ABSTRACT

This thesis investigates the relationship between quantitative correlates of diffuse brain damage and neurological and psychiatric manifestations in Systemic Lupus Erythematosus (SLE). A group of 37 patients with a primary diagnosis of SLE (mean age 43.97±12.55) were compared to 29 matched healthy controls. The SLE group were subdivided into those who had experienced neuropsychiatric (NP) manifestations (NPSLE – n=15) and those who had never had NP manifestations (non-NPSLE). Participants completed a broad cognitive test battery, neuropsychological measures and quantitative MRI (magnetisation transfer (MTI) and diffusion tensor imaging (DTI)). From MTI the magnetisation transfer ratio (MTR) was measured, which can be a marker for demyelination. Using DTI the extent (apparent diffusion coefficient) and directionality (fractional anisotropy) of diffusion were assessed, which are sensitive measures of brain structural integrity.

Results indicate that both SLE groups had significantly higher scores on depression and anxiety and lower quality of life compared to healthy controls. The only difference between the NPSLE and non-NPSLE groups was lower physical health related quality of life in the former group. On cognitive tasks the NPSLE group scored significantly worse than controls on multiple domains, and worse than the non-NPSLE group on memory and speed of processing. There were no differences between the non-NPSLE patients and controls. On DTI measures the NPSLE group showed increased white matter ADC and a non significant decrease in FA, changes which are consistent with subtle brain damage in this group. The non-NPSLE group had higher ADC than controls if measured in the whole brain. There were no differences on MTI and few differences on measures of brain volume, suggesting demyelination and atrophy were not noteworthy in this cohort.

Correlations were assessed between cognition and the other factors. In the NPSLE group cognitive function correlated with white matter FA suggesting this was driven by changes in brain parenchyma. Cognitive function also correlated with pain, fatigue, physical health, disease activity and anxiety scores suggesting general health related factors also play a role in cognitive dysfunction. In the non-NPSLE group processing speed correlated with depression scores, but no other relationships were evident. The role of anti-phospholipid antibodies, anti-Ro antibodies, corticosteroid dose and confounds such as renal involvement in SLE, hypertension and motor speed differences were considered. None of these factors could explain cognitive dysfunction in the patient group. These findings are interpreted as indicating that cognitive performance in NPSLE is unlikely to be driven by emotional health. Instead performance related to white matter integrity and general illness, two factors which may be interlinked.
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AUTHOR’S DECLARATION

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to these or any other university for a degree, and does not incorporate any material already submitted for a degree.

Signed

Date
**LIST OF KEY ABBREVIATIONS**

<table>
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<tr>
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<tr>
<td>ACR</td>
<td>American college of rheumatology</td>
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<tr>
<td>ADC</td>
<td>Apparent diffusion coefficient</td>
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<td>APS</td>
<td>Anti-phospholipid syndrome</td>
</tr>
<tr>
<td>CFQ</td>
<td>Cognitive failures questionnaire</td>
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<td>CII</td>
<td>Cognitive impairment index</td>
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<tr>
<td>COWAT</td>
<td>Controlled oral word association test</td>
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<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<td>CV</td>
<td>Coefficient of variation</td>
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<td>DTI</td>
<td>Diffusion tensor imaging</td>
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<td>FA</td>
<td>Fractional anisotropy</td>
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<td>GIS</td>
<td>Global impairment score</td>
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<td>HADS</td>
<td>Hospital anxiety and depression scale</td>
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<td>ISD</td>
<td>Intra-individual standard deviation</td>
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<td>LupusQol</td>
<td>Lupus Quality of life</td>
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<td>MCS</td>
<td>Mental component score (of SF-36)</td>
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<td>MTI</td>
<td>Magnetisation transfer imaging</td>
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<td>MTR</td>
<td>Magnetisation transfer ratio</td>
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<td>NART</td>
<td>National adult reading test</td>
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<td>NPSLE</td>
<td>Neuropsychiatric systemic lupus erythematosus</td>
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<tr>
<td>PCS</td>
<td>Physical component score (of SF-36)</td>
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<tr>
<td>RAVLT</td>
<td>Rey auditory verbal learning test</td>
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<tr>
<td>RVIP</td>
<td>Rapid visual information processing</td>
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<td>SF-36</td>
<td>Short form-36</td>
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<td>SLE</td>
<td>Systemic lupus erythematosus</td>
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<td>SLEDAI</td>
<td>Systemic lupus erythematosus disease activity index</td>
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<tr>
<td>SOP</td>
<td>Speed of processing</td>
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<td>SSAl</td>
<td>Spielberger state anxiety inventory</td>
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<td>VBM</td>
<td>Voxel based morphometry</td>
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CHAPTER 1

INTRODUCTION

1.1 Lupus as a clinical problem

Systemic Lupus Erythematosus (SLE) or “Lupus” is a chronic inflammatory, immune mediated disease. In SLE the immune system produces antibodies (auto-antibodies) that attack DNA and other material in the nuclei the patient’s own cells, causing inflammation and damage to joints, muscles and other organs. As the name ‘systemic’ implies, almost any organ may be affected, leading to a wide range of symptoms including generalised symptoms such as fatigue, joint/muscular pain, feverishness, rashes, weakness and weight gain or loss, and specific symptoms of particular organ involvement. These can include cardiovascular symptoms such as chest pain, renal complications, mucosal ulcers and alopecia.

SLE affects approximately 1:35000 of the population (A. E. Johnson, Gordon, Palmer, & Bacon, 1995), and is more prevalent in people of Afro-Caribbean or Asian descent than European (Hopkinson, Doherty, & Powell, 1993; Samanta, Roy, Feehally, & Symmons, 1992). It is also more common in females, with a male to female ratio of 1:9. This is thought to be due to the action of sex hormone, as oestrogens can enhance the immune system, whereas androgens and progesterone suppress it (Rubtsov, Rubtsova, Kappler, & Marrack, 2010).

SLE is characterised by flares and remissions in symptoms. It is currently incurable, and therefore treatments focus on managing symptoms. Common drug treatments include; corticosteroids, which affect inflammation and dampen disease activity; cytotoxic or immunosuppressive drugs; anti-malarials such as hydroxychloroquin, which has anti-inflammatory properties; and non-steroidal anti inflammatory drugs as a high proportion of SLE patients develop joint pain (Bernknopf, Rowley, & Bailey, 2011).

1.2 Neuropsychiatric SLE (NPSLE)

As previously mentioned, SLE can affect any organ system, and this includes the brain. Involvement of the brain has been termed Neuropsychiatric SLE or NPSLE. In 1999 the American College of Rheumatology defined 19 neuropsychiatric manifestations of SLE to allow...
classification for research purposes (ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999a). Prior to 1999 NPSLE was not well defined, with studies using different classifications and terminology. This included CNS lupus or cerebral lupus, which ignored the involvement of the peripheral nervous system. The neuropsychiatric manifestations of SLE are shown in table 1.1.

### Neuropsychiatric manifestations of SLE

#### Central Nervous System

<table>
<thead>
<tr>
<th>Neurological</th>
<th>Psychiatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aseptic Meningitis</td>
<td>Acute confusional state</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>Anxiety disorder</td>
</tr>
<tr>
<td>Demyelinating syndrome</td>
<td>Cognitive dysfunction</td>
</tr>
<tr>
<td>Headache</td>
<td>Mood disorder</td>
</tr>
<tr>
<td>Movement disorder (chorea)</td>
<td>Psychosis</td>
</tr>
<tr>
<td>Myelopathy</td>
<td></td>
</tr>
<tr>
<td>Seizure disorder</td>
<td></td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td></td>
</tr>
</tbody>
</table>

#### Peripheral Nervous System

- Acute inflammatory demyelinating polyradiculoneuropathy
- Autonomic disorder
- Guillain-Barre syndrome
- Neuropathy
- Mononeuropathy (single/multiplex)
- Plexopathy
- Polyneuropathy

Table 1.1: Neuropsychiatric manifestation of SLE, defined by the American College of Rheumatology (ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999a)

The proportion of patients displaying neuropsychiatric (NP) involvement varies widely across studies by as much as 14-91% (Ainiala, Loukkola, Peltola, Korpela, & Hietaharju, 2001). This is in part due to the different criteria used to define what constitutes NPSLE, but also the heterogeneous nature of NPSLE itself. NPSLE presents a diagnostic challenge as it is not clear to what extent subtle psychiatric manifestations, such as cognitive dysfunction, depression and anxiety are direct consequences of SLE disease activity or are secondary responses to chronic illness or treatment with corticosteroids. A second issue that arises is whether the NPSLE and non-NPSLE patients form two distinct groups, or whether they show a continuum of severity of CNS involvement with subclinical involvement in non-NPSLE.
1.3 Differentiation of NPSLE and non-NPSLE groups

As depression, anxiety and cognitive dysfunction have all been incorporated into the NPSLE nomenclature, it might be expected that there would be a distinction between patients with NPSLE and non-NPSLE on these measures, depending on how the groups have been defined. On the other hand a high prevalence of cognitive impairment has also been shown in SLE patients without overt neuropsychiatric manifestations, with recent studies reporting impairment in 15-55% of non-NPSLE patients (Denburg & Denburg, 2003). This compares to prevalence rates ranging from 40-81% in NPSLE patients (Carbotte, Denburg, & Denburg, 1986; Carlomagno, et al., 2000; Hanly, Fisk, et al., 1992; Hay, et al., 1992; Kozora, Ellison, & West, 2004; Monastero, et al., 2001; Sailer, et al., 1997). Studies comparing participants with NPSLE and non-NPSLE on cognitive functioning have gave generally found greater impairment in the NPSLE group (Kozora, et al., 2004; Kozora, Ellison, & West, 2006; Loukkola, et al., 2003; Monastero, et al., 2001) however, this does not preclude the idea that the patients fall on a continuum with the NPSLE group at the more extreme end.

Prevalence studies also suggest a high rate of depression in NPSLE with prevalence rates of 23-44% (Ainiala, Loukkola, et al., 2001; Brey, et al., 2002; Robert, Sunitha, & Thulaseedharan, 2006). Some studies have also found higher depression scores in non-NPSLE patients than in controls (Kozora, Arciniegas, et al., 2008; Kozora, et al., 2006) although other studies have not found this (Monastero, et al., 2001; Olazaran, Lopez-Longo, Cruz, Bittini, & Carreno, 2009). Previous research into the distinction between NPSLE and non-NPSLE patients on a variety of measures of mental health and wellbeing is introduced in chapter 3. In general the NPSLE participants show worse scores on depression and anxiety than non-NPSLE patients, but there is also evidence of emotional disturbance in non-NPSLE patients.

These mixed findings mean the question of whether the NPSLE and non-NPSLE form distinct groups on the basis of diffuse psychiatric symptoms is still unanswered. This thesis addresses this question focussing on psychiatric manifestations of depression, anxiety and cognitive dysfunction.
1.4 Why is cognitive dysfunction important?

Cognitive impairment is widely acknowledged to affect a sizable proportion of SLE patients (Benedict, Shucard, Zivadinov, & Shucard, 2008; Denburg & Denburg, 2003). The prevalence varies widely across studies due to factors such as methodological variation and differences in samples (Benedict, et al., 2008). However, cognitive dysfunction has been shown to be one of the most prevalent neuropsychiatric manifestations of SLE in prevalence studies (Ainiala, Loukkola, et al., 2001; Brey, et al., 2002). As acknowledged in the ACR case definitions, cognitive dysfunction can have an impact on social, educational and occupational functioning. The likelihood of being unemployed has been related to the presence and number of cognitive domains impaired (Appenzeller, Cendes, & Costallat, 2009) and to severity of memory impairment (Panopalis, et al., 2007). An association between employment status and cognitive impairment has also been found in non-NPSLE (Olazaran, et al., 2009). This can have implications for the patient’s quality of life and wider implications such as economic costs if the patient is unable to work. It is important to understand the pattern of deficits in SLE, and the potential correlates of impairment in order to better treat patients who present with cognitive complaints or mild cognitive impairment.

Cognitive dysfunction is an important area for research in chronic illness. Neuro-inflammatory conditions such as multiple sclerosis have been associated with significant cognitive impairment (Benedict, et al., 2008). However, cognitive dysfunction has also been related to a wide range of chronic illnesses that are not directly related to the brain, such as inflammatory bowel disease and irritable bowel syndrome (Attree, Dancey, Keeling, & Wilson, 2003), liver disease, (Hilsabeck, Hassanein, Carlson, Ziegler, & Perry, 2003), diabetes (Kodl & Seaquist, 2008), following chemotherapy for breast cancer (Tannock, Ahles, Ganz, & van Dam, 2004) and cardiac bypass surgery (van Dijk, et al., 2000). These diverse conditions are likely to have a variety of different mechanisms that lead to the same outcome of cognitive dysfunction. This highlights the importance of assessing the extent to which cognitive performance is associated with general aspects of illness, or whether cognitive dysfunction in SLE is a consequence of lupus specific disease activity and damage to brain parenchyma.

Understanding the causes of psychiatric manifestations such as cognitive dysfunction is important in a clinical context as this can affect how the patient is treated. If these manifestations reflect the direct consequence of disease activity on the nervous system, then
treatment using immunomodulatory drugs should benefit the patient. If instead cognitive dysfunction arises from secondary causes, such as co-existing emotional disturbance, then treatment should instead focus instead on the emotional disturbance.

1.5   Theories behind cognitive dysfunction in SLE

1.5.1   Lupus specific damage to brain parenchyma

Mechanisms for Lupus pathology involve vascular damage and autoantibody mediated injury to neuronal cells. At least 20 auto-antibodies have been associated with NPSLE. Of these 11 act on brain components and the remaining nine act systemically (Zandman-Goddard, Chapman, & Shoenfeld, 2007). The most widely investigated of these are anti-Cardiolipin and Lupus anticoagulant antibodies, which are associated with Antiphospholipid syndrome (APS). APS is a disorder of coagulation, which induces a pro-thrombotic state, and as such, it is linked with an increased risk of thrombosis. Vascular abnormalities such as multifocal microinfarcts have been linked to focal neuropsychiatric manifestations of SLE (Abbott, Mendonca, & Dolman, 2003). However, these changes may also occur independent of APS (Kozora, Hanly, Lapteva, & Filley, 2008).

Other antibodies may affect neuronal tissue, but it is not clear whether they are able to act on the central nervous system (CNS) due to disruption to the blood-brain barrier (BBB) or whether they are produced within the CNS. One hypothesis is that either vasculopathy of small vessels, or an immune mediated attack on the endothelium, enhances BBB permeability. This may then allow access of pathogenic autoantibodies to the brain, and if these antibodies act against neuronal proteins then neurological damage may occur (Abbott, et al., 2003). Thus Zvaifler and Bluestein (1982), suggest that the coexistence of serum antibodies against brain tissue and disruption to the BBB are needed, and neither alone is sufficient.

Autopsy studies indicate small vessel vasculopathy as a common finding (Brooks, Jung, Ford, Greinel, & Sibbitt, 1999; Ellis & Verity, 1979; Hanly, Walsh, & Sangalang, 1992; R. T. Johnson & Richardson, 1968; Sipek-Dolnicar, et al., 2002). This supports the first part of the model. Hanly, Walsh et al. (1992) also found 2 (of 10) patients showing diffuse astrogliosis, which is usually a response to longstanding neuronal injury. They suggest this was not clinically explained and could reflect auto-antibody damage. However, there was no association between astrogliosis
and detectable auto-antibodies in these patients, or between specific antibodies and clinical NPSLE or neuropathogenic findings. Additionally, immunohistological examinations did not find surface reactivity on neuronal or glial cells (in three patients studied). On the other hand animal models using a lupus prone mouse (NZM88 strain) have shown a functional link between auto-antibodies, activation of microglia, and neuronal function associated with dopamine production (Mondal, Saha, Miller, Seegal, & Lawrence, 2008).

In clinical studies, there is some evidence for a link between specific neuropsychiatric manifestations and certain auto-antibodies, but the research is far from conclusive and at the moment no antibody has been shown to be highly sensitive or specific for NPSLE or for cognitive dysfunction (Zandman-Goddard, et al., 2007). Another way to approach this question is to look at in vivo metrics of brain structural integrity. Brain imaging research has focussed on identifying structural changes to brain parenchyma in SLE patients (Kozora & Filley, 2011; Peterson, Axford, & Isenberg, 2005, see for review), with the assumption that differences from matched healthy controls are the result of lupus disease. If cognitive dysfunction does result from the direct action of lupus disease on brain tissue, then we can hypothesise, (1) there would be a difference between patients and controls on brain imaging measures, (2) there would be a correlation between the imaging parameters and cognitive function, (3) if damage to the nervous system only occurs in patients with NPSLE then this group would differentiate from healthy controls whereas the non-NPSLE patients would not.

1.5.2 The effect of emotional disturbance

Mood and psychological factors have been associated with cognitive performance in psychiatric patients and patients with neurological disorders (Sweet, Newman, & Bell, 1992). As both depression and cognitive dysfunction are prevalent in SLE it has been proposed that cognitive impairment in SLE is related to co-existing symptoms of depression or anxiety.

There is some evidence to support this idea. In a longitudinal study, Hay (1994) found cognitive function followed the course of psychiatric status, with patients showing improved psychiatric status also improving on cognitive testing. Another study used multivariate analysis to predict cognitive performance. Depression and level of education were the only significant variables (age, neuropsychiatric involvement, disease duration, disease activity, current steroid dose, and anxiety were not) (Monastero, et al., 2001). Conversely other studies have found no
relationship between psychiatric disorder and cognitive impairment (Carlomagno, et al., 2000; Denburg, Carbotte, & Denburg, 1997) or have found cognitive dysfunction in the absence of emotional disturbance (Segui, et al., 2000). Kozora, Arciniegas, Zhang, and West (2007) compared cognitive impairment in depressed SLE patients, depressed controls and non depressed controls. They found the overall magnitude and pattern of cognitive impairment in depressed SLE patients could not be explained by depression alone. These data suggest that although in some patients psychiatric symptoms such as depression may explain their cognitive performance, there is not enough of a link to argue this is the case in all patients.

The correlation between mood and cognitive performance is addressed in chapter 7. If cognitive dysfunction is related to emotional disturbances then a few predictions can be made; (1) there would be a significant negative correlation between scores on measures of depression and anxiety and cognitive function (2) differences between NPSLE and non-NPSLE patients would only be expected if there are also differences on measures of emotional disturbance.

1.5.3 Non-specific aspects of chronic illness

Cognitive dysfunction could be a response to non specific aspects of ill-health, such as symptoms including fatigue or pain or generally feeling unwell or the effect of treatment, such as corticosteroids. Animal models suggest links between corticosteroids and hippocampal damage, and deficits in memory (McEwen, 2000). This link has also been substantiated by similar findings in humans (Brown, et al., 2004; Keenan, et al., 1996). However, corticosteroids may also help repair damage to the blood brain barrier, and therefore may be protective of neuropsychiatric manifestations of SLE. This is supported by evidence that steroid use can improve cognitive dysfunction and mood (Denberg, Carbotte and Denberg, 1994). The effect of chronic illness including treatment with corticosteroids is assessed in chapter 7 of the current thesis.

Fatigue following prolonged wakefulness has been shown to have detrimental effects on cognitive function (Broadbent, 1958). Correlations have also been identified between fatigue and cognition in Multiple Sclerosis (Diamond, et al., 2006) Parkinson’s Disease (Friedman, et al., 2007) and cognitive dysfunction has been seen in chronic fatigue syndrome without co-morbid psychiatric disorder (DeLuca, Johnson, Ellis, & Natelson, 1997). Chronic pain has also
been associated with neuropsychological impairment, particularly attention, psychomotor speed and memory (Hart, Martelli, & Zasler, 2000). Research also suggests that systemic infection can elicit characteristic behavioural responses such as reduced motivation, psychomotor slowing, mild cognitive impairment and affective change. These have been termed “sickness behaviour” and may be mediated by pro-inflammatory cytokines. These normally coordinate the immune response to microbial pathogens, but may also act on the brain producing the stereotypical sickness behaviours, as reviewed in (Dantzer, O’Connor, Freund, Johnson, & Kelley, 2008).

A possible link between non-specific aspects of chronic illness and cognition is not necessarily distinct from either of the above options as it may be that health related symptoms are related to the same disease processes that may lead to immune mediated damage to brain parenchyma, or may be related to co existing emotional disturbance. Nonetheless, if cognitive dysfunction in SLE is related to non specific aspects of chronic illness then a few predictions can be made, (1) there would be a correlation between cognitive function and systemic disease activity or measures of physical health, pain or fatigue, (2) no difference in cognitive performance would be expected between NPSLE and non-NPSLE patients, or other chronic illness controls assuming the groups have similar levels of systemic disease activity.

1.6 Purpose and structure of the thesis

Previous research suggests that cognitive impairment and mood disorders are prevalent in NPSLE and these have been incorporated into the American College of Rheumatology (ACR) nomenclature for NSPLE (ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999a). However, mild cognitive impairment and depression have also been found in non-NPSLE leading to the suggestion that these two groups may not be distinct, and instead form a continuum of neuropsychiatric involvement. This is addressed in the current thesis looking at measures of mental health and wellbeing, including self reported symptoms of depression, anxiety and quality of life (chapter 3), cognitive function (chapters 4 and 5) and quantitative magnetic resonance imaging (MRI)(chapter 6). Quantitative MRI refers to structural imaging methods that can be used to quantify changes in brain structural integrity, for example magnetisation transfer imaging and diffusion tensor imaging.

The primary focus of the thesis is to describe differences in cognitive function between the groups. Methodological variation in previous studies has prevented direct comparison of
results. As previously noted there is a wide range in the proportion of patients classed as impaired, and this is partially due to differences in test batteries used and the method used to detect impairment. To allow comparability with previous studies a broad cognitive test battery has been developed that is primarily based on one proposed by the ACR (ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999b). Previous studies have used a mixture of analytic methods, including categorical analysis with the group divided into impaired and not impaired, group comparisons on individual tasks and comparisons on different cognitive domains. These methodological considerations are discussed in section 4.1.3 and different analysis methods are compared. Cognitive performance is further analysed by investigating group differences on three tasks in more detail (chapter 5). This more sophisticated analysis has two purposes; first to see whether differences between NPSLE and non-NPSLE patients can be clarified by looking at tasks in more detail and secondly to see whether the cognitive processes involved in cognitive deficits can be elucidated.

The first aim of the analysis is to identify differences between SLE patients and controls in terms of cognitive performance, psychology and imaging. The second aim of the research programme is to investigate the extent to which the differences from controls are specific to those with neuropsychiatric manifestations of SLE (NPSLE). The third aim is to investigate the relationship between cognitive performance and the clinical, emotional and imaging parameters (chapter 7). This is assessed in the SLE group as a whole, and then in the NPSLE and non-NPSLE subgroups separately to see whether these groups show different correlates of cognitive function. Additionally, to address the question of whether observed changes are specific to SLE or related to chronic illness in general, a group of illness controls have been recruited for comparison with other groups on all measures.
CHAPTER 2

METHODOLOGIES

2.1 Design

This study had a cross sectional design. An opportunistic sample of SLE patients was recruited from one rheumatology clinic at the Royal Sussex County Hospital, led by consultant rheumatologist Professor K Davies. A comparison group of age and sex matched controls were identified and recruited from the community. In order to reduce experimenter effect all cognitive testing was completed by the lead researcher. The design meant it was impossible to have randomisation, or for the researcher to be completely blind to the status of the participants. However, SLE participants were not categorised into NPSLE and non-NPSLE subgroups until after all cognitive assessments were completed. Additionally, standard procedures were followed during the cognitive assessment and standard instructions given for all tasks. The study was approved by the East Kent Local Research Ethics Committee (REC reference 08/H1103/29) on the 1st May 2008.

2.1.1 Justification for choice of participants.

Previous studies have focussed on either NPSLE or non-NPSLE groups. Whilst making sense in a research context, this does not necessarily translate into clinical practice, where categorisation may not be clear cut. At present if a patient is identified as having possible NPSLE they are usually referred for an MRI scan and based on the finding this diagnosis of probable NPSLE is confirmed or more usually denied. Therefore for initial recruitment a general group of SLE patients were selected and later categorized into NPSLE and non-NPSLE on the basis of symptoms for a final sub-group analysis. This allows analysis of whether it is more meaningful to treat NPSLE and non-NPSLE patients as qualitatively different or whether they form a continuum. Additionally participants were not screened or excluded for co-morbidities as we wanted to represent the “normal” SLE patient seen in the clinic, but had to have a primary rather than secondary diagnosis of SLE. In this sample 32/37 (86.5%) of patients had at least one co-morbidity as shown in table 2.3.
Two control groups were selected for the study, the first being a group of age matched healthy controls selected to represent the performance of the general “normal” population. This group formed the main comparison group for the initial analyses.

In addition, a chronic illness control group of rheumatology conditions with no SLE was recruited. This group predominantly consisting of patients with Rheumatoid Arthritis, however also included three patients, two with Primary Sjögren’s syndrome, both with no symptoms of central nervous system involvement and one with urticarial vasculitis. Analyses were repeated using only the RA patients to assess whether the presence of these other conditions within the group were affecting results and conclusions. The illness control group was selected to give information about the effects of either having a long term condition, medications fatigue or pain on cognition and mental health and wellbeing. It was hypothesised that these patients would show “normal” brain scans but may differ from healthy controls on scores of quality of life, depression and anxiety and cognition. The comparison with this group has been included in chapter 7.

2.2 Eligibility

SLE group

Any SLE patient attending the rheumatology clinics at either the Royal Sussex County Hospital or the Princess Royal Hospital was eligible to take part in the study.

Exclusion criteria for the SLE group were:

- They were aged less than 18 years old
- They were aged over 68 years old
- They were a non-Native English speaker
- They had contraindications for MRI

Exclusion criteria for the healthy control comparison group were:

- They were aged less than 18 years old
- They were aged over 68 years old
They were a non-Native English speaker
They had contraindications for MRI
They had a long term illness including depression
They had known neurological problems

Exclusion criteria for the Rheumatoid arthritis group were as above with the addition that they were excluded for any concurrent medical conditions and were especially screened (and excluded) for SLE, anti-phospholipid antibodies and fibromyalgia.

2.3 Power analysis

Power analysis was undertaken to calculate the minimum sample size needed to obtain 80% power based on using an independent samples t-test with a significance level of 0.05. The data (means and standard deviations) were taken from a study (Kozora, et al., 2006) which used the SLE–ACR battery to calculate a cognitive impairment index. These scores were comparable to other studies using the same measure. Performance difference (d effect size 0.72) between an NPSLE/SLE group and control group suggested a sample size of 32 per group was needed (power 0.80, p<0.05, two tailed). This was then weighed against data from a study that compared an SLE patient group to a control group on MRI measures of diffusion (Zhang, et al., 2007) (d effect size 0.78) which suggested a sample size of 27 per group was needed (power 0.80, p<0.05, two tailed). Finally even larger effect sizes have been found (d > 0.8) (Kozora, et al., 2006; Monastero, et al., 2001) for differences between SLE patients and controls on measures of depression and anxiety again indicating a sample of 32 per group should pick up differences on these measures.

2.4 Recruitment

SLE group

Patients were identified in clinic by the rheumatology consultant. In all cases but one these were identified by Professor K Davies. Patients were informed that there was a study being conducted and asked if they could be contacted by the researcher by telephone. Potential participants were then contacted and asked if they would be interested in receiving the patient information leaflet about the study. After a short delay to allow them time to read the information, they received a follow-up phone call to see if they would be interested in
participating. Participants were then invited for the first study visit at which point they were formally recruited into the study through an informed consent procedure.

Healthy control group

The members of the comparison group were recruited from a number of sources including university staff (n=9) a local woman’s running group (n=7) partners or spouses of participants (n=1) word of mouth (n=9) and participants in a previous study assessing the factor structure of the test battery (see section 4.3) (n=2).

Rheumatoid arthritis group

Patients were identified through the rheumatology clinics by consultant rheumatologists Professor K Davis and Dr K Walker-Bone. Patients were contacted by the consultant by post and sent a copy of the patient information leaflet, inviting them to contact the research team if they had any questions or were interested in taking part.

2.5 Participant demographics

Table 2.1 shows the participant demographics for age, gender, years in education, handedness and number of errors on the National Adult Reading Test (NART) (Nelson, 1982) which is a measure of pre-morbid IQ. The groups were compared using univariate ANOVA tests for continuous variables (age, education, NART) and chi-square test for categorical variables. No significant differences were found for age, gender, years in education, or handedness, indicating the groups were well matched on these attributes. However a significant group difference was found on NART scores with the SLE group making significantly more errors than the healthy controls while the illness controls did not differ from either group. This difference equates to an 8 point difference in IQ between the healthy controls and SLE patients. As many of the cognitive tests depend on IQ, NART error score was added as a covariate to all group comparisons on the cognitive test battery. Additionally the results of the chi-square test should be interpreted with caution as 50% of cells had frequencies less than five. To ensure any differences found on any measure were not due to the lower percentage of males in the control group, (3.6% compared to 8-9% in the other groups) the data was checked to ensure the males were not acting as outliers and influencing the statistical tests. Additionally the
imaging data was assessed for the influence of left-handers as the illness control group contained a greater percentage (36% compared to 11% in the other groups).

<table>
<thead>
<tr>
<th></th>
<th>Control (n=28)</th>
<th>Illness controls (n=11)</th>
<th>SLE all (n=37)</th>
<th>Between groups difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>43.8 (11.5)</td>
<td>48.2 (11.9)</td>
<td>44.7 (12.7)</td>
<td>F(2,73)=0.52, n.s</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>96.4%</td>
<td>90.9%</td>
<td>91.9%</td>
<td>χ²(2)=0.67, n.s</td>
</tr>
<tr>
<td>Years in education</td>
<td>15.5 (2.2)</td>
<td>14.6 (2.8)</td>
<td>14.3 (3.5)</td>
<td>F(2,73)=1.31, n.s</td>
</tr>
<tr>
<td>NART (number of errors)</td>
<td>13.0 (5.5)</td>
<td>17.7 (5.8)</td>
<td>19.2 (8.3)</td>
<td>F(2,30)=7.29, p&lt;0.01^</td>
</tr>
<tr>
<td>Corresponding IQ (from NART)</td>
<td>113 (6.3)</td>
<td>107 (6.6)</td>
<td>105 (9.5)</td>
<td>-</td>
</tr>
<tr>
<td>Handedness (% right)</td>
<td>89.3%</td>
<td>63.3%</td>
<td>89.2%</td>
<td>χ²(2)=4.98, n.s</td>
</tr>
</tbody>
</table>

Table 2.1: Participant demographics for the current study
^ SLE > control

The SLE group were further subdivided into neuropsychiatric SLE (NPSLE) and non-NPSLE. This was done by consultant rheumatologist Professor Davies on the basis of their clinical picture using the American College of Rheumatology criteria for NPSLE (ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999a). Fifteen patients were identified as having current or previous neuropsychiatric manifestations, while 22 were considered to have no evidence of NPSLE. The neuropsychiatric symptoms are shown in table 2.2. Only two participants had been formally assessed for cognitive dysfunction (required for classification according to ACR criteria), however a further four participants within the NPSLE group had documented subjective cognitive complaints. With all these participants included, cognitive dysfunction was the most prevalent manifestation, affecting 40% of participants. This was followed by headache, mononeuropathy and seizure disorder affecting 27% each. Comparison of the prevalence of neuropsychiatric manifestations to previous published studies is difficult due to the inconsistency of findings across studies; nonetheless consistent with the present findings, cognitive dysfunction and headache have been found to be the most frequent manifestations across three prevalence studies (Ainiala, Hietaharju, et al., 2001; Ainiala, Loukkola, et al., 2001; Brey, et al., 2002; Robert, et al., 2006). However the prevalence may be underestimated in the present sample as cognitive dysfunction was found in around 80% of
NPSLE patients and headache in approximately 50%, whilst myelopathy was not seen in any of the three studies, but affected 20% of participants in the present study. Differences within populations may reflect the heterogeneity of SLE and NPSLE or may suggest that some more subtle manifestations have been missed.

<table>
<thead>
<tr>
<th>Neuropsychiatric manifestation</th>
<th>Number of participants (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive dysfunction (ACR)</td>
<td>2 (13.3 %)</td>
</tr>
<tr>
<td>Subjective cognitive complaints</td>
<td>6 (40.0 %)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (26.7 %)</td>
</tr>
<tr>
<td>Mononeuropathy</td>
<td>4 (26.7 %)</td>
</tr>
<tr>
<td>Seizures and Seizure disorder</td>
<td>4 (26.7 %)</td>
</tr>
<tr>
<td>Mood disorder</td>
<td>3 (20.0 %)</td>
</tr>
<tr>
<td>Myelopathy</td>
<td>3 (20 %)</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>1 (6.7 %)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1 (6.7 %)</td>
</tr>
<tr>
<td>Demyelinating syndrome</td>
<td>1 (6.7 %)</td>
</tr>
<tr>
<td>Movement disorder</td>
<td>1 (6.7 %)</td>
</tr>
</tbody>
</table>

Table 2.2: Neuropsychiatric manifestations of SLE volunteers in the current sample.

The two SLE populations are compared in table 2.3. There are no significant group differences on any of the demographic variables, clinical variables, concurrent medical conditions or current medications indicating the groups are well matched on these variables; however the NPSLE group did have a greater proportion with concurrent Sjogren’s syndrome (SS) and anti-phospholipid syndrome (APS) (60 versus 40% for SS and 27 versus 13% for APS) and a greater proportion currently on a high dose (greater than 10 mg per day) of corticosteroids (27 versus 5%). The affect of these factors on cognitive performance is discussed in chapter 7.

A significantly greater number of NPSLE participants had previous MRI scans (73.3% compared to 22.7%). But they were not more likely to have had an abnormality reported on the scan. Around half the patients in each group who had a previous MRI, had an abnormality reported.
<table>
<thead>
<tr>
<th>Participant demographics</th>
<th>SLE all (n=37)</th>
<th>Non-NPSLE (n=22)</th>
<th>NPSLE (n=15)</th>
<th>Between groups difference (non-NPSLE vs NPSLE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44.7 (12.7)</td>
<td>42.9 (13.9)</td>
<td>47.3 (10.6)</td>
<td>t(35)=-1.03, n.s</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>91.9%</td>
<td>90.9%</td>
<td>93.3%</td>
<td>χ^2(1)=0.07, n.s</td>
</tr>
<tr>
<td>Years in education</td>
<td>14.3 (3.5)</td>
<td>14.1 (3.00)</td>
<td>14.7 (4.3)</td>
<td>t(35)=-0.58, n.s</td>
</tr>
<tr>
<td>NART (errors)</td>
<td>19.1 (8.4)</td>
<td>20.7 (8.3)</td>
<td>16.5 (8.0)</td>
<td>t(35)=1.5, n.s</td>
</tr>
<tr>
<td>Corresponding IQ</td>
<td>105 (9.5)</td>
<td>104 (9.5)</td>
<td>108 (9.1)</td>
<td>-</td>
</tr>
<tr>
<td>Handedness (% right)</td>
<td>89.2%</td>
<td>90.9%</td>
<td>86.7%</td>
<td>χ^2(1)=0.17, n.s</td>
</tr>
<tr>
<td>Disease information</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>7.9 (7.1)</td>
<td>8.5 (7.9)</td>
<td>7.1 (5.9)</td>
<td>t(35)=0.53, n.s</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>36.6 (11.8)</td>
<td>34.4 (10.4)</td>
<td>40.1 (13.5)</td>
<td>t(35)=-1.41, n.s</td>
</tr>
<tr>
<td>SLEDAI score †</td>
<td>2.8 (2.5)</td>
<td>3.0 (2.4)</td>
<td>2.5 (2.7)</td>
<td>t(35)=0.56, n.s</td>
</tr>
<tr>
<td>Current hypertension (%)</td>
<td>2.7 %</td>
<td>4.5 %</td>
<td>0.0 %</td>
<td>-</td>
</tr>
<tr>
<td>On anti-hypertensive drugs (%)</td>
<td>24.3 %</td>
<td>22.7 %</td>
<td>26.7 %</td>
<td>χ^2(1)=0.08, n.s</td>
</tr>
<tr>
<td>Current renal involvement</td>
<td>8.1 %</td>
<td>13.6 %</td>
<td>0.0 %</td>
<td>-</td>
</tr>
<tr>
<td>Renal involvement ever</td>
<td>13.5 %</td>
<td>13.6 %</td>
<td>13.3 %</td>
<td>χ^2(1)=0.27, n.s</td>
</tr>
<tr>
<td>Concurrent medical conditions (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sjogrens syndrome</td>
<td>48.6 %</td>
<td>40.9 %</td>
<td>60.0 %</td>
<td>χ^2(1)=1.30, n.s</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>18.9 %</td>
<td>13.6 %</td>
<td>26.7 %</td>
<td>χ^2(1)=0.98, n.s</td>
</tr>
<tr>
<td>Fibromyalgia syndrome</td>
<td>10.8 %</td>
<td>9.1 %</td>
<td>13.3 %</td>
<td>χ^2(1)=0.17, n.s</td>
</tr>
<tr>
<td>Reynauds Phenomena</td>
<td>59.4 %</td>
<td>59.1 %</td>
<td>60.0 %</td>
<td>χ^2(1)=0.03, n.s</td>
</tr>
<tr>
<td>Mean number of co-morbidities</td>
<td>1.4 (0.8)</td>
<td>1.3 (0.9)</td>
<td>1.6 (0.5)</td>
<td>t(33.6)=1.37, n.s</td>
</tr>
<tr>
<td>Prior Imaging (%)</td>
<td>43.2 %</td>
<td>22.7 %</td>
<td>73.3 %</td>
<td>χ^2(1)=9.3, p&lt;0.01</td>
</tr>
<tr>
<td>% of MRIs abnormal</td>
<td>50.0%</td>
<td>40.0%</td>
<td>54.4%</td>
<td>χ^2(1)=0.29, n.s</td>
</tr>
<tr>
<td>Drugs (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease modifying</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current corticosteroid‡</td>
<td>59/27/14</td>
<td>59/36/5</td>
<td>60/13/27</td>
<td>χ^2(2)=4.98, n.s</td>
</tr>
<tr>
<td>Previous corticosteroid‡</td>
<td>27/27/46</td>
<td>36/18/45</td>
<td>13/40/47</td>
<td>χ^2(2)=3.32, n.s</td>
</tr>
<tr>
<td>Hydroxyclochoquin</td>
<td>67.6 %</td>
<td>72.7 %</td>
<td>60.0 %</td>
<td>χ^2(1)=0.69, n.s</td>
</tr>
<tr>
<td>Micophenolate</td>
<td>18.9 %</td>
<td>9.1 %</td>
<td>33.3 %</td>
<td>χ^2(1)=3.44, n.s</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>10.8 %</td>
<td>13.6 %</td>
<td>6.7 %</td>
<td>χ^2(1)=0.45, n.s</td>
</tr>
<tr>
<td>Non disease modifying</td>
<td>16.2 %</td>
<td>13.6 %</td>
<td>20.0 %</td>
<td>χ^2(1)=0.27, n.s</td>
</tr>
<tr>
<td>Drugs affecting CNS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-depressants</td>
<td>27.0 %</td>
<td>22.7 %</td>
<td>33.3 %</td>
<td>χ^2(1)=0.51, n.s</td>
</tr>
<tr>
<td>Anti-convulsant</td>
<td>8.1 %</td>
<td>0.0 %</td>
<td>20.0 %</td>
<td>-</td>
</tr>
<tr>
<td>Other (Sumatriptan)</td>
<td>2.7 %</td>
<td>0.0 %</td>
<td>6.7 %</td>
<td>-</td>
</tr>
<tr>
<td>Drugs not affecting CNS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>16.2 %</td>
<td>13.6 %</td>
<td>20.0 %</td>
<td>χ^2(1)=0.27, n.s</td>
</tr>
<tr>
<td>Anti-coagulant for APS</td>
<td>13.5 %</td>
<td>9.1 %</td>
<td>20.0 %</td>
<td>χ^2(1)=0.91, n.s</td>
</tr>
<tr>
<td>Other</td>
<td>40.5 %</td>
<td>36.4 %</td>
<td>46.7 %</td>
<td>χ^2(1)=0.39, n.s</td>
</tr>
</tbody>
</table>

Table 2.3. Demographics of NPSLE and non-NPSLE groups in the current study

† SLEDAI – systemic lupus disease activity index (Bombardier, Gladman, Urowitz, Caron, & Chang, 1992)
‡ Corticosteroid dose was quantified as % not on steroids/ % on low dose (<5mg per day) and high dose (>5 mg).
* Analysis of categorical variables used Fisher’s exact test due to small numbers in some groups.
- Analysis was not completed where 0% was included in one group.
Participant numbers differ across sections of the study as six participants (one NPSLE, two non-NPSLE, two illness controls and one healthy control) were unable to complete the imaging session. This was due to contraindications for MRI in five cases (cardiac pacemaker; cardiac stent; hair extensions with metal clips; claustrophobia and clips from previous surgery that we were unable to verify if MR safe) and lack of time in the sixth case. Two SLE participants only completed half of the cognitive test battery. One due to the participant having a broken wrist of her dominant hand at the time of testing, and the other participant did not have time to complete the testing session. Questionnaire data is missing for three participants who did not return the forms.

2.6 Measures

A number of different outcome measures were assessed; these can be divided into imaging measures, mental health and well being, cognitive assessment and clinical measures. The choice of individual tasks, and details of the materials used and testing procedure will be covered in the individual chapters.

<table>
<thead>
<tr>
<th>Mental health and wellbeing (chapter 3)</th>
<th>Cognitive assessment (chapters 4 and 5)</th>
<th>Magnetic Resonance Imaging (chapter 6)</th>
<th>Clinical variables (Chapter 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Depression</td>
<td>1. Memory</td>
<td>1. $T_1$ weighted MP range structural scan</td>
<td>1. Specific autoantibodies</td>
</tr>
<tr>
<td>3. Quality of life</td>
<td>3. Executive function</td>
<td>3. Diffusion tensor imaging</td>
<td></td>
</tr>
<tr>
<td>4. Subjective cognitive failures</td>
<td>4. Psychomotor speed</td>
<td>4. $T_2$ weighted structural scan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Visuospatial processing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2.4: Outcome measures acquired in the current study

2.7 Testing procedure

Figure 2.1 indicates the procedure followed by participants. Testing took place in two sessions. In one session, demographic data was taken, the participants filled in a questionnaire measuring state anxiety (Speilberger State Anxiety Inventory) and the cognitive assessment was completed. During this session, the SLE patients were assessed clinically to measure disease activity (SLEDAI score) and a 20 ml blood sample was taken for serum stored for
antibody testing. The data from this antibody testing is unavailable at the time of writing this thesis, but is considered in the future work section, chapter 8, section 8.6. Finally the participants either filled in the other questionnaires or took them home and returned them during the second session. During the second session the participants had an MRI scan of the brain. Other clinical data was extracted from the patient’s medical notes. This included current medications, results of any previous imaging or neurological assessment, co-morbidities including current or previous renal involvement, current or previous hypertension, disease duration and recent results of serological assessment for routine clinical monitoring.

Disease activity was assessed using the SLE disease activity index (SLEDAI) (Bombardier, et al., 1992). This scale measures disease activity in the last 10 days using 24 weighted laboratory and clinical variables. Scoring was completed by a rheumatology trained clinician. Proteinuria and haematuria were assumed to be absent if they were not clinically indicated. A copy of the SLEDAI scoring sheet is included in appendix 2.

As much as possible the test sessions were kept the same for all participants. The cognitive assessments were all conducted by the lead researcher giving standard instructions for each test, and using rigid criteria for determining if an item was correct. The SLEDAI scoring was performed by one doctor using objective criteria to establish if the participant should score for a particular item. The MRI scans followed a standardised protocol, and all imaging analysis was performed by the same researcher using automated procedures where possible.

The two testing sessions were generally completed on separate days, though where it was necessary to test on the same day the cognitive assessment was conducted before the MRI scan to avoid any carry over affects from the scan such as fatigue or feeling disorientated (n=5 patients, 10 healthy controls). The median time between assessments was 8.5 days (range 0-67) for the SLE participants. Six participants had delays greater than 21 days due to time constraints but they were re-assessed to ensure they had not had any change in their symptoms during this time. For the healthy controls and illness controls the median delay was 16 days and 0 days respectively.
2.8 Statistical analysis

SPSS version 18 was used for all analyses. The first part of the study involved comparing two (SLE versus healthy controls) or more (SLE versus NPSLE versus healthy controls) groups on the main outcome measures separately. T-tests were used for group comparisons of continuous data (MRI measures, cognitive assessment, psychological assessment and some of the serology data) and one-way ANOVAs for more than two groups. Where Levene’s test of homogeneity of variances was significant the Welsh correction was used. To assess the location of the significance post hoc tests were carried out using Gabriel’s procedure as the sample sizes were not equal. These were verified using the Games-Howell procedure which should be used when sample variances are not equivalent (Field, 2005).

The impact of covariates was assessed using ANCOVAs. The National Adult Reading Test (NART) scores were added as a covariate in all analyses of cognitive assessment scores as the
groups were not matched on this variable. In other analyses where covariates have been
added this is specified in the text. Where variables did not meet parametric criteria non-
parametric versions of statistical tests were used (Wilcoxon’s and Kruskal Wallis test).
Categorical measures were assessed using chi-squared tests or Fisher’s exact test where
indicated. The second aim of the research programme was to look at the relationship between
the different outcome variables. Correlation analysis was performed using Pearson’s Product
Moment Correlation Coefficient. For all analyses the significance level was set at 0.05 except
where mentioned that adjustments had been made.

For consistency of interpretation, effect sizes for t-tests and correlations are reported as r
values and ω for one-way ANOVAs. The results are reported as ω rather than r as this is
generally a more accurate estimate of the effect in the population. These can be interpreted as
values greater than .1 indicating a small effect, values greater than .3 indicating a medium
effect and values greater than .5 indicating a large effect (Cohen, 1992). For t-tests r can be
calculated using the following formula: 
\[ r = \frac{t^2}{(t^2 + df)} \]
For correlations r is the value of the
correlation coefficient and finally for ANOVAs
\[ \omega = \sqrt{\frac{(SS_m - df_m MS_e)}{(SS_T + MS_e)}} \]
(Where
\[ SS_m = \text{Sum of squares between groups}, \]
\[ SS_T = \text{total sum of squares}, \]
\[ MS_e = \text{Mean squares error}, \]
and \[ df_m = \text{the degrees of freedom for the effect (number of groups minus 1)}. \]

2.9 Evaluation of possible confounding factors

2.9.1 Patient selection

As mentioned in the recruitment section, patients were identified by the consultant
rheumatologist and then later sent the patient information leaflet. Of these 12 participants
were unable to participate. One possibility is that those patients who agreed to participate
differ from the general population in some way, such as age or health. Reasons for non
participation included ill health (n=1), contraindications for MRI (n=2, one for anxiety about
the scan and one for a tattoo on the neck), they did not answer the phone for follow up calls
(n=4), they declined to participate (n=6) with the most common reason being lack of time. This
indicates only one patient did not participate specifically due to ill health. It is also possible this
group has better general health than the participants who did complete the research, as many
of them were too busy to participate or were not home to answer their phone. However there
was a broad range of employment statuses across the participants who did complete the
research including a large percentage in full time employment and only two participants on current sick leave at the time of the study, suggesting differences with controls are not purely down the SLE group being out of work. The only demographic features that are available on the non-participants are age and gender, and as the NPSLE status of these patients is unknown these were compared with the SLE group as a whole. There were no significant differences between those who did and did not participate on either age or gender. Mean age of participants (44.68 ±12.68) non-participants (46.83±14.32) (t(47)=0.497, p>0.1) gender 12 female 0 male compared to 32 female 3 male who agreed to participate.

2.9.2 Testing setting

The majority of patients (30) were tested on the cognitive test battery at the Royal Sussex County Hospital, whereas the controls were tested at the University of Sussex. For both locations testing occurred in a quiet, private room and it is unlikely there were effects of testing location. However, seven SLE patients were tested at the University and this allows an analysis of whether there were any systematic differences between testing location. Due to the discrepancy in group size (30 versus 7) non-parametric tests were used to see if there were differences on cognitive test scores between the patients tested at the University versus those tested at the Hospital. The only task on which there was a significant difference between locations was the time taken to complete the complex figure, with the University participants completing it in an average of 79.14 seconds compared to 124.38 seconds for those tested at the hospital and this would not survive correction for multiple comparisons. Given the non-significant finding across all other tasks it is hard to argue that group differences between patients and controls are down to testing location.
3.1 Introduction

3.1.1 Depression and Anxiety.

It is generally accepted that SLE is associated with a high prevalence of psychological distress including depression and anxiety, (Barbosa, et al., 2011; Kozora, et al., 2006; Nery, et al., 2008; Stojanovich, Zandman-Goddard, Pavlovich, & Sikanich, 2007) with patients with SLE showing significantly higher levels of depression and anxiety compared to healthy controls (Barbosa, et al., 2011). Mood disorders have been incorporated into the American College of Rheumatology (ACR) nomenclature for NPSLE and prevalence studies suggest anxiety disorder is present in 13-24% of NPSLE patients and depression in 23-44% (Ainiala, Loukkola, et al., 2001; Brey, et al., 2002; Robert, et al., 2006). This suggests that patients with NPSLE would be likely to score higher than those with non-NPSLE on measures of depression and anxiety, and this was supported in a study that found significantly higher depression and anxiety in an NPSLE group compared to non-NPSLE (Monastero, et al., 2001). However Kozora et al. (2006) found no differences between their sample of patients with NPSLE and non-NPSLE on depression, with both groups scoring significantly higher than healthy controls. Interestingly in both these studies approximately 48% of the NPSLE participants had mood disorders suggesting it is not simply the presence of participants with mood disorders in the NPSLE group that can account for differences between NPSLE and non-NPSLE groups on measures of depression (e.g. Monastero, et al., 2001). In the present sample 3/15 (20%) NPSLE participants had a diagnosed mood disorder and 1/15 (6.7%) a diagnosed anxiety disorder. Removal of these participants allows an analysis of whether any potential differences identified between the groups are due to the inclusion of these participants in the NPSLE group.

The Hospital Anxiety and Depression scale (Zigmond & Snaith, 1983) was designed for use in physically ill patients and does not contain somatic items, which might artificially increase depression scores in patient populations. It is a 14 item questionnaire that scores depression and anxiety on a scale from 0-21 with higher scores indicating worse symptoms. The original paper suggested that scores 8 or above indicate possible mood disorder, and scores of 11 and
above for probable mood disorder. These cut-offs have been supported to a good degree across other studies in a variety of patient groups (Bjelland, Dahl, Haug, & Neckelmann, 2002; Herrmann, 1997). For the current analysis both raw scores and the proportion of participants falling above and below the cut-off were compared across groups. Using raw scores is a more sensitive analysis; however although studies have found significant increases in depression and anxiety in SLE patients compared to controls, the mean scores found by Monastero et al, (2001) were below the cut off for clinical depression. Looking at the proportion falling into each category will give an idea whether the patients score higher, but are still within the normal range, or whether the patients are likely to have possible or probable mood disorder.

As studies have suggested that SLE patients have higher anxiety in general than healthy controls this could impact on performance on cognitive testing. A number of studies have reported a relationship between anxiety and test performance in academic settings (Zeidner, 1998); additionally higher state anxiety has been associated with poorer performance on cognitive tasks in normal ageing (Wetherell, Reynolds, Gatz, & Pedersen, 2002).

The Speilberger State Anxiety Inventory (SSAI) (Speilberger, Gorsuch, & Lushene, 1970) was incorporated into the testing session and was completed immediately before commencing the cognitive assessment. This questionnaire asks participants to rate how they feel at this moment in time. Two studies have used the SSAI to measure state anxiety in SLE patients, however they did not correlate this with task performance and did not split the group into NPSLE and non-NPSLE patients, instead focussing their analysis on NR2a antibody positive versus NR2a antibody negative patients (Harrison, Ravdin, & Lockshin, 2006) or correlations with disease activity (Ward, Marx, & Barry, 2002).

3.1.2 Perceived cognitive failures

In addition to assessing depression and anxiety the American College of Rheumatism (ACR) recommend including self reported measures of cognitive function in research into SLE. (ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999b). The Cognitive Failures Questionnaire (CFQ) (Broadbent, Cooper, FitzGerald, & Parkes, 1982) is widely used to assess lapses in memory and attention in everyday life. It has been suggested that scores on the CFQ relate to symptoms of depression or stress rather than objective impairment, and this was supported by a study that showed higher correlations between depression and perceived
cognitive failures, than actual cognitive impairment in patients with SLE (Vogel, Bhattacharya, Larsen, & Jacobsen, 2011). de Groot et al. (2001) showed a relationship between periventricular white matter hyperintensities and subjective cognitive failures in a sample of older adults even in the absence of objective cognitive impairment. This suggests that increased subjective complaints may indicate damage to brain parenchyma and would be expected to be higher in patients with NPSLE compared to non-NPSLE. One study compared scores on the CFQ between patients with NPSLE and non-NPSLE and controls and found the NPSLE group reported significantly more cognitive failures than the non-NPSLE group, and this difference occurred in the absence of differences on depression scores (Kozora, et al., 2006). The CFQ provides an overall score of perceived cognitive failures, however several investigators have examined the factor structure, and suggested it can be divided into between two and five separate domains. These are reviewed in Wallace (2004). One factor solution divided the CFQ into four domains; memory, blunders, distractibility and names (Wallace, Kass, & Stanny, 2002) and these have been replicated in a confirmatory factor analysis, along with verification of the construct validity (Wallace, 2004). Scores across separate domains have not previously been assessed in patients with SLE and for this reason the current study will include them.

3.1.3 Approach to assessing quality of life

SLE has been associated with reduced health related quality of life compared to healthy controls (McElhone, Abbott, & Teh, 2006) and comparable or worse quality of life compared to patients with other rheumatological conditions (McElhone, et al., 2006) or other chronic illnesses (Jolly, 2005). Only patients with fibromyalgia (Da Costa, et al., 2000) have been shown to have significantly worse quality of life than those with SLE (although it’s worth noting that fibromyalgia also occurs in SLE). The majority of studies into health related quality of life in SLE have used the Medical Outcomes Study Short Form-36 (SF-36)(Ware & Sherbourne, 1992) a measure that has eight subscales that can be combined to provide a physical component score (PCS) and a mental component score (MCS). Two studies from the same group have directly compared patients with NPSLE and non-NPSLE on SF-36, and both found the NPSLE group had significantly lower scores on both the PCS and MCS, indicating worse quality of life (Hanly, McCurdy, Fougere, Douglas, & Thompson, 2004; Hanly, et al., 2007; Hanly, et al., 2010). However the differences found by Hanly et al. (2007) were relatively small, 6-10 points (out of 100), and both groups scored more than one standard deviation below the normative data for
healthy controls indicating reduced quality of life in non-NPSLE participants. On the other hand in support of this difference Tam et al. (2008) found the NP-involvement was associated with reduced quality of life on the general health subscale of the short form-36.

The short form-36 is a generic measure that is widely used to assess quality of life. Its generic nature means that it can be used to compare scores across different patient groups or with healthy controls. On the other hand this also means it may not accurately represent some aspects of quality of life that are specific to SLE, for example issues with body image which may arise from symptoms such as a butterfly rash on the face, hair loss or weight gain. Recently a lupus specific quality of life measure has been developed, LupusQoL (McElhone, et al., 2007) and its generation was based on a sample of SLE participants who were asked about issues relating to their lupus that were relevant to them. The LupusQoL questionnaire can be used to generate eight domains; physical health, pain, planning, intimate relations, burden to others, emotional health, body image and fatigue. The planning domain asks how frequently the patient has problems with planning or committing to social occasions as a result of their lupus. The intimate relations measure asks about a lack of interest in sexual relationships either as a direct result of lupus or due to pain caused by lupus. Burden to others asks about feelings of concern that the patient’s lupus makes them a burden on friends and family.

The authors have published three studies that use the LupusQol, the first validating its use in a US-based sample (Jolly, Pickard, Wilke, et al., 2010) and the others looking at correlated factors such as age and disease activity in a US-based (Jolly, Pickard, Mikolaitis, et al., 2010) and UK-based sample(McElhone, et al., 2010). None of these studies separated participants into NPSLE and non-NPSLE groups therefore it is unclear whether these groups would (a) score differently on this measure or (b) have a different pattern of results across the subscales. These issues will be addresses in the present study.

3.1.4 Link between quality of life and depression or anxiety.

The relationship between anxiety and depression and quality of life has been investigated using the SF-36. Three studies found a consistent relationship between anxiety and the MCS but not with the PCS (Navarrete-Navarrete, et al., 2010; Wang, Mayo, & Fortin, 2001) or the mental health subscale but not other subscales (Tam, et al., 2008). The association with depression has been less consistent. Two studies found significant negative correlations
between depression and all subscales of the SF-36 (Stoll, et al., 2001; Tam, et al., 2008). Wang et al. (2001) found an association between depression and the mental component score but not the physical component score; finally Navarrete-Navarrete et al. (2010) found depression was not related to either component score. This could possibly reflect sample sizes as Navarrete-Navarrete et al. (2010) had only 34 participants compared to 60 and 291 in the other studies. However Stoll et al. (2001) reported large effect sizes for the correlation between depression and all subscales of the SF-36 suggesting this is unlikely and may instead reflect heterogeneity of participant across studies. Both Navarrete-Navarrete et al. (2010) and Stoll et al. (2001) were European studies so should have similar ethnicity. These studies have all correlated depression and anxiety with quality of life measured by the SF-36. It is likely that similar correlations exist with quality of life measured by the LupusQoL. If the relationship mirrors the SF-36 then anxiety would be expected to only correlate with the mental health subscale, while depression would be expected to correlate more broadly.

3.1.4.1 Factors predicting depression and anxiety in the SLE group.

Finding a relationship between mental health components of quality of life and anxiety and depression is unsurprising as it is likely that these measures are tapping into the same thought processes. For example the mental health subscale of the SF-36 asks the participant about the frequency of symptoms that relate to depression and anxiety. Of more interest is the relationship that has been shown between depression and physical health. Monaghan et al. (2007) investigated the relationship between physical disability (measured by SF-39 physical composite score) and psychological distress in patients with rheumatic diseases, and the mediator role of body image. Using hierarchical multiple regression, they found a significant relationship between physical health and depression, which did not remain significant when appearance was added to the analysis. No relationship was found with anxiety. The body image measure in the LupusQoL questionnaire allows a similar analysis. This can also be extended by adding other possible mediator variables such as the pain, intimate relations, burden to others, planning and fatigue subscales that can also be taken from the LupusQoL.

Monaghan et al. (2007) also included other variables in the first block of their analysis including age, disease duration, education level, living arrangements and employment situation. None of these were significant independent predictors of either depression or anxiety. Other studies have looked at the relationship between disease activity or damage and
mood disorders. These have tended to find no relationship or weak associations (Jarpa, et al., 2011; Lisitsyna, et al., 2009; Nery, et al., 2008; Stoll, et al., 2001).

### 3.1.4.2 Association of quality of life to clinical variables

In a review of studies into quality of life, McElhone et al. (2006) suggest that quality of life measured by the SF-36 was not well correlated with disease activity or damage in SLE. Studies that have reported significant correlations tended to have small to medium effect sizes ($r$ values .2 to .4). Other factors such as age and disease duration have also been considered. Age tended to show negative correlations with quality of life, while disease duration effects have varied across studies some showing a positive association and others a negative one. A similar pattern has been found using the LupusQoL measure with weak correlations ($r$ values .2 to .3) with disease activity (Jolly, Pickard, Wilke, et al., 2010; McElhone, et al., 2010).

Other factors may relate to health related quality of life such as objective measures of physical or motor function. The present test battery included the finger tapping test as a measure of motor speed and this may predict physical health but not mental health aspects of quality of life.

### 3.1.6 Research questions

The present study addresses the following specific questions that arise from a review of previous literature:

1. Do the SLE participants differ from healthy controls on measures of depression, anxiety, perceived cognitive failures and quality of life?
   Based on previous research it is hypothesised that the SLE group will show higher depression, anxiety and perceived cognitive failures and lower quality of life.

2. Is there a difference between the NPSLE and non-NPSLE group on these measures?
   Based on previous research it is hypothesised that the NPSLE will show the most extreme scores on these measures, but it is unclear whether they will show significantly different scores from the non-NPSLE group.
(3) Is there a relationship between quality of life and depression or anxiety?
   It is hypothesised that there will be a significant relationship between both anxiety and depression and mental composite score on the SF-36, but only depression will relate to the physical composite score.

(4) Are there mediator variables in the relationship between physical health and depression?
   It is hypothesised following Monaghan et al. (2009) body image may mediate this relationship, however other variables such as pain, fatigue, intimate relationships and feelings of being a burden may also have a mediator role.

(5) Do clinical variables explain quality of life in the SLE group?
   Previous research suggests clinical variables may play a moderate role in explaining quality of life. It was hypothesised that finger tapping, a measure of physical/motor ability may predict physical health aspects of quality of life.

3.2 Methods

3.2.1 Participants

Data is missing from three participants; one NPSLE patient, one non-NPSLE patient and one healthy control. These participants all completed the Spielberger State anxiety Inventory (SSAI) but not the other questionnaires. Scores on the SSAI indicate the control had low state anxiety with a score of 27 that is within one standard deviation of the group mean (32.32±5.42). The non-NPSLE participant scored 39, also within one standard deviation of the group mean (35.12±7.90). Finally the NPSLE participant scored 62, the highest score across all participants and just within two standard deviations above the group mean (39.63±11.91). Assuming a moderate correlation between the SSAI and other measures (correlation coefficients ranged from .44 to .64) these results suggest that inclusion of these participants would be likely to increase any group differences found, rather than change them. The demographics of the participants for which questionnaire data is available is shown in table 3.1.
<table>
<thead>
<tr>
<th></th>
<th>Control (n=27)</th>
<th>Non-NPSLE (n=21)</th>
<th>NPSLE (n=14)</th>
<th>Between groups difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44.3 (11.5)</td>
<td>42.8 (14.0)</td>
<td>46.3 (10.3)</td>
<td>F(2,59)=0.41, n.s</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>96.2%</td>
<td>90.5%</td>
<td>100%</td>
<td>χ²(2)=.595, n.s</td>
</tr>
<tr>
<td>Years in education</td>
<td>15.5 (2.3)</td>
<td>14.2 (3.0)</td>
<td>15.1 (4.3)</td>
<td>F(2,59)=1.08, n.s</td>
</tr>
<tr>
<td>NART (number of errors)</td>
<td>13.2 (5.5)</td>
<td>20.6 (8.5)</td>
<td>16.5 (8.0)</td>
<td>F(2,59)=6.18, p&lt;.01*</td>
</tr>
<tr>
<td>Corresponding IQ (from NART)</td>
<td>114 (6.8)</td>
<td>105 (10.6)</td>
<td>110 (9.9)</td>
<td>F(2,59)=6.18, p&lt;.01*</td>
</tr>
</tbody>
</table>

Table 3.1: Mean (SD) values for demographics of the participants who completed the mental health and wellbeing questionnaires.

* non-NPSLE group>controls. NPSLE group did not differ from either group.

3.2.2 Materials

3.2.2.1 Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983)

The HADS is a 14 item questionnaire assessing the frequency of symptoms of depression and anxiety in the past week. Each question is rated on a four point scale from 0-3 giving a maximum total score out of 42. The HADS can be divided into two subscales; the HAD-A measuring anxiety and HAD-D measuring depression. These are both addressed by seven items, giving a possible score from 0-21 with higher scores indicating higher anxiety or depression. A cut off of 8 can be used to indicate possible mood disorder, and 11 to indicate probable mood disorder. A copy of the questionnaire and detail on how subscales were generated can be found in appendix 1.

3.2.2.2 Spielberger State Anxiety Inventory (SSAI) (Spielberger, et al., 1970)

The SSAI was chosen as a measure of state anxiety. This questionnaire asks participants to rate how they feel at this moment in time. The SSAI consists of 20 items rated on a four point scale from “not at all” to “very much so.” Scores are summed to give an overall anxiety measure ranging from 20-80 with higher scores indicating higher anxiety.
3.2.2.3 Cognitive Failures Questionnaire (Broadbent, et al., 1982)

The cognitive Failures Questionnaire is widely used to assess participant’s perceptions of the frequency of cognitive failures over the past six months. This questionnaire consists of 25 items such as “Do you find you forget appointments?” and the respondent must rate how often they have happened to them in the past six months on a scale from “never” to “very often”. This can be used to generate a total score out of 100 (maximum number of errors, scoring 4 on every item) or can be divided into four separate measures; memory; distractibility; blunders and names. These take the form of average scores and are out of 4 with higher scores indicating more frequent cognitive failures.

3.2.2.4 Medical Outcomes Survey Short Form 36 (SF-36) (Ware & Sherbourne, 1992)

The short Form-36 (SF-36) is a generic measure of health related quality of life. It includes 36 questions which ask about various aspects of quality of life over the past four weeks. The SF-36 can be used to generate an overall score; SF-36 total or eight subscales; physical function; role physical; body pain; general health; vitality; social functioning; role emotional; emotional health. These can be combined to create two domain scores the physical component score (PCS) and the mental component score (MCS). To avoid too many comparisons these two component scores were compared across groups in the present study. The SF-36 total score and all domain scores were converted to a scale from 0-100 with higher scores indicating higher health related quality of life.

3.2.2.5 LupusQoL © (McElhone, et al., 2007)

The LupusQoL is a lupus specific measure of quality of life. This asks patients about health related quality of life, but makes specific reference to Lupus, e.g. “because of my Lupus I.....” There are 34 questions asking the participant to rate the frequency of symptoms over the past four weeks on a five point scale from “all of the time” to “never”. A total score out of 100 can be generated where higher scores indicate better quality of life. The LupusQoL questionnaire can be used to generate eight domains; physical health, pain, planning, intimate relations, burden to others, emotional health, body image and fatigue. The planning scale asks how frequently the patient has problems with planning or committing to social occasions as a result of their lupus. The intimate relations measure asks about a lack of interest in sexual
relationships either as a direct result of lupus or due to pain caused by lupus. Burden to others asks about feelings of concern that the patient’s lupus is stressful for other people, or makes them a burden on friends and family.

3.2.2.6 Finger Tapping (Reitan & Wolfson, 1988)

This test is widely used to test manual dexterity. The participant was asked to tap a key on the keyboard as fast as they could for 10 seconds with a single finger. This was repeated four times with each hand with the number of taps averaged across both hands to give an overall measure.

3.2.3 Regression analysis

A series of hierarchical multiple regression analyses were run to look at the relationship between quality of life and clinical variables with depression and anxiety as outcome measures. Due to small numbers in the subgroups this was conducted in the SLE group as a whole. In a first step, physical health from the LupusQoL, age, years in education, disease activity (SLEDAI), and disease duration were entered. In a second block, pain, planning, intimate relationships, burden to others, body image and fatigue were added to see if any of them played a meditational role.

A second set of analyses were run to assess the factors predicting scores on the different subscales of the LupusQoL. Age disease duration, disease activity, years in education, HADS-D, HADS-A and finger tapping were added as independent variables. The significance level for each regression model was set at 0.0065 (0.05/8) to account for multiple comparisons.

3.3 Results

3.3.1 Depression and anxiety

Table 3.2 shows the mean scores and standard deviation on the HADS-A and HADS-D. The SLE group had a higher mean anxiety score than the healthy controls (8.09 versus 5.67) t(60) = -2.27, p<0.05, r=.28. This represents a small to medium effect size. The SLE group also had
significantly higher mean depression scores (6.49 versus 1.96) and this difference had a large effect size \( t(58)=-5.74, p<0.001, r=.62 \).

Table 3.2 also shows scores with the SLE group split into NPSLE and non-NPSLE patients. Parallel to the results from the first analysis, there was a significant difference in anxiety scores with a small to medium effect size \( F(2,59)=3.39, p<0.05, \omega=.27 \). Gabriel’s post hoc tests revealed the non-NPSLE group had significantly higher scores than the control group, whereas the NPSLE group did not differ significantly from either group. The effect size for the difference between patient groups was small \( (r=.2) \).

There was also a significant difference in depression scores \( F(2,27)=16.35, p<0.001, \omega=.54 \). This again indicates a large effect size. Post-hoc tests indicate that both patient groups had higher depression scores than the healthy controls but did not differ significantly from each other, and the effect size for this difference was very small \( (r=.08) \).

<table>
<thead>
<tr>
<th></th>
<th>Control (n=27)</th>
<th>SLE all (n=35)</th>
<th>Non-NPSLE (n=21)</th>
<th>NPSLE (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAD-A</td>
<td>5.67 (3.70)</td>
<td>8.09 (4.50)</td>
<td>8.81 (4.79)</td>
<td>7.00 (3.92)</td>
</tr>
<tr>
<td>HAD-D</td>
<td>1.96 (2.16)</td>
<td>6.49 (4.01)</td>
<td>6.24 (3.43)</td>
<td>6.86 (4.77)</td>
</tr>
</tbody>
</table>

Table 3.2: Mean scores (standard deviation) on HAD-A and HAD-D for controls, all SLE patients (left), and the SLE group split into NPSLE and non-NPSLE subgroups (right).

Despite these difference, the mean scores (aside from non-NPSLE group HAD-A score) all fall below the cut off for probable depression or anxiety. Another way to assess the data is to look at the number of participants that fall above and below these cut offs. Table 3.3 shows the number of participants falling into each category split by subgroup. Due to small numbers falling in the probable case category (less than 5 in all but one cell) statistical testing was performed on the proportion in each group scoring greater than 8 versus less than 8. Fisher’s exact tests were performed to test the null hypothesis that the distribution of those scoring above and below the cut off was the same across the groups. In contrast to the results of the ANOVA no difference was found on the proportion falling above and below the cut off for anxiety \( \chi^2(2)=2.73, p>0.05 \). This possibly represents the loss of sensitivity from reducing a 21 point scale to a two point scale. The depression scores confirm the result of the ANOVA with a greater proportion falling above the cut off in both patient groups compared to healthy
controls $\chi^2(2)=10.18, p<0.01$ and no difference between the patient groups $\chi^2(1)=0.79, p>0.05$. It is worth noting that only 5% of non-NPSLE patients scored above 11 for depression whereas 21% NPSLE patients did and this difference may have been significant if greater numbers allowed testing.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Non-NPSLE</th>
<th>NPSLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (score \leq 7)</td>
<td>18 (67%)</td>
<td>9 (43%)</td>
<td>8 (57%)</td>
</tr>
<tr>
<td>Possible case score (\geq 8)</td>
<td>9 (33%)</td>
<td>12 (57%)</td>
<td>6 (43%)</td>
</tr>
<tr>
<td>Probable case score (\geq 11)</td>
<td>2 (7%)</td>
<td>5 (24%)</td>
<td>3 (21%)</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (score \leq 7)</td>
<td>26 (96%)</td>
<td>13 (62%)</td>
<td>8 (57%)</td>
</tr>
<tr>
<td>Possible case score (\geq 8)</td>
<td>1 (4%)</td>
<td>8 (38%)</td>
<td>6 (43%)</td>
</tr>
<tr>
<td>Probable case score (\geq 11)</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td>3 (21%)</td>
</tr>
</tbody>
</table>

Table 3.3: Number of participants in each group scoring above/below cut off for depression and anxiety according to the HADS.

These results indicate that despite 3/15 in the NPSLE group presenting with depression and 1/15 with anxiety there was no difference between the two patient groups on these measures. Interestingly the HADS identified these three participants as having probable depression. The HADS also identified one non-NPSLE participant as having probable depression and four further participants as having probable anxiety. The question of whether these patients should be classed as having NPSLE (as depression and anxiety are both in the ACR nomenclature for NPSLE) then arises. None of these patients had any other neuropsychiatric manifestations, and in all five patients there are personal and social issues that can explain their raised scores on the HADS that in some cases predated their SLE.

3.3.1.1 Speilberger State Anxiety Inventory

The results on the SSAI comparing the SLE group as a whole to the controls was similar to the HADS-A. The SLE group as a whole showed a slightly higher mean score compared to healthy controls (36.93 versus 32.32) and this difference was significant with a medium effect size $t(54.89) = -2.37; p<0.05, r=.30$. Splitting the SLE group into subgroups revealed a different
pattern to the HADS-A as the NPSLE group showed the highest mean scores, however the group difference was not significant when the Welch correction for inhomogeneity of variance was used $F(2,27)=2.89; \ p>0.05, \ \omega=.29$, although this difference did approach significance ($p=0.072$). This result could reflect a loss of power resulting from splitting the SLE group.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>SLE all</th>
<th>Non-NPSLE</th>
<th>NPSLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSAI</td>
<td>32.32 (5.42)</td>
<td>36.93 (9.80)</td>
<td>35.12 (7.90)</td>
<td>39.64 (11.91)</td>
</tr>
</tbody>
</table>

Table 3.4: Mean (standard deviation) scores for Spielberger State Anxiety Inventory (SSAI) for controls and SLE all (left) and the SLE group divided into NPSLE and non-NPSLE subgroups (right).

3.3.2 Perceived cognitive failures

On the Cognitive Failures Questionnaire the SLE patients had a significantly higher total score than the healthy controls, with a mean score of 50.71 compared to 34.80 $t(52.97)=4.21$, $p<0.001, \ r=.50$. This equates to the patients rating cognitive failures overall as happening occasionally, compare to the controls rating them as happening very rarely. Splitting the SLE group into NPSLE and non-NPSLE revealed a significant effect of group $F(2,27)=10.37; \ p>0.001, \ \omega=.49$. Post hoc tests revealed both patient groups reported significantly more cognitive failures than the healthy controls but did not differ from each other. The effect size for the comparison between SLE group was small to medium ($r=.25$). The mean total scores are shown in table 4.5.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>SLE all</th>
<th>Non-NPSLE</th>
<th>NPSLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (max 100)</td>
<td>33.30 (9.67)</td>
<td>50.71 (19.20)</td>
<td>46.76 (17.06)</td>
<td>56.64 (21.30)</td>
</tr>
</tbody>
</table>

Table 3.5: Mean (standard deviation) for CFQ total score for controls and SLE all (left) and the SLE group divided into NPSLE and non-NPSLE subgroups (right).

The CFQ divides into four domains, memory, distractibility, blunders and names. Figure 3 shows the mean scores for each domain split by group. A series of ANOVAs were run to assess whether group differences were evident on all domains using a Bonferroni correction for multiple comparisons (significance level 0.05/4=0.0125). Significant group differences were found on memory $F(2,27)=8.64; \ p<0.001, \ \omega=.51$, distractibility $F(2,59)=8.80; \ p<0.001, \ \omega=.45$ and blunders $F(2,27)=10.82; \ p<0.001, \ \omega=.51$ whereas the names domain approached corrected significance $F(2,59)=4.34; \ p=0.017, \ \omega=.31$. Post hoc tests revealed that the NPSLE group
differed from the healthy controls on all domains but only reported significantly more cognitive failures than the non-NPSLE group on the memory domain and this difference has medium to large effect size \((r=.44)\). The difference between NPSLE and non-NPSLE mean scores was small to medium on the other domains; \(r=.30\) for distractibility; \(r=.24\) for blunders and \(r=.14\) for names. The non-NPSLE group reported more significantly more cognitive failures than controls on the blunders and distractibility domains, but not on memory.

![Figure 3.1](image.png)

Figure 3.1: Mean scores on the domains of the Cognitive Failures Questionnaire split by group. Error bars represent ± 1 standard error.

Comparing scores across domains it is clear that there is a similar pattern across groups, with the most frequent failures happening in the names domain and the least frequent in the memory domain. Anecdotally many of the NPSLE participants complained of problems with their memory, however on this questionnaire they report failures within this domain as happening on average “occasionally” (compared to very rarely for the control and non-NPSLE groups).

### 3.3.3 Quality of life

Table 3.4 shows the mean scores on the SF-36 physical component score (PCS) and mental component score (MCS). The SLE group showed significantly lower scores than controls on both subscales indicating poorer quality of life, and these differences had large effect sizes \(t(47)=8.03; p<.001, r=.76\) for PCS and, \(t(55)=7.48; p<.001, r=.71\) for MCS.

This was further analysed by splitting the SLE group into NPSLE and non-NPSLE sub groups. The mean scores and standard deviations can also be seen in table 3.6. The NPSLE group show the lowest quality of life scores, with a mean score of 29.79 for PCS and 43.86 for MCS compared...
to 55.14 and 55.62 in the non-NPSLE group and 82.81 and 80.22 in the control group. The results of two one-way ANOVAs reveal these differences are significant $F(2,28)=86.08; p>0.001$, $\omega=.78$ for PCS and $F(2,30)=41.59; p>0.001$, $\omega=.68$ for MCS. Gabriel’s post hoc tests reveal that all three groups separate significantly from each other on PCS and the difference between NPSLE and non-NPSLE groups had a large effect size ($r=.54$). In contrast on the MSC both patient groups score significantly lower than the controls but do not differ from each other, although the effect size for this comparison was medium ($r=.3$).

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=27)</th>
<th>SLE all (n=35)</th>
<th>Non-NPSLE (n=21)</th>
<th>NPSLE (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 PCS</td>
<td>82.81 (9.58)</td>
<td>45.00 (23.50)</td>
<td>55.14 (23.37)</td>
<td>29.79 (13.76)</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>80.22 (10.73)</td>
<td>50.91 (19.70)</td>
<td>55.62 (21.94)</td>
<td>43.86 (13.61)</td>
</tr>
</tbody>
</table>

Table 3.6: Mean scores (standard deviation) on SF-36 physical component score and mental component score for controls and SLE all (left) and the SLE group split into NPSLE and non-NPSLE (right). Higher scores indicate better quality of life.

The results from the previous two one-way ANOVAs indicate the NPSLE group is particularly affected by reduced quality of life relating to physical health and do not score significantly lower than the non-NPSLE group on the MCS. Figure 1 indicates that the control and non-NPSLE groups showed similar scores on the two subscales while the NPSLE group scored lower on PCS compared to MCS. The difference in scores within the NPSLE group was statistically significant with a large effect size, $t(13)=4.47; p<.01$, $r=.77$, while within the other groups no difference in scores were found, $t(26)=1.60; p>.05$, $r=.30$ (controls) and $t(20)=0.225; p>.05$, $r=.05$ (non-NPSLE).

3.3.3.1 LupusQoL©

The NPSLE group had a significantly lower mean overall score on the Lupus QoL questionnaire, with a mean score of 45.98 (22.77) compared to 70.28 (23.54) for the non-NPSLE group $t(33)=3.03; p<.01$, $r=.47$. This difference relates to the NPSLE participants rating themselves as being affected by their Lupus on average “a good bit of the time,” while the non-NPSLE participants rated themselves as being affected “occasionally.” Figure 3.2 shows the mean scores for each subscale split by group. From this it is clear that the NPSLE patients scored lower on all subscales. A series of t-tests using a Bonferroni correction for multiple comparisons (significant level 0.05/8=0.006) revealed the difference in mean scores was...
significant for “planning” \( t(33)=3.04; \ p<0.006, \ r=.47, \) “physical health,” \( t(33)=2.99; \ p<0.006, \ r=.46 \) and approached significance for “burden to others” \( t(33)=2.86; \ p=0.007, \ r=.45 \) and “pain” \( t(33)=2.77; \ p=0.009, \ r=.43. \) Thus the largest differences tended to occur on subscales asking about physical health aspects of quality of life, whilst smaller effect sizes were found on those relating to emotional health, which supports the findings from the SF-36.

![Figure 3.2](image)

**Figure 3.2**: Mean (± 1 standard error) subscale scores on LupusQoL spilt by group.

It is clear from figure 3.2 that the two groups show a similar pattern of scores across the different domains with both groups scoring lowest on “fatigue” and highest on “body image” and “emotional health”. Table 3.7 shows the mean scores collapsed across both groups.

To illustrate the differences across the subscales the number scoring below 50 (indicating this factor affects them at least a good bit of the time) and the number scoring 100 (indicating this item never bothers them) has been recorded. Nearly 37% of participants indicated that body image issues relating to SLE never bothered them and only 17% were bothered by this a good bit of the time or more. This could relate to these symptoms not affecting all participants or affecting them infrequently rather than participants not being bothered by them and in support of this 8 of the 13 participants who scored 100 for this subscale used the “not applicable” option for the specific questions about hair loss, weight gain and rashes.
The other issues not covered by generic quality of life measures affected participants more frequently, with just over a third of participants rating intimate relationships or feelings of being a burden affecting them a good bit of the time. Again, five participants did not answer the items on intimate relations indicating that either they were not in a relationship or did not have issues relating to this factor.

### 3.3.4 Does quality of life relate to anxiety and/or depression?

Table 3.8 shows the correlation coefficients for the relationship between quality of life and depression and anxiety split into SLE patients and controls. Both groups had significant correlations between mood and MCS on the SF-36 with large effect sizes ($r > .50$). Within the SLE group depression then correlated with PCS whereas anxiety did not. The same result was found for the LupusQol where both depression and anxiety correlated with emotional health, but only depression correlated with all subscales with moderate effect sizes.
Table 3.8: Correlation between HADS and SF-36 for all SLE patients and controls, and between HADS and LupusQoL subscales for the SLE patients.

<table>
<thead>
<tr>
<th></th>
<th>SLE all (n=35)</th>
<th>Controls (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HAD-A</td>
<td>HAD-D</td>
</tr>
<tr>
<td><strong>SF-36</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental composite score</td>
<td>-.52**</td>
<td>-.66**</td>
</tr>
<tr>
<td>Physical composite score</td>
<td>-.18</td>
<td>-.43*</td>
</tr>
<tr>
<td><strong>LupusQoL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Image</td>
<td>-0.33*</td>
<td>-0.50**</td>
</tr>
<tr>
<td>Emotional health</td>
<td>-0.68**</td>
<td>-0.60**</td>
</tr>
<tr>
<td>Pain</td>
<td>-0.25</td>
<td>-0.37*</td>
</tr>
<tr>
<td>Planning</td>
<td>-0.24</td>
<td>-0.43*</td>
</tr>
<tr>
<td>Intimate Relationships</td>
<td>-0.05</td>
<td>-0.39*</td>
</tr>
<tr>
<td>Physical Health</td>
<td>-0.18</td>
<td>-0.39*</td>
</tr>
<tr>
<td>Burden to others</td>
<td>-0.31</td>
<td>-0.32</td>
</tr>
<tr>
<td>Fatigue</td>
<td>-0.24</td>
<td>-0.36*</td>
</tr>
</tbody>
</table>

3.3.4.1 *Factors predicting depression and anxiety in the SLE group.*

Adding anxiety as the outcome measure revealed than none of the variables were significant predictors of anxiety. The model was not significant at either step and explained only 12% of the variance in anxiety at step 1 and 10% at step 2. There were no independent predictors of anxiety in either step.

When depression was added as the outcome measure the first step of the regression model was significant $F(5,24)=3.21; \ p<0.05$, and accounted for 28% of the variance in depression. There were two independent predictors of depression; physical health $t(1,24)=-2.62; \ p<0.05$ and years in education $t(1,24)=-2.27; \ p<0.05$. When the second block was added the overall model remained significant $F(11,18)=2.89; \ p<0.05$, and now accounted for 42% of the variance in depression. In this model years in education remained a significant independent predictor of depression $t(1,24)=-2.61; \ p<0.05$ while physical health was no longer significant $t(1,18)=0.15$;
Of the variables added in the second block only body image was a independent predictor of depression $t(1,18)=-2.73$; $p<0.05$, suggesting that this mediates the relationship between physical health and depression. The model summary is shown in table 3.9. This analysis was repeated excluding the two male participants. Both scored 100 on the body image subscale indicating they were never bothered by appearance because of their lupus, however both scored above the cut off for possible depression indicating any relationship between body image and depression may be different in males and females. The exclusion of the two male participants did not change the result for the regression model but did increase adjusted $R^2$ to .44 for the first step and .67 for the second step.

<table>
<thead>
<tr>
<th></th>
<th>Adjusted $R^2$</th>
<th>$\beta$</th>
<th>df</th>
<th>F</th>
<th>t</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Significant predictors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical health</td>
<td>0.28</td>
<td>-0.44</td>
<td>1.24</td>
<td>-2.62</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Years in education</td>
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<td>-0.37</td>
<td>1.24</td>
<td>-2.27</td>
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<tr>
<td><strong>Step 2</strong></td>
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<td></td>
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<tr>
<td>Independent predictors</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical health</td>
<td>0.42</td>
<td>0.09</td>
<td>1.18</td>
<td>0.15</td>
<td>0.879</td>
<td></td>
</tr>
<tr>
<td>Years in education</td>
<td></td>
<td>-0.40</td>
<td>1.18</td>
<td>-2.61</td>
<td>0.018</td>
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</tr>
<tr>
<td>Body Image</td>
<td></td>
<td>-0.55</td>
<td>1.18</td>
<td>-2.73</td>
<td>0.014</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.9: Model summary for regression model with HADS-D as the outcome variable, physical health, age, years in education, disease activity, and duration were entered in the first block, pain, planning, intimate relations, burden to others, body image and fatigue in the second block.

3.3.4.2 Factors predicting quality of life in the SLE group

The overall model was significant for body image, emotional health, pain and physical health. Finger tapping was independently associated with physical health and pain scores, with a better motor speed relating to better quality of life. Age was associated with emotional health and body image and it was older age that was predictive of better quality of life. Finally there was a negative relationship between anxiety and emotional health and depression and body image with lower scores indicating better quality of life. The overall model was not significant for planning, intimate relationships, burden to others and fatigue subscales, but finger tapping
emerged as a significant predictor of quality of life in all these analyses. The model summaries are reported in table 3.10.

This analysis suggests that depression is not related to emotional health, even though the correlations in table 3.8 would suggest that there should be a significant relationship. Removal of anxiety from the analysis resulted in depression emerging as a significant predictor of emotional health, indicating anxiety was acting as a suppressor variable. In a similar analysis removing depression from the model with body image, anxiety emerged as significant. Removal of finger tapping from the other models did not reveal any other significantly independent variables suggesting this was not acting as a suppressor in these analyses.

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Significant predictors</th>
<th>Adjusted $R^2$</th>
<th>$\beta$</th>
<th>df</th>
<th>$F$</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Image</td>
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<td>3.70</td>
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<td>Emotional health</td>
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<td>HADS-A</td>
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<td></td>
<td>-3.92</td>
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<td>Pain</td>
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<td>7,26</td>
<td>7.06</td>
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<td></td>
</tr>
<tr>
<td>Physical health</td>
<td>Finger tapping</td>
<td>0.42</td>
<td>0.61</td>
<td>7,26</td>
<td>4.45</td>
<td>5.50</td>
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</tr>
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<td>Planning</td>
<td>Finger tapping</td>
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<td>0.44</td>
<td>7,26</td>
<td>2.24</td>
<td>2.62</td>
<td>0.068</td>
</tr>
<tr>
<td>Intimate relationships</td>
<td>Finger tapping</td>
<td>0.29</td>
<td>0.23</td>
<td>7,22</td>
<td>2.69</td>
<td>2.64</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>HADS-D</td>
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<td>1,22</td>
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<td>-2.23</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td>Burden to others</td>
<td>Finger tapping</td>
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<td>0.48</td>
<td>7,26</td>
<td>2.49</td>
<td>2.97</td>
<td>0.006</td>
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<tr>
<td>Fatigue</td>
<td>Finger tapping</td>
<td>0.21</td>
<td>0.36</td>
<td>7,26</td>
<td>2.27</td>
<td>2.20</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Table 3.10: Model summary for regression analysis with LupusQol subscales as the outcome variables. Age, disease duration, disease activity, years in education, HADS-D, HADS-A and finger tapping as independent variables.

3.4 Discussion

3.4.1 Group comparisons

The SLE group showed significantly increased depression compared to healthy controls with a large effect size. Splitting the SLE group revealed that both the NPSLE and non-NPSLE participants had increased depression and did not differ from each other. On anxiety measures
the comparison of the SLE group as a whole with the control group had a moderate effect size. On the HADS-A it was the non-NSPLE group that had significantly increased anxiety compared to controls, while on the SSAI the NPSLE group had the highest scores, but when the SLE group was split this analysis did not reach statistical significance. The increased depression and anxiety compared to healthy controls supported the findings of previous studies (Barbosa, et al., 2011; Kozora, et al., 2006; Monastero, et al., 2001).

The NPSLE and non-NPSLE groups did not differ from each other on depression or anxiety measured by HADS-D, HADS-A or SSAI. This supports Kozora et al. (2006) who found no difference on a depression measure, but contrasts with Monastero et al. (2001) who showed significantly increased scores on both depression and anxiety in their NPSLE group compared to non-NPSLE. One possibility is that this relates to reduced power in the present study as the group size is relatively small, although comparing effect sizes reveals this is unlikely. The effect size for the difference on depression was 0.08 which is lower than 0.29 found by Monastero et al. (2001) and on anxiety the non-NPSLE group actually scored higher. A second possibility is that this relates to the criteria used to define the NPSLE group. In the present study only 20% of the NPSLE sample was classified as having depression and 6.7% anxiety, which is a lower proportion than the prevalence studies indicate (e.g. Ainiala, Loukkola, et al., 2001). This suggests some milder cases may have been missed and placed in the non-NPSLE group. On the other hand, both Monastero et al. and Kozora et al. used the ACR criteria to define NPSLE and both had approximately 48% of their NPSLE participants listed as having depression, suggesting the differences are not due to Monastero et al. (2001) including more NPSLE patients with depression. Either way, the current data was unable to test the assumption that increased scores on depression or anxiety in an NPSLE group compared to non-NPSLE simply relates to the presence of participants with mood or anxiety disorders, as no differences were found between them even with the inclusion of these participants.

On the cognitive failures questionnaire the SLE group as a whole scored higher than the healthy controls on total score. Splitting the SLE group revealed the mean scores for both NPSLE and non-NPSLE were higher than the healthy controls and did not differ from each other. This contrasts with Kozora et al. (2006), who found a significant difference between reported cognitive failures in their NPSLE and non-NPSLE groups. Comparing effect sizes across the two studies indicates Kozora et al. found a slightly larger effect ($r=0.30$ compared to 0.25).
and had a marginally larger sample size suggesting the present study may not have sufficient statistical power to find an effect of this size.

Dividing the CFQ into the four domains revealed the NPSLE group had the highest mean score on all subscales, and reported significantly more cognitive failures than the healthy controls on the memory, distractibility and blunders. The non-NPSLE group differed from the control group on distractibility and blunders. Finally although both patient groups had the highest mean score for the names subscale, the group difference did not reach significance when a Bonferroni correction was used for multiple comparisons. NPSLE and non-NPSLE participants have not previously been compared on these separate domains of the CFQ. Memory was the only domain on which the NPSLE and non-NPSLE were separated and this difference had a medium to large effect size compared to small to medium for the other domains. This suggests that it is cognitive failures relating to memory that separate the NPSLE and non-NPSLE groups. Wallace (2004) reported a moderate correlation between scores on the memory subscale and a measure of everyday memory. Anecdotally some of the NPSLE participants complained of memory problems and an interesting further comparison would be to see if scores on the memory domain of the CFQ correlate with objective memory performance. This will be addressed in chapter 7, section 7.4.2, of this thesis.

On the SF-36 the SLE group as a whole had reduced quality of life compared to healthy controls on both the physical component score and the mental component score. This supports the findings of previous studies (McElhone, et al., 2006). When the SLE group was split, the NPSLE participants had significantly lower quality of life on the PCS but not on the MCS. Hanly and colleagues have found a significant difference on both scales (Hanly, et al., 2004; Hanly, et al., 2007) and the later study had a larger difference in scores on the MCS compared to PCS, which contrasts with the pattern shown in the present study. The main difference between the current report and Hanley et al. (2007) is that they studied patients with a recent diagnosis, and mean disease duration of 5 months, whilst in the current study the patients had mean disease duration of 8 years. It may be that the pattern of scores on quality of life measures change over time. For example, ill-health may have a greater impact of quality of life around the time of diagnosis if patients have not come to terms with the diagnosis and what it will mean for them.
In support of the findings on the SF-36, the NPSLE group also had significantly reduced quality of life compared to non-NPSLE participants on physical health components but did not differ significantly on emotional health components of the LupusQol. This indicates both measures were equally good at separating the two lupus groups. This is important as many studies select a generic quality of life measure to allow comparison with control groups.

On the LupusQol the item most affected was fatigue and the least affected were body image and emotional health. This mirrors the findings of the three other studies using the LupusQoL where fatigue has consistently been the most affected domain (Jolly, Pickard, Mikolaitis, et al., 2010; McElhone, et al., 2007; McElhone, et al., 2010) and body image one of the least affected (McElhone, et al., 2007; McElhone, et al., 2010). Body image had the highest mean score of all subscales which corresponded to this factor only affecting participants on average “occasionally,” additionally 13 participants rated this factor as never bothering them. The questionnaire gives participants the option of saying an item was not applicable, and 8 of the 13 used this option for all three of the specific questions about hair loss, weight gain and rashes. Future work could specifically ask about the frequency of these symptoms and relate this to scores on this item.

3.4.2 Relationship between mood and quality of life.

Across all groups depression and anxiety had a significant relationship with the MCS of the SF-36, but only depression correlated with the PCS. Within the SLE group anxiety also correlated with the emotional health subscale of the LupusQol but not physical health while depression correlated with all of the subscales with correlation coefficient greater than 0.30. This pattern of results echoes that found in previous research (Navarrete-Navarrete, et al., 2010; Stoll, et al., 2001; Tam, et al., 2008; Wang, et al., 2001). This implies there is a greater link between physical health and depression than anxiety.

3.4.2.1 Factors predicting depression and anxiety in the SLE group.

The relationship between physical health and anxiety and depression was further analysed using hierarchical multiple regression. Physical health and years in education were significant independent predictors of depression and the relationship with physical health was mediated by body image. None of the variables were related to anxiety. The main findings confirm the
results of a previous study that found the same relationship between physical health and depression (Monaghan, et al., 2007), however in the present study years in education was also negatively associated with associated with depression. As an extension to Monaghan et al. other possible mediator variables were also added; pain, planning; intimate relationships and fatigue subscales form the LupusQol. None of these were independent predictors of depression in the analysis. In the first block of the model other clinical variables were added (age, disease duration and disease activity). None of these were related to either depression or anxiety and this supports previous research which have tended to find no relationship or weak associations between disease activity or damage and mood disorders (Jarpa, et al., 2011; Lisitsyna, et al., 2009; Nery, et al., 2008; Stoll, et al., 2001). This suggests that mood disorders are not related to systemic aspects of disease, and are not simply a response to ill health. This has clinical implications as it means that simply treating the systemic disease activity is not likely to also improve mood disorders and these need to be treated independently.

3.4.2.1 The association of quality of life to clinical variables.

In a series of regression analyses clinical variables were related to the subscales of the LupusQol questionnaire. Disease activity, disease duration and years in education were not associated with any aspect of quality of life. This somewhat supports previous studies that have found weak correlations between LupusQol subscales and disease duration or activity (Jolly, Pickard, Mikolaitis, et al., 2010; McElhone, et al., 2010). Motor speed measured by finger tapping was the only significant predictor of the physical health and pain subscales. Although the overall model was not significant for intimate relationships, burden to others, planning and fatigue finger tapping also emerged as an independent predictor on all these analyses. It is interesting that a simple measure of motor speed was predictive of various aspects of physical health related quality of life, and this is something that would be easy to use clinically to get an objective measure of physical impairment.

Anxiety, depression and age were associated with emotional health and body image. The relationship with mood is unsurprising the questions generating the emotional health subscale directly relate to feelings of depression and anxiety, and body image has previously been associated with both depression and anxiety in healthy and clinical populations. Surprisingly it was older age that was associated with better quality of life. Previous studies investigating the correlation between age and SF-36 have tended to either find the opposite relationship with
better quality of life associated with younger age, or no association (McElhone, et al., 2006). This pattern was also found with the LupusQoL in a UK sample (McElhone, et al., 2010). Only one study has shown older age associated with better quality of life, and this was between improvements in quality of life and age at diagnosis rather than current age (Thumboo, et al., 2000). The relationship between older age and body image could perhaps be explained by research showing a decrease in appearance anxiety with ageing, however this finding needs to be confirmed in a larger sample.

3.5 Summary

(1) The SLE group as a whole scored significantly higher than controls on measures of depression, anxiety and perceived cognitive failures, and lower on quality of life. The largest effect sizes were for physical health related quality of life and depression.

(2) The NPSLE and non-NPSLE groups did not differ on depression, anxiety, overall cognitive failures or mental health aspects of quality of life. The NPSLE group had significantly reduced quality of life on physical health aspects of quality of life and reported more cognitive failures relating to memory.

(3) There were significant correlations between both depression and anxiety and mental health aspects of quality of life. Only depression correlated with physical health.

(4) Body image emerged as a mediator variable between physical health and depression.

(5) Anxiety, depression and age were related to emotional health and body image explaining 56% and 40% of the variance in them. Finger tapping was associated with pain and physical health explaining 51% and 40% of the variance. Other variables such as disease activity, disease duration and years in education did not relate to quality of life.
CHAPTER 4

COGNITIVE ASSESSMENT

4.1 Introduction

Cognitive dysfunction was included in the American College of Rheumatism case definitions as one of the neuropsychiatric manifestations of NPSLE. Cognitive dysfunction is defined as ‘Significant deficits in any or all of the following cognitive functions: simple or complex attention, reasoning, executive skills (e.g., planning, organizing, sequencing), memory (e.g., learning, recall), visual-spatial processing, language (e.g., verbal fluency), and psychomotor speed’ (ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999a). This is an important area for research as cognitive dysfunction has been shown to be the most common neuropsychiatric manifestation in prevalence studies (Ainiala, Loukkola, et al., 2001; Brey, et al., 2002), although prevalence rates vary across studies by as much as 20-60% (Denburg & Denburg, 2003). A high prevalence of cognitive impairment has also been shown in SLE patients without overt neuropsychiatric manifestations (non-NPSLE). Again this has varied widely but recent have put this prevalence as 20-35% (Kozora, et al., 2005; Kozora, Arciniegas, et al., 2008; Kozora, et al., 2004; Monastero, et al., 2001; Nelson, 1982; Olazaran, et al., 2009). Studies comparing participants with NPSLE and non-NPSLE on cognitive functioning have gave generally found greater impairment in the NPSLE group (Kozora, et al., 2004, 2006; Loukkola, et al., 2003; Monastero, et al., 2001), but as Benedict, Shucard, Zivadinov, & Shucard, (2008) point out this is not really surprising given that cognitive dysfunction is included as a criterion for NPSLE. However, neither Kozora et al., (2006) nor Monastero et al., (2001) report including participants in their NPSLE group on the basis of cognitive dysfunction. In the present study six (40%) of the NPSLE group had subjective cognitive complaints, but these patients also had other neuropsychiatric manifestations.

Benedict et al., (2008) argue against the distinction into NPSLE and non-NPSLE, instead arguing it is more important to focus on patients who do not have focal injury such as stroke. In their review of cognition in SLE they found only seven studies that conformed to their criteria that included exclusion of patients with previous cerebrovascular disease, and reporting of sufficient data to allow the calculation of effect sizes. It can be argued that it is meaningful to assess whether the differences identified in previous studies between patients with NPSLE and
non-NPSLE were due to the presence of participants with overt strokes or whether these differences persist when these participants are excluded.

4.1.1 Pattern of deficits in SLE

Although there is some variation in the findings of individual studies into cognitive dysfunction, there is some consensus. Two studies have pooled data from previous publications to assess the pattern of deficits. Denburg and Denburg (2003) grouped previous findings into the domains of general intelligence, verbal learning/memory, visuospatial skills, psychomotor speed/manual dexterity and attention/mental flexibility, and counted the number of studies citing impairment in these areas. 10 out of 12 studies cited impairment in attention/mental flexibility compared to five citing impairment in general intelligence. Nine studies found impairment in visuospatial skills, and eight in the other two areas. The majority found impairment in three of the five areas.

Benedict et al., (2008) reviewed seven studies that met their criteria of excluding participants with focal injury or stroke. They grouped findings into the domains of language, spatial ability, verbal memory, spatial memory, psychomotor speed/complex attention/working memory and executive function. Psychomotor speed and attention were combined as tasks included in neuropsychological testing often required both these factors, (e.g. the trail making test both require rapid responding and attention). The effect sizes for the difference between patients with SLE and healthy controls combined from separate studies. On all domains the effect sizes ranged from Cohen's $d=0.2$ to 0.5, which are small to medium effects and equate to $r = .1$ to .3. The largest effect sizes were found in the domains of spatial memory and psychomotor speed/attention. The pattern across the domains was very similar to that seen in multiple sclerosis (MS), but the effect sizes seen in SLE were generally lower than MS indicating less severe impairment.

These reviews both indicate the deficits in SLE are broad, but suggest they do not extend to general intelligence as much as other areas. Both implicate attention and visuospatial skills and memory as key areas of impairment, and there were only two overlapping studies between the reviews, indicating this consensus was not simply due to assessing the same data.
4.1.2 Methodological considerations

The first consideration is task selection, as this can impact on the results that are obtained. The cognitive test battery was developed with two factors in mind, comparability with previous studies of cognition in patients with SLE and a broad selection of tests to allow discrimination of impairment on different cognitive domains. To allow comparison with previous studies, the cognitive test battery was primarily based on one proposed by the American College of Rheumatism (ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999b). This one-hour battery has been validated against a four hour one, (Kozora, et al., 2004) and tasks were chosen to reflect domains of complex attention, executive skills, memory, visuo-spatial processing, language and psychomotor speed. Some additions were made to the ACR battery. Firstly, to extend its scope, we added a prospective memory test, a mental rotation task and a computerised sustained attention test that looked at rapid visual information processing. Prospective memory has not previously been assessed in SLE, but is sensitive to the effects of ageing and general damage to the brain. Mental rotation was added because visuospatial skills were identified by Denburg and Denburg (2003) as frequently being impaired in SLE. The ability to perform mental rotations and other spatial transformations is sensitive to various brain disorders (Lezak, Howieson, & Loring, 2004). Second, the California verbal learning test (Delis, et al., 1991) was substituted for the Rey auditory verbal learning test (RAVLT) (Rey, 1964). These tasks have similar properties, and the RAVLT has been used extensively in neuropsychological testing, including patients with SLE (Paran, et al., 2009). Finally, the category fluency task (animal naming) was replaced with a test of cognitive flexibility (Alternative uses test) (Guilford, 1967). This is a test of executive function and fluency, but is more dissimilar to a phonemic fluency task that is also included in the ACR battery.

There are two methodological considerations for analysing the data from the cognitive test battery. The first is whether to analyse the tasks individually or combine them to generate domain scores. The second is whether to analyse the data parametrically or to categorise performance according to impairment. Analysing the tasks individually has the benefit of highlighting whether deficits are general or specific to particular aspects of cognition, however with a large battery there is the problem of multiple comparisons. If the significance level is not adjusted there is a risk of making a type 1 error, whereas using a Bonferroni comparison may make the required significance too small to pick up any group differences that do exist. Generating domain scores reduces the number of comparisons, but the question arises how
best to combine the data. A number of studies in SLE have combined performance on multiple tasks into a single measure of performance (Kozora, et al., 2004; Lapteva, et al., 2006) which has the advantage of generating a single score that can then be used in further correlations for example with imaging or clinical parameters. Kozora et al., (2004) gave all measures equal weighting in generating a performance index, while Lapteva et al., (2006) first combined tasks into domain scores. This allowed an initial investigation of which domains the SLE group showed impairment, and also avoided the potential problem that a participant may score as globally impaired if they show specific impairment on related tasks. For example a participant may only perform worse on tasks that all relate to memory, but if there are multiple memory tasks in the battery these combined could imply global impairment. For the present study multiple approaches were used. The battery was combined using a factor analysis to generate domain scores based on linked performance rather than theoretical constraints. Individual tasks within each domain were then assessed separately. Finally a single global score was generated, first using the same method as Kozora et al., and second using the domains taken from the factor analysis to see whether they gave a different interpretation to the data.

The second consideration was whether to analyse the data parametrically or categorically. Parametric analysis has the advantage of using all the data so can pick up subtle differences in performance and the use of ANCOVAs also allows covariates to be added to the analysis. However this can only give information about group performance and not about individuals. Where the group data shows a large overlap categorical analysis would highlight whether the individuals in the tails show impaired performance. This then leads to further consideration such as how to class performance as normal or not normal. Most previous studies into SLE have used published norms and then classed an individual’s performance as impaired if they score more than one or two standard deviations below the norm. Published norms usually have the benefit of accommodating differences in age, gender and level of education; however they can only be used if the same procedure has been followed at testing as was used to generate the norm. This is unlikely when the tasks are embedded within a battery and performance may be better on the early tasks that later ones. For the current study therefore the control group data was used as the normative sample. To ensure that this data was not unsuitable, especially given the mean number of errors on the NART implies a mean IQ of 115 for this group, then performance was compared on to the available normative data. Eleven scores (taken from seven tasks) were converted to z-scores using age adjusted norms. The mean z-score across tasks was 0.18±0.05 and fell within ±1 standard deviation of the
normative data mean for all tasks, indicating the control group was an appropriate substitute for published norms. Finally in the generation of categorical scores the raw data was adjusted for NART errors and age where appropriate. This procedure is described in section 4.7.

4.2 The cognitive test battery

The tasks included in the test battery are listed in table 4.1. The order presented here is the order the battery was conducted for all participants. Some task aspects involve a delay; the delayed recall and recognition trials from the Rey Auditory Verbal Learning Test, and the delayed trial from the Rey-Osterreith complex figure were completed at the end of the battery. The prospective memory component of the card sorting test was completed after the alternative uses test.

<table>
<thead>
<tr>
<th>Test</th>
<th>Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>National adult reading test</td>
<td>Pre-morbid IQ</td>
</tr>
<tr>
<td>Rey-auditory verbal learning test</td>
<td>Verbal learning and memory</td>
</tr>
<tr>
<td>Rey-Osterreith complex figure</td>
<td>Perceptual organisation and visual memory</td>
</tr>
<tr>
<td>Rapid visual information processing</td>
<td>Sustained attention</td>
</tr>
<tr>
<td>Digit symbol substitution test</td>
<td>Sustained attention, speed of processing and visuo-motor coordination</td>
</tr>
<tr>
<td>Card sorting and prospective memory</td>
<td>Prospective memory</td>
</tr>
<tr>
<td>Trail making test</td>
<td>Speed of processing and attention</td>
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<td>Controlled oral word association test</td>
<td>Verbal fluency</td>
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<tr>
<td>Mental rotation</td>
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<td>Letter number sequencing</td>
<td>Working memory</td>
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<td>Alternative uses test</td>
<td>Fluency and mental flexibility</td>
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<tr>
<td>Finger tapping test</td>
<td>Motor speed</td>
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<tr>
<td>Stroop test</td>
<td>Executive functioning and response inhibition</td>
</tr>
</tbody>
</table>

Table 4.1: Tasks that were included in the cognitive test battery
4.2.1 National Adult Reading Test (NART)

The National Adult Reading Test (NART) (Nelson, 1982) has become a widely accepted method for estimating pre-morbid levels of intelligence in neuropsychological research. In the current study it was included to allow the matching of the experimental groups on approximate IQ. The NART assesses the ability to read irregular words that do not follow common grapheme-phoneme representations, or common stress rules. These words can only be read correctly if the participant recognises their written form through previous knowledge of the word. Reading ability is used as it is highly correlated with general IQ in the normal population (Nelson, 1982; Nelson & McKenna, 1975). This task is suitable for use in participants aged 18-70 as this was the range used in the validation sample. During administration the number of errors made by the participant is recorded and from this the premorbid IQ can be estimated using the following formula: Predicted WAIS-R Full Scale IQ = 130.6 - 1.24 x NART error score. The ACR battery uses the North American Reading Test, a version of the NART that is suitable for American and Canadian participants. However the original NART was used in the current study as the participants were all recruited and lived in the UK.

4.2.2 Rey Auditory Verbal Learning Test

The Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964) consists of two 15 item word lists, list A and List B. The words are all high frequency concrete items e.g. “drum” see appendix 4.2 for full lists.

Administration

On trial I List A was read to the participant at a rate of one word per second. The participant was instructed to repeat back as many words as they could remember in any order. The list was then repeated (with immediate recall trials) a further four times (trials II – V). An interference trial then followed in which list B was read to the participant, and they were instructed to repeat as many words that they could remember from this second list and not the first list. On trial VI the participant was asked to recall the words from list A without them being read out again. A final delayed recall trial (trial VII) was completed at the end of the battery (a delay of approximately 1 hour). Following this the participant was given a recognition test, consisting of a sheet with 50 words – the 15 words from list A, 15 words from
list B and 20 words that were either semantically related, phonetically related or both. The participant was instructed to mark the words that were on list A.

**Scoring**

A number of dependent measures can be taken from this task, however for purposes of the current study the following measures were used; immediate span (total correct on trial I), Learning (total correct on trials I-V), delayed recall (trial VII), recognition (recognition trial) and retroactive interference (total correct on trial V – trial VI). Other measures are discussed in section 5.2.

4.2.3 Rey-Osterreith Complex Figure (Corwin & Bylsma, 1993)

**Administration**

During this task the participant was presented with a printed version of the figure (see appendix 4.3) and instructed to copy it. The time taken to complete the figure was recorded though it was emphasised that speed was not a requirement. At the end of the battery a delayed recall trial was administered, approximately 60 minutes after the copying trial. Participants were not forewarned about the delayed recall trial at the time of copying the figure.

**Scoring**

The scoring system for the figure is given in appendix 4.3. This divides the figure into 18 elements which are scored in terms of their accuracy and relative position within the figure. Items are given two points if correct and placed properly, one point if correct and placed poorly or distorted/incomplete but placed correctly, and finally ½ a point if poorly placed and distorted/incomplete but recognisable. This gives a total possible score of 36.
4.2.4 Rapid Visual Information Processing (RVIP) (Wesnes & Warburton, 1984)

**Administration**

The participant was presented with a series of numbers that flash on the screen at a rate of 80 per minute. They were instructed to press the spacebar when a series of three odd or three even numbers occurred in succession. The task lasted for 4 minutes and there were 8 targets and 72 non-targets per minute, giving a total of 32 targets and 288 non-targets.

**Scoring**

The number of hits, false alarms and misses were recorded which allowed a d’ analysis to measure response bias. This was calculated using the formula; 
\[ d' = \frac{z(\text{hit rate}) - z(\text{false alarm rate})}{\sqrt{\frac{1}{n} + \frac{1}{m}}} \]
This accounts for both the hits and false alarms as having a high response rate irrespective of whether it was a target, would artificially increase accuracy scores. The reaction time to hits was also recorded. To account for RTs slower than 750 ms a response was considered correct if it was made up to 1500 ms following target presentation.

4.2.5 Digit symbol substitution test (Wechsler, 1981)

**Administration**

This task consists of first a copying trial and then a substitution trial. In the copying trial the participant was given a sheet with a series of nonsense symbols in boxes and was asked to copy them in the box underneath. They were given 90 seconds to complete as many as they could, and were instructed to do this as quickly and as accurately as possible. In the subsequent substitution trial the boxes were randomly labelled with the numbers 1-9 and a key matched each number to the symbols from the previous trial. Again the participant was asked to fill in as many as they could in 90 seconds.

**Scoring**

The number of correct symbols copied or substituted was the main outcome measure. At the end of administration, the paper was folded over and the participant was asked to fill in as
many boxes as they could without looking at the key. This provided an additional measure of incidental learning and was scored as the number of correct pairings out of 9.

4.2.6 Card sorting and Prospective Memory (Rusted, Sawyer, Jones, Trawley, & Marchant, 2009)

Prospective Memory (PM) is the memory to perform a pre-planned action. This can be measured experimentally using an event based paradigm, where a predesigned prospective cue is established and the participant must perform an action (the PM intention) whenever the target is detected. The prospective memory targets are typically embedded in an ongoing task, which is used to engage attention. Reaction time on the ongoing task with an embedded PM can be compared to RT on the same task without the PM intention. The difference in RT represents the cost of holding a PM intention in mind (R. E. Smith, Hunt, McVay, & McConnell, 2007).

Administration

This task was divided into two parts. The first was a simple card sorting task, where the participant was shown a deck of cards on a computer screen and instructed to sort by suit. The participant was instructed to respond with a key press for hearts and spades and not to respond to diamonds or clubs. The procedure involved randomly showing all the cards from one deck of cards, therefore there were 52 trials; 26 requiring the participant to sort the cards and 26 non-sort trials. In the second element of the task the participant was additionally instructed to press the spacebar to particular target cards (cards with the number 7), rather than responding to its suit. These target cards constitute the prospective memory trials. In the second variant there were two decks of cards, and so a total of 8 PM, 48 sort and 48 non-sort trials. The card sorting task with additional PM trials was conducted after a delay of approximately 20 minutes from the instructions, in this case after the alternative uses test. This delay is thought to increase the ecological validity of PM laboratory experiments, as prospective memory in the real world typically involves holding an intention in mind over a variable period of time.
Scoring

The number of correct card sort and PM responses, and reaction times to correct responses was recorded. PM trials were classed as correct even if the sort button was pressed first and the spacebar afterwards. The cost of holding a PM intention in mind was measured as the difference in reaction time to sorted cards with and without the PM intention.

4.2.7 Trail making test (Reitan & Wolfson, 1988)

Administration

The participant was presented with a series of circles containing either numbers (part A) or numbers and letters (part B). The participant was instructed to join them in the correct order as quickly as possible. In part A the numbers ran from 1-25 and the participant had to join them in numerical order. In part B there the numbers 1-13 and letters A-L were used and the participant was asked to join them in the order 1-A-2-B-3-C.... etc. The time taken to complete each part was measured using a stopwatch, which was stopped as soon as the participant reached the final circle. Any errors were pointed out to the participant who then had to correct them in order to progress. In this way error was conflated into the total time to complete and so number of errors was not recorded.

Scoring

Two outcome measures were taken, time to complete part A and time to complete part B. Each was measured in seconds using a stop watch.

4.2.8 Controlled Oral Word Association Test (COWAT) (Borkowski, Benton, & Spreen, 1967)

Administration

The participant was instructed to generate as many words as they could within the time limit beginning with a certain letter, and following certain rules; words could not be proper nouns, and could not start with the same suffix (such as bash, bashes and bashing). Three letters were used (F, A and S) with one minute given for each letter. The participant was given a sheet of
paper to write down the words, although an oral response is sometimes used in this task. Written responses allow the participant to check what they have written and may reduce errors such as repetitions. The normative data suggests similar performance for the two response formats (Spreen & Strauss, 1991)

Scoring

The main outcome measure was the total number of correct words generated over the three minutes. Words that were misspelt but recognisable were scored as correct. A further analysis looking at chunking is addressed in chapter 5 section 5.3.

4.2.9 Mental Rotation (Shepard & Metzler, 1971)

Administration

The letter “R” was presented on a computer screen and was either a normal presentation or mirror reversed. The letters also were rotated 0°, 45°, 90°, 135° and 180° in either a clockwise or anticlockwise directions. The participant was instructed to make a key press with “z” for mirror reversed and “m” for normal. There were four mirror and four normal trials per angle of rotation giving a total of 64 trials. Items remained on the screen until a response was made.

Scoring

Overall accuracy and response times to all correct trials were recorded. Increased rotation from upright increased the angle to which the target required rotation, and thus task difficulty. There was little difference in reaction times to targets rotated clockwise or anticlockwise therefore these trials were collapsed together. Response times were slower to normally presented trials, but there was no difference in response pattern, therefore trials were also collapsed over presentation. This resulted in 8 trials for upright or upside down presentations and 16 trials for each angle of rotation. The overall mean RT and accuracy for all trial types was recorded. A measure of task performance relating to increase task difficulty was generated by subtracting the mean RT for targets with a 0°or 45° rotation from the mean RT for 135° or 180°rotation.
4.2.10  Letter number Sequencing (Wechsler, 1997)

*Administration*

The participant was given a sequence of numbers and letters such as (Q-1-B-3-J-2) presented aurally at a rate of one item per second. They were asked repeat the sequence back but place the numbers first in numerical order, then the letters in alphabetical order (response 1-2-3-B-J-Q). The trials started with one number and one letter, and get progressively longer up to trials of eight items. There were three trials per list length and the test was stopped when the participant failed three trials at the same length.

*Scoring*

One point was scored for each correct trial and the total number completed successfully was the main outcome measure.

4.2.11  Alternative Uses Test (Guildford, 1967)

*Administration*

The participant was given the name of a common object and instructed to generate as many alternative uses for this object as they could within a one minute period. Two different objects were used, a shoe and a button, with one minute given for each. The procedure used in the current study is the same as the used in the Cambridge Mental Disorders in the Elderly Examination, Section B CAMCOG (Roth, et al., 1986).

*Scoring*

The main outcome measure was the total number of uses generated for both objects. To be scored as correct the response had to be a use for the object rather than something you could do to it. For example if the participant said you could “bury the button” this was not considered a use, however if they said you could “bury the button and use this as the treasure in a treasure hunt game for children” this was considered a use. Instructions emphasised that the uses had to be difference from each other and different from the usual use. For example if
the participant said you could “swat a fly” with the shoe followed by “swat a wasp” this second use would not be scored.

4.2.12 Finger tapping test (Reitan & Wolfson, 1988)

Administration

The participant was instructed to tap a key on the computer keyboard as many times as they could in a 10 second period. The letter “a” was used for left hand responses and “l” for right hand. Four trials were completed per hand.

Scoring

The mean number of taps in a 10 second period for each hand was the main outcome measure. Any trial with a grossly different number of tap, for example if the participant stopped in the middle for any reason, was excluded from the average. Trials were scored for dominant and non-dominant hands.

4.2.13 Stroop test (Golden, 1978)

The stroop test measures the Stroop effect, whereby if you are shown the word “blue” displayed in coloured ink, it is more difficult to name the ink colour when it is incongruent to the word. For example it is more difficult to name the ink colour if the word “blue” is displayed in red ink than if the word “red” is displayed in red ink. The effect occurs as you have to inhibit the task irrelevant stimuli (reading the colour word name).

Administration

The participant was shown a colour word displayed in coloured ink on a computer screen, and had to respond with a button press indicative of the colour of the ink. This was divided into congruent and incongruent trials. On the congruent trials the ink matched the printed colour word, whereas on the incongruent trials the two did not match. Trials were presented in blocks of 20, alternating between congruent and incongruent trials. Overall there were 160
trials, 80 congruent and 80 incongruent. Each trial remained on screen until a response was made and overall this task took approximately 3 ½ minutes to complete.

Scoring

The total number of errors was calculated along with mean reaction times to congruent and incongruent correct trials. These outcome measures were calculated for all congruent and incongruent trials overall. A measure of the magnitude of stroop effect was calculated as reaction time to incongruent trials minus the reaction time to congruent trials.

4.3 Preliminary analysis of the test battery

In order to assess the structure of the battery and to generate domain scores to reduce the number of analyses a factor analysis was conducted using the data from 77 healthy participants. This sample included the healthy control group from the main study along with additional participants recruited from the University population. The mean age of this sample was 33.5±14.5, mean years in education 15.1±2.2, mean number of errors on the NART 16.3±6.3 and female to male ratio 58:19.

The correlation matrix was screened to identify items that did not correlate with any other items and these were removed from subsequent analysis. Scores on the finger tapping test and difference scores in reaction time on computerised tasks were removed at this point. The factor analysis was run using an oblique (direct oblimin) rotation as there was a high likelihood that factors would correlate due to an overlap of cognitive domains. Eigenvalues greater than one were retained and the scree plot was checked to assess the suitability of this factor structure. Items with factor loadings greater than .5 were considered significant and items which did not meet this criterion were removed from the analysis. RVIP reaction time, the alternative uses test and prospective memory accuracy scores were removed at this point and the analysis rerun to ensure these items had not affected results. The items included in the final analysis are listed in table 4.1 along with the factor loadings for these items. Bartlett’s test for sphericity was highly significant (p<0.001) and the Kaiser-Meyer-Olkin measure of sampling adequacy was good at 0.742 indicating factor analysis was suitable for this data (Field, 2005).
Four factors were extracted and these accounted for 62% of the total variance. The first factor incorporated items from the RAVLT and has therefore been termed ‘memory’. The second factor included pencil-and-paper timed tasks (digit symbol copying and substitution, trail making test A and B, time to complete the complex figure copying trial and total number of words on the COWAT), this has been named ‘speed of processing’ (SOP). The third factor included tests that can be considered to have executive control components and included letter number sequencing (working memory), COWAT (fluency), RVIP d’ (sustained attention) and trial I from RAVLT (span). It also included incidental leaning and complex figure recall, which are not classically considered tasks of executive control, but both involve non-strategic learning and may depend on working memory capacity. This factor has been termed ‘executive control’. The final factor included the reaction times for computerised tasks and the digit symbol substitution test. These are reaction times with an additional decision making component therefore this factor was named ‘compound reaction time’ (Compound RT).

The factors were assessed using Cronbach’s $\alpha$ in (1) the factor analysis sample and (2) the SLE group. This was greater than .74 for all scales in both samples indicating good internal reliability.

<table>
<thead>
<tr>
<th>Test Item</th>
<th>Memory</th>
<th>Speed of processing</th>
<th>Executive control</th>
<th>Compound RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVLT trial I</td>
<td>.77</td>
<td>.21</td>
<td>.52</td>
<td>.09</td>
</tr>
<tr>
<td>RAVLT learning</td>
<td>.87</td>
<td>.10</td>
<td>.44</td>
<td>.05</td>
</tr>
<tr>
<td>RAVLT delayed recall</td>
<td>.91</td>
<td>.02</td>
<td>.28</td>
<td>.26</td>
</tr>
<tr>
<td>RAVLT delayed recognition</td>
<td>.81</td>
<td>.14</td>
<td>.03</td>
<td>.34</td>
</tr>
<tr>
<td>RAVLT retroactive interference†</td>
<td>-.79</td>
<td>.15</td>
<td>-.13</td>
<td>-.36</td>
</tr>
<tr>
<td>Complex figure copying time†</td>
<td>.29</td>
<td>-.55</td>
<td>.13</td>
<td>-.17</td>
</tr>
<tr>
<td>Digit symbol copying trial</td>
<td>.09</td>
<td>.80</td>
<td>.16</td>
<td>.12</td>
</tr>
<tr>
<td>Digit symbol substitution trial</td>
<td>.20</td>
<td>.65</td>
<td>.27</td>
<td>.53</td>
</tr>
<tr>
<td>Trail making test part A†</td>
<td>-.01</td>
<td>-.66</td>
<td>-.02</td>
<td>-.16</td>
</tr>
<tr>
<td>Trail making test part B†</td>
<td>-.10</td>
<td>-.69</td>
<td>-.33</td>
<td>-.36</td>
</tr>
<tr>
<td>COWAT fluency</td>
<td>.03</td>
<td>.56</td>
<td>.56</td>
<td>.01</td>
</tr>
<tr>
<td>Letter number sequencing</td>
<td>.12</td>
<td>.19</td>
<td>.85</td>
<td>.22</td>
</tr>
<tr>
<td>RVIP d’</td>
<td>.35</td>
<td>.20</td>
<td>.63</td>
<td>.13</td>
</tr>
<tr>
<td>Incidental learning</td>
<td>.46</td>
<td>-.14</td>
<td>.61</td>
<td>.34</td>
</tr>
<tr>
<td>Complex figure recall</td>
<td>.36</td>
<td>-.28</td>
<td>.60</td>
<td>.17</td>
</tr>
<tr>
<td>Stroop incongruent reaction time†</td>
<td>-.30</td>
<td>-.14</td>
<td>-.10</td>
<td>-.83</td>
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<tr>
<td>Mental rotation test reaction time†</td>
<td>-.11</td>
<td>-.20</td>
<td>-.26</td>
<td>-.72</td>
</tr>
<tr>
<td>Card sorting test reaction time†</td>
<td>-.24</td>
<td>-.36</td>
<td>-.18</td>
<td>-.65</td>
</tr>
</tbody>
</table>

Table 4.2: Factor loadings for each test item. Significant loadings (greater than .50) are highlighted. † These items show negative loadings as lower values signify better performance.
4.4 Missing data

Some participants did not have data for particular tasks due to problems with the computer programme or not completing the task correctly (for example two participants responded to the word rather than colour on all incongruent Stroop trials). Missing data was not further analysed but there were no obvious group differences in non compliance to task instructions. Participants with missing data were excluded from that particular analysis when looking at individual tasks. When generating domain scores the available data was used to calculate averages. For the categorical analysis it was assumed that the participant was not impaired on any task for which data was missing. This is a conservative assumption.

4.5 Parametric analysis

Domain scores were generated from the factor analysis using the following method, (1) raw scores were converted to z-scores using the mean and standard deviation of all participants combined. (2) Items with negative factor loadings were inverted so that higher scores indicated better performance on all measures. (3) Items for each domain were averaged to generate domain z-scores. (4) These were then converted to t scores ($t = z*10 + 50$) to maintain separation from the z-scores used in the categorical analysis (section 4.6).

Within each domain the individual tasks were also compared to see where any differences lay. The distributions were checked for normality and the following tasks were normalised using a log transformation; trail making test part A, letter number sequencing, stroop RT, Card sort RT and mental rotation RT. The recognition trial from the RAVLT and prospective memory accuracy were not normally distributed in the control group as they showed ceiling effects. There is no simple transformation to account for ceiling effects, and using non parametric tests would not take into account the effects of covariates, therefore these were still analysed parametrically. Delayed recall from the RAVLT showed a mild negative skew in the control group, but applying a square root transformation skewed the data in the other groups therefore this was also left and analysed parametrically for the reasons given above.
4.5.1 Results for parametric analysis SLE versus controls

The groups were compared on the four cognitive domains. ‘Memory’ included RAVLT trial I, learning, delayed recall, delayed recognition and retroactive interference. ‘Speed of processing (SOP)’ included complex figure copying time, digit symbol copying trial and substitution trial, trail making test parts A and B and COWAT fluency. ‘Executive control’ included RAVLT trial I, COWAT fluency, Letter number sequencing, RVIP d’, incidental learning and complex figure recall. ‘Compound reaction time’ included digit symbol substitution, Stroop RT, Mental rotation RT and card sorting RT.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=28)</th>
<th>SLE all (n=35)</th>
<th>p</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>53.56 (7.57)</td>
<td>47.28 (8.46)</td>
<td>0.050</td>
<td>.24</td>
</tr>
<tr>
<td>Speed of processing</td>
<td>53.75 (5.00)</td>
<td>46.84 (8.89)</td>
<td>0.017</td>
<td>.30</td>
</tr>
<tr>
<td>Executive control</td>
<td>53.93 (6.35)</td>
<td>46.81 (7.51)</td>
<td>0.014</td>
<td>.30</td>
</tr>
<tr>
<td>Compound RT</td>
<td>53.19 (6.09)</td>
<td>46.95 (10.15)</td>
<td>0.035</td>
<td>.26</td>
</tr>
</tbody>
</table>

Table 4.3: Mean (standard deviation) cognitive domain t-scores for control and SLE participants and effect size r for the difference.

The SLE group as a whole were compared to the healthy controls using four ANCOVAs with NART error score added as a covariate. The mean (standard deviation) t scores for each domain are shown in table 4.3. The SLE group had significantly lower scores on all domains; memory \( t(63)=-2.00, p<0.05, r=.24 \); speed of processing (SOP) \( t(63)=-2.45, p<0.05, r=.30 \); compound RT \( t(63)=-2.15, p<0.05, r=.26 \) and executive control \( t(63)=-2.52, p<0.05, r=.30 \), although none would remain significant if a Bonferroni correction was used for multiple comparisons. The effect sizes were small to medium, and were similar for all domains.

4.5.2 Results splitting the SLE group

Splitting the SLE group into NPSLE and non-NSPLE participants indicated that it was the NPSLE group who had the lowest scores. Using a Bonferroni correction \( p = 0.05/4 = 0.0125 \) there were significant group differences on all domains; memory \( F(2,61)=6.44, p<0.01, \omega=.35 \); SOP \( F(2,61)=6.32, p<0.01, \omega=.35 \); executive control \( F(2,61)=6.29, p<0.01, \omega=.32 \) and compound RT.
$F(2,61)=4.77$, $p<0.05$, $\omega=.31$. Post hoc tests using a Bonferroni correction indicated that the NPSLE group had significantly lower scores than the controls on all domains, and these had medium effect sizes ranging from $r=.36$ for compound RT to $r=.40$ for SOP and executive control. The NPSLE group had significantly lower mean scores than the non-NPSLE group on memory and SOP with medium effect sizes ($r=.34$ and $.30$) but did not have significantly lower scores on compound RT or executive control. Finally although the non-NPSLE participants had a lower mean score than controls on all domains this was not statistically significance and effect sizes were negligible or small ranging from $r=.05$ for memory to $r=.12$ for SOP.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=28)</th>
<th>Non-NPSLE (n=22)</th>
<th>NPSLE (n=15)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw score</td>
<td>53.56 (7.57)</td>
<td>47.28 (8.46)</td>
<td>43.79 (9.76)</td>
<td></td>
</tr>
<tr>
<td>Adjusted score</td>
<td>52.16 (7.79)</td>
<td>51.30 (7.82)</td>
<td>44.00 (7.39)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Speed of processing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw score</td>
<td>53.56 (5.34)</td>
<td>48.73 (6.39)</td>
<td>44.05 (11.32)</td>
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</tr>
<tr>
<td>Adjusted score</td>
<td>52.33 (7.44)</td>
<td>50.19 (7.47)</td>
<td>44.23 (7.06)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Executive control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw score</td>
<td>53.93 (6.35)</td>
<td>48.11 (6.63)</td>
<td>44.91 (8.52)</td>
<td></td>
</tr>
<tr>
<td>Adjusted score</td>
<td>52.18 (6.43)</td>
<td>50.16 (6.46)</td>
<td>45.17 (6.10)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Compound RT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw score</td>
<td>53.19 (6.09)</td>
<td>48.89 (7.20)</td>
<td>43.80 (12.91)</td>
<td></td>
</tr>
<tr>
<td>Adjusted score</td>
<td>52.21 (7.75)</td>
<td>50.04 (8.78)</td>
<td>43.95 (8.30)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 4.4: Mean (sd) cognitive domain t-scores separated into NPSLE, non-NPSLE and controls. The adjusted scores show the estimated marginal means with NART added as a covariate.

4.5.2.1 Memory

Looking at the individual tasks that make up the memory domain, it is evident that the NPSLE performed worse than the other groups on all measures. There were significant group differences on learning, delayed recall and recognition. On post hoc test the NPSLE group had significantly lower scores than controls on these three tasks, and scored significantly lower than the non-NPSLE group on delayed recall and recognition. There were no group differences on the interference measure even though the NPSLE group lost on average 2.87 words following the interference trial, compared to 1.61 for controls. The large standard deviation indicates the NPSLE group were variable on this measure, and inspection of the scores
obtained indicate one participant in the NPSLE group gained five words following presentation of list B. This pattern of performance is abnormal; on normative data most participants lose 1.5 words between trials V and VI, and in the current sample only one other (control) participant showed this pattern. Removal of both these participants resulted in the ANCOVA reaching significance $F(2,59)=3.26$, $p<0.05$, and the NPSLE group showing significantly higher interference than controls. The NPSLE participant also showed no learning curve from trials I to V (normative data suggests a gain of five words across trials is normal) and this gain to trial VI suggests this was not a true reflection of her ability. As a final check to ensure the differences between the NPSLE and other groups was not due to the abnormal performance of this one participant analyses on the memory domain were repeated with her data removed, but this did not affect the pattern of other results.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=28)</th>
<th>Non-NPSLE (n=22)</th>
<th>NPSLE (n=15)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAVLT trial I (max 15)</td>
<td>7.71 (2.55)</td>
<td>6.91 (2.07)</td>
<td>5.73 (1.91)</td>
<td>0.051</td>
</tr>
<tr>
<td>RAVLT learning (max 75)</td>
<td>57.57 (8.76)</td>
<td>51.05 (9.65)</td>
<td>45.00 (14.21)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RAVLT trial VII (max 15)</td>
<td>12.14 (3.03)</td>
<td>10.36 (2.56)</td>
<td>7.87 (4.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recognition (max 15)</td>
<td>13.58 (1.70)</td>
<td>13.50 (1.60)</td>
<td>11.36 (3.08)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Retroactive interference</td>
<td>1.61 (1.73)</td>
<td>2.50 (1.63)</td>
<td>2.87 (3.18)</td>
<td>0.305</td>
</tr>
</tbody>
</table>

Table 4.5. Mean (sd) scores for the individual tasks that were included in the Memory domain t-score.

### 4.5.2.2 Speed of processing (SOP)

On the individual tasks that make up the SOP domain, there were significant group differences on all tasks except the trail making test. On post hoc tests the NPSLE group were slower than the controls on COWAT and digit symbol copying and substitution. These had medium effect sizes with values between $r=.30$ and .37. On other tasks the effect sizes ranged from .23 for trail making test part A to .28 for trail making test B which are marginally smaller effects.
Although overall the NPSLE group had a significantly lower mean t-score than the non-NPSLE group, the only individual task on which they showed a significant difference was the time to complete the complex figure. The non-NPSLE and control groups did not differ on any task. Effect sizes for the contrast between them were small ($r < .20$).

<table>
<thead>
<tr>
<th>Speed of processing</th>
<th>Control (n=28)</th>
<th>Non-NPSLE (n=22)</th>
<th>NPSLE (n=15)</th>
<th>$p$</th>
<th>$3 &lt; 1, 2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure copy time (s)</td>
<td>105.68 (35.01)</td>
<td>97.86 (35.76)</td>
<td>140.40 (75.73)</td>
<td>0.029</td>
<td>$3 &gt; 2$</td>
</tr>
<tr>
<td>Digit symbol copying</td>
<td>122.39 (18.10)</td>
<td>108.10 (32.22)</td>
<td>96.62 (34.18)</td>
<td>0.041</td>
<td>$3 &lt; 1$</td>
</tr>
<tr>
<td>Digit symbol substitution</td>
<td>61.14 (10.48)</td>
<td>51.33 (11.90)</td>
<td>50.77 (13.73)</td>
<td>0.026</td>
<td>$3 &lt; 1$</td>
</tr>
<tr>
<td>Trail making test A (s)</td>
<td>32.74 (12.07)</td>
<td>36.68 (13.01)</td>
<td>43.06 (18.52)</td>
<td>0.167</td>
<td></td>
</tr>
<tr>
<td>Trail making test B (s)</td>
<td>61.17 (19.57)</td>
<td>80.93 (34.00)</td>
<td>95.51 (60.31)</td>
<td>0.064</td>
<td></td>
</tr>
<tr>
<td>COWAT (n in 3 minutes)</td>
<td>43.54 (10.29)</td>
<td>32.41 (9.74)</td>
<td>31.64 (9.97)</td>
<td>&lt;0.01</td>
<td>$3 &lt; 1$</td>
</tr>
</tbody>
</table>

Table 4.6: Mean (sd) scores for the individual tasks that were included in the speed of processing domain score.

4.5.2.3 Executive control

There were significant group differences on RALT trial I, complex figure recall, incidental learning and COWAT. On post hoc test the NPSLE performed significantly worse than controls on these three tasks, and the differences had medium effect sizes, ranging from $r = .29$ for incidental learning to $r = .37$ for COWAT. The non-NPSLE group did not differ from either the NPSLE group or controls on any task. The performance of the non-NPSLE group was closer to that of the controls for RAVLT trial I and complex figure recall, but was closer to the NPSLE group for incidental learning and COWAT.
### Table 4.7: Mean (sd) scores for the individual tasks that were included in the executive control domain score.

<table>
<thead>
<tr>
<th>Task</th>
<th>Control (n=28)</th>
<th>Non-NPSLE (n=22)</th>
<th>NPSLE (n=15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Executive control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAVLT trial I</td>
<td>7.71 (2.55)</td>
<td>6.91 (2.07)</td>
<td>5.73 (1.91)</td>
<td>0.051</td>
</tr>
<tr>
<td>Complex figure recall</td>
<td>20.75 (4.50)</td>
<td>19.05 (5.85)</td>
<td>15.53 (5.00)</td>
<td>0.017</td>
</tr>
<tr>
<td>(maximum score 36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidental learning</td>
<td>5.19 (2.26)</td>
<td>4.00 (2.27)</td>
<td>3.00 (2.45)</td>
<td>0.029</td>
</tr>
<tr>
<td>(maximum score 9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COWAT</td>
<td>43.54 (10.29)</td>
<td>32.41 (9.74)</td>
<td>31.64 (9.97)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LNS (maximum score 21)</td>
<td>12.65 (2.64)</td>
<td>11.16 (2.71)</td>
<td>10.29 (4.21)</td>
<td>0.144</td>
</tr>
<tr>
<td>RVIP d’</td>
<td>2.93 (0.95)</td>
<td>2.30 (1.07)</td>
<td>2.74 (1.12)</td>
<td>0.950</td>
</tr>
</tbody>
</table>

4.5.2.4 Compound Reaction Time

Although there was a significant group difference on the compound RT domain score, the only individual task that showed a significant group difference was the digit symbol substitution, where the NPSLE had a lower mean score than the control group (r=.30). However, the effect sizes for the other comparisons were similar ranging from r=.23 for stroop RT to r=.30 for rotation RT. The non-NPSLE group did not differ from either the NPSLE group of the controls on any task.

### Table 4.8: Mean (sd) scores for the individual tasks that were included in the Compound RT domain score.

<table>
<thead>
<tr>
<th>Task</th>
<th>Control (n=28)</th>
<th>Non-NPSLE (n=22)</th>
<th>NPSLE (n=15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compound RT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Card sort RT (ms)</td>
<td>570.49 (96.36)</td>
<td>630.84 (110.14)</td>
<td>644.64 (124.84)</td>
<td>0.120</td>
</tr>
<tr>
<td>Mental rotation RT (ms)</td>
<td>1129.85 (262.63)</td>
<td>1247.61 (253.70)</td>
<td>1508.43 (777.51)</td>
<td>0.056</td>
</tr>
<tr>
<td>Stroop incongruent RT (ms)</td>
<td>1360.59 (251.53)</td>
<td>1418.15 (332.92)</td>
<td>1594.93 (456.79)</td>
<td>0.113</td>
</tr>
<tr>
<td>Digit symbol substitution</td>
<td>61.14 (10.48)</td>
<td>51.33 (11.90)</td>
<td>50.77 (13.73)</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Table 4.8: Mean (sd) scores for the individual tasks that were included in the Compound RT domain score.
4.5.2.5 Measures not included in the factor analysis

These measures were not included in the factor analysis as they did not correlate with other items or did not load on any of the factors. These measures were; RVIP RT, alternative uses test, prospective memory (PM) accuracy, PM cost (card sort RT with embedded PM minus card sort RT without PM), the stroop effect (incongruent trials RT minus congruent), mental rotation difficulty (RT to trials with >135° rotation minus trials with <45° rotation) and the finger tapping test. Table 4.9 shows the mean scores for these tasks with the SLE group split into NPSLE and non-NPSLE. There was a significant group difference on finger tapping $F(2,47)=10.67; p<0.01$, $\omega=.30$, with the NPSLE group having significantly lower scores than both other groups which did not differ from each other. The NPSLE group had 1.6-2 fewer taps per second than the other groups.

On the other tasks there were no significant group differences, although the alternative uses test and mental rotation difficulty approached significance. Both patient groups generated fewer uses than the controls on the alternative uses test, and had a larger effect of rotation difficulty. Combining the SLE group resulted in a significant difference with controls on both the alternative uses test, $t(61)=2.40, p<0.05$, $r=.29$, and mental rotation difficulty, $r(55)=2.54, p<0.05, r=.32$.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=28)</th>
<th>Non-NPSLE (n=22)</th>
<th>NPSLE (n=15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVIP RT</td>
<td>525.48 (74.78)</td>
<td>603.40 (140.86)</td>
<td>591.84 (149.97)</td>
<td>0.274</td>
</tr>
<tr>
<td>Alternative uses test</td>
<td>11.82 (3.35)</td>
<td>7.48 (3.22)</td>
<td>9.07 (5.44)</td>
<td>0.052</td>
</tr>
<tr>
<td>PM accuracy (max 8)</td>
<td>7.22 (1.74)</td>
<td>6.52 (2.04)</td>
<td>6.20 (1.74)</td>
<td>0.305</td>
</tr>
<tr>
<td>PM intention cost †</td>
<td>115.68 (92.02)</td>
<td>80.09 (72.95)</td>
<td>75.59 (54.70)</td>
<td>0.157</td>
</tr>
<tr>
<td>Stroop effect †</td>
<td>73.85 (92.02)</td>
<td>149.88 (221.27)</td>
<td>69.43 (104.97)</td>
<td>0.513</td>
</tr>
<tr>
<td>Rotation difficulty†</td>
<td>502.42 (270.82)</td>
<td>744.98 (572.32)</td>
<td>783.68 (445.67)</td>
<td>0.073</td>
</tr>
<tr>
<td>Finger tapping dominant hand</td>
<td>63.00 (6.49)</td>
<td>59.25 (13.16)</td>
<td>43.19 (18.32)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 4.9: Mean (sd) for tasks that were not included in the factor analysis.

† All measured in milliseconds.
The non-significant difference on prospective memory accuracy was further investigated as this was a task that was expected to be sensitive. The groups were compared on the PM cost and the correlation between cost and PM detection. There was no group difference on the PM cost $F(2,61)=1.65$, $p=0.20$, with the NPSLE group showing a mean increase of 74.60 ms compared to 89.09 in the non-NPSLE group and 115.68 for controls. However, within the NPSLE group there was a significant correlation between PM accuracy and PM intention cost $r(15)=.54$, $p<0.05$, and this was not present in the other groups.

4.5.2.6 Accuracy measures

Overall accuracy was fairly high on the computerised tasks. The mental rotation test was the only task that showed significant group differences, $H(63)=5.99$, $p<0.05$. The median number of errors (range) was 3 (0-32) for NPSLE, 2 (0-16) for non-NPSLE and 0 (0-4) for controls. On post hoc test the NPSLE group was less accurate than the control group, and the non-NPSLE group did not differ from either.

4.6 Categorical analysis

Raw scores were converted to categorical scores (impaired or not impaired) by converting them to z-scores using the mean and standard deviation of the control group as a reference. As the control group was used rather than normative data, which usually adjusts for age and education, prior to converting to z-scores the raw scores were adjusted to account for covariates. First, correlations between raw scores and covariates were assessed, and where these were significant, scores were adjusted for this covariate. All tasks except time to complete the complex figure were adjusted for NART error scores, and the following tasks were also adjusted for age: complex figure recall, digit symbol substitution, trail making test B, finger tapping, card sort RT and stroop RT. Adjusted scores were calculated by regressing the covariate onto the raw score to find $\beta$, then adjusting the raw score by $\beta$ multiplied by the difference between an individual’s score and the group mean. Thus an individual who made few errors on the NART would have their score reduced whereas an individual making more errors than the group mean would have their score increased. As an example an individual who scored 47 for learning on the RAVLT ($\beta=-.604$) and made 25 errors on the NART (group mean 16.71) would have their score adjusted in the following way: adjusted score = 47 + ($-.604*(16.71-25)) = 52.
Z-scores more than one standard deviation below the control mean were classed as impaired for that task. Although some studies use two rather than one standard deviation as the cut-off for impairment, one standard deviation was selected to allow comparability with other studies that have used the ACR battery (Kozora, Arciniegas, et al., 2008; Kozora, et al., 2004, 2006). The categorical scores were combined to produce an impairment index using the method employed by Kozora et al., (2004) using the tasks included in the ACR battery. This involved scoring one point for each task on which the individual’s performance was classed as impaired from the following tasks: RAVLT learning trial, RAVLT trial VII, complex figure copying and delayed recall, DSST, trail making test- part B, letter number sequencing, COWAT, alternative uses test (replaced animal fluency in the ACR battery), Stroop test (incongruent trials reaction time was used) and finger tapping in the dominant and non-dominant hand. Therefore the cognitive impairment index had a range from 0-12 and, in accordance with Kozora et al. (2004) a score of four or more was classed as global impairment.

Secondly, to check whether this overestimated global impairment where only certain domains were affected, a global score based on the domains taken from the factor analysis was generated by scoring the number of domains on which a participant was impaired (out of four). Scores of two or more were classed as global impairment. These differed from the z-scores generated in the parametric analysis as they refer to the deviation from the control group mean rather than the mean for the entire group. As such the parametric analysis was more conservative.

4.6.1 Results for categorical analysis

Figure 4.1 clearly highlights the group differences in mean z-scores for the four domains taken from the factor analysis and the items that make up the ACR cognitive impairment index. On the majority of tasks the NPSLE group had a mean z-score of around -1, compared to -0.2 for the non-NSPLE participants and 0 for healthy controls (as the z-scores were generated with respect to the group mean). The dotted line indicates one standard deviation below the control mean, which is the cut off for classification as impaired on that task. The percentage of participants scoring below the cut off for impairment is also shown. This was on average 43% for the NPSLE group (range 13-73%), 18% for the non-NSPLE group (range 0-36%) and 14% for the control group (range 3-21%).
<table>
<thead>
<tr>
<th>Control</th>
<th>Non-NP</th>
<th>NPSLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.7</td>
<td>27.3</td>
<td>46.7</td>
</tr>
<tr>
<td>14.3</td>
<td>18.2</td>
<td>53.3</td>
</tr>
<tr>
<td>14.3</td>
<td>4.5</td>
<td>13.3</td>
</tr>
<tr>
<td>17.9</td>
<td>18.2</td>
<td>46.7</td>
</tr>
<tr>
<td>14.3</td>
<td>27.3</td>
<td>46.7</td>
</tr>
<tr>
<td>21.4</td>
<td>18.2</td>
<td>33.3</td>
</tr>
<tr>
<td>14.3</td>
<td>0.0</td>
<td>53.3</td>
</tr>
<tr>
<td>17.9</td>
<td>22.7</td>
<td>40.0</td>
</tr>
<tr>
<td>17.9</td>
<td>27.3</td>
<td>26.7</td>
</tr>
<tr>
<td>10.7</td>
<td>9.1</td>
<td>33.3</td>
</tr>
<tr>
<td>10.7</td>
<td>36.4</td>
<td>73.3</td>
</tr>
<tr>
<td>14.3</td>
<td>18.2</td>
<td>73.3</td>
</tr>
<tr>
<td>14.3</td>
<td>9.1</td>
<td>53.3</td>
</tr>
<tr>
<td>14.3</td>
<td>18.2</td>
<td>40.0</td>
</tr>
<tr>
<td>3.6</td>
<td>9.1</td>
<td>26.7</td>
</tr>
<tr>
<td>10.7</td>
<td>18.2</td>
<td>40.0</td>
</tr>
</tbody>
</table>

**Individual tasks**

- RAVLT learning
- RAVLT trial VII
- Complex figure copy
- Complex figure recall
- Digit symbol substitution
- Trail making test – part B
- Letter number sequencing
- COWAT
- Alternative uses
- Stroop reaction time
- Tapping Dominant
- Tapping non-dominant

**Domain scores**

- Memory
- Speed of processing
- Executive control
- Compound reaction time

Figure 4.1: NPSLE and non-NPSLE (non-NP) z-scores for domain scores and tasks included in the ACR cognitive impairment index, along with the percentage of participants impaired on each task. Error bars indicate ±1 standard error.

* p<0.05, ** p<0.01
Although a greater proportion of the NPSLE group were classed as impaired on all tasks compared to the other two groups, this was only significant for the memory domain score, RAVLT learning and delayed recall, letter number sequencing and finger tapping in both the dominant and non-dominant hand. Tapping showed the largest group differences with 73% of the NPSLE group being classified as impaired, and a z-score of approximately -3 for both hands indicating a number of participants scored as significantly impaired on this measure.

Table 4.10 displays the average score on the cognitive impairment index (CII) based on the ACR battery and global impairment score (GIS) based on the domains from the factor analysis. The number of participants classed as showing global impairment (scores of 4 or more on the CII or more than 2 on the GIS) is also displayed.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=28)</th>
<th>Non-NPSLE (n=22)</th>
<th>NPSLE (n=15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive impairment index (maximum 12)</td>
<td>1.79 (2.00)</td>
<td>2.41 (2.20)</td>
<td>5.40 (3.29)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Percentage impaired</td>
<td>17.9</td>
<td>27.3</td>
<td>66.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Global impairment score (max 4)</td>
<td>0.43 (0.69)</td>
<td>0.59 (0.91)</td>
<td>1.67 (1.54)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Percentage impaired</td>
<td>10.7</td>
<td>18.2</td>
<td>53.3</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 4.10: Mean (sd) for scores on the cognitive impairment index and global domain score, and the percentage of participants that are classed as impaired based on these measures.

On both indices the NPSLE group had significantly higher scores and a greater percentage of participants were classed as impaired compared to the other groups. Although the two indices gave the same overall pattern of results the CII identified a greater proportion of participants as impaired, including 18% of control participants. One possibility for this difference is that the CII includes finger tapping, a measure on which 73% of NPSLE participants and up to 36% of non-NPSLE participants were impaired on. Removal of this item resulted in a reduction in the proportion of patients classed as impaired, in both patient groups, to the level suggested by the GIS, but did not impact on the control group.
4.7 Discussion

The SLE group as a whole performed worse than healthy controls in relation to cognitive performance, and these differences were significant on all four domains with the largest effects in speed of processing (SOP) and executive control. Splitting the SLE group into NPSLE and non-NPSLE indicated it was the NPSLE participants who performed worse than controls on these four domains. The NPSLE group scored significantly worse than the non-NPSLE participants on SOP and memory, but not on executive control or compound RT. The non-NPSLE group did not differ from controls on any of the domain scores or any individual task within the battery. These findings imply, in contrast to the suggestion of Benedict et al., (2008), that it is important to distinguish between patients with NPSLE and non-NPSLE. This is more remarkable given that no participants in the NPSLE group recruited for the present study had previous focal brain injury or stroke.

Effect sizes for the difference between NPSLE participants and controls were similar for all domains, but were largest on executive control and SOP, which supports the findings of Benedict et al., (2008), who reviewed previous studies and found the largest effect sizes in psychomotor speed/attention. The effect sizes in the current study ($r = .40$) were slightly larger than those described by Benedict et al., (2008), probably reflecting the fact that they combined studies looking at non-NPSLE and NPSLE participants. In fact the effect sizes for the whole SLE group compared to controls ($r = .30$) were akin to those of Benedict et al., (2008).

The categorical analysis suggested cognitive impairment for 18-27% of non-NPSLE participants, and 53-67% of NPSLE participants. However it also identified impairment in 11-18% of controls. Previous studies have estimated cognitive impairment in up to 80% of NPSLE participants (Ainiala, Loukkola, et al., 2001) and between 15 and 50% of patients with non-NPSLE. Using the ACR battery 48% of NPSLE and 21-23% non-NPSLE patients have been classed as impaired (Kozora, Arciniegas, et al., 2008; Kozora, et al., 2004). These values are slightly lower than those found in the present sample. This is unlikely to be due to a high scoring control group used as a comparison, as Kozora et al., (2008) also found impairment in 14% of controls, which is comparable with the 18% found in the present data. The cognitive impairment index (CII) raw scores can be compared to those seen in other studies. In the present sample the scores were 1.79 for controls, 2.41 for non-NPSLE and 5.40 for NPSLE. The first two scores are very similar to those obtained by Kozora and colleagues; 1.44-1.90 for
controls and 2.41-2.30 for non-NPSLE (Kozora, Arciniegas, et al., 2008; Kozora, et al., 2006). However the NPSLE mean score is higher than the 3.74 obtained by Kozora et al., (2006). One possibility is that this reflects the fact that 73.3% of NPSLE participants were impaired on finger tapping, and this contributed two points of 12 to the total CII score. Although the previous studies do not specify what percentage of NPSLE participants were impaired on this measure, only 20% of the NPSLE and non-NPSLE participants combined were impaired on finger tapping (Kozora, et al., 2004). Other studies that have compared NPSLE and non-NPSLE participants (Loukkola, et al., 2003; Monastero, et al., 2001) did not include motor speed measures. It would be interesting to see whether these motor impairments would be seen in another, or larger NPSLE sample.

4.7.2 Parametric analysis versus categorical

The parametric analysis picked up more group differences than the categorical analysis. RAVLT learning, delayed recall, finger tapping and the memory domain score showed significant group differences on both analyses. Parametric testing established additional group differences on complex figure recall and digit symbol substitution along with the other three domain scores. This reveals the additional sensitivity associated with parametric testing. Letter number sequencing was the only task to reveal group differences on categorical testing and not on parametric. This could be because large variability within the NPSLE group masked the fact that 50% of participants were impaired on this task relative to controls.

4.7.2 Individual tasks versus combined scores

Combined scores identified greater group differences than the analysis of individual tasks. During the parametric analysis the NPSLE group separated from controls on all four domains, and from the non-NPSLE group on speed of processing and memory. However the patient groups were only different on individual tasks of delayed recall, recognition and time to complete the complex figure. The difference in sensitivity is evident when considering the compound RT domain, on which the NPSLE group had significantly lower overall scores than the controls but the digit symbol substitution test was the only individual task on which the groups differed. This could reflect the heterogeneity of cognitive dysfunction in NPSLE; participants were impaired on slightly different tasks and combining scores across tasks them therefore was better able to pick up group differences.
The cognitive impairment index (CII) identified two more participants in each group as impaired compared to the global impairment index (GIS). One possibility is that this overestimates global impairment if the participant is only impaired in one domain, but this is covered by multiple tasks that are combined in the cognitive impairment index. Inspection of the participants who were impaired on CII but not GIS suggest a more likely explanation is that the difference is due to the inclusion of finger tapping in the CII and not in the GIS. A high proportion of patients were impaired on this task and this contributed two points (out of 12) to the overall CII score. Removal of finger tapping from the CII resulted in a similar proportion of participants being classified as impaired as using the GIS.

4.7.3 Tasks not included in the ACR battery

The current battery included a few tasks had not previously been assessed in SLE. These were prospective memory (PM) accuracy and cost, the alternative uses test, mental rotation and rapid visual information processing (RVIP). Although patient groups were less accurate on prospective memory than controls, this difference was not significant, and generally accuracy was high; even the NPSLE group had a mean accuracy of 78%. The lack of PM effect was further investigated. One possibility was that, although there was no group difference on PM accuracy, the patient groups had a greater cost to the ongoing task. This was not supported as there was no group difference in PM cost, and in fact the control group showed the biggest PM cost. However, the within the NPSLE group there was a significant correlation between PM accuracy and cost; the more accurate participants showed a greater cost to the ongoing task. No correlation was found in the other groups. In an identical task to the present study, Rusted, Sawyer, Jones, Trawley, and Marchant (2009) found no correlation between PM detection and the size of the PM cost. Thus this pattern of performance in the NPSLE group is abnormal and suggests participants in the NPSLE group were directing resources away from the ongoing task in order to complete the PM task. This did not translate into an overall group difference in PM intention cost, however, suggesting that added resources were needed by this group to maintain PM performance.

The group difference on the alternative uses test approached significance for the comparison between controls, NPSLE and non-NPSLE participants. The control group suggested more uses for the objects than the other groups, and this was one task where mean performance in the NPSLE group was above that in the non-NPSLE participants. Approximately 27% of participants
in both patient groups were impaired on this measure. This compares to 40% of NPSLE participants who were impaired on the COWAT, which also measures fluency. This suggests the COWAT is a more sensitive measure. The NPSLE group had a larger standard deviation than the other groups, and inspection of the range of scores shows the best (21 uses) and worst (0 uses) performers were in this group. Thus cognitive flexibility/divergent thinking is something that is not necessarily impaired in NPSLE.

Neither accuracy nor RT on the RVIP separated the groups. This was surprising as both Benedict et al., (2008) and Denburg and Denburg (2003) implicated attention as a key area of impairment in SLE. One possibility is that the task was not long enough to detect group differences in sustained attention. A second possibility is that this is the effect of missing data, as four non-NPSLE participants were unable to complete the task correctly, due to not understanding the task instructions. However this does not explain the lack of difference between the NPSLE and control group. Participants in all groups reported that this task was difficult, and its lack of sensitivity here suggests that it is perhaps not a suitable task for this type of investigation.

The mental rotation test was the only computerised task that separated the groups in terms of accuracy, with the NPSLE group making more errors than controls. The group difference in RT also approached significance (p=0.056), with a medium effect size for the difference between the NPSLE and control groups. Both patient groups showed an effect of task difficulty; measured by subtracting the mean RT for targets with a 0°or 45° rotation from the mean RT for 135° or 180° rotation. The difference between large and small rotations was significantly increased in the SLE group compared to controls, indicating they were differentially affected by the trials that required a greater rotation. These findings add support to the idea that SLE is associated with impairment in visuospatial abilities.

4.8 Summary

(1) Across multiple domains the SLE group performed worse than the controls, with small to medium effect sizes (r=.24 to .30)

(2) The NPSLE group had significantly lower scores than controls on all four domains. They also had lower scores than the non-NPSLE participants on the memory and speed of
processing domains. The non-NPSLE group did not differ from controls on any domain or on any individual task.

(3) On the categorical analysis the NPSLE group had significantly higher scores of global impairment and a significantly higher proportion were classed as showing cognitive impairment than both other groups.

(4) Combining tasks into domain scores or into an impairment index was more sensitive at detecting group differences than the individual tasks.

(5) Altogether these results suggest mild cognitive impairment in prevalent in NPSLE, and although the non-NPSLE group had an intermediate performance, it did not differ significantly from that of the control group. Group differences are further assessed in chapter 5 where three tasks are investigated in more detail.
CHAPTER 5

FURTHER INVESTIGATION OF COGNITIVE PERFORMANCE DIFFERENCES

5.1 Introduction

In chapter 4 the NPSLE group performed worse than healthy controls on a variety of tasks, and showed reduced performance compared to non-NPSLE participants on memory related tasks. In this chapter these differences are clarified by looking at three separate tasks in more detail. (1) Group differences on the Rey Auditory verbal Learning Test (RAVLT) were further studied looking at the pattern of responses across trials and other performance indicators. The aim was to get a better understanding of the processes that may explain impaired performance such as encoding or retrieval deficits or learning strategies. (2) The Controlled Oral Word Association test (COWAT) was further analysed looking at strategies such as phonemic or semantic clustering, and switching between clusters during word generation. The aim was to investigate whether group differences on the COWAT were related to differences in clustering or switching, and if this could be related to other cognitive processes previously associated with these parameters (Unsworth, Spillers, & Brewer, 2011). (3) Reaction time on the Stroop test was further assessed looking at intra-individual variability, which has been described as a behavioural marker for central nervous system integrity (Bunce, et al., 2007; Hultsch, Strauss, Hunter, & MacDonald, 2008; Strauss, Bielak, Bunce, Hunter, & Hultsch, 2007). The aim was to investigate whether the patient groups showed greater reaction time variability than controls, and whether this was predominantly seen in the NPSLE group who were thought to have central nervous system damage.

5.2 Analysis of the Rey Auditory Verbal Learning Test (RAVLT)

In the previous chapter the NPSLE group were shown to have lower scores than the controls on the RAVLT learning, delayed recall, recognition, and reduced performance on trial I though this did not reach significance. Each participant’s performance was analysed in more detail to see whether there were also qualitative difference in the pattern of performance. The detailed analysis can be split into three sections; first the pattern of performance across trials was assessed, looking for group differences in learning rates, forgetting rates and retrieval efficiency. In a similar analysis Paran et al. (2009) compared a mixed SLE group and healthy
controls on the RAVLT. The SLE group showed a significant reduction in learning rate (learning curve from trial I to V), no difference on forgetting rate (trial VII minus trial V) and a significant increase in improvement from recall to recognition. This pattern typifies the pattern seen in subcortical rather than cortical dementias (Delis, et al., 1991) and has been interpreted as indicating impaired retrieval processes. Paran et al. (2009) assessed 40 patients and stated that 21 fulfilled the criteria for NPSLE, but they did not split the group or indicate whether the differences identified were due to the presence of the NSPLE participants (though they did reanalyse the data excluding the influence of patients with previous strokes or depression and found no differences). Therefore in the current analysis the SLE group was split into NPSLE and non-NPSLE to see whether the same pattern as seen in Paran et al. (2009) was evident and whether the deficits were seen in both patient groups.

Secondly the serial position of recalled words was investigated. Normal performance on list learning typically shows a U-shape curve with items at the beginning and end of the list having a higher probability of being recalled compared to the middle. Primacy and recency effects can provide evidence of processes responsible for memory performance. Reduced primacy effects are indicative of impaired encoding for long term memory, and is seen in Alzheimer’s disease (Delis, et al., 1991) whereas reduced recency effects would indicate impaired short term memory (Mitrushina, Satz, Chervinsky, & D’Elia, 1991). One study of HIV associated dementia (HAD) showed an increase in percentage recalled from the end of a list and reduced recall from the middle compared to healthy controls and HIV patients without dementia (Scott, et al., 2006). However after a short delay words at the end of the list were less likely to be recognised despite better immediate recall. This suggests an ineffective encoding style with the HAD patients simply outputting the words at the end of the list whilst they were in their auditory attention span. Serial position within list learning has not been assessed in SLE but this could give further insight into whether poor performance on memory testing is due to impaired encoding or retrieval.

Finally other performance measures were investigated including the number of omissions (words omitted on the next trial that were recalled on the previous trial) and additions (words added that were missed on the previous trial) from trial to trial during the learning phase, and repetitions and intrusions. Paran et al. (2009) found significantly more omissions in the SLE group and a significant group x trial interaction, with the controls omitting a stable number of words, whilst they increased in the SLE group as the trials progressed. They interpreted this as
inefficient and impaired learning strategies in SLE. There was no group difference in additions, or interaction with trial. In the current study the same analysis was completed splitting the SLE group into NPSLE and non-NPSLE subgroups to see whether the impaired strategies were evident in both groups.

Intrusions can take the form of confabulations (words not on the list) or intrusions from the interference trial (list B) on subsequent recall and repetition trials. Lezak, Howieson, & Loring, (2004) state that intrusions on the RAVLT show impairment in distinguishing external or internally generated information, or in source monitoring for information coded at different times. These have not previously been assessed in patients with SLE. In the present study participants were instructed to mark 15 items on the recognition trial and this may increase the number of intrusions if the participant is guessing on the last few words marked. In a subset of participants this was investigated by recording whether errors were made in the last few items marks or whether they were spread throughout the trial indicating confusion between the lists. Finally increased repetitions in the context of poor recall may indicate poor self monitoring (Lezak, et al., 2004).

5.2.1 Methods for assessing RAVLT

5.2.1.1 Pattern of performance across trials

Three specific areas were focused on; learning rate, forgetting rate and retrieval. Learning rate was assessed using a 5 x 3 mixed ANCOVA, with trials I to V added as a within subjects factor, group as a between subjects factor and NART error score as a covariate. Forgetting rate is usually calculated as the difference between trial VII and trial VI. However performance on trial VI is confounded by interference from list B, and the difference between trial VII and trial V may represent a better measure of what has been lost from previous learning. This was the measure used by Paran et al. (2009) to assess retention. Retrieval was assessed by looking at the difference between recall (trial VII) and recognition.

5.2.1.2 Serial position of recalled words

Correct answers on each trial were divided by serial position into start (first five words in the list), middle (middle five) and end (final five) to assess primacy and recency effects. To remove
the effect of group differences in overall recall performance a proportional measure was used, whereby the number of words recalled from each serial position was divided by the total number of correct words for that trial. Primacy and recency effects were assessed on trial I, as it has been recommended that the first presentation of a list captures a purer measure of regional recall, (Delis, Kramer, Kaplan, & Ober, 2000) cited in Scott et al., (2006). This was compared to the pattern on trial VII (delayed recall). Finally, the difference between the number of recalled words on trial V and VII was analysed by position, to see whether words were lost from all sections equally and if the pattern was the same for patients and controls. For these analyses NART was not added as a covariate as proportions were used which already removed differences in overall performance.

5.2.1.3 Omissions, additions, repetitions and intrusions

Successful performance on the RAVLT may relate to a number of factors including omissions, additions, intrusions and repetitions. Omissions were calculated at the number of words that were remembered on the previous trial but omitted on the current trial. Additions were the number of words added on the current trial that were omitted on the previous one. Confabulations were classed as words not on the learning list, and intrusions were words from list B that were recalled or recognised on later trials. Lastly, repetitions were any repeated word that had already been said. These were categorised as noticed if the participant asked “have I said drum?” or corrected themselves, and were categorised as unnoticed if they did not comment.

5.2.2 Results

5.2.2.1 Pattern of performance across trials

Figure 5.1 shows the number of correct items recalled on trials I to V. The ANCOVA revealed a main effect of trial $F(4,244)=27.18; p<0.001, \omega=.65$, and a main effect of group $F(2,61)=5.41; p<0.01, \omega=.38$ but no interaction $F(2,61)=1.00; p=0.42$, indicating the learning curves were equal across groups. This was confirmed by analysing the learning rate (number correct on trial V minus trial I) where there was no significant group difference $F(2,62)=0.37; p=0.63, \omega<.01$. The learning rate was $5.33 \pm 2.92$ words for NPSLE, $5.41 \pm 1.84$ for non-NPSLE and $5.64 \pm 2.02$ for controls.
Figure 5.1: Learning rate. Estimated marginal mean number of words recalled on trials I-V of the RAVLT, with NART as a covariate.

Figure 5.2 shows the number of correct items for trials V, VI and VII. All groups showed retroactive interference (the difference between trials VI and V) and the group difference for this was discussed in section 4.5.1. There was no group difference in forgetting rates measured from trial VI to trial VII $F(2,62)=1.98; p=0.15, \omega=.17$, however there was a significant difference from trial V to trial VII $F(2,62)=3.37; p<0.05, \omega=.26$, and post hoc tests revealed the NPSLE group showed a significantly larger forgetting rate than the controls with a medium effect size $t(63)=2.553; p<.05, r=.30$, and a trend for greater forgetting rate than the non-NPSLE group, $t(63)=1.954; p=.055, r=.24$.

Figure 5.2: Forgetting rate. Estimated marginal mean number of words recalled on trials V-VII of the RAVLT, with NART as a covariate.

There was a significant group difference on retrieval efficiency, $F(2,62)=4.92; p<0.01, \omega=.31$, with the NPSLE group showing a mean improvement of 3.5 ±1.9 words from recall to recognition, compared to 2.9±2.0 for non-NPSLE and 1.6±2.0 for controls. Post hoc tests indicated that the NPSLE group showed a significantly larger improvement than the controls.
$t(63)=3.01; p<0.01, r=.35$ but did not differ from the non-NPSLE group. Despite the non-NPSLE group showing an improvement of 1.3 words more than the controls, the difference between them also did not reach significance.

5.2.2.2 Serial position of recalled words

Figure 5.3 shows the mean number of words recalled split by position for trial I (left) and trial VII (right). On trial I all groups showed primacy and recency effects, with the worst performance on the middle section of the list. This was analysed using a 2x3 mixed ANOVA. There was no main effect of group. There was a significant main effect of position $F(2,122)=10.21; p<0.001, \omega=.38$ with pairwise comparisons indicating there was a smaller proportion of words recalled from the middle position compared to the first and last ($p<0.001$), but no difference between primacy and recency effects ($p>0.1$). Although both patient groups showed an increased recency effect the group x position interaction was not significant $F(4,122)=1.21; p=0.31$.

On trial VII there was also a main effect of position, $F(2,122)=7.88; p<0.01, \omega=.33$, but a different pattern was evident with fewer words recalled from the last section compared to the start ($p<0.001$) and middle ($p<0.05$) sections. Again the group x position interaction was not significant $F(4,122)=0.37; p=0.83$.

Figure 5.3: Primacy and recency effects. Proportion of recalled words that came from the first, middle and last sections of the list, for immediate, (trial I, left) and delayed recall (trial VII, right).

The lack of a significant interaction indicates that although the NPSLE group had reduced performance compared to the other two groups, it was equally reduced across all sections of the list. All groups recalled fewer words from the middle part of the list compared to the start.
and end on the immediate recall trials, and then showed worse performance on the end of the list on the delayed recall trial.

5.2.2.3 Omissions, additions, repetitions and intrusions

Figure 5.4 shows the number of omission and additions across the learning trials. These were analysed using 3x4 mixed ANCOVAs with group and trial as independent variables. For omissions there was no main effect of group $F(2,61)=1.90; \ p=0.16, \ \omega=.17$ or trial $F(3,183)=1.46; \ p=0.23, \ \omega=.09$ and no group x trial interaction $F(6,183)=0.20; \ p=0.97$, indicating the number of omissions were stable across trials and did not differ between the groups.

Figure 5.4: Mean number of words omitted (left) and added (right) on the learning trials II-V.

For additions there was also no main effect of group $F(2,61)=1.04; \ p=0.36, \ \omega=0.03$, but there was a main effect of trial, $F(3,183)=6.27; \ p<0.001, \ \omega=.29$ and a significant group x trial interaction $F(6,183)=3.02; \ p<0.01$. Post hoc tests indicate there were more additions at trial II then the other trials ($p<0.001$) and more additions at trial III than trial V, indicating additions dropped off over time. The group x trial interaction occurred as the control group had fewer additions than the non-NPSLE group at trial III ($p<0.01$), and fewer additions that both patient groups at trial VI ($p<0.05$). This indicates the number of additions per trial dropped off faster in the control group. This difference in the pattern of additions did not translate into an overall difference in learning curve.

The mean total number of repetitions is shown in table 4.1 along with the percentage of repetitions that were noted by the participant. There was a significant group difference in number of repetitions, $F(2,61)=16.16; \ p<0.001, \ \omega=.31$ with both the control and non-NPSLE
repeating significantly more words than the NPSLE group. There was no significant difference in the proportion that were noted $F(2,61)=2.67; p=0.08, \omega=.22$.

<table>
<thead>
<tr>
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<th>Control (n=28)</th>
<th>Non-NPSLE (n=22)</th>
<th>NPSLE (n=15)</th>
<th>p</th>
</tr>
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<td>Repetitions</td>
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<tr>
<td>Proportion noted</td>
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<td>0.45 (0.29)</td>
<td>0.31 (0.30)</td>
<td>0.078</td>
</tr>
</tbody>
</table>

Table 5.1: Mean total number of repetitions across all trials (I-VII), and proportion that were noted by the participant.

Confabulations have been separated into those occurring in trials I to V, and those in trials VI, VII and the recognition trial individually. The latter trials may also include intrusions from list B. Overall intrusions and confabulations were relatively rare, therefore as well as displaying the mean number, the percentage of participants experiencing each type of intrusion/confabulation has been presented in table 5.2. These were analysed using Kruskal-Wallis tests due to a large proportion of participants having zero in most categories.

A larger proportion of patients experienced confabulations and intrusions compared to controls and this difference was just significant for confabulations $H(65)=6.08; p<0.05$, and almost reached significance for intrusions $H(65)=5.88; p=0.052$. The effect sizes for post hoc comparisons indicate both patient groups had more intrusions and confabulations than controls. On the recognition trials there was a trend for a difference between the NPSLE group and controls on both confabulations and intrusions. For a subset of participants (n=26) it was recorded whether the errors were made throughout the recognition trial, or whether they occurred in the last few words marked, indicating the participant may have been guessing. Of these, 13 participants made at least one error on the recognition trial and 61% of confabulations and 89% of intrusions occurred in the final five words marked. This pattern did not differ across the groups.
Table 5.2. Mean number of confabulations and intrusions from list B for RAVLT recall trials (I-VII) and recognition trial.

† Figures in brackets indicate the percentage of participants who had at least one error.
‡ Effect size1 = NPSLE versus controls and effect size 2 = non-NPSLE versus controls.

5.2.3 Discussion of further assessment of the RAVLT

5.2.3.1 Pattern of performance across trials

Although the NPSLE group showed significant reduction in total number of words learnt, there was no difference in learning rate on trials I to V. This contrasts with Paran et al. (2009) who showed a reduced learning rate in their SLE group. In the present study, however, seven controls (25%) had reached ceiling by trial IV compared to one NPSLE patient, therefore a longer list could perhaps better distinguish differences in learning rates.

The NPSLE group showed larger forgetting rates if the difference between trial V and VII was used, but there were no group differences on forgetting rates measured as trial VII minus trial VI. This again contrasts with Paran et al. (2009) who found no differences on forgetting rate measured form trial V to VII. The main difference between the studies is that Paran et al. had a delay of 20 minutes, whereas in the current study the delay was approximately one hour. This implies that larger forgetting rates in SLE participants are only evident after a longer delay.

The NPSLE group showed a significantly larger improvement from recall to recognition compared to the controls. Although the non-NPSLE group did not differ from controls on post hoc tests they showed nearly twice the improvement (2.6 words compared to 1.3). This finding supports Paran et al. (2009) and suggests that impaired performance reflects difficulty with effortful retrieval. However the NPSLE group had reduced recognition performance on the
recognition trial compared to the other groups, which also reflects impaired encoding (Delis et al, 2000).

5.2.3.2 Serial position of recalled words

Neither patient group showed differential effects relative to controls when serial position was analysed in detail. This pattern differs from that shown in HIV associated dementia (Scott, et al., 2006) and suggests that group differences were not likely to be due to deficient encoding in the NPSLE group.

5.2.3.3 Omissions, additions, repetitions and intrusions

In the present sample there were no group differences on number of omissions or additions and no group x trial interaction for omissions. This differs from Paran et al. (2009) who found more omissions in their SLE group and an interaction whereby the SLE group made increasingly more omissions as the trials progressed. This could in part explain why Paran et al. (2009) found differences in learning rate, which were not found in the present sample.

The control and non-NPSLE groups had significantly more repetitions than the NPSLE participants. There was no difference in the proportion of repetitions that were noted by the participant, suggesting repetitions did not reflect failure of monitoring in the NPSLE group. The pattern of increased repetitions in non impaired participants was also shown a sample of chronic lead exposed participants (Bleecker, et al., 2005). They suggest increased repetitions without confabulations or intrusions may reflect increased effort to recall as many words as possible.

On the recall trials, (I-VII) intrusions and confabulations were more common in the SLE group than controls and this difference just reached significance for confabulations, and was almost significant for intrusions. However, this is unlikely to be a significant factor in overall group differences because (1) only 20% of NPSLE patients experienced intrusions and 25% confabulations, while 53.3% of patients were classed as impaired on the memory domain (see figure 4.1) (2) both the NPSLE and non-NPSLE groups had an increase in confabulations and intrusions compared to controls whereas only the NPSLE group had significantly worse memory performance. On the recognition trials participants were instructed to mark 15 items
and therefore all errors would be scored as an intrusion or confabulation. Analysis of a subset of participants indicates the errors tended to occur in the final few words marked, and this pattern did not differ across the groups. This suggests the NPSLE group did not have poorer recognition performance because they experienced more intrusions from list B, but instead made more errors towards the end of the trial when they may have been guessing.

4.3 Cluster analysis of verbal fluency task

Most studies that use the controlled oral word associate test (COWAT) use the total number of words generated as the primary outcome measure. However performance on this task has been related to a number of different processes. Troyer and colleagues (Troyer, Moscovitch, & Winocur, 1997; Troyer, Moscovitch, Winocur, Alexander, & Stuss, 1998) suggested that effective performance on the COWAT related to two processes; clustering and switching. Clustering refers to the generation of words within a category, such as words beginning with fol (e.g. follow, folder, folk) and switching refers to the creation of new categories. Troyer et al. (1997) suggested that these processes are dissociable with clustering relating to automatic processing relying on temporal lobe structures, and switching relating to more effortful frontal lobe processing. Unsworth, Spillers, and Brewer (2011) investigated the relationship between the cognitive constructs of working memory capacity, inhibition, vocabulary and processing speed and clustering and switching. They found clustering was related to both working memory capacity and vocabulary, whilst switching was related to working memory capacity and processing speed, suggesting there may not be an automatic/strategic distinction between clustering and switching. However, despite stating they used the exact same scoring procedures as Troyer et al. (1997), Unsworth et al. (2011) in fact did not calculate cluster size in the same manner as Troyer et al. Unsworth et al. (2011) used only clusters larger than one in their calculation, whilst Troyer et al. (1997) included all clusters, giving single words a size of 0. Thus, Troyer’s measure relates to the absolute size of each cluster, but also correlates highly with the percentage of words within a list that are part of a cluster, whereas Unsworth’s measure relates only to absolute cluster size. This means the interpretation of what cognitive processes relate to cluster size is potentially problematic, nonetheless their research suggests these are somewhat separate processes both contributing to performance on fluency tasks.

Previous neuropsychological studies have shown fewer words generated on verbal fluency tasks (both phonological and semantic) with fewer switches, but normal cluster sizes in frontal
lobe patients (Troyer, Moscovitch, Winocur, Leach, & Freedman, 1998) and patients with Multiple Sclerosis or Parkinson’s disease (Troster 1998). They also report deficits in both in Alzheimer’s disease, (Troster, et al., 1998; Troyer, Moscovitch, Winocur, Leach, et al., 1998) and Huntingdon’s disease (Troster, et al., 1998). These factors have not previously been assessed in SLE, but it could be predicted that a similar pattern would be evident to that shown in multiple Sclerosis, with a significant difference in switching but not in cluster size.

5.3.1 Method for analysing clusters and switching

Previous studies investigating clustering and switching have used the COWAT to measure phonological fluency and a categorical task such as animal naming to measure semantic clustering. However it is possible for an individual to use a semantic strategy in performing the COWAT; for example words linked to the beach (sun, sand, sea, swimming). Therefore both phonemic and semantic clusters were measured in the present data set. Inter-rater reliability was assessed using kappa statistic on the agreement between two raters. \( \kappa = 0.86 \) for phonological clusters and \( \kappa = 0.58 \) for semantic clusters. This indicates almost perfect agreement for the phonological categorisation, and moderate agreement for semantic clustering (Landis & Koch, 1977). The difference in semantic clustering was due to less prescriptive rules as to what constituted a shared association. However as the same coder assessed all the word lists within this study, differences between coders would not affect comparisons between groups.

Phonemic clusters were defined using the methods of Troyer et al. (1997) in brief these were consecutive words that began with the same two letters, rhymed, were homonyms or had the same first and last sound separated by a vowel. Semantic clusters were classified as words that had a shared meaning, or shared words associates. Switches were calculated as the number of transitions to a new cluster, including single words. Clusters size was measured starting with the second word (e.g. a cluster of one would score zero, a cluster of two would score one) and these were then averaged across all trials. A second cluster size measure (cluster size 2) was also generated in accordance with Unsworth et al. (2011) using only the clusters with a size greater than 1. The details of coding and scoring rules can be found in appendix 5.

To understand the impact of cluster size and switching on task performance and how these related to working memory, vocabulary, speed of processing and motor speed, a series of
correlations were run on the whole group together. These factors were assessed as they were previously implicated in cluster size and switching (Unsworth, et al., 2011). Speed of processing was measured using the domain score (with COWAT total score removed) generated in section 4.5.1.4. Letter number sequencing was used as a measure of working memory, and the number of errors on the NART was used as the measure of vocabulary. The effect of motor speed was assessed as the task was administrated with a written response and therefore task differences could relate to differences in motor performance. Finger tapping with the dominant hand was used as a measure of motor speed.

4.3.2 Results

The mean number of switches, cluster size and percentage switches are shown in table 5.3. Participants were more likely to use phonological clustering than semantic, with all participants including at least one phonological cluster, whereas only 69% included at least one semantic cluster. There was no group difference in the proportion of participants generating semantic clusters $\chi^2(2)=2.4; ns$.

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<tr>
<td>Switches</td>
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</tr>
</tbody>
</table>

Table 5.3: Mean number of switches and cluster size for phonological and semantic clusters.

†One NPSLE participant did not complete the COWAT due to time constraints.
‡Cluster size 1 used all clusters including single words; cluster size 2 did not include single words. Values are < 1 for semantic cluster 2 as some participants had no semantic clusters.

As predicted there was a significant group difference in mean number of switches $F(2,60)=5.24; p<0.008, \omega=.29$ for phonological switches and $F(2,60)=5.94; p<0.004, \omega=.29$ for semantic switches. Post hoc tests with a Bonferroni correction, indicate the NPSLE group had significantly fewer switches than the controls, with medium effect sizes for both phonological
Correlations between switching and cluster size total performance, working memory, speed of processing and motor speed are shown in table 5.4. As not all participants used semantic clusters this was only assessed using phonological cluster and switching measures. As 18 separate correlations were performed the significance level was set to 0.003.

<table>
<thead>
<tr>
<th></th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>COWAT total</th>
<th>LNS†</th>
<th>SOP†</th>
<th>Finger tapping</th>
<th>NART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switches</td>
<td>-0.05</td>
<td>-0.07</td>
<td>0.86**</td>
<td>0.55**</td>
<td>0.56**</td>
<td>0.32*</td>
<td>-0.53**</td>
</tr>
<tr>
<td>Cluster size 1</td>
<td></td>
<td></td>
<td>0.44**</td>
<td>0.10</td>
<td>0.09</td>
<td>0.03</td>
<td>-0.22</td>
</tr>
<tr>
<td>Cluster size 2</td>
<td></td>
<td></td>
<td>0.15</td>
<td>-0.05</td>
<td>0.13</td>
<td>0.08</td>
<td>-0.00</td>
</tr>
</tbody>
</table>

Table 5.4: The correlations between switching and cluster size and task performance, working memory, speed of processing and motor speed (finger tapping).

** p<0.003; *p=0.017
† LNS = Letter number sequencing, SOP = Speed of processing

The number of switches did not correlate with either cluster size measure, however these factors showed significant negative correlations when total number correct was partialled out, r(64) =-0.93; p<0.001 for the correlation with cluster size 1, and, r(64)=0.38; p<0.003 for cluster size 2. Number of switches and cluster size 1 both correlated with COWAT total correct, but cluster size 2 did not. This was further assessed using multiple regression, F(2,61)=1073; p<0.001 where switches, t(1,61)=41.43; p<0.001 and cluster size 1, t(1,61)=22.95; p<0.001 were both independent predictors of overall task performance. Letter number sequencing, speed of processing and NART all correlated with number of switches but not with either measure of cluster size. Motor speed was also associated with switches but this did not reach corrected significance.

4.3.3 Discussion of clustering and switching

The NPSLE group had significantly fewer switches than the control group but no difference in mean cluster size, and this was found for both phonemic and semantic clusters. This indicates that the groups were equally likely to use a clustering strategy and generated clusters that did not differ in size. This suggests differences in total task performance related to a reduced
ability to switch between clusters in the NPSLE group. One possibility is that this relates to motor slowing in the NPSLE group as the task used a written response. Switching had a moderate correlation with finger tapping; however when split into subgroups the relationship did not remain suggesting reduced motor speed did not account for the group differences in switching. This suggestion is also supported by the fact that the pattern of reduced switching and normal cluster size has also been seen in patients with Multiple Sclerosis and Huntingdon’s disease when using a verbal response format (Troster, et al., 1998). These are typically seen as white matter disorders and Multiple sclerosis has been shown to have a similar pattern of deficits to SLE (Benedict, et al., 2008).

Unsworth et al. (2011) suggest switching is related to working memory and processing speed, while cluster size relates to working memory and vocabulary. This is partially supported by the present data, where number of switches correlated with the speed of processing domain score, and letter number sequencing. However, cluster size did not correlate with the working memory measure or the vocabulary measure. This could be because these single measures were not as good at picking up working memory or vocabulary differences as the composite measures used by Unsworth et al. (2011).

5.4 Reaction time variability

Reaction time (RT) variability or Intra-individual variability refers to the within person deviation in RTs across multiple trials. This measure has been proposed as a behavioural marker for central nervous system integrity (Bunce, et al., 2007; Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000; Hultsch, et al., 2008; Strauss, et al., 2007; ter Borg, Horst, Hummel, Limburg, & Kallenberg, 1990). Variability increases have been shown to occur with age, mild cognitive impairment, traumatic brain injury, Parkinson’s disease and epilepsy (Hultsch, et al., 2008) and to correlate with frontal white matter hyperintensities in community dwelling middle aged adults (Bunce, et al., 2007). One proposal is that increased variability reflects lapses or fluctuations in executive control, which increase the RTs on certain trials and thus increase the overall variability (R. West, Murphy, Armilio, Craik, & Stuss, 2002). Whilst variability does consistently correlate with overall mean RT, in logistic regression variability has been shown to be a more sensitive predictor of group membership in Alzheimer’s disease (Hultsch, et al., 2000) and mild cognitive impairment (Dixon, et al., 2007).
Additionally, studies have found group differences on variability measures in the absence of group differences on mean RT (Rentrop, et al., 2010).

There are a number of methods that have been used to assess RT variability. The simplest is to calculate a coefficient of variation (standard deviation of RT/mean RT), which provides a measure of variation that is independent of the mean. However this relies on the assumption that individual standard deviations and means have an invariant and linear relationship, assumptions that have been shown to be false (Schmiedek, Lovden, & Lindenberger, 2009).

A second method was developed by Hultsch and colleagues (Hultsch, et al., 2000; Hultsch, et al., 2008) this involves using regression to partial out the effect of extraneous variables on RT on a trial by trial basis. Variables usually include trial and block which removes some of the effects of practice or fatigue which could increase or decrease RT over time. Participant factors such as age, gender and IQ can also be removed at this stage. The standard deviation of the residuals (intra-individual standard deviations or ISDs) from the regression model is then used as the outcome measure for analysis.

Other studies have looked at the distribution of reaction times, such as fitting an ex-Gaussian distribution. This assumes that the distribution of RTs can be modelled as having a Gaussian and an exponential component showing a longer right tail. RTs can be described by three parameters; \( \mu \), the mean of the normal component; \( \sigma \), the standard deviation of the normal component and \( \tau \) which is the tail of the exponential. Researchers have proposed cognitive interpretations of ex-Gaussian parameters, particularly \( \mu \) and \( \tau \), but these vary across researchers. However there is some consistency in that higher order processes, such as decision making, are typically ascribed to \( \tau \), while lower order processes, such as sensory ones, are ascribed to \( \mu \) (Matzke & Wagenmakers, 2009). West et al., (2002) propose lapses of attention show up as increases in \( \tau \) as these exceptional RTs would fall in the tail of the distribution. In support of this, older adult’s performance is typically associated with larger values of \( \tau \) compared to young adults (Madden, et al., 1999; McAuley, Yap, Christ, & White, 2006; Spieler, Balota, & Faust, 1996; R. West, et al., 2002) although increases in the other parameters have also been found. West et al., (2002) suggest this reflects an increase in the skew of the distribution. However, Myerson, Robertson, & Hale (2007) point out that simple slowing in which all RTs are multiplied by a constant would increase \( \tau \) but would leave the shape of the distribution unchanged. They suggest using \( \tau/\sigma \) ratio as a measure of skew.
in the RT distribution or taking parameters from another distribution – the Weibull distribution which has a parameter that measures skewedness.

The Weibull distribution is another approach to comparing the shape of RT histograms. This provides three parameters; shift, scale and shape. The shift parameter represents the position of the leading edge of the RT distribution and could reflect sensory or motor speed components of reaction time. Scale represents the spread of the distribution and may reflect speed of processing. The shape parameter is a measure of the skew of the distribution, with values of one indicating an exponential distribution, and values approaching 3.4 indicating a normal distribution (Myerson, et al., 2007).

Reaction time variability has not been assessed in SLE patients. As Hultsch and colleagues suggest increased variability is indicative of central nervous system damage, it is hypothesised that the NPSLE group would show larger ISDs and larger values of \( \tau \). In section 4.5.1.4 the NPSLE group showed significantly slower scores on tasks measuring speed of processing, therefore it is hypothesised that they will show larger values for the scale parameter from the Weibull distribution.

5.4.1 Reaction time variability methods

Intra-individual variability was assessed using two different methods. The first was the method described in Hulsch et al., (2008) which involved using a regression model to generate intra-individual standard deviations (ISD). The second involved the calculations of distribution parameters by fitting an ex-Gaussian and Weibull distribution to each individual’s raw data. Prior to either calculation outliers were removed, which were any RTs less than 500 ms and any that were more than three standard deviations from the individual’s mean RT.

5.4.1.1 Calculation of Intra-individual standard deviations (ISDs)

Any RTs that had been removed during data stripping were replaced by the individual’s mean RT. This is a conservative method as it reduces the variability; however data stripping removed less than 1.5% of trials. The effect of variables that could influence variability; age, IQ, gender and trial number and block were partialled out using a split-plot regression procedure with the RT for each individual trial as the dependent variable. This removed the effect of these
variables, plus the higher order interactions between them from the RTs. The residuals from the regression model were normalised and converted to t-scores to ease interpretation. The standard deviation of each individual’s t-scores was calculated and used for inferential statistics.

5.4.1.2 Calculation of distribution parameters.

Outliers were not replaced during the calculation of distribution parameters as this could change the overall shape of the distribution, and this method did not need the RT for every trial. Parameters were generated using QMPE software (Cousineau, Brown, & Heathcote, 2004; Heathcote, Brown, & Mewhort, 2002) which fits the required distribution (ex-Gaussian or Weibull) to the data using maximum likelihood fitting. This programme generates the parameters for each individual along with the observed and expected values allowing the calculation of chi-square on the fit of the model. For congruent trials one NPSLE participant’s data did not have a good fit for ex-Gaussian parameters. This participant was a significant outlier with a mean RT of 3059 ms when the group mean was 1487 ms, therefore her data was excluded from further analysis. For incongruent trials nine (15%) participants did not have a good fit for ex-Gaussian parameters even at the 0.005 significance level. Therefore analysis of distribution parameters was only conducted on congruent trials.

5.4.2 Reaction time variability results

The distributions of the reaction times for congruent and incongruent trials can be seen in figure 5.5. The NPSLE group show a shift towards higher RTs for congruent and incongruent trials. This graph was very similar if the participant with extreme RT values was removed.

Figure 5.5: Frequency distribution graphs for reaction times to congruent (left) and incongruent (right) trials on the Stroop test.
The mean values (standard deviation) for mean RT, ISD, ex-Gaussian parameters (\(mu\), \(sigma\) and \(tau\)) and Weibull parameters (shift, scale and shape) and shown in table 5.5. On congruent trials there were significant group differences on ISD \(F(2,59)=3.36, p=0.042\), ex-Gaussian components of \(sigma\) \(F(2,59)=5.50, p=0.016\) and \(tau\) \(F(2,59)=3.11, p=0.050\) and the Weibull scale parameter \(F(2,59)=6.04, p=0.004\). The non-NPSLE group had significantly lower values than the NPSLE group on all these parameters (\(p<0.05\) on post hoc tests with Bonferroni correction) with medium effect sizes (\(r=.31\) to \(.40\)). Only \(sigma\) and scale separated the NPSLE group from controls and these also had medium effect sizes (\(r=.31\) and \(.33\)). The difference on mean RT approached significance \(F(2,59)=2.74, p=0.072\), with the NPSLE participants showing the slowest RTs and the non-NPSLE group the fastest. The difference between these groups had a medium effect size despite the overall ANCOVA not reaching significance. The other parameters (ex-Gaussian \(mu\), and the \(sigma/tau\) ratio, and Weibull parameters shift and shape) did not show group differences and effect sizes for the individual group comparisons were all small (\(r=.19\) or lower).

<table>
<thead>
<tr>
<th></th>
<th>Control (n=27)†</th>
<th>Non-NPSLE (n=20)†</th>
<th>NPSLE (n=13)†</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congruent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean RT</td>
<td>1286.74 (208.42)</td>
<td>1269.60 (164.08)</td>
<td>1409.57 (314.33)</td>
<td>0.074</td>
</tr>
<tr>
<td>ISD</td>
<td>4.09 (1.84)</td>
<td>4.03 (1.46)</td>
<td>5.47 (2.41)</td>
<td>0.042</td>
</tr>
<tr>
<td>Ex-Gaussian</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mu)</td>
<td>1134.78 (148.80)</td>
<td>1140.99 (134.74)</td>
<td>1209.58 (127.68)</td>
<td>0.30</td>
</tr>
<tr>
<td>(sigma)</td>
<td>69.99 (27.19)</td>
<td>64.03 (29.18)</td>
<td>99.90 (50.10)</td>
<td>0.016</td>
</tr>
<tr>
<td>(tau)</td>
<td>148.74 (92.26)</td>
<td>127.86 (63.33)</td>
<td>201.04 (139.73)</td>
<td>0.050</td>
</tr>
<tr>
<td>Sigma/(tau)</td>
<td>0.51 (0.22)</td>
<td>0.59 (0.43)</td>
<td>0.71 (0.48)</td>
<td>0.22</td>
</tr>
<tr>
<td>Weibull</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shift</td>
<td>1001.07 (143.56)</td>
<td>1010.29 (141.29)</td>
<td>1017.35 (136.69)</td>
<td>0.89</td>
</tr>
<tr>
<td>Scale</td>
<td>288.02 (99.63)</td>
<td>263.40 (98.89)</td>
<td>399.51 (155.31)</td>
<td>0.004</td>
</tr>
<tr>
<td>Shape</td>
<td>1.79 (0.80)</td>
<td>1.75 (0.67)</td>
<td>1.72 (0.74)</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Incongruent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean RT</td>
<td>1360.59 (251.53)</td>
<td>1418.15 (332.92)</td>
<td>1486.54 (218.83)</td>
<td>0.41</td>
</tr>
<tr>
<td>ISD</td>
<td>4.65 (2.23)</td>
<td>5.33 (3.26)</td>
<td>5.91 (2.89)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Table 5.5: Group mean values for mean RT and intra-individual standard deviation for congruent and incongruent trials, and ex-Gaussian (\(mu\), \(sigma\) and \(tau\)) and Weibull (shift, scale and shape) parameters for congruent trials only.

† One control and one non-NPSLE participant was excluded as they responded to the word rather than the colour on incongruent trials. One NPSLE participant did not complete the Stroop test due to time constraints. One NPSLE participant was excluded due to extreme values on mean RT and poor fit of ex-Gaussian parameters.
On the incongruent trials mean RT and ISD did not show significant group differences although both patient groups had slightly slower mean RTs and larger ISD than the control group. This suggests that the other not analysed variability measures would not have shown significant group differences.

The relationships between the different parameters were assessed in the whole group. As this involved a large number of comparisons only correlations with a large effect size ($r>.5$) will be discussed, and these were all significant at $p<0.002$ which is the Bonferroni corrected significance level. Mean RT had the largest correlation with $\mu$ ($r=.89$), but also positively correlated with ISD, $\tau$, shift and scale. These parameters fell into two groups; shift and $\mu$ correlated with each other ($r=.79$); and ISD, $\tau$ and scale all showed larger positive correlations, with the largest correlation between ISD and $\tau$ ($r=.92$). Finally shape and sigma/tau ratio were significantly related ($r=.79$) indicating they both assessed the skew of the distribution. Tau also showed a moderate negative correlation with both these parameters ($r=-.41$ to $-.44$) indicating that this does relate to the skew of the distribution. Finally as the Weibull scale parameter has been suggested to reflect speed of processing, the relationship between the domain for speed of processing generated in section 4.5.1.4 and the variability parameters was assessed. Scale showed a moderate correlation with SOP and this just reached significance $r(60)=-0.26; p<0.05$.

Variability measures all correlated with mean RT, therefore this was further assessed to see whether differences in variability simply reflected the difference in mean RT. The scatter plot for the relationship between mean RT and $\tau$ is shown in figure 5.6. The beta coefficients for the regression of mean RT and $\tau$ were compared to see whether an increase in mean RT led to a greater increase in variability in the NPSLE group compared to the other groups (i.e. a steeper slope on the regression line). There were no group differences in beta coefficients; $t(29)=0.72, ns$ for the comparison between non-NPSLE and NPSLE, and $t(36)=0.40, ns$ for controls versus NPSLE group. A similar comparison for ISD gave the same result.
Figure 5.6: The relationship between mean RT and the ex-Gaussian tau parameter for congruent trials.

5.4.3 Reaction time RT discussion

Overall the different methods for assessing variability and RT distribution provided outcome variables that were highly correlated. Ex-Gaussian tau parameter correlated highly with ISD indicating they had 85% shared variance, and as such were probably measuring the same process, the Weibull scale parameter also correlated with both of these but to slightly lesser degree. Parameters relating to the position of the distribution (shift and mu) and the skew of the distribution (shape and sigma/tau ratio) also correlated with each other.

The NPSLE group showed an increase in variability compared to the non-NPSLE participants but did not differ from the healthy controls. This makes the findings somewhat more difficult to interpret. If differences had been found between the NPSLE group and both the other groups, this could be interpreted as being due to differences in central nervous system integrity. There are a few possibilities why the NPSLE group did not differ from controls; one is that there was insufficient power to select this difference. However, the effect size for the group comparison was small (r=.15 for ex-Gaussian tau parameter and .22 for ISD) and there were group differences between NPSLE and controls on other parameters; sigma and scale, indicating this better represents the difference between the NPSLE participants and other groups. This suggests that the NPSLE group did not have an increase in the extreme values in the tail of the distribution, but instead had a greater spread of values around the mean. This is also supported by the lack of difference in the Weibull shape parameter, or in the sigma/tau ratio indicating the distribution of RTs in the NPSLE group was not more skewed. The Weibull scale parameter has been associated with speed of processing (Myerson, et al., 2007) which indicated processing speed differences may underlie the present findings. In partial support of
this, a moderate significant correlation was found in the whole group between the scale parameter and the speed of processing domain score.

Another possibility is that these effects relate to differences in improvement with practice. Participants only have 20 practice trials prior to commencing the experimental trials and as such may have been improving during the session. A greater improvement in RT would show up as an increase in variability. The calculation of ISDs does take this into account, however this removed the effect of trial across the whole sample, and it is possible if the groups improved at different rates, this would not be accounted for by the model.

The variability measures showed a significant and large correlation with mean RT. The relationship was investigated by comparing the beta coefficients from the regression of mean RT on tau were compared. Although beta was larger in the NPSLE group, this was not significant, suggesting that increased RT in the NPSLE group was not a confound in this analysis.

5.5 General discussion

Three disparate areas of cognition have been discussed in this chapter. Although different tasks and analyses have been used, some common themes have emerged. Firstly, the main difference between the NPSLE group and controls on the RAVLT indicates a retrieval deficit. The NPSLE group had increased forgetting rates compared to controls and a significant improvement form recall to recognition. In contrast there was no difference in omissions from trial to trial, and no difference in primary and recency effect, suggesting the NPSLE group did not have impaired encoding strategies. Performance on the COWAT could also be interpreted in terms of a retrieval deficit as the NPSLE group had fewer switches, indicating less efficient retrieval of new categories.

A second theme relates to possible speed of processing deficits in the NPSLE group. On the COWAT the NPSLE group showed reduced switching between clusters, but no differences in cluster size compared to controls. Switching has previously been associated with speed of processing and working memory (Unsworth, et al., 2011). It can tentatively be concluded that speed of processing is playing a bigger role in the group differences as there were no differences on cluster size, which also relates to working memory (Unsworth, et al., 2011). On
the RT variability measure, the largest group differences were seen on the Weibull scale parameter. This has also previously been associated with speed of processing (Myerson, et al., 2007) and a moderate correlation was found between this measure and the speed of processing domain score.

Retrieval deficits and cognitive slowing have both been included in the behavioural profile of white matter dementia (Filley, 2010). This profile also includes deficits in executive function, sustained attention and visuospatial processing, while memory encoding and language are relatively spared. This suggests white matter dysfunction is likely to underlie the deficits found in the NPSLE group and this is explored in the next chapter using quantitative imaging.

5.6 Summary

(1) Although the NPSLE group had worse performance overall on the RAVLT, the learning rates, primacy and recency effects, omissions, additions, confabulations and intrusions did not differ between the groups. There were however significant differences in forgetting rates, and improvement from recall to recognition indicating retrieval deficits.

(2) On the COWAT, the NPSLE group had reduced switches compared to controls, but no difference in cluster size. This indicates they were no less likely to use a clustering strategy, but were less able to switch between clusters.

(3) On measures of RT variability the NPSLE group was more variable that the non-NPSLE group, but did not differ from healthy controls. This did not seem to result from an increase in the skew of the distribution, but instead indicates a broadening of the distribution.

(4) These results can mostly be interpreted using a framework of the NPSLE group showing deficits associated with white matter disruption.
CHAPTER 6

QUANTITATIVE MAGNETIC RESONANCE IMAGING IN SLE

6.1 Introduction

Magnetic resonance imaging (MRI) has become an important tool in identifying and classifying disease in the brain. Typically, MRI is used to provide structural images of the brain that are qualitatively analysed to observe the presence of lesions or gross abnormalities. The most common abnormalities observed on such MRI scans of NPSLE individuals are multiple hyperintense foci in the deep white matter, (Benedict, et al., 2008), but these are neither sensitive nor specific for NPSLE. Some patients display severe neuropsychological problems but have normal-appearing MRI, whilst others show abnormalities in the absence of neuropsychological symptoms (Sibbitt, Sibbitt, & Brooks, 1999; S. G. West, Emlen, Wener, & Kotzin, 1995). This led researchers to look at quantitative imaging techniques, such as Magnetisation Transfer Imaging (MTI), Diffusion Tensor Imaging (DTI) and spectroscopy, which could potentially reveal finer grained changes in brain parenchyma.

6.1.1 Magnetisation Transfer Imaging (MTI)

The microstructure of tissue may be thought of as a mixture of free, water-like protons (such as those found in intra- and extra-cellular water) and bound protons (such as those found in large macromolecules like myelin). However, in conventional MRI only the signals from the free water protons are retained. The bound protons do not contribute to the overall image intensity due to their very short T2 relaxation time; the signal dies away before it can be recorded by the scanner. Consequently, we lose the opportunity to directly observe the changes that occur in this environment. MTI provides an indirect method of probing the bound protons by measuring the exchange of magnetisation between bound and free proton environments. A radiofrequency (RF) pulse (the MT pulse) is applied at a frequency offset from that of the free water protons, thereby ensuring that the bound protons are selectively saturated. Bound and free water protons that are close in space may be magnetically coupled and magnetization may be transferred between the two, resulting in a reduction of the free water magnetisation - the magnetisation transfer (MT) effect, which is proportional to the amount of bound protons. The amount of MT can be expressed as the magnetisation transfer
ratio (MTR) which is the ratio between signal intensity when the saturation pulse is applied ($M_s$) and the intensity without saturation ($M_0$).

$$MTR = \frac{(M_s + M_0)}{M_0} \times 100\% \quad (6.1)$$

The MTR value can be affected by a number of parameters including normal biological variation, tissue type (white matter has a higher MTR than grey matter) and clinical factors, such as demyelination. In white matter, the majority of bound protons are found in the myelin sheath that surrounds the axons, and thus a loss of myelin decreases the amount of magnetisation transfer (and hence the MTR). Multiple Sclerosis (MS) has been extensively studied using MTI and a variety of different MTR values have been found within MS lesions, reflecting their diverse underlying histology. However, of more interest in the context of NPSLE, an illness that is often characterised by the normal appearing of the brain, is the finding of lower than normal MTR values in the normal appearing white matter in MS patients (Dousset, et al., 1992; Filippi, et al., 1995). This is thought to reflect widespread microscopic damage separate from the lesions.

The MTR value can be measured in a single region of interest, or can be calculated for each individual voxel in the brain and the resultant values displayed as a histogram that plots the number of voxels for a given MTR value. This can be done for the whole brain, or segmented into grey matter and white matter. When looking at a particular tissue class the histogram is characterized by a single peak. From this a number of parameters can be taken, including the peak height (the number of voxels at the histogram mode), the peak location (the histogram mode) and mean MTR. The peak height is dependent on factors such as bin width, the quality of the segmentation process, and brain size. Therefore the histograms are usually normalised by an arbitrary value to remove the effect of brain size, and identical methods of segmentation and histogram generation are used throughout a study. A diffuse disease process that manifests in an inhomogeneity of MTR across the brain will lead to a broadening of the histogram, and therefore a reduction in peak height. The peak height then represents the homogeneity of brain tissue, with lower values indicative of pathological processes that cause a shift in MTR values and a broadening of the histogram. Van Buchem et al. (1997)suggest the peak height represents the amount of remaining normal brain parenchyma, and this is supported by a significant correlation between peak height and physical disability in MS (van Buchem, et al., 1998).
Using MTR histograms differences have been shown between NPSLE patients and controls, with the NPSLE group having a reduced peak height on whole-brain histograms (Bosma, Rood, Zwinderman, Huizinga, & van Buchem, 2000; Steens, Admiraal-Behloul, Bosma, et al., 2004). Four studies compared patients with NPSLE, non-NPSLE and controls (Bosma, Rood, Huizinga, et al., 2000; Bosma, Rood, Zwinderman, et al., 2000; Dehmeshki, Van Buchem, Bosma, Huizinga, & Tofts, 2002; Emmer, et al., 2008; Rovaris, et al., 2000). Bosma, Rood, Huizinga et al. (2000) and Rovaris et al. (2000) both found a significant difference between patients with NPSLE and non-NPSLE, with the NPSLE group showing a significant reduction in mean MTR (Rovaris et al., 2000) and peak height (Bosma et al., 2000), while the non-NPSLE group did not differ from controls. Dehmeshki et al. (2002) used multivariate discriminate analysis to separate the groups based on MTR histogram parameters. When compared to either controls or non-NPSLE patients, the NPSLE group were well classified with 17/20 correct. However, the histogram parameters of the non-NPSLE group could also be distinguished from controls relatively well, with 15/20 correctly classified, indicating their histograms were not completely ‘normal’. This is supported by Emmer et al. (2008) who found no difference between the two patient groups.

One study investigated the difference between acute NPSLE and chronic NPSLE on MTR parameters (Bosma, Rood, Huizinga, et al., 2000). Both NPSLE groups had a significant reduction in peak height compared to controls and non-NPSLE patients. The acute group also had significantly higher mean MTR values compared to all other groups including the patients with chronic NPSLE. Steens et al. (2006) also investigated the impact of disease activity on MTR peak height. They scanned 19 patients on two or more occasions and found a significant increase in peak height in the patients whose clinical condition improved, whilst a decrease in peak height was observed in those who deteriorated and no change in peak height was seen in patients who remained stable.

These studies all used MTR measurements in the whole of the brain parenchyma. Two studies looked at histograms in white matter and grey matter separately. Steens et al. (2004) showed a selective reduction in peak height in the grey matter of patients with NPSLE, and Emmer et al. (2008) only found peak height differences in the whole brain analysis and not in either white matter or grey matter alone. However, in both studies the NPSLE group had a lower peak height than controls in all tissue types indicating the difference was in the expected direction, it just did not reach significance.
6.1.2 Diffusion Tensor Imaging (DTI)

DTI is based on the diffusion of water molecules, which shift in position in the brain due to thermal agitation. The extent of diffusion is measured by the Apparent Diffusion Coefficient (ADC). In free water the molecules can move around easily, and this has a high ADC. In the brain, ADC depends on the biological barriers to water movement, such as cell walls and nerve fibres, with more barriers resulting in a reduced ADC. DTI data is acquired with diffusion weighting along six or more orientations. This is used to calculate the diffusion tensor, and can be depicted as a diffusion tensor ellipsoid (see figure 6.1). The diffusion tensor has three orthogonal eigenvectors \( \varepsilon_1, \varepsilon_2, \) and \( \varepsilon_3 \), which represent the principle axes of the tensor. These axes are scaled by the extent of diffusion along the direction; this is represented by the eigenvalues of the diffusion tensor \( \lambda_1, \lambda_2 \) and \( \lambda_3 \). The advantage of measuring diffusion in this way is that it is rotationally invariant, and does not depend on the orientation or positioning of the participant.

![Figure 6.1: Schematic representation of the diffusion tensor. The arrows represent the orientation of the three orthogonal eigenvectors. The axes are scaled by the eigenvalues, \( \lambda_1, \lambda_2 \) and \( \lambda_3 \).](image)

ADC describes the mean diffusivity within a voxel and is calculated as the average diffusion along three orthogonal directions, as described in equation 6.2.

\[
ADC = \frac{(ADC_x + ADC_y + ADC_z)}{3} \quad (6.2)
\]

The directionality of diffusion is measured by the fractional anisotropy (FA). The anisotropy of diffusion is influenced by the directional nature of tissue. For example in long thin fibres, such as white matter tracts, diffusion occurs preferentially along the fibre than across it. Therefore diffusion in white matter is anisotropic, and has a high FA. In contrast, grey matter diffusion is not restricted in any particular direction, therefore diffusion is more isotropic and grey matter has a lower FA.
FA is a scalar value between 0 and 1, where 0 indicates isotropic diffusion (equal in all directions), and larger values indicate greater anisotropy. FA is calculated from the eigenvalues in the diffusion tensor.

\[
FA = \frac{\sqrt{2} \sqrt{(\lambda_1 - \lambda)^2 + (\lambda_2 - \lambda)^2 + (\lambda_3 - \lambda)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \quad (6.3a)
\]

\[
\lambda = \frac{(\lambda_1 + \lambda_2 + \lambda_3)}{3} \quad (6.3b)
\]

Anything that affects the molecular environment, or changes the tissue compartments in the brain, will have a quantifiable effect on the diffusion tensor. In general, ADC and FA can be used to detect damage to brain parenchyma, as destruction of biological barriers to diffusion will result in an increase in ADC and a decrease in FA in directional fibres (Tofts, 2003).

As with MTI, the diffusion parameters may be measured in a region of interest (including the whole of the white matter or grey matter). This can be described as a mean value, or displayed as a histogram. Other analysis methods include tract-based spatial statistics (TBSS) which is a voxel-wise analysis method that looks for group differences in the white matter tracts.

Compared to controls, SLE patients generally show higher mean ADC (Bosma, Huizinga, Mooijaart, & Van Buchem, 2003; Hughes, et al., 2007; Jung, Caprihan, et al., 2010; Welsh, Rahbar, Foerster, Thurnher, & Sundgren, 2007; Zhang, et al., 2007) and reduced FA. (Emmer, et al., 2010; Hughes, et al., 2007; Jung, Caprihan, et al., 2010; Zhang, et al., 2007). One study contrasted with this general finding of increased ADC, and instead found significantly reduced values in the amygdala in SLE compared to controls, which the authors interpret as evidence of cytotoxic edema, despite the majority of patients having inactive disease at the time of the scan (Emmer, van der Grond, Steup-Beekman, Huizinga, & van Buchem, 2006).

Two studies directly compared patients with NPSLE versus non-NPSLE. Jung et al. (2010), found significant differences in FA between patients with NPSLE and non-NPSLE in certain regions, but these were less extensive than the differences with controls. No regions separated the non-NPSLE and control participants. In contrast, Emmer et al. (2006) looked at mean ADC across the whole grey matter and white matter, and found no significant difference between the patient groups. However this study also found no difference in mean ADC between the
controls and NPSLE group, contrasting with previous studies. Emmer et al. (2006) found selective involvement of the amygdala, and ADC values differed from controls in both the NPSLE and non-NPSLE groups. These studies suggest DTI differences are evident in NPSLE, but whether they are also found in non-NPSLE has not completely been resolved.

Six studies have tried to localise the DTI differences between SLE patients and controls. Two looked at values in the whole grey matter or white matter, two used regions of interest, and two used TBSS. In the first category, Welsh et al. (2007) found significant differences in ADC between patients with NPSLE and controls in both grey and white matter. Emmer et al. (2006) did not find significant differences in either white matter or grey matter, although the percentage difference was slightly larger in white matter. The region of interest and TBSS studies do show slightly different results, but all identified diffuse white matter structures as showing differences in NPSLE or mixed SLE groups. Hughes et al. (2007), Zhang et al. (2007) and Jung, Caprihan et al. (2010) all identified differences in the corpus callosum.

Although some of these studies did use participants with acute disease (Emmer, van der Grond, et al., 2006; Welsh, et al., 2007), none directly compared acute versus chronic NPSLE. The majority of studies investigated patients who did not have acute disease, indicating DTI differences do not purely represent active disease. Welsh et al. (2006) is the only study to suggest grey matter differences (apart from subcortical gray matter structures such as the thalamus). Therefore there is scope to see whether there are differences in both grey and white matter histograms in non acute NPSLE. Emmer et al. (2010) state that direct damage caused by antibodies against neuronal receptors would be expected to occur at the areas with the highest concentration of these receptors – i.e. the grey matter.

6.1.3 Magnetic resonance Spectroscopy

Spectroscopy ($^1$HMRS) is a non invasive technique that measures brain metabolites such as $N$-acetylasparate (NAA), creatine (Cr), Choline (Cho) and Myoinositol (mI). NAA is found in neuronal cells, and is a marker for axonal integrity. Choline is associated with membrane breakdown, and is possibly related to inflammation. Creatine is involved in cell metabolism, and is often used as a reference standard for the other metabolites as it is thought to be stable, thus concentrations are often reported as ratios to Creatine. Myoinositol is found in glial cells, and is thought to increase with inflammation. The main findings in NPSLE are a
reduction in NAA/Cr ratio and an increase in Cho/Cr ratio (Peterson, et al., 2005) and these changes have been shown in normal appearing white matter in chronic and acute NPSLE. One study looked at the absolute concentrations of metabolites and found an increase in NAA, an increase in Cho and increase in ml (Axford, Howe, Heron, & Griffiths, 2001). Kozora and colleagues investigated ¹H-MRS in patients with non-NPSLE. They showed increased Ch/Cr in frontal white matter (Filley, et al., 2009) and decreased NAA/Cr in the right hippocampus (Kozora, et al., 2011). These parameters, along with Glutamate+Glutamine/Cr ratio (Kozora, et al., 2011), also correlated with cognitive performance, indicating pathological processes in non-NPSLE.

6.1.4 Atrophy

Imaging studies suggest cerebral atrophy is a prevalent finding in NPSLE (Appenzeller, Bonilha, et al., 2007; Jung, Segall, et al., 2010). Whole brain atrophy can be measured as the ratio of cerebrospinal fluid (CSF) to intracranial volume (ICV), with a higher relative volume indicating increased atrophy. Another method is to assess the volume of specific structures, either using a region of interest approach, or using voxel-based methods such as voxel-based morphometry (VBM). VBM looks for regions of reduced volume across the whole brain, and hence does not suffer from biases that affect region of interest analyses (Tofts, 2003).

Reduced whole brain volume (measured as CSF/ICV) has been shown in NPSLE compared to controls (Ainiala, et al., 2005; Bosma, Rood, Huizinga, et al., 2000) and in NPSLE versus non-NPSLE patients (Ainiala, et al., 2005). In one study, no difference in total brain volume was found between non-NPSLE patients and controls (Filley, et al., 2009). Two studies have used VBM to localised differences between patients with SLE and controls. The first found diffuse white and grey matter volume reduction, particularly in the corpus callosum, frontal, occipital and temporal lobes, limbic areas and cerebellum (Appenzeller, Bonilha, et al., 2007). This study had a wide age range (18-60), but did not correct the analysis for age or total intracranial volume. The second only looked at white matter, and found less extensive differences, but did identify differences in the anterior and posterior internal capsule, subgyral frontal lobe, and left temporal lobe (Xu, et al., 2010). Appenzeller et al. (2007) also split the SLE group, and revealed the NPSLE group showed volume reduction, while the non-NPSLE patients did not differ from controls. These findings have been supported by an investigation of cortical
thickness, where the NPSLE group had a significant reduction compared to both healthy controls and non-NPSLE patients (Jung, Segall, et al., 2010).

Xu et al. (2010) compared patients with active versus inactive systemic disease, and found a correlation between disease activity and white matter volume in the internal capsule. In contrast, Appenzeller et al. (2007) found no relationship between volume and current systemic disease activity, and patients with past central nervous system involvement had greater volume reduction that those with active CNS involvement. The cohort studied by Appenzeller et al. (2007) had a mean SLEDAI score of 15.9 (range 9-24) and thus all had active systemic disease. Why this should impact on the relationship between disease activity and volume is unclear, however as both Appenzeller et al. (2007) and Jung et al. (2010) had patient groups with high mean SLEDAI scores (>9) there is scope to establish whether volumetric analysis would identify differences between controls and patients with low systemic disease activity.

6.1.5 Summary of previous imaging findings

Taken together these results suggest there are subtle diffuse changes to normal appearing brain matter in SLE, and these are detectable by quantitative MRI. Differences have predominantly been detected in patients with NPSLE rather than non-NPSLE, although recent studies using $^1$H-MRS have suggested there are also some changes present in non-NPSLE. Dehmeshki et al. (2002) were able to correctly separate non-NPSLE patients using MTR histogram parameters from controls in 15/20 cases indicating there are some difference between the groups. One study using MTI suggested differences were primarily in the grey matter, whereas DTI investigations have indicated white matter changes are also present. VBM and $^1$H-MRS both also point towards changes in both grey and white matter in NPSLE. Finally, differences have been found between NPSLE patients with non acute disease and controls, suggesting changes persist beyond a disease flare.

6.2 Methodological considerations

To gain an understanding of grey and white matter integrity in the current SLE cohort Magnetisation Transfer Imaging and Diffusion Tensor Imaging were used along with voxel-based morphometry to assess volume loss. Although Spectroscopy may also have provided an
insight into the disease process in SLE, this technique was not available when the study began and would have increased the scanning time beyond that tolerated by the subject group.

The imaging techniques described allow analysis of the whole brain, the whole grey or white matter segment of the brain, or voxel-based approaches that identify where differences occur. Whilst voxel-based analyses have the advantage of localising differences, these require correction for multiple comparisons, perhaps restricting their sensitivity. Their use also requires the assumption that there are common brain regions affected in SLE. This assumption may be correct if antibody mediated damage is more likely to occur at areas with the highest concentration of a particular receptor targeted by the antibody, or areas where the blood brain barrier is disrupted. On the other hand, white matter lesions have been found to occur throughout the brain in SLE (Appenzeller, Faria, Li, Costallat, & Cendes, 2008) and a pathological study described widely scattered microinfarcts in cortical grey matter that were not limited to vascular territories or watershed zones (Hanly, Walsh, et al., 1992). This suggests there may not necessarily be common areas of pathology across patients. Histogram analyses provide a few simple parameters that have been suggested to measure structural integrity. A combination of these approaches was used; histogram analysis for MTI and DTI data and a VBM brain volume analysis of the T1 weighted structural scan.

6.3 Aims of the current research

The main aim was to investigate quantitative MRI measures of DTI and MTI, and VBM analysis in a cohort of patients with low systemic disease activity (mean SLEDAI score 2.8, range 0-11).

(1) To see whether differences are specific to NPSLE or also found in non-NPSLE patients.
(2) To see whether differences are seen in grey matter or white matter.
(3) To see whether there are correlations between quantitative imaging and clinical parameters, including disease duration and disease activity. Correlations were also assessed with cognitive function and these are discussed in chapter 7.
6.4 Imaging methods

6.4.1 Participants

The details of the participants who completed the imaging session are shown in table 6.1. There were not significant group differences on age, gender or handedness. One NPSLE, one control and three non-NPSLE participants were unable to attend the MRI scan. The reasons are covered in chapter 2, section 2.5.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=27)</th>
<th>Non-NPSLE (n=20)</th>
<th>NPSLE (n=14)</th>
<th>Between groups difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44.3 (11.5)</td>
<td>44.8 (13.1)</td>
<td>46.3 (10.3)</td>
<td>F(2,58)=0.14, n.s</td>
</tr>
<tr>
<td>Gender (%) female</td>
<td>96.3%</td>
<td>90.0%</td>
<td>100.0%</td>
<td>$\chi^2(2)=1.53$, n.s</td>
</tr>
<tr>
<td>Handedness (%) right</td>
<td>88.9%</td>
<td>90.0%</td>
<td>85.7%</td>
<td>$\chi^2(2)=0.60$, n.s</td>
</tr>
</tbody>
</table>

Table 6.1: Demographics for the participant who completed the MRI session.

Incidental findings were found in four patients, two participants presented with subarachnoid cysts, and one with large sulci, which were deemed unlikely to be of clinical significance. In one participant a possible aneurysm was identified. The segmentation process used to separate the grey and white matter, was not adversely affected by these irregularities and classified these areas as cerebrospinal fluid, thereby excluding them from further analysis. However, it is conceivable that some residual areas of fluid remained within the brain parenchyma used in the analysis. The analysis was repeated with these participants excluded and it was shown that they did not change the results. Consequently, the data from these participants are included in the histogram analyses presented here.

Participants for VBM analysis

The two patients with subarachnoid cysts and one with large sulci were excluded from the VBM analysis as these could affect the VBM registration process. The number of participants in the control group was increased to match the total number in the SLE group, using data obtained for repeatability analysis. The VBM analysis was repeated with and without the inclusion of left handed and male participants, and this did not affect results. Therefore the
results from the whole group have been reported. The demographics are displayed in table 6.2.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=31)</th>
<th>SLE (n=31)</th>
<th>Between groups difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>43.9 (11.2)</td>
<td>44.6 (11.6)</td>
<td>t(60)=-0.22, n.s</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>96.8%</td>
<td>96.8%</td>
<td>χ²(1)=0.00, n.s</td>
</tr>
<tr>
<td>Handedness (% right)</td>
<td>90.3%</td>
<td>87.1%</td>
<td>χ²(1)=0.16, n.s</td>
</tr>
</tbody>
</table>

Table 6.2: Participant demographics for VBM study

6.4.2 Imaging protocol

MRI was performed using a Siemens Avanto 1.5 T scanner. A high-resolution 3D structural scan was acquired using a T₁-weighted MP-RAGE sequence. Images were prescribed in a transverse-oblique plane using the following acquisition parameters: TR/TE/TI=1160/4.44/600 ms, NEX=1, flip angle = 15°, in-plane FOV = 230x230 mm, matrix size = 256x256x192 with voxel dimensions 0.9x0.9x0.9 mm³. The acquisition time was 5 minutes.

MTI was performed using a 3D gradient echo pulse sequence acquired in a transverse-oblique plane, with TR/TE=30/5 ms, NEX=1, flip angle=5°, FOV 220x220 mm, matrix size=256 (read) x192(phase) x 64 (slice). The partition (slice) thickness was 2.5mm covering the whole brain with in-plane resolution 0.859 x 1.1 mm. Two consecutive image volumes were acquired: the first with the addition of an off-resonance radiofrequency MT saturation pulse, flip angle = 500°, and the second volume without. Each MT scan lasted 6 minutes 10 seconds leading to a total scan time of 12 minutes 20 seconds for MTI.

DTI was acquired using a diffusion-weighted 2D echo planar imaging (EPI) sequence. The images were acquired in the transversal-oblique plane, with TR/TE = 6400/110ms, NEX=2, flip angle= 90°, FOV = 220x220 mm, matrix size = 128x128. 22 slices were obtained with a slice thickness of 5 mm and an in-plane resolution of 1.719x1.719 mm. Diffusion-weighted images were acquired with one b-value = 0 (b₀) and b-value = 1000 s/mm², along 30 optimised diffusion gradient directions. DTI scan time was 6 minutes 45 seconds.
At each scanning session the imaging protocol was conducted in the order: localiser, T$_1$ weighted MP-RAGE (structural scan), 3D gradient echo (with MT pulse on), 3D gradient echo (without the MT pulse), Diffusion-weighted EPI. Overall the scanning session lasted approximately 35 minutes.

6.4.3 Imaging analysis

Image analysis was carried out on a Sun Microsystems computer running the Suse 11 Linux operating system.

6.4.3.1 MTI analysis

The following steps were taken to produce the MTR histograms

1. The MTI images were co-registered to the high resolution structural images and re-sliced using SPM 5 (Wellcome Department of Cognitive Neurology, London, UK, http://fil.ion.ucl.ac.uk).
2. The co-registered images were used to calculate MTR (using eqn 6.1) on a pixel-by-pixel basis with an in-house computer program developed in the MATLAB computing environment (Mathworks Inc, http://www.mathworks.com).
3. Random noise was added to the images. As the image pixels are stored as integer values, the calculation of the MTR map can cause spikes to appear in the final histograms. In order to avoid this, random noise with a standard deviation of ±0.5 percentage units was added to the images. This was done using ImageJ (National Institute of Health, USA, http://rsb.info.nih.gov/ij/).
4. The T$_1$ weighted structural image was segmented into grey matter, white matter and CSF using the segmentation algorithm provided by SPM 5. The segmentation results in an output in the form of three probability maps with each voxel representing the probability that it was a particular tissue type. Whole brain probability maps were generated by summing together the individual grey and white matter probability maps.
5. A masking programme in MATLAB was used to create separate MTR maps for the grey and white matter. The probability maps were used to create tissue-type masks using a threshold of 95%.
(6) The histograms were generated using a bin width of 0.2 percentage units.
(7) The histograms were normalised to remove the effect of brain size by dividing each histogram value by the sum of all values x the bin width. These values were normalized to give an area under the curve of 500 units.
(8) The histograms were smoothed using a Gaussian line broadening with a standard deviation of 0.4 percentage units. The peak height, peak position and mean value were extracted from the smoothed histogram. These metrics were used for inferential statistics.

6.4.3.2 DTI Analysis

(1) Initial analysis was conducted using FSL (www.fmrib.ox.ac.uk/fsl/). The first stage of the analysis is to correct for geometric distortions in the images caused by the presence of eddy currents during acquisition. Eddy currents are formed in the scanner gradient coils by the rapid switching imaging gradients. Eddy-current effects can be reduced by using FSL’s “eddy correct” function. This function corrects for these distortions, and for simple head motion, using affine registration to the first volume of the DTI acquisition.
(2) The apparent diffusion coefficient (ADC) and a fractional anisotropy (FA) maps were created from the eddy corrected data set using FSL. The eigenvalues were calculated from the diagonalised diffusion tensor, these were then used in the formulae described in equations 6.2 (ADC) and 6.3 (FA) to calculate the values for each individual voxel.
(3) Segmented grey matter and white matter maps were produced using each subject’s b=0 second/mm² image. This is a non diffusion-weighted image (T₂ weighted) that is intrinsically co-registered to the ADC and FA maps as it is acquired during the same imaging process. SPM 5 was used to produce the segmented maps.
(4) The masking programme in MATLAB was used to create separate ADC/FA maps for the grey and white matter. The probability maps were used to create tissue-type masks using a threshold of 80%, and the histograms were generated using a bin width of 5 x10⁻¹²m²/s for ADC and 0.005 units for FA.
(5) The histograms were normalised to remove the effect of brain size by dividing each histogram values by the sum of all histograms x the bin width. This resulted in an area under the curve of 20 units.
(6) To aid extraction of peak height, position and mean, Gaussian smoothing was applied using a standard deviation of $20 \times 10^{-12} \text{m}^2/\text{s}$ for grey matter ADC, $10 \times 10^{-12} \text{m}^2/\text{s}$ for white matter and whole brain ADC, $0.009$ for grey matter FA, $0.02$ for white matter FA and $0.015$ for whole brain FA. These values were chosen as they gave smooth histogram line shapes whilst closely fitting the original data.

6.4.3.3 VBM analysis

For the VBM analysis the DARTEL tool box from SPM8 was used (Wellcome Department of Cognitive Neurology, London, UK, [http://fil.ion.ucl.ac.uk](http://fil.ion.ucl.ac.uk)).

The analysis was conducted by following the tutorial of Ashburner (2010) ([http://www.fil.ucl.ac.uk/~john/misc/VBMclass10.pdf](http://www.fil.ucl.ac.uk/~john/misc/VBMclass10.pdf)).

(1) Pre-processing for VBM analysis involved three steps.
   a. The T$_1$ weighted structural scans were segmented using “new segment”, which generated grey and white matter maps and DARTEL imported versions of the masks.
   b. The DARTEL imported images were used to generate a template from all the participants’ images. This stage also generates a flow field for each participant, which represents the translation from the individual to the template.
   c. Images were normalised to MNI space using the group template and the flow fields. Voxel size was specified as $1.5 \times 1.5 \times 1.5$ to reduce the number of comparisons in the voxel-wise statistical analysis. A Gaussian smoothing kernel was applied with a size of 10mm FWHM.

(2) The statistical analysis.
   a. The analysis was conducted comparing the SLE group (n=31) to the healthy controls (n=31), then comparing the NPSLE (n=13) and non-NPSLE (n=18) group separately to the controls.
   b. To account for differences in brain size, total intercranial volume (TIV) was added as a global value. TIV was calculated by summing the total number of voxels in the white matter, grey matter and CSF masks generated using the “new segment” SPM function. An ANCOVA method of global normalisation was used, which treats “globals” as covariates in the general linear model.
c. Age was also added as a covariate in the analysis.
d. Group comparisons of white matter volume and grey matter volume were made using a two-sample t-test. The result was defined as statistically significant at a threshold of voxel-wise uncorrected $p<0.001$, with 30 continuous voxels. With a 1.5x1.5x.5 voxel size, this included clusters that had a volume greater than 101 mm$^3$. Clusters that reached corrected significance have also been reported. This was either voxel level family-wise error (FWE) corrected significant (this corrects the significance level to account for the number of voxels included in the comparisons) or cluster level FWE significance (this accounts for the size of the cluster).

6.4.3.3 General analysis methods

Two main analyses were conducted, the first investigated group differences on the imaging parameters, and the second investigated the relationship between imaging parameters and clinical variables. This included the correlation with disease duration (measured in years) and disease activity, measured using the SLEDAI (Bombardier, et al., 1992). Age was included as a covariate in the analyses with disease duration as duration may be confounded by age.

6.4.4 Pre-analysis of variability of MRI measures

It is important to assess within person variability of quantitative MRI measures, as instrumental variation can mask within group differences in a cross-sectional study. MTR mapping particularly relies on short-term stability, since the MTR map is formed from the difference between two consecutive images. The variability of the MTR and DTI was assessed by calculating the percentage coefficient of variation (CV%) for measures taken in nine healthy volunteers (mean age 38±13) (CV%=100 x standard deviation/mean). This provides a measure of variability that is independent of the mean, and allowed comparability of our data to published normal values. Repeated measures of each were taken within the same session and the root mean squared difference was calculated.

$$\text{RMSD} = \sqrt{\frac{\sum_{i=1}^{n}(x_{1i}-x_{2i})^2}{n}}$$ (6.4)
Since MTR is calculated from two 3D gradient echo acquisitions (with and without a MT pulse) it is important that the scanner provides repeatable measurements between each consecutive volume acquisition. The long-term stability of the scanner was assessed by repeatedly scanning a test object (phantom) overnight for approximately 15 hours, using the 3D gradient echo sequence used in the MTR calculations. The phantom was a 20 cm diameter bottle containing a 10 mM solution of nickel sulphate. A region of interest was drawn in the centre of the central slice and signal intensity was compared in each scan to the previous one, which resembles what happens in MTR analysis where the ratio of two consecutive scans is calculated.

Although variability in imaging parameters was studied in all tissue types, only the results relating to white matter will be described as very similar effects were found in grey matter. For MTR, the CV% was 1.87 which is within the same range as other published studies, which tend to be less than 2% (Tofts & Collins, In Press). For DTI measures the CV% was 3.29 (ADC) and 3.87 (FA). Published studies have found ADC CV% 3-5% (Tofts & Collins, In Press), indicating our method was as good as previous studies.

However, within some sessions there was a large shift in MTR values, in some cases as much as two percentage units (see figure 6.2, panel c). The RMSD for within session scans was 0.9 pu. Repeated scans of the phantom indicated the scanner was sometimes stable, but could have shifts in signal intensity between consecutive scans of up to 8% (figure 6.1, panel a). Due to the variability in signal intensity a hardware change was made and the RF transmitter boards were replaced in October 2009.

Following the change of RF transmitter boards, the RMSD improved to 0.17 percentage units (from 0.9 pu) and there were no large within session shifts as seen before. Overnight repeated scanning of the phantom revealed good stability with an average between scan difference of 0.2% (figure 6.2, panel B). The coefficient of variation% for the group also decreased to 0.79% (from 1.87%).
Figure 6.2: Repeated measures of mean signal intensity in a region of interest in the centre of a bottle phantom measures before hardware replacement (A) and after (B). MTR histograms of one participant (P-5) within the same session before (C) and after (D) changing the RF transmitter boards.

The change in RF transmitter boards had little effect on DTI parameters, with a slight reduction in CV% (ADC=2.08\% compared to 3.29\%; FA=3.16\% compared to 3.87\%) and a slight increase in RMSD (ADC=5.08 \times 10^{-12} \text{m}^2 \text{s}^{-1} compared to 3.59; FA=0.006 compared to 0.005). The RF transmitter boards were changed after the first 11 SLE and 11 controls had been scanned. As there was little effect on DTI parameters, it can be concluded that the DTI data obtained before and after the changing of the transmitter boards is likely to be equivalent. The MTR measures from after the changing of the transmitter boards show good reliability, but even the group measures before had CV\% in a similar range to previous published studies. Therefore in the present study the analysis was conducted on the whole sample, but any differences were also confirmed by looking at the data from after October 2009 only.
6.5 Results

6.5.1 DTI

The Apparent Diffusion Coefficient (ADC) group histograms for grey and white matter are displayed in figure 6.3. In both tissue types the SLE group show a shift towards higher values, and a slight drop in peak height. The differences in ADC were significant in the white matter; mean ADC $t(59)=2.68, p<0.01, r=.33$; peak location; $t(59)=2.42, p<0.05, r=.30$; and in the whole brain; mean ADC $t(59)=2.72, p<0.01, r=.33$; peak location, $t(59)=2.73, p<0.01, r=.34$. However the reduction in peak height in the SLE group was not significant in either the white matter, $t(59)=1.07, p=0.29, r=.14$ or whole brain, $t(59)=1.01, p=0.31, r=.13$. In contrast none of the parameters reached significance in the grey matter. The mean values can be seen in table 6.3.

![Figure 6.3: Apparent Diffusion Coefficient group histograms for controls (solid line) and SLE group (broken line) for white matter (left) and grey matter (right).](image)

The Fractional Anisotropy parameters did not show any significant group differences, although the SLE group had lower mean values, the difference approached significance for whole brain FA, $t(59)=-1.97, p=0.053, r=.25$. The mean values can be seen in table 6.3.
<table>
<thead>
<tr>
<th></th>
<th>Control (n=27)</th>
<th>SLE all (n=34)</th>
<th>Non-NPSLE (n=20)</th>
<th>NPSLE (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>White matter</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADC</td>
<td>Mean</td>
<td>738.6 (15.2)</td>
<td>752.0 (22.1)**</td>
<td>749.01 (18.2)</td>
</tr>
<tr>
<td></td>
<td>Peak location</td>
<td>730.2 (17.3)</td>
<td>742.9 (22.6)*</td>
<td>738.8 (18.8)</td>
</tr>
<tr>
<td></td>
<td>Peak height</td>
<td>.521 (.04)</td>
<td>.508 (.05)</td>
<td>.509 (.04)</td>
</tr>
<tr>
<td>FA</td>
<td>Mean</td>
<td>.373 (.02)</td>
<td>.369 (.03)</td>
<td>.372 (.02)</td>
</tr>
<tr>
<td></td>
<td>Peak location</td>
<td>.344 (.02)</td>
<td>.340 (.03)</td>
<td>.344 (.03)</td>
</tr>
<tr>
<td></td>
<td>Peak height</td>
<td>.256 (.01)</td>
<td>.263 (.02)</td>
<td>.261 (.02)</td>
</tr>
<tr>
<td><strong>Grey matter‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADC</td>
<td>Mean</td>
<td>918.7 (39.3)</td>
<td>939.5 (44.9)</td>
<td>940.3 (47.9)</td>
</tr>
<tr>
<td></td>
<td>Peak location</td>
<td>853.5 (23.1)</td>
<td>867.7 (32.8)</td>
<td>866.8 (30.71)</td>
</tr>
<tr>
<td></td>
<td>Peak height</td>
<td>.324 (.05)</td>
<td>.301 (.05)</td>
<td>.300 (.06)</td>
</tr>
<tr>
<td><strong>Whole brain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADC</td>
<td>Mean</td>
<td>817.0 (24.1)</td>
<td>835.6 (28.3)**</td>
<td>836.3 (25.5)†</td>
</tr>
<tr>
<td></td>
<td>Peak location</td>
<td>759.3 (16.0)</td>
<td>773.2 (22.4)**</td>
<td>770.3 (17.4)</td>
</tr>
<tr>
<td></td>
<td>Peak height</td>
<td>.370 (.04)</td>
<td>.360 (.04)</td>
<td>.354 (.04)</td>
</tr>
<tr>
<td>FA</td>
<td>Mean</td>
<td>.266 (.01)</td>
<td>.258 (.01)</td>
<td>.257 (.01)</td>
</tr>
<tr>
<td></td>
<td>Peak location</td>
<td>.139 (.03)</td>
<td>.130 (.02)</td>
<td>.126 (.02)</td>
</tr>
<tr>
<td></td>
<td>Peak height</td>
<td>.323 (.03)</td>
<td>.337 (.03)</td>
<td>.343 (.03)</td>
</tr>
</tbody>
</table>

Table 6.3: Group means (standard deviation) for ADC and FA histogram peak height, peak location and mean ADC/FA for white matter, grey matter and whole brain.

* p < 0.05 for the t-test between the control group and SLE all.
** p < 0.01 for the t-test between the control group and SLE all.
† The ANOVA for the comparison between control, non-NPSLE and NPSLE was significant (p<0.05). The symbol denotes which group differs from the control group on post hoc tests.
‡ FA values have not been reported for grey matter as this does not have a directional structure and it is unclear whether values could meaningfully change with disease.

The group differences were further assessed by splitting the SLE group into NPSLE and non-NPSLE participants. The mean group values for the ADC and FA parameters are displayed in table 6.3. A series of ANOVAs were run, and these confirmed the non significant difference in grey matter ADC. In the white matter there was a significant difference on mean ADC; $F(2,58)=4.18$, $p<0.05$, $\omega=.31$, and ADC peak location; $F(2,58)=4.03$, $p<0.05$, $\omega=.30$, but again, no
difference in peak height. On post hoc tests, it was the NPSLE group that had significantly higher ADC than the controls ($p<0.05$), and this comparison had a medium effect size for both parameters ($r=.34$). The non-NPSLE group fell between the other groups, but did not differ significantly from either and had a small effect size for the comparison ($r=.2$). There were no group differences on white matter FA.

In the analysis of ADC and FA in the whole brain, there were significant group differences in mean ADC, $F(2,58)=3.66$, $p<0.05$, $\omega=.28$; and peak location, $F(2,58)=34.29$, $p<0.05$, $\omega=.31$ but no differences in FA. On post hoc test the NPSLE group differed from controls on ADC peak location ($p<0.05$) with the NPSLE group showing a shift towards higher ADC values. Neither group differed from the non-NPSLE group ($p>0.05$). For mean ADC it was the non-NPSLE group who differed from controls on post hoc tests, with the non-NPSLE group showing higher mean ADC values ($p<0.05$), whilst the NPSLE participants did not differ from either group, although they had a higher mean ADC value than controls.

Although the NPSLE group had significantly higher mean ADC in the white matter than the controls, there were no group differences on mean white matter FA. As both parameters are markers for structural integrity, both would be expected to show differences with damage. The NPSLE group mean FA was lower than the control mean FA, which is in the expected direction based on the assumption of reduced structural integrity in the NPSLE group. Therefore, the CV% for these parameters was compared, to see whether the lack of difference was due to increased variability in the FA measurement, or whether it indicated something about the disease process in NPSLE. The CV% values for the three groups are shown in table 6.4. In all three groups the CV% in FA was approximately double the value in ADC, which suggests the lack of group difference on the FA parameter was due to increased variability in this measure and not due to a disease process that specifically impacted on ADC and not on FA.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Non-NPSLE</th>
<th>NPSLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC CV%</td>
<td>2.05</td>
<td>2.43</td>
<td>3.56</td>
</tr>
<tr>
<td>FA CV%</td>
<td>4.06</td>
<td>4.83</td>
<td>6.64</td>
</tr>
</tbody>
</table>

Table 6.4: Percentage Coefficient of variation (CV%) for white matter ADC and FA parameters.
6.5.1.1 Using DTI to detect NPSLE

For DTI to have clinical utility, it would need to be able to differentiate between individual patients and controls. This was investigated by calculating the percentage from each group for whom ADC or FA values were more than 1 or 2 standard deviations from the control mean. Raw scores were adjusted for differences in age using the same method outlined in chapter 4, section 4.6. Only results relating to white matter mean ADC and mean FA have been reported since the grey matter and whole brain analyses were less sensitive. Using a cut off of 2 standard deviations, 28.6% of NPSLE patients were detected as having abnormally high mean ADC, compared to 0% of non-NPSLE and 3.7% of controls. This has a sensitivity of 0.29, and a specificity of 0.96 for the comparison with controls and 1.00 for comparison with non-NPSLE. Changing the cut off to 1 standard deviation above the control mean had a sensitivity of 0.43 and a specificity of 0.85 against controls and 0.60 against non-NPSLE. FA was less sensitive at detecting differences at both cut off values (0.14 and 0.21). The proportion of participants with values outside of either 1 or 2 times the standard deviation from the control group mean is shown in table 6.5.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Non-NPSLE</th>
<th>NPSLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC</td>
<td>2*SD</td>
<td>1 (3.7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>1*SD</td>
<td>4 (14.8%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>FA</td>
<td>2*SD</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td></td>
<td>1*SD</td>
<td>4 (14.8%)</td>
<td>5 (25%)</td>
</tr>
</tbody>
</table>

Table 6.5: Number (and percentage) of participants classified as having abnormally high ADC or abnormally low FA. Abnormality was defined as either 2 standard deviations (2*SD) or 1 standard deviation (1*SD) above/below control mean.

6.5.1.2 The relationship with clinical parameters

There were no significant relationships in the SLE group between any of the DTI parameters and disease duration ($r < \pm 0.29, p > 0.10$) or SLEDAI score ($r < \pm 0.24, p > 0.17$). Separating the group into NPSLE and non-NPSLE patients did not affect this result for disease duration, but SLEDAI scores showed a significant relationship with white matter ADC in the NPSLE group, $r(14) = 0.54$, $p < 0.05$, and for this group approached significant for white matter FA, $r(14) = 0.52$, $p = 0.058$. There was no relationship in the non-NPSLE group.
6.5.2 MTR

Figure 6.4 shows the average MTR histograms for the control group and SLE group. In both the white matter and grey matter there is almost complete overlap on the histogram, indicating very little difference between the groups.

![Figure 6.4: MTR histograms for controls (solid line) and SLE patients (broken line) for white matter (left) and grey matter (right)](image)

This was analysed using a series of t-tests, where there were no significant group differences on any parameter (mean MTR, peak location or peak height). For all comparisons t(59)<1.4, p>0.1, r<.18. Splitting the SLE group into NPSLE and non-NPSLE did not affect this result; the histograms showed almost complete overlap and for all parameters the ANOVAs were not significant; F(2,58)<1.72, p>0.19, ω<.15.

Figure 6.5 shows the range of values for white matter mean MTR and peak height split into participants scanned before and after the transmitter boards were changed. For mean MTR there were two outlying participants scanned before the transmitter boards were changed (crosses on graph); one control with a low mean MTR and one NPSLE participant with a high value. Removal of these two participants did not change the non significant group differences. Restricting the analysis to those scanned after the transmitter boards were changed (black dots on graph, did not reveal any group differences.
In the grey matter however, there was a non significant trend\(^1\) towards lower peak height in the NPSLE group compared to controls ($p=0.09$). This can be seen in figure 6.6 where the NPSLE values fall to the bottom end of the control range. However, these NPSLE participants had a higher mean age at 55(±7.3) years old compared to 46 (±13.1) in the control group and 43(±15.0) in the non-NPSLE group, so the possibility that this was an age effect cannot be ruled out.

---

\(^1\) The NPSLE group was restricted to $n=6$ which reduces the statistical power to detect a significant difference.
matter areas in which the NPSLE group had a larger volume than either the non-NPSLE group or controls, and no regional differences between the control group and non-NPSLE participants. These are listed in table 6.6.

<table>
<thead>
<tr>
<th>$K_e$</th>
<th>Z</th>
<th>MNI coordinates</th>
<th>Side</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>$Control &gt; SLE$</th>
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</thead>
<tbody>
<tr>
<td>36</td>
</tr>
<tr>
<td>3.2</td>
</tr>
<tr>
<td>(-33, -21, 60)</td>
</tr>
<tr>
<td>L</td>
</tr>
<tr>
<td>Frontal lobe, precental gyrus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>$Control &gt; NPSLE$</th>
</tr>
</thead>
<tbody>
<tr>
<td>324</td>
</tr>
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<td>4.0</td>
</tr>
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<td>(-33, -24, 57)</td>
</tr>
<tr>
<td>L</td>
</tr>
<tr>
<td>Frontal lobe, precental gyrus</td>
</tr>
<tr>
<td>86</td>
</tr>
<tr>
<td>3.8</td>
</tr>
<tr>
<td>(24, -27, 60)</td>
</tr>
<tr>
<td>R</td>
</tr>
<tr>
<td>Frontal lobe, precental gyrus</td>
</tr>
<tr>
<td>31</td>
</tr>
<tr>
<td>3.2</td>
</tr>
<tr>
<td>(30, 15, 20)</td>
</tr>
<tr>
<td>L</td>
</tr>
<tr>
<td>Frontal lobe, sub gyrual</td>
</tr>
</tbody>
</table>

<table>
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<th>$Non-NPSLE &gt; NPSLE$</th>
</tr>
</thead>
<tbody>
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<td>(24, 44, 21)</td>
</tr>
<tr>
<td>R</td>
</tr>
<tr>
<td>Frontal lobe, superior frontal gyrus</td>
</tr>
</tbody>
</table>

Table 6.6: Areas of significant white matter volume difference. $K_e$ represents the number of 1.5x1.5x1.5 voxels in the cluster. Only contrasts with significant clusters at $p<0.001$ have been reported.

Figure 6.7: Areas of reduced white matter volume in the NPSLE group compared to controls showing bilateral differences in the frontal precentral gyrus. The bar indicates z-scores, $p<0.001$. Slices taken at coordinates x=25, y=-27, z=63.

**ORIGINAL IN COLOUR**
Table 6.7: Areas of significant grey matter volume difference. $K_e$ represents the number of 1.5x1.5x1.5 voxels in the cluster. BA represents the nearest Brodmann area for the cluster. Only contrasts with significant clusters at $p<0.001$ have been reported.

Several areas of grey matter volume difference emerged. The control group showed greater volume in a few regions in the left frontal and temporal lobe. Separating the SLE group again indicated areas of reduced volume in the patient groups in the left hemisphere, with the NPSLE
group showing reduced volume in the left insula and fusiform gyrus and the non-NPSLE group showing reduced volume in the middle temporal gyrus/occipital lobe border. The opposite contrast (control group showing reduced volume) tended to find regions in the right hemisphere. The significant clusters are listed in table 6.7.

Comparing the two patient groups, indicated reduced volume in the NPSLE group bilaterally in the thalamus, and significant clusters in the right inferior frontal gyrus and post central gyrus. The opposite contrast revealed reduced volume in the non-NPSLE group in the right frontal lobe, superior temporal gyrus. This region almost overlapped with an area of white matter difference that showed the opposite effect (smaller volume in the NPSLE group). This suggests that this regional difference reflected the segmentation method, as in the case of the non-NPSLE group it has been allocated to the grey matter comparison and in the NPSLE group to the white matter comparison. A threshold of 0.2 was used for inclusion in the analysis, which included voxels that have a 20% chance of being a certain tissue type in the analysis. In reality voxels in these borderline regions contain a mixture of grey and white matter.

6.5.3.1 The relationship with clinical parameters

One grey matter region displayed a negative correlation with disease duration (e.g. reduced volume with longer disease duration) this was in the left temporal lobe, middle temporal gyrus. This also approached voxel-level family-wise error (FWE) corrected significance (p=0.06). This region did not overlap with any of the regions that differentiated the patient groups from healthy controls. A large, bilateral area encompassing the part of the cerebellum, and stretching into the temporal and occipital lobes showed the opposite correlation (e.g. larger volume with longer disease duration). Both these regions can be seen in figure 6.8a. A few white matter regions showed a negative correlation with disease duration. These were in the parietal and temporal lobe, and were posterior to the grey matter region showing this negative correlation. The opposite contrast revealed the cuneus as the only region with a positive correlation with disease duration. These can also be seen in figure 6.8b.
There was a negative correlation between grey matter volume and SLEDAI scores in a few diffuse regions in the right hemisphere, including the parietal lobe, frontal lobe and limbic lobe (figure 6.8c). The region in the post-central gyrus (parietal lobe) also reached voxel level FWE corrected significance. No regions showed the opposite correlation. In the white matter there were negative correlations with SLEDAI score in clusters in the frontal, limbic and temporal lobes (figure 6.8d). The opposite contrast indicated one area in the subcallosal frontal white matter that was larger in the patients with higher SLEDAI scores. This was in a similar location to grey matter regions that displayed the opposite correlation, but did not overlap.
<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td></td>
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**Negative correlation with disease duration**

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<th>Structure</th>
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<td>89</td>
<td>3.7</td>
<td>(-21, -54, 50)</td>
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<td>Parietal lobe, precuneus</td>
</tr>
<tr>
<td>136</td>
<td>3.7</td>
<td>(-46, -38, -4)</td>
<td>L</td>
<td>Temporal lobe, subgyral</td>
</tr>
<tr>
<td>105</td>
<td>3.5</td>
<td>(22, -52, 48)</td>
<td>R</td>
<td>Parietal lobe, precuneus</td>
</tr>
<tr>
<td>47</td>
<td>3.4</td>
<td>(-38, -64, -2)</td>
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<td>Temporal lobe, subgyral</td>
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**Positive correlation with disease duration**

<table>
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<th>Structure</th>
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<td>Occipital lobe, cuneus</td>
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</table>

**Negative correlation with SLEDAI score**

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<th>Z</th>
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<th>Structure</th>
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<tr>
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<td>Frontal/limbic lobe, sub gyral</td>
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<tr>
<td>119</td>
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<td>Limbic lobe, cingulate gyrus</td>
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<tr>
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<td>R</td>
<td>Temporal lobe, middle temporal gyrus</td>
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<td>Sub-lobar, extra nuclear white matter, pulnivar</td>
</tr>
<tr>
<td>58</td>
<td>3.2</td>
<td>(20, -30, 38)</td>
<td>R</td>
<td>Limbic lobe, cingulate gyrus</td>
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</table>

**Positive correlation with SLEDAI score**

<table>
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<th>Z</th>
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<th>Side</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>3.7</td>
<td>(15, 18, -16)</td>
<td>R</td>
<td>Frontal lobe, subcallosal gyrus</td>
</tr>
</tbody>
</table>

Table 6.9: White matter regions that showed a significant relationship with clinical variables. Ke represents the number of 1.5x1.5x1.5 voxels in the cluster. Only contrasts with significant clusters at p<0.001 have been reported.

† This also reached cluster level family-wise error corrected significance.
‡ This also reached voxel level family-wise error corrected significance.
Cross-hair coordinates (x=13, y= -54, z= -14)  Cross-hair coordinates (x=12, y= -51, z= -6)

Cross-hair coordinates (x=0, y= -20, z= -17)  Cross-hair coordinates (x=-14, y= -32, z= -17)

Figure 6.8: Grey and white matter regions that showed a significant relationship between volume and clinical variables. The correlation between (a) disease duration and grey matter volume. Reduced volume (red) in the left middle temporal gyrus, increased volume (blue) bilaterally in cerebellum. (b) Disease duration and white matter. Reduced volume (red) bilaterally in the precuneus and in the left sub-gyral temporal lobe, increased volume (blue) in the cuneus. (c) SLEDAI score and grey matter. Reduced volume in the parietal lobe, post central gyrus and subcolossal frontal lobe. (d) SLEDAI score and white matter. Reduced volume (red) bilaterally in the cingulate gyrus and in left sub-nuclear white matter, increased volume (blue) in subcallosal frontal lobe.
6.6 Discussion

6.6.1 Diffusion tensor imaging

There were significant differences between the SLE group and controls on white matter and whole brain mean ADC and peak location, with the SLE group showing higher ADC values. Higher ADC values have been interpreted as being indicative of cell breakdown, as with cell breakdown there are fewer biological barriers to diffusion. This supports previous studies that have shown increased white matter ADC in patients with SLE (Hughes, et al., 2007; Welsh, et al., 2007; Zhang, et al., 2007). The current study found no ADC or FA differences in the grey matter. Two previous studies have investigated ADC in the grey matter in SLE. One (Welsh, et al., 2007) also found grey matter differences in NPSLE, while Emmer et al. (Emmer, van der Grond, et al., 2006) did not (but they also did not find white matter differences either). The main difference with Welsh et al. (2007) was that they studied patients with new acute neurological symptoms, and it may be that grey matter differences are only evident during active disease. In support of this, the authors interpret their finding as indicating inflammation and/or vasculitis of the grey matter.

Separating the SLE group into NPSLE and non-NPSLE indicated it was predominantly the NPSLE group who differed from controls, although there was a significant difference between controls and the non-NPSLE group on whole brain mean ADC. In the white matter, the non-NPSLE group had intermediate values, and did not differ from either the NPSLE or control groups. Jung, Caprihan et al. (2010) suggested ADC differences in NPSLE, but not non-NPSLE while Emmer et al. (2006) did not find any differences between their NPSLE and non-NPSLE groups. The current results suggest there is a slight increase in ADC in non-NPSLE patients, particularly evident in the whole brain analysis. In support of this, the evaluation of participants with abnormally high ADC values, detected a similar proportion of NPSLE and non-NPSLE participants (about 40%) at the less stringent cut off of one standard deviation above the control mean. At the more stringent cut off nearly 30% of NPSLE patients were detected compared to nearly zero in the other groups. Thus there may be subtle damage occurring in both NPSLE and non-NPSLE patients, but this was more widespread in a subset of NPSLE patients. The difference between groups may reflect the heterogeneity of different NPSLE or non-NPSLE cohorts. Even if studies use the ACR criteria for defining NPSLE, there may be differences in the manifestations that are included in the research group.
Differences were identified in white matter ADC but not FA. This was surprising as it might be expected that pathological processes would affect both FA and ADC, and the two parameters were highly correlated. One possibility is that this reflects the variability of the two measures. FA had nearly double the coefficient of variation of ADC, and this could make it more difficult to detect a difference statistically. The mean white matter FA was reduced in the NPSLE group, which would be expected with subtle damage. FA might be more variable because each λ value is used multiple times in its calculation, whereas in calculating ADC they are only used once. The λ values have some uncertainty/error attached and this uncertainty could be multiplied in calculating FA. This increased variability in FA has been previously reported (Paldino, Barbriak, Desjardins, Friedman, & Vredenburgh, 2009; Tofts & Collins, In Press). On the other hand, previous studies have shown a significant reduction FA in SLE (Emmer, et al., 2010; Hughes, et al., 2007; Jung, Caprihan, et al., 2010; Zhang, et al., 2007). The main difference is that these all used regionally specific measurement rather than global. It may be that FA differences are better detected if measured regionally.

The DTI parameters were explored for their potential to detect participants with abnormally high ADC or low FA (possible pathology). Two cut offs for detecting pathology were compared – one standard deviation from the control mean or two standard deviations. The more stringent cut-off had high specificity for NPSLE (0.96 – 1.00 compared to controls or non-NPSLE) but fairly low sensitivity (0.29). Methods for diagnosing NPSLE include conventional MRI, spectroscopy, Computerised tomography (CT), Electroencephalography (EEG), Positron emission tomography (PET) and serological evaluation of antibodies in the blood serum or CSF. Conventional MRI has been shown to have fairly low sensitivity (0.47) and specificity (0.43) for diffuse NPSLE (S. G. West, et al., 1995) but does have high sensitivity (1.0) for focal manifestations. CT scans may be abnormal in 35-59% of NPSLE patients (Sibbitt, et al., 1999) but is insensitive to small, diffuse lesions that are visible on MRI. West et al. (1995) obtained a sensitivity of 0.57 for CT. Abnormal EEGs have been found in up to 70% of NPSLE patients (Hermosillo-Romo & Brey, 2002), but does not distinguish between NPSLE and non-NPSLE groups (S. G. West, et al., 1995). Serological evaluation suggests a high sensitivity (0.74) and specificity (1.0) for an elevated CSF IgG index, which is a measure of antibody synthesis within the CNS (S. G. West, et al., 1995). Assessment of serum had mixed results and it has been proposed that in NPSLE auto-antibodies in serum do not reflect their behaviour in CSF (e.g. Fragoso-Loyo, et al., 2008). On the other hand, evaluation of the CSF requires a lumbar puncture, which is an invasive test necessitating a hospital admission and this would not be
justifiable for patients with mild disease. Therefore it is promising that DTI had a high
specificity for NPSLE when a stringent cut off for abnormality was used but to be clinically
useful it would need to be used in conjunction with other diagnostic methods due to the low
sensitivity.

6.6.2 Magnetisation transfer imaging

There were no group differences on any of the MTR parameters when looking at the whole
group or the NPSLE and non-NSPLE group separated. This contrasts with previous research that
indicates a reduction in mean MTR (Rovaris, et al., 2000) and peak height (Bosma, Rood,
Huizinga, et al., 2000; Steens, Admiraal-Behloul, Bosma, et al., 2004) in NPSLE. One previous
study also found no difference between NPSLE, non-NPSLE patients and controls on MTR
measures in the grey and white matter, but this study did have a trend towards lower peak
heights in the NPSLE group, and did find significant differences in the whole brain analysis
(Emmer et al., 2008). One possibility is that this reflects the instability of the scanner during
the initial stages of the project, which was in unfortunately when 60% of the NPSLE group
were scanned. On the other hand, in those scanned after the hardware upgrade there was no
evidence of, or even a trend towards, reduced mean MTR of peak height in the white matter.
This suggests demyelination was not present in these patients. There was a trend to lower
peak height values in grey matter of the NPSLE group compared to controls. This was the
parameter identified by Steens et al. (2004) as showing group differences. But as the NPSLE
patients in this cohort were older than the control group or non-NSPLE group, the effect of age
cannot be ruled out.

6.6.3 Voxel-based morphometry

Reduced brain volume was found in several small grey and white matter regions in the SLE
group compared to controls. These were mainly found in the posterior frontal lobe and
temporal lobe. Separating the SLE group indicated it was the NPSLE group that showed
reduced volume in white matter regions compared to controls, whereas the non-NPSLE group
did not. Previous studies have found white matter volume differences in SLE compared to
controls, and suggest greater volume reduction in NPSLE compared to non-NPSLE patients
(Appenzeller, Bonilha, et al., 2007). This study found extensive white matter differences, which
would overlap the areas identified in the current study, but also extended well beyond them. A
Second VBM study identified a few regions of reduced white matter volume in SLE (Xu, et al., 2010). These included the internal capsule, the right post-central gyrus in the frontal lobe and the parahippocampal gyrus in the temporal lobe. Only one of these clusters was in a similar location to the differences identified in the current study and Xu et al, only found differences in the right hemisphere, whereas they were bilateral in the comparison with NPSLE in the current study.

In the grey matter there was no clear pattern of results. A few regions were significantly reduced in the NPSLE group compared to controls, and different regions were reduced compared to non-NPSLE patients. On the other hand small regions also emerged as showing increased volume in the NPSLE group compared to the other groups. In contrast, previous studies have suggested widespread atrophy in NPSLE. Appenzeller et al. (2007) found extensive regions of grey matter volume reduction in SLE patients, and again suggest these differences were more important in the NPSLE group. Jung, Segall et al. (2010) compared patients with NPSLE, non-NPSLE and controls on cortical thickness and also found thickness differences across the cortex in the NSPLE group.

There were some regions of overlap between the current study and previous studies of volume. For example Jung, Segall et al. (2010) identified regions of reduced cortical thickness in the middle frontal gyrus, and post-central gyrus. These are in similar locations identified as showing reduced volume in the NPSLE group compared to controls (middle frontal gyrus) and compared to non-NPSLE participants (post-central gyrus). However there was not a systematic pattern of differences in grey matter volume across the different studies. This converges with the lack of overlap with the white matter volume findings of Xu et al. (2010) and the fact that in two voxel-wise (TBSS) diffusion studies, different tracts were identified as showing differences between patients with SLE and controls. The use of regional analyses requires the assumption that there will be common areas of damage within a patient group, and generalisability relies on the assumption that these regions would be matching in other patient samples. Unlike disease such as Parkinson’s disease or Multiple Sclerosis, NPSLE does not have a particular presentation. Instead there are variable neuropsychiatric manifestations across patients, which suggests diffuse damage to the CNS. Typical autopsy findings are of bland vasculopathy (e.g. Zvaifler & Bluestein, 1982) and this may occur throughout the brain. Perhaps the aim of imaging studies should not be identify specific regions that show damage in NPSLE, but instead to identify and quantify diffuse damage.
6.6.4 The relationship between imaging parameters and clinical variables

Using VBM, one grey matter region in the left middle temporal gyrus emerged as showing reduced volume with increased disease duration. This cluster approached family-wise error corrected significance. Several white matter regions also correlated with disease duration, these were found bilaterally in the precuneus, and in the left sub-gyral temporal lobe. Appenzeller et al. (2007) also found a relationship between disease duration and white matter volume loss, although again they found more extensive differences. In contrast, Xu et al. (2010) found no relationship between volume and disease duration; however, they simply split the group into two: those with duration less than 12 and those longer than 12 months. This may be a less sensitive approach because this reduces duration to a categorical variable. In the current study, a larger region of the cerebellum emerged as showing the opposite relationship with disease duration (larger volume with longer duration). This is a surprising finding, and it is difficult to hypothesise why this should occur, especially given that cerebellar involvement in SLE is relatively rare (Alarfaj & Naddaf, 1995; Chan, Li, Wong, & Liu, 2006) and none of the patients had any symptoms associated with cerebellar damage, such as a loss of coordination of movement. Appenzeller et al. (2007) do not report any regions that showed increased volume with disease duration, which might be expected if this is a generalisable finding. It is possible this reveals registration problems with the template, but why this should only emerge in the correlation with disease duration is not clear.

There was no relationship between disease duration and any of the DTI measures. Previous studies have not reported any association between disease duration and DTI, although whether this is because no relationship has been found, or whether it has not been investigated is not clear. Only one publication has investigated the relationship with MTR histogram parameters, where no relationship was evident (Bosma, et al., 2002). One possibility for the relationship between disease duration and volume, but not with DTI is that these parameters could reflect distinct aspects of the disease process, one which affects volume and changes linearly over time, and one which affects structural integrity and does not change linearly over time. This would need to be assessed using longitudinal measurements.

Several grey and white matter regions displayed a relationship with current disease activity. This was surprising as none of the patients had significantly active disease at the time of the scan. This suggests that there may be ongoing pathological processes outside of disease flares
that are reflected in slightly increased SLEDAI scores. Xu et al. (2010) also reported correlations between white matter volume and SLEDAI scores in the left posterior internal capsule and right anterior internal capsule. This latter region was in a similar location to one of the significant clusters found in the present study in the sub-lobar, extra nuclear white matter. In contrast, Appenzeller et al. (2007) did not find a relationship between disease activity (also measured by the SLEDAI) and volume in any region. Xu et al. (2010) explain their correlation as potentially reflecting significant vasculopathy in the active stage. This explanation seems an unlikely explanation for the current finding as none of the patients had significantly active disease. SLEDAI scores measure systemic disease activity, and may show elevation from zero outside of an active disease flare due to persisting signs such as elevated anti-double-stranded DNA antibody levels, low complement levels or symptoms such as arthritis. It is possible that it also reflects concurrent low grade cerebral inflammation. Within the NPSLE group there was also a correlation between SLEDAI score and white matter ADC and FA. This suggests more research is needed on the impact of current disease on MRI parameters in order to ascertain their utility in differentiating acute versus chronic effects of SLE.

6.7 Summary

(1) Compared to controls, the SLE group as a whole showed elevated ADC in the white matter and whole brain histogram analyses. Separating the SLE group indicated it was the NPSLE group that differed from controls on white matter ADC. The non-NPSLE group differed from controls on whole brain mean ADC.

(2) There were no group differences on any of the FA histogram parameters. This may reflect increased variability and therefore poor sensitivity in this measure.

(3) There were no group differences on MTR, but there was a trend towards lower grey matter peak height in the NPSLE group.

(4) On VBM a few areas of reduced grey and white matter volume in the NPSLE group emerged. However, the opposite contrast also revealed regions of increased volume suggesting there was not clear atrophy in this cohort.

(5) A few diffuse regions showed a correlation between volume loss and disease duration, but a significant region of the cerebellum showed increased volume with disease duration, making these findings difficult to interpret.

(6) Correlations were found between a) disease activity and volume and b) disease activity and ADC and FA mean values. This suggests there may be low level cerebral
inflammation even in the absence of significantly active disease, and that these techniques are sensitive enough to measure this change in activity.
CHAPTER 7

PORTMANTEAU\textsuperscript{2} CHAPTER

7.1 Introduction

The previous four chapters have discussed the group differences on mental health and wellbeing (chapter 3), cognition (chapters 4 and 5) and imaging (chapter 6). The main aim of this chapter is to look at the relationships between different parameters and cognitive performance.

7.1.2 The relationship between mood and cognitive performance

The correlation between depression/anxiety and cognitive performance was addressed as psychological factors have been shown to influence performance on neuropsychological tests. Depression has been associated with deficits in cognitive performance both in psychiatric patients and in patients with neurological disorders (Sweet, et al., 1992). A number of studies have reported a relationship between anxiety and test performance in academic settings (Zeidner, 1998); additionally higher state anxiety has been associated with poorer performance on cognitive tasks in normal ageing (Wetherell, et al., 2002). In the volunteers tested here, there were no differences between the NPSLE and non-NPSLE participants on measures of depression or anxiety, and both had significantly higher depression scores than the healthy controls. In contrast, significant differences were evident between NPSLE and non-NPSLE participants on the cognitive domains of memory and speed of processing (SOP) and global cognitive impairment (CII) (chapter 4). Kozora, Ellison, & West. (2006) had the same pattern of results, (increased depression in both non-NPSLE and NPSLE patients, but only increased cognitive impairment in the NPSLE group) and found a significant relationship between CII scores and depression in the NPSLE group, but not the non-NPSLE group. It would be interesting to see whether this finding is replicated in the current sample.

\textsuperscript{2} Portmanteau

1. (formerly) a large travelling case made of stiff leather, especially one hinged at the back so as to open out into two compartments

2. (modifier) embodying several uses or qualities
7.1.3 The relationship between perceived cognitive failures and objective performance

Kozora et al. (2006) found higher cognitive impairment (CII) and higher self reported cognitive failures (CFQ) in their NPSLE group than in non-NPSLE patients. They suggest that subjective cognitive complaints tend to be associated with depression, but, despite similar depression scores, the group (NPSLE) with higher objective impairment also had greater subjective impairment. This same overall pattern was evident of the data reported in the current thesis, although the difference between the NPSLE and non-NPSLE group scores on the CFQ total score did not reach significance. The NPSLE group did have a significantly higher mean score on the CFQ memory subscale than the non-NPSLE participants, and they also had significantly worse performance on the memory domain. Therefore two relationships were selected for further assessment; the relationship between total score on CFQ and global cognitive impairment, and CFQ memory subscale and the memory domain t-score. Kozora et al. (2006) found a significant correlation between CFQ and cognitive impairment (CII) in the NPSLE participants, but not in the non-NPSLE group or controls. This mirrored their finding of a correlation between CII and depression in the NPSLE group, but non-NPSLE. Again it would be interesting to see whether this finding is replicated in the present sample, and whether this pattern is also evident in the relationship between the CFQ memory subscale and the memory domain t-score.

7.1.4 The relationship between Imaging parameters and cognitive performance

7.1.4.1 Diffusion Tensor Imaging

In the imaging chapter the NPSLE group was shown to have higher Apparent Diffusion Coefficient (ADC) than healthy controls in the white matter. ADC refers to the extent of diffusion and is a marker to brain structural integrity. The NPSLE group also performed worse than the controls on cognitive measures, as discussed in chapter 4. If cognitive performance is related to damage to brain parenchyma, then it might be expected that there would be a correlation between imaging parameters and cognition in the NPSLE group. Ageing has been associated with lower FA and higher ADC (Bendlin, et al., 2010; Bennett, Madden, Vaidya, Howard, & Howard, 2010; Hsu, et al., 2008; Kennedy & Raz, 2009; Pfefferbaum, et al., 2000; Salat, et al., 2005). Additionally there may be age related differences in cognitive performance, particularly in cross sectional studies (Hedden & Gabrieli, 2004). Therefore, in a cohort with a
large age range, it might be expected that imaging parameters would show a relationship with cognition independent of disease. A partial correlation controlling for age would show if a relationship exists in the patient cohort over and above any effect of age.

As yet no published studies have correlated DTI parameters with cognitive performance in SLE. Mandelli et al. (2011) presented data at a recent conference, where SLE patients with cognitive impairment showed increased ADC and reduced FA compared to healthy controls. Cognitively normal SLE patients also showed reduced FA compared to controls, but this was less widespread. They found no correlation between white matter changes and broad-based cognitive impairment indices. However, correlations have been identified between other imaging parameters and cognition, such as Magnetisation Transfer Imaging (Bosma, et al., 2002) and spectroscopy (Kozora, et al., 2005; Lapteva, et al., 2006). This suggests there should be a relationship between cognition and DTI if it is identifying the same damage processes as other imaging methods.

7.4.1.2 Voxel-based morphometry

Widespread correlations have previously been identified between volumetric analysis and cognitive function (Appenzeller, Bonilha, et al., 2007). Patients with severe cognitive impairment had more severe volume loss than patients with no cognitive impairment, and there was a negative correlation between volume and the number of domains impaired. Memory scores correlated with grey and white matter volume in the temporal and frontal lobes, while attention correlated with volume in the parietal lobe. The authors propose that cognitive impairment is the clinical expression of the atrophy. Appenzeller et al. (2007) found broader atrophy differences in their SLE sample than were evident in the imaging chapter of the present thesis. It would be interesting to see whether there were still correlations between cognitive function and volume in patients without such widespread atrophy.

7.1.5 The relationship between clinical variables and cognitive performance

A number of clinical variables were selected for analysis, including disease related factors such as disease duration and disease activity levels, specific auto antibodies, general health and the use of corticosteroid drugs.
7.1.5.1 The relationship between disease activity and cognitive performance

There are a number of different measures for assessing disease activity in SLE. One such measure is the SLE disease activity index (SLEDAI) (Bombardier, et al., 1992). The SLEDAI measures disease activity in the past 10 days using weighted clinical and laboratory variables. There are several serological components that change during an SLE flare, including complement levels C3 and C4, erythrocyte sedimentation rate (ESR), levels of C-reactive protein (CRP) and anti-double-stranded DNA antibodies (anti-dsDNA). The ESR and CRP are both general markers of inflammation. In SLE the ESR is used to follow disease activity and is usually elevated during a flare, whereas the CRP levels are typically normal or only slightly raised (Griffiths, Mosca, & Gordon, 2005). During a disease flare the complement levels C3 and C4 typically decrease, (Abbas & Lichtman, 2006), while levels of anti-dsDNA increase (ter Borg, et al., 1990). These last two serological factors are both incorporated into the SLEDAI scoring system.

Research into the relationship between disease activity and cognition in SLE has had mixed findings. Two studies identified disease activity as a predictor of later impairment (Gladman, et al., 2000; Mikdashi & Handwerger, 2004). In Gladman et al. (2000), though, the patients had no disease activity at the time of testing, suggesting cognitive dysfunction may be caused by previous disease. Kozora et al., (2006), however, found a significant correlation between current disease activity and cognitive performance in both NPSLE and non-NPSLE participants. In fact this was one of few correlations with cognitive performance in the non-NPSLE group, where cognition did not relate to depression, pain or fatigue. The mean SLEDAI Score was approximately 7±5 in both patient groups. In the present study the mean SLEDAI score was lower, at 2.8±2.5 and few patients had scores greater than 8 (suggesting active disease). Therefore it would be interesting to see whether this correlation could be replicated in the present sample.

The impact of other health related factors, such as physical health, pain and fatigue were also considered. These factors can be generated from the subscales from the LupusQol questionnaire, which asks about the frequency of symptoms over the past four weeks. Kozora et al., (2006) also investigated the relationship between fatigue and pain and cognitive impairment in patients with NPSLE and non-NPSLE. There were significant correlations between these factors in the NPSLE group, but not in the non-NPSLE group.
7.1.5.2 Serology

A number of auto antibodies have previously been associated with cognitive dysfunction including anti-neuronal, anti-N-methyl-D-aspartate, anti-cardiolipin (aCL), Lupus-anticoagulant (LA) and anti-Ro antibodies.

Anti-cardiolipin and lupus anticoagulant antibodies are both involved in antiphospholipid syndrome (APS), which is a disorder of coagulation and is therefore associated with an increased risk of thrombosis. There are therefore well researched links between aCL antibodies and focal neurological symptoms of SLE, such as stroke, seizure, epilepsy and migraines (Zandman-Goddard, et al., 2007). They have also been associated with diffuse neuropsychiatric manifestations, such as cognitive dysfunction (Stojanovich, et al., 2007). Although all areas of cognitive function have been implicated in antiphospholipid antibody positive patients, the majority of studies support a relationship with specific functions of psychomotor speed and attention and mental flexibility (Denburg & Denburg, 2003).

Anti-Ro antibodies are associated with Sjogren’s syndrome, which may itself have related cognitive dysfunction of a similar prevalence to SLE (Harboe, et al., 2009). In a longitudinal study of predictors of neuropsychiatric damage in SLE patients, anti-Ro antibodies were related to severe neuropsychiatric damage. However, they were not predictive of cognitive impairment in a multivariate analysis (Mikdashi & Handwerger, 2004). Other studies, however, have related anti-Ro antibodies to cognitive impairment in SLE patients (Zandman-Goddard, et al., 2007). aCL and anti-Ro antibodies are routinely screened for during clinical monitoring and therefore were included in the current analysis.

7.1.5.3 Corticosteroid use

Corticosteroids, such as Prednisone, are a common treatment for rheumatological conditions including SLE. At the time of testing 41% of participants in the current sample were being treated with steroids, and 73% had used them at some point. Animal models suggest an association between corticosteroids and memory impairment and hippocampal damage (McEwen, 2000). Human studies have also indicated an association between acute corticosteroid administration and memory retrieval deficits in healthy volunteers (de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; Young, Sahakian, Robbins, & Cowen, 1999) and
in patients on long term corticosteroid therapy (Brown, et al., 2004; Keenan, et al., 1996). In SLE, long-term corticosteroid use has been associated with cortical atrophy (Zanardi, Magna, & Costallat, 2001). Cumulative steroid dose correlated with degree of grey matter atrophy (Appenzeller, Bonilha, et al., 2007) and hippocampal volume loss (Appenzeller, D Carnevalle, Li, Costallat, & Cendes, 2006). However in studies of cognition, cognitive impairment did not correlate with current steroid dose (Kozora, Arciniegas, et al., 2008; Monastero, et al., 2001).

7.1.6 Illness controls

As previously mentioned, the current programme of research included a chronic illness control group. This was to allow comparison with a group of patients with similar confounding factors, such as chronic illness, medications or features such as fatigue or pain. Rheumatoid arthritis was predominantly selected for the comparison group as this is thought to have few symptoms of central nervous system involvement. It was hypothesised that this group would show normal brain scans, but may differ from healthy controls on quality of life, depression anxiety and cognition. Of particular interest was the comparison between illness controls and the NPSLE and non-NPSLE groups.

7.1.7 Confounding factors

Possible confounding factors were considered, including group differences in motor speed, and secondly concurrent or previous risk factors for poor cognitive performance, such as renal involvement in SLE and hypertension.

7.1.7.1 Motor speed

All six tasks that were included in the speed of processing (SOP) and compound RT domains had a manual (computer keypress or written) response. 73.3% of NPSLE patients compared to 36.6% of non-NPSLE and 10% of controls were classed as impaired on the finger tapping test, a test of manual dexterity (chapter 4). It is therefore possible that differences identified on the SOP and compound RT domains were related to group differences in motor speed, rather than cognitive deficits. Therefore the correlations between these parameters were investigated.
7.1.7.2 Renal involvement

Although estimates vary, approximately 40% of SLE patients may have abnormalities of renal function (Dooley, 2007), and this may vary according to ethnicity, with Lupus nephritis more common in Afro-Caribbean, Chinese and indo-Asian populations than Caucasian (Patel, Clarke, Bruce, & Symmons, 2006). Chronic kidney disease has been linked with cognitive deficits (Madero, Gul, & Sarnak, 2008; Murray, 2008). There is little research on the cognitive impact of renal involvement in SLE, but there may be common pathogenesis such as vasculopathy, which may affect both the kidneys and the central nervous system, or there may be causal links between renal involvement and cognition. Therefore renal involvement was considered as a confounding variable, with analyses conducted to see whether SLE patients with renal involvement had poorer performance than those without, and whether differences were still evident between SLE patients and controls with renal patients excluded.

7.1.7.3 Hypertension

Similar to kidney disease, hypertension may be associated with cognitive decline in older (Lopez, et al., 2003; Tzourio, Dufouil, Ducimetiere, & Alperovitch, 1999) and middle aged adults (Knopman, et al., 2001). In the general population hypertension is linked to vascular events, including cerebrovascular disease. Hypertension in SLE may be incidental, with similar risk factors that are seen in the general population, such as smoking, family history or obesity, or may be related to renal disease or corticosteroid treatment. One study analysed factors affecting cognition in SLE, including cardiovascular risk factors such as hypertension. Hypertension was the most important generic risk factor and significantly affected both the presence and severity of cognitive impairment (Tomietto, et al., 2007). In the current analysis, the confounding effect of hypertension was addressed by comparing performance of normotensive and hypertensive patients, and by seeing if group differences were still evident between normotensive patients and healthy controls.

7.1.8 Research questions

(1) Are there significant relationships between mood, imaging and clinical factors and cognitive performance? Are these relationships the same for the NPSLE and non-NPSLE groups?
(2) Are group differences in cognitive performance between patients and healthy controls driven by auto-antibodies such as anti-Ro and anti-Cardiolipin antibodies?

(3) Does cognitive performance relate to corticosteroid use?

(4) How does the performance of illness controls compare to the NPSLE and non-NPSLE groups?

(5) Do confounding factors such as motor speed, renal involvement or hypertension explain the group differences in cognitive performance?

### 7.2 Summary of main group differences

Table 7.1 recapitulates the main group differences on measures of mental health and wellbeing, cognitive performance and quantitative imaging. Rather than reporting where the overall ANOVAs were significant, the results have been separated into pair-wise comparisons on post hoc tests, as this emphasises where group differences occurred. Cells have been highlighted in grey where the group comparisons were significant using Gabriel’s procedure to correct for multiple comparisons.

<table>
<thead>
<tr>
<th></th>
<th>NPSLE vs Controls</th>
<th>Non-NPSLE vs controls</th>
<th>NPSLE vs non-NPSLE</th>
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<tbody>
<tr>
<td><strong>Mental health and wellbeing</strong></td>
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<tr>
<td>Depression</td>
<td>NPSLE &gt; controls</td>
<td>Non-NPSLE &gt; controls</td>
<td>No differences</td>
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<tr>
<td>Anxiety</td>
<td>NPSLE &lt; controls</td>
<td>Non-NPSLE &lt; controls</td>
<td>No differences</td>
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<td>QoL</td>
<td>NPSLE &lt; controls</td>
<td>Non-NPSLE &lt; controls</td>
<td>NPSLE &lt; non-NPSLE on physical health QoL</td>
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<td><strong>Cognitive performance</strong></td>
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<tr>
<td>Memory</td>
<td>NPSLE &lt; controls</td>
<td>No differences</td>
<td>NPSLE &lt; non-NPSLE</td>
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<tr>
<td>SOP</td>
<td>NPSLE &lt; controls</td>
<td>No differences</td>
<td>NPSLE &lt; non-NPSLE</td>
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<tr>
<td>Executive control</td>
<td>NPSLE &lt; controls</td>
<td>No differences</td>
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<td>Compound RT</td>
<td>NPSLE &lt; controls</td>
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<td>Overall impairment</td>
<td>NPSLE &gt; controls</td>
<td>No differences</td>
<td>NPSLE &gt; non-NPSLE</td>
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<td><strong>MRI (White matter)</strong></td>
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<tr>
<td>DTI</td>
<td>NPSLE &gt; controls</td>
<td>No differences</td>
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<td>MTI</td>
<td>No differences</td>
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<tr>
<td>VBM</td>
<td>NPSLE &lt; controls in small white matter regions</td>
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<td><strong>MRI (grey matter)</strong></td>
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<td>DTI</td>
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<tr>
<td>MTI</td>
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<td>VBM</td>
<td>No differences</td>
<td>No clear result pattern</td>
<td>No clear result pattern</td>
</tr>
</tbody>
</table>

Table 7.1: The main group differences identified in chapters 3 to 6. Cells highlighted in grey indicate where significant group differences were found on post hoc test.
7.3 Methods

To reduce the number of comparisons only a subset of variables were selected from the previous chapters to investigate the relationship between cognition and other factors, including mental health and wellbeing, quantitative imaging parameters, clinical variables and finally other potentially confounding factors.

7.3.1 Measures of cognitive performance

The domain t-scores (memory, speed of processing (SOP), executive control and compound RT) generated in chapter 4, section 4.5 were used for the analysis, rather than the scores from individual tasks. Additionally, the cognitive impairment index (CII) generated in chapter 4, section 4.6 was included as a measure of global cognitive performance. This was chosen rather than the global domain score (also generated in section 4.6) as this had a wider range of scores and hence would have more scope to demonstrate a relationship with other variables.

7.3.2 Mental health and well being

The Hospital Anxiety and Depression Sale depression (HAD-D) and anxiety (HAD-A) were used as measures of depression and anxiety. The Speilberger State Anxiety Inventory (SSAI) was also included as a measure of state anxiety. This was completed immediately prior to the cognitive assessment and therefore it provides a better estimate of anxiety at the time of cognitive testing.

7.3.3 Perceived cognitive failures

As mentioned in chapter 3, section 3.3.2 the NPSLE group had higher overall scores on the cognitive failures questionnaire (CFQ) than healthy controls, and higher scores on the memory subscale than the non-NPSLE participants. Therefore two relationships were assessed; total score on the CFQ and the cognitive impairment index (CII), and score on the CFQ memory subscale and the memory domain t-score.
7.3.4 Imaging parameters

Diffusion tensor imaging parameters (Apparent Diffusion Coefficient (ADC) and Fractional Anisotropy (FA)) taken from the analysis of white matter integrity were included. White matter ADC differentiated the NPSLE group from the controls. As ADC and FA are likely to indicate the same underlying pathology, both were included in the correlational analysis. The cognitive domain scores were included as correlates in a VBM analysis to see areas of grey and white matter volume that correlated with cognitive function.

7.3.5 Clinical measures

A number of clinical measures were included in the analysis and these can be divided into general disease related factors, drugs and serology.

7.3.5.1 Disease and health related factors

Disease duration was considered to be the time (in years) since SLE was first diagnosed. Although this may exclude some time during which the patient was potential symptomatic but undiagnosed, this was deemed the safest method rather than attempting to retrospectively diagnose SLE. Disease activity was assessed using the SLE disease activity index (SLEDAI) (Bombardier, et al., 1992). Three measures of general health were taken from the LupusQoL questionnaire subscales (chapter 3, section 4.2.12). These were physical health, pain and fatigue subscale scores.

7.3.5.2 Serology

Data from routine clinical management was taken from the patients’ medical notes. This included the erythrocyte sedimentation rate (ESR), levels of C-reactive protein (CRP) and anti-double-stranded DNA antibodies (Anti-dsDNA). Patients were categorised according to the presence or absence of anti-Ro antibodies, based on their antibodies to extractable nuclear antigens (ENA) screen taken for routine clinical monitoring. This was confirmed by inspecting serology results from multiple clinic visits to ensure patients had a persistent positive or negative result over the time period that included their cognitive assessment and MRI scan. Patients were also categorised into antiphospholipid syndrome (APS) positive or negative.
based on either a persistently elevated titre of anti-Cardiolipin antibodies (>15 IgG Phospholipid units/mL) taken from medical notes over a time period that included cognitive assessment, or a diagnosis of APS due to clinical symptoms such as vascular thrombosis.

7.3.5.4 Corticosteroid drug use

The effect of current or previous steroid use was assessed. Steroid dose was divided categorically into high (greater than 10 mg per day), low (less than 10 mg per day) and absent. Previous dose was calculated in the same way.

7.3.6 Illness controls

The participant characteristics for the illness control group are described in chapter 2 section 2.5. Eight patients had rheumatoid arthritis, two Primary Sjögren’s syndrome, with no evidence of central nervous system involvement, and one Urticarial Vasculitis. Two participants did not complete the MRI scan, one due to a cardiac stent and the other severe claustrophobia.

7.3.7 Confounding factors

7.3.7.1 Motor Speed

The finger tapping test was included as a measure of motor speed. The mean number of taps was recorded over a 10 second period was recorded. Although this was measured using the dominant and non-dominant hand, only the number of taps with the dominant hand was used for correlations.

7.3.7.2 Renal involvement

The effect of renal involvement was assessed in two ways; first the scores on cognitive tasks were compared for the patients who had current or previous renal involvement (renal +) and those who had never had renal involvement (renal -). Secondly the renal- group was compared to healthy controls to see whether group differences identified in chapter 4, section 4.5.1.1 were still evident.
7.3.7.3 Hypertension

Blood pressure readings were taken from the patient’s medical notes. Patients were classified as having normal blood pressure (normotensive) if they were not on any anti-hypertensive treatment. Patients who were concurrently on anti-hypertensive treatment were placed in a hypertensive group, even if their blood pressure readings were normal at the time of testing. This classification has been used in previous studies (e.g. E. R. Smith, Nilforooshan, Weaving, & Tabet, 2011). The hypertensive patients were compared to normotensive patients. Secondly the normotensive group was compared to healthy controls so see whether group differences identified in chapter 4, section 4.5.1.1 were still evident.

7.4 Results

7.4.1 The relationship between mood and cognitive performance

Within the whole SLE group, there were significant correlations between both depression (HAD-D) and anxiety (SSAI) and SOP and compound RT domain t-scores. The cognitive impairment index (CII) also correlated with anxiety, but not HAD-D. None of the domains correlated with HAD-A.

These relationships were further assessed by splitting the SLE group. It was evident that the correlations between anxiety and cognitive performance were driven by a relationship in the NPSLE group. Although correlations did not reach significance due to sample size, the correlation coefficients ranged from $r=-.41$ to $r=-.51$ for the relationship between SSAI and the cognitive domain scores and from $r=-.29$ to $r=.52$ for HAD-A. HAD-D did not show a relationship with cognitive performance in the NPSLE group ($r<-.21$). The correlation coefficients can be seen in table 7.2.
<table>
<thead>
<tr>
<th></th>
<th>Memory</th>
<th>SOP</th>
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<th>Compound RT</th>
<th>CII</th>
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<tbody>
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<td>-.43**</td>
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<td>-.52</td>
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<td>-.51</td>
<td>-.50</td>
<td>-.41</td>
<td>.42</td>
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Table 7.2: The correlation coefficients for the relationship between depression (HAD-D) anxiety (HAD-A and SSAI) and cognitive performance.

* $p<0.05$; ** $p<0.01$

The scatter plot for relationship between SOP and anxiety in the NPSLE group is shown in figure 7.1. One NPSLE participant (P 7) is a clear outlier with low anxiety and low cognitive performance. Removal of this participant resulted in significant correlations between SSAI and all domains and CII, ranging from, $r(13)= -.58$; $p<0.05$ for memory to, $r(13)= -.79$; $p<0.001$ for SOP. There were also significant correlations between HAD-A and SOP, $r(13)= -68$, $p<0.05$, and executive control, $r(13)= -68$, $p<0.05$. The relationship with HAD-D remained non significant.
In the non-NPSLE group cognitive performance was not related to anxiety; $r < .17$ for all variables. In contrast, the observed correlations with depression in the overall group analysis were clearly driven by the non-NPSLE group. For the non-NPSLE patients, HAD-D significantly correlated with SOP $r(21) = -.43; p < 0.05$ and compound RT $r(21) = -.59; p < 0.01$ and approached significance for executive control $r(21) = -.40; p = 0.07$.

### 7.4.2 The relationship between perceived cognitive failures and cognitive performance

In the SLE group as a whole there was no significant correlation between CFQ total score and the CII, $r(35) = .25; p > 0.05$. Splitting the SLE group into subgroups did not change this; however figure 7.2 shows the scatter plot for this relationship in the NPSLE group. Again, the same participant (P 7) acts as an outlier with the highest cognitive impairment score, but the lowest score on perceived cognitive failures. Removal of this participant resulted in a significant correlation between these parameters, $r(13) = .57; p < 0.05$.

The relationship between CFQ memory and the memory domain t-score was also not significant in the SLE group as a whole, $r(35) = -.13; p > 0.05$. This was not affected by splitting the SLE group or removing the previously mentioned NPSLE participant.
7.4.3 The relationship between imaging parameters and cognitive performance

7.4.3.1 Diffusion Tensor Imaging

In the SLE group overall there was no relationship between imaging parameters and cognitive performance ($r < .22$). However, splitting the SLE group revealed a different pattern; within the NPSLE group there was a significant correlation between white matter FA and SOP, executive control and compound RT domain scores. The correlation with the CII did not reach significance but also has a large effect size ($r = .50$). Participants with lower white matter FA values (indicating reduced structural integrity) had worse performance on cognitive tasks. The correlation coefficients are displayed in table 7.3. There was no correlation with ADC.

In the non-NPSLE group the opposite pattern was seen; when controlling for age, better performance was associated with lower FA and higher ADC, and this reached significance for the relationship with executive control. However, controlling for NART removed this relationship.

Within the control group the relationship between compound RT and white matter FA was significant, $r(27) = .40$. $p < .05$, with higher FA values associated with better performance, i.e. the same pattern as in the NPSLE group. For the other domains the relationship was not significant with correlation coefficients smaller than $r = .20$.  

Figure 7.2: The relationship between cognitive impairment (CII) and perceived cognitive failures (CFQ total score) in the NPSLE group. One participant (P7) does not show the same relationship as the rest of the group. The regression line is for the NPSLE group excluding P7.
<table>
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<th>Executive control</th>
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<th>CII</th>
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<td>.26</td>
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<td>-.51*</td>
<td>-.28</td>
<td>.05</td>
</tr>
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</table>

Table 7.3: The correlation coefficients for the relationship between Diffusion Tensor Imaging Parameters and cognitive performance for the NPSLE and non-NPSLE groups.

* p<0.05; **p<0.01
ADC=Apparent Diffusion Coefficient – the extent of diffusion; FA=Fractional Anisotropy – directionality of diffusion; Memory, SOP, Executive control, Compound RT=domain t-scores; CII=Cognitive Impairment Index.

7.4.3.2 Voxel-based morphometry

In the SLE group as a whole there were several regions where grey or white matter volume showed a correlation with performance on cognitive domains. These displayed in figure 7.3 and 7.4, with the peak coordinates listed in table 7.4. Generally there was a large overlap between the domains, with all domains showing a relationship with grey matter in the left inferior temporal gyrus (figure 7.3a). Memory scores alone correlated with the volume of the right thalamus (figure 7.3b). The other domains all showed a correlation with an overlapping region in the left middle frontal gyrus (figure 7.3c). All domains had a relationship with a region of the post central gyrus, on the left for SOP, compound RT and executive control, and right for memory (figure 7.3d).

In the white matter SOP and compound RT scores correlated with white matter volume in a large region running from the sub-gyral frontal lobe to the parietal lobe (figure 7.4a and b). Executive control scores showed a relationship with a region in the sub-gyral left frontal lobe. All domains correlated with volume region of the left temporal lobe/occipital lobe border, with the peak in the temporal lobe for memory and executive control (figure 7.4c). Memory correlated with a cluster in the body of the corpus collosum, while compound RT correlated with volume on the splenium (figure 7.4d).
Figure 7.3: Grey matter regions that showed a significant relationship between volume and cognitive domain t-scores. Blue=memory, yellow=SOP, cyan=executive control, red=compound RT (CRT). Relationship between; (a) all domains and left inferior temporal gyrus, (b) memory showed and the right thalamus (c) CRT/SOP and bilateral middle frontal gyrus, executive control and left middle frontal gyrus, (d) CRT/SOP and left post central gyrus/parietal lobule, memory and right parietal lobule.

Figure 7.4: White matter regions that showed a relationship with cognitive domain t-scores. Blue=memory, yellow=SOP, cyan=executive control, red=compound RT (CRT). Relationship between; (a-b) CRT/SOP and bilateral sub-gyral white matter running from frontal to parietal lobe. Executive control and left sub-gyral frontal lobe, memory and right parietal lobe (c) all domains and sub-gyral temporal lobe (d) memory and body of corpus callosum, CRT and sphenium of corpus callosum.

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### Memory

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<td>(30, -48, 44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>3.4</td>
<td>(4, -16, 24)</td>
<td>$R$</td>
<td>Corpus collosum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Speed of processing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>348</td>
<td>4.4</td>
<td>(26, 15, 38)</td>
<td>$R$</td>
<td>Frontal lobe, sub-gyral</td>
</tr>
<tr>
<td>1065</td>
<td>3.8</td>
<td>(20, -10, 45)</td>
<td>$R$</td>
<td>Frontal lobe, sub-gyral/pre-central gyrus/</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(28, 32, 56)</td>
<td></td>
<td>post-central gyrus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(28, -32, 45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>325</td>
<td>3.7</td>
<td>(-32, -75, 10)</td>
<td>$L$</td>
<td>Occipital lobe, middle occipital gyrus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-28, -82, 6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>395</td>
<td>3.7</td>
<td>(-33, 6, 42)</td>
<td>$L$</td>
<td>Frontal lobe, sub-gyral/pre-central gyrus</td>
</tr>
<tr>
<td>105</td>
<td>3.6</td>
<td>(38, 2, 38)</td>
<td>$R$</td>
<td>Frontal lobe, pre-central gyrus</td>
</tr>
<tr>
<td>33</td>
<td>3.5</td>
<td>(27, -48, 42)</td>
<td>$R$</td>
<td>Parietal lobe, sub-gyral</td>
</tr>
<tr>
<td>35</td>
<td>3.4</td>
<td>(10, -18, -39)</td>
<td>$R$</td>
<td>Brain stem, pons</td>
</tr>
<tr>
<td>31</td>
<td>3.4</td>
<td>(22, 48, 18)</td>
<td>$R$</td>
<td>Frontal lobe, medial frontal gyurs</td>
</tr>
<tr>
<td>81</td>
<td>3.4</td>
<td>(9, -15, -18)</td>
<td>$R$</td>
<td>Brain stem, midbrain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Executive control</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>187</td>
<td>4.1</td>
<td>(-22, -66, 20)</td>
<td>$L$</td>
<td>Temporal lobe, sub-gyral</td>
</tr>
<tr>
<td>119</td>
<td>3.8</td>
<td>(-18, 14, 46)</td>
<td>$L$</td>
<td>Frontal lobe, sub-gyral/inferior frontal gyrus</td>
</tr>
<tr>
<td>44</td>
<td>3.3</td>
<td>(-18, -76, 2)</td>
<td>$L$</td>
<td>Occipital lobe, middle occipital gyrus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Compound reaction time</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2893†</td>
<td>4.6*</td>
<td>(21, -9, 44)</td>
<td>$R$</td>
<td>Frontal lobe/parietal lobe, sub-gyral</td>
</tr>
<tr>
<td>3.9</td>
<td>(26, 14, 38)</td>
<td>$R$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.8</td>
<td>(27, -32, 44)</td>
<td>$R$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3463†</td>
<td>4.0</td>
<td>(-28, -2, 34)</td>
<td>$L$</td>
<td>Frontal lobe/parietal lobe, sub-gyral</td>
</tr>
<tr>
<td>3.9</td>
<td>(-26, 4, 40)</td>
<td>$L$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.7</td>
<td>(-28, -38, 50)</td>
<td>$L$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>297</td>
<td>3.9</td>
<td>(0, -39, 21)</td>
<td></td>
<td>Corpus callosum</td>
</tr>
<tr>
<td>247</td>
<td>3.8</td>
<td>(-28, -82, 6)</td>
<td>$L$</td>
<td>Occipital lobe, middle occipital gyrus</td>
</tr>
<tr>
<td>3.6</td>
<td>(32, -69, 9)</td>
<td>$L$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>3.7</td>
<td>(14, -21, -39)</td>
<td>$R$</td>
<td>Brain stem, pons</td>
</tr>
<tr>
<td>41</td>
<td>3.6</td>
<td>(22, 50, 18)</td>
<td>$R$</td>
<td>Frontal lobe, sub gyral</td>
</tr>
</tbody>
</table>
Table 7.4: Grey and white matter regions that showed a significant relationship with cognitive domain t-scores. \( K_E \) represents the number of 1.5x1.5x1.5 voxels in the cluster. Significant clusters at \( p<0.001 \) have been reported.

<table>
<thead>
<tr>
<th>( K_E )</th>
<th>( Z )</th>
<th>MNI coordinates</th>
<th>Side</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>81</td>
<td>3.6</td>
<td>(26, -50, 44)</td>
<td>( R )</td>
<td>Parietal lobe, sub-gyral/precuneus</td>
</tr>
<tr>
<td>82</td>
<td>3.5</td>
<td>(-16, -32, 9)</td>
<td>( L )</td>
<td>Sub-lobar, extranuclear</td>
</tr>
<tr>
<td>83</td>
<td>3.4</td>
<td>(12, -16, -21)</td>
<td>( R )</td>
<td>Brain stem, midbrain</td>
</tr>
<tr>
<td>251</td>
<td>3.4</td>
<td>(-32, 54, 27)</td>
<td>( L )</td>
<td>Parietal lobe, sub-gyral</td>
</tr>
<tr>
<td>34</td>
<td>3.3</td>
<td>(34, -56 ,26)</td>
<td>( R )</td>
<td>Temporal lobe, sub-gyral</td>
</tr>
</tbody>
</table>

† This also reached cluster level family-wise error corrected significance.

To clarify these relationships, similar analyses were conducted for the control group, and for the SLE group separated into NPSLE and non-NPSLE. There were no regions that correlated with cognitive performance in the control group. Significant regions of correlation between white matter volume and SOP and compound RT remained in the NPSLE group, but not the non-NPSLE group. Memory and executive control correlations did not remain in either group. In the grey matter there were regions in which volume correlated with cognitive scores emerged in both patient groups, but these did not overlap with each other or with the whole group correlations.

7.4.4 The relationship between clinical factors and cognitive performance

7.4.4.1 Disease and health related factors

The cognitive impairment index (CII) showed a significant relationship with physical health \( r(35)= -.35; p<0.05 \), fatigue, \( r(35)= -.35; p<0.05 \), and pain, \( r(35)= -.44; p<0.01 \) in the SLE group as a whole. There was no correlation with either disease activity \( r(37)=.19; p>0.05 \) or disease duration \( r(37)=.19; p>0.05 \).

Splitting the SLE group indicates that within the NPSLE group the only significant relationship was between CII and SLEDAI score, with higher disease activity associated with greater impairment \( r(15)=.54; p<0.05 \). However, the highest SLEDAI score was eight, which indicates low disease activity.
The correlation coefficients displayed in table 7.5 suggest the relationship with physical health, fatigue and pain were driven by relationships in the NPSLE group, though with a small sample these did not reach significance. Figure 7.5 shows the scatter plot for the relationship between fatigue and pain and cognitive impairment. Again, one participant (P 7 - the same outlying participant mentioned in earlier sections) does not show the same pattern as the rest of the NPSLE group. Removal of this participant resulted in the correlation with CII reaching significance for physical health, r(13)=.60; p<0.05, fatigue r(13)= -.70; p<0.01 and pain, r(13)= -.76; p<0.01. None of the clinical factors showed a significant correlation with CII in the non-NPSLE group.

Looking at the individual cognitive domains, in the NPSLE group with P7 excluded, the domain t-scores all showed medium to large (r=.34 to r=.68) correlations with fatigue and pain. This reached significance for the correlation between fatigue and SOP and memory, and between pain and SOP and compound RT.
7.4.4.2 Serology

The relationship between erythrocyte sedimentation rate (ESR), complement levels (C3 and C4) and anti double-stranded DNA antibodies (anti-dsDNA) and cognitive performance was assessed. There was no significant correlation between any of these measures and scores on cognitive assessment, either in the SLE group together or separate subgroups.

Ten participants were positive for anti-Ro antibodies at the time of testing. There were no group differences in age (anti-Ro+ mean age=46.3±10.9, anti-Ro- mean age=44.1±13.4; U=149.5, p=0.62) or NART errors (anti-Ro+ mean=16.7±9.0, anti-Ro- mean=20.2±8.0; U=104, p=0.29). Figure 7.6 presents the mean domain t-scores with the patient group split by anti-Ro antibody status. Comparing the two groups revealed no significant differences on domain t-scores or on the cognitive impairment index. Comparing the anti-Ro- patients to healthy control revealed significant differences remained on all domains, t(53)>2.07, p<0.05, r >.27, except compound RT. Group differences still remained, F(2,51)=5.83, p<0.01 after separating the anti-Ro- group into NPSLE (n=11) and non-NPSLE (n=16) subgroups.

Figure 7.6: The cognitive domain t-scores, for healthy controls and SLE group separated into anti-Ro positive and anti-Ro negative patients. Error bars ±1 standard error.

SOP=speed of processing; EC=executive control; CRT=compound RT.

Six participants were positive for anti-cardiolipin antibodies (aCL). These all had low positive results, with a median titre of 24 IgG Phospholipid units/mL. A further three participants were included in the APS+ group due to clinical symptoms and the APS- group contained the remaining 28 SLE patients. There were no group differences in age (APS+ mean age=44.3±13.6, APS- mean age=44.8±12.6, Mann-Whitney U=127, p=0.97) or NART errors (APS+ mean=20.9±7.8, APS- mean=18.7±8.5; U=150, p=0.39). The mean domain t-scores split by APS
status are displayed in figure 7.7. There were no significant differences between groups on any domains (U=117, \( p=.75 \), for memory and compound RT; U=129, \( p=.92 \), for SOP and executive control). Using the cognitive impairment index (CII), a greater proportion of APS+ (55.6%) compared to APS- (39.3%) were classified as showing cognitive impairment (CII scores of 4 or greater). This difference also did not reach statistical significance \( \chi^2(1)=.74, p=0.35 \).

A second analysis was conducted comparing the APS- participants to the healthy controls. The APS- group had lower scores on all domains, and this was significant for SOP \( t(53)=2.64, p<0.05, r=.34 \), executive control \( t(54)=2.67, p<0.01, r=.34 \) and compound RT \( t(53)=2.40, p<0.05, r=.26 \) but not memory \( t(54)=1.85, p=0.07, r=.24 \). However splitting the APS- SLE group into NPSLE (n=10) and non-NPSLE (n=18) subgroups revealed a significant difference on all measures including memory, \( F(2,52)=4.33, p<0.05 \), with post hoc tests indicating that the NPSLE group differed significantly from the controls.

![Figure 7.7: Cognitive Domain t-scores](image)

7.7: The cognitive domain t-scores, for healthy controls and SLE group separated into Anti-Phospholipid syndrome positive (APS+) and anti- Phospholipid syndrome negative (APS-) patients. Error bars ±1 standard error.

SOP=speed of processing; EC=executive control; CRT=compound RT.

### 7.4.4.3 Corticosteroid use

Overall 22 participants were in the no steroid group (59%), 10 were in the low dose group (27%) and 5 were in the high dose group (14%). There were no group differences on age, \( H(2)=0.18, p=0.92 \), or NART error scores, \( H(2)=0.19, p=0.91 \). The mean scores for the four cognitive domains are shown in figure 7.8. The SLE groups had lower mean scores than the control group on all four domains, and had similar scores to each other for speed of processing, executive control and compound RT. The high steroid group showed a lower mean
score on the memory domain than the other two groups. This was compared using a Kruskal Wallis test (due to the small numbers in the steroid groups). The overall group comparison for the memory domain reached significance $H(2)=6.33$, $p<0.05$, however none of the group differences were significant on post hoc tests. Group comparisons on the other three domains were all non significant, as was the difference on the cognitive impairment index.

![Figure 7.8](image_url)

Figure 7.8: The cognitive domain t-scores, for healthy controls and SLE group separated by current steroid dose (no steroid, <10 mg of Prednisolone per day and >10 mg per day). Error bars ±1 standard error.

SOP=-speed of processing; EC=executive control; CRT=compound RT.

7.4.5 Comparison with illness controls

7.4.5.1 Mental health and well being

The mean scores for depression (HAD-D), anxiety (HAD-A and SSAI), perceived cognitive failures (CFQ) and quality of life mental component score (SF-36 MCS) and physical component score (SF-36 PCS) are shown in table 7.5. There were significant group differences on HAD-D, $F(3,26)=11.41$; $p<0.001$, $\omega=.47$, CFQ, $F(3,69)=6.74$; $p<0.001$, $\omega=.44$, the SF-36 MCS, $F(3,27)=27.86$; $p<0.001$, $\omega=.61$ and PCS, $F(3,26)=58.35$; $p<0.001$, $\omega=.74$. All three patient groups had higher scores on HAD-D than healthy controls, but did not differ from each other; all three patient groups had lower scores on SF-36 MCS than healthy controls but did not differ from each other; the non-NPSLE and illness controls had significantly lower scores on the SF-36 PCS than controls, but significantly higher scores than the NPSLE group. The CFQ did not show the same pattern as the non-NPSLE group had significantly higher scores than the healthy controls on post hoc tests, whereas the illness controls did not. However, the two groups had
very similar mean scores and standard deviations, suggesting this reflected the small sample in
the illness control group rather than a meaningful difference between these two groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Healthy Controls (27)</th>
<th>Illness controls (11)</th>
<th>Non-NPSLE (21)</th>
<th>NPSLE (14)</th>
<th>Group differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAD-D</td>
<td>1.96 (2.16)</td>
<td>5.82 (5.27)</td>
<td>6.24 (3.43)</td>
<td>6.86 (4.77)</td>
<td>1 &lt;2,3,4</td>
</tr>
<tr>
<td>HAD-A</td>
<td>5.67 (3.70)</td>
<td>7.18 (6.03)</td>
<td>8.81 (4.79)</td>
<td>7.00 (3.92)</td>
<td>n.s.</td>
</tr>
<tr>
<td>SSAI</td>
<td>32.32 (5.42)</td>
<td>40.27 (14.60)</td>
<td>35.12 (7.90)</td>
<td>39.64 (11.91)</td>
<td>n.s.</td>
</tr>
<tr>
<td>CFQ</td>
<td>33.30 (9.67)</td>
<td>46.45 (20.35)</td>
<td>46.76 (17.06)</td>
<td>56.64 (21.30)</td>
<td>1&lt;3,4</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>80.22 (10.73)</td>
<td>49.45 (24.82)</td>
<td>55.62 (21.94)</td>
<td>43.86 (13.61)</td>
<td>1&gt;2,3,4</td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>82.81 (9.58)</td>
<td>56.64 (25.65)</td>
<td>55.14 (23.37)</td>
<td>29.79 (13.76)</td>
<td>1&gt;2,3&gt;4</td>
</tr>
</tbody>
</table>

Table 7.6: Mean (sd) scores for illness controls on measures of mental health and wellbeing.

Hospital Anxiety and Depression scale depression (HAD-D) and anxiety (HAD-A) subscales, Spielberger
State Anxiety Inventory (SSAI), Cognitive Failures Questionnaire (CFQ), and Short-Form 36 Mental
Component Score (SF-36 MCS) and Physical Component Score (SF-36 PCS)

7.4.5.2 Cognitive performance

Using the Cognitive impairment index (CII) 0% of the illness controls were classified as
impaired (CII ≥ 4). This compared to 17.9% of healthy controls, 27.1% of non-NPSLE
participants and 66% of NPSLE participants. The mean (± standard deviation) score was
1.64±1.03 for the illness controls, compared to 1.79±2.0 for healthy controls, 2.41±2.20 for
non-NPSLE and 5.4±3.29 for the NPSLE group. On statistical testing ($\chi^2$ test for proportion
impaired and Kruskall-Wallis for CII scores) there were significant group differences
($\chi^2(3)=15.7, p<0.001$; $H(3)=16.2, p<0.001$), and on post hoc test the NPSLE group had
significantly higher scores, and a higher proportion impaired than the other groups, which did
not differ from each other.

Estimated marginal mean (NART as a covariate) cognitive domain t-scores split by group are
shown in figure 7.9. There were significant group differences on all four domains; $F(3,71)=4.55$;
p<0.01, $\omega=.33$ for memory, $F(3,71)=4.79$; p<0.01, $\omega=.33$ for SOP, $F(3,71)=4.59$; p<0.01, $\omega=.30$
for executive control and $F(3,71)=3.48$; p<0.05, $\omega=.29$ for compound RT. On post hoc tests the
illness controls did not differ significantly from the other groups, including the NPSLE group,
whereas the non-NPSLE group had significantly higher scores than the NPSLE group for
memory and SOP. The group comparisons between illness controls or non-NPSLE and NPSLE group had similar effect sizes ($r=.32$ versus $.29$ for memory and $r=.29$ versus $.29$ for SOP), suggesting the lack of a significant difference between illness controls and NPSLE participants was due to the small numbers in these groups.

![Figure 7.9: Mean domain t-scores for healthy controls, illness controls, non-NPSLE and NPSLE participants. Error bars± 1 standard error.](image)

SOP=speed of processing; EC=executive control; CRT=compound RT.

### 7.2.5.3 Diffusion Tensor Imaging data

The mean ADC and FA values for white matter, grey matter and whole brain are shown in table 7.7. The illness controls had similar values to the healthy controls for all parameters. In chapter 6, section 6.5.1, significant group differences were found on white matter mean ADC and peak location, and whole brain mean ADC and peak location. These remained significant with the illness controls included in the ANOVA; $F(3,66)=3.09$, $p<0.05$, for white matter mean ADC, $F(3,66)=2.94$, $p<0.05$, for white matter ADC peak location, $F(3,66)=3.83$, $p<0.05$ for whole brain mean ADC and $F(3,66)=3.12$, $p<0.05$ for whole brain ADC peak location. On post hoc tests the illness controls did not differ from any of the other groups, although the difference between the NPSLE group and illness controls on whole brain ADC peak location approached corrected significance ($p=0.066$).
Table 7.7: Mean (sd) scores for ADC and FA (Fractional Anisotropy) for illness controls, split into WM (white matter), GM (grey matter) and WB (whole brain).

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls (n=27)</th>
<th>Illness controls (n=9)</th>
<th>Non-NPSLE (n=21)</th>
<th>NPSLE (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WM mean ADC</td>
<td>738.6 (15.2)</td>
<td>740.0 (17.9)</td>
<td>749.0 (18.2)</td>
<td>756.2 (26.9)</td>
</tr>
<tr>
<td>WM mean FA</td>
<td>.373 (.02)</td>
<td>.372 (.01)</td>
<td>.372 (.02)</td>
<td>.365 (.02)</td>
</tr>
<tr>
<td>GM mean ADC</td>
<td>918.7 (39.3)</td>
<td>917.7 (37.8)</td>
<td>940.3 (47.9)</td>
<td>938.3 (42.2)</td>
</tr>
<tr>
<td>WB mean ADC</td>
<td>817.0 (24.1)</td>
<td>815.5 (20.2)</td>
<td>836.3 (25.5)</td>
<td>834.7 (32.9)</td>
</tr>
<tr>
<td>WB mean FA</td>
<td>.266 (.01)</td>
<td>.268 (.02)</td>
<td>.257 (.02)</td>
<td>.260 (.01)</td>
</tr>
</tbody>
</table>

7.4.6 Confounding variables

7.4.6.1 The relationship between cognition and finger tapping

In the combined SLE group there was a significant correlation between finger tapping in the dominant hand and SOP, \( r(36)=.63, p<0.001 \) and compound RT, \( r(36)=.50, p<0.01 \). Separating into NPSLE and non-NPSLE subgroups revealed the relationship was stronger in the non-NPSLE participants; \( r(21)=.82, p<0.001 \) (non-NPSLE) compared to \( r(15)=.48, p=0.07 \) (NPSLE) for SOP and \( r(21)=.62, p<0.01 \) (non-NPSLE) compared to \( r(15)=.37, p=0.18 \) (NPSLE) for compound RT. In the control group the correlation was \( r(27)=.19, p=.34 \) for both domains. Figure 7.10 shows the scatter plot for the correlation between finger tapping and SOP.

![Figure 7.10: The relationship between finger tapping and speed of processing (SOP) domain t-score in the NPSLE (plusses), non-NPSLE (open circles) and control (black dots) groups.](image)

However, correlations were also evident between finger tapping and memory, \( r(36)=.60, p<0.001 \), and executive control, \( r(36)=.47, p<0.01 \). The majority of tasks within these domains...
did not require written responses. This suggests that there are other variables that may be related to both finger tapping and cognitive tasks.

### 7.4.6.2 Renal involvement

Five patients had either current (n=1) or previous (n=4) renal involvement (renal+) in their SLE. There were no significant group differences on age or NART, (mean age: 38.6±16.4 compared to 45.6±12.0, U=56, \( p=0.29 \)) (NART errors: 23.6±6.0 compared to 18.6±8.5, U=122, \( p=0.16 \)). The mean domain t-scores are shown in figure 7.9. There were no significant differences between renal+ and renal- participants.

![Figure 7.11: The cognitive domain t-scores, for healthy controls and SLE group separated into current or previous renal involvement (renal+) and no renal involvement ever (renal-). Error bars ±1 standard error. SOP=speed of processing; EC=executive control; CRT=compound RT.](image)

The mean domain t-score for renal- participants are shown in table 7.8 along with the effect sizes for the comparison with healthy controls. There were significant group differences on all domains, and effect sizes were slightly larger than the group comparisons involving all SLE participants. These were all medium effects (\( r = .27 \) to .40).

### 7.4.6.3 Hypertension

One participant had raised blood pressure (taken from notes) around the time of cognitive testing. However, approximately 25% (9/37) of patients were on anti-hypertensive drugs. The groups were well matched on age, (hypertensive mean age=43.6±12.7, normotensive mean age=45.0±12.9; U=123, \( p=0.93 \)) and NART errors (hypertensive mean=19.2±9.3, normotensive mean=19.3±8.1; U=134, \( p=0.79 \)).
Figure 7.12 shows the mean scores for the four cognitive domains with the SLE patients split into normotensive and those on antihypertensive medication (labelled hypertensive). The hypertensive patients had lower scores on the memory domain, but equivalent scores on the other domains.

Figure 7.12: The cognitive domain t-scores, for healthy controls and SLE group separated into normotensive or hypertensive. Error bars ±1 standard error.

SOP=speed of processing; EC=executive control; CRT=compound RT.

The mean domain t-scores and effect sizes for the comparisons between the normotensive participants and the control group are displayed in table 7.8, along with the data for all SLE participants. Removing the patients on antihypertensive drugs increased the effect sizes slightly for speed of processing, executive control and compound RT, but removed the significant difference between patients and controls for the memory domain. Using the cognitive impairment index (CII) instead of the domains scores resulted in the same finding; there were still significant group differences between the SLE group and controls when patients with renal involvement or on anti-hypertensive drugs were removed.
Table 7.8: Mean domain t-scores for healthy controls and all SLE, renal- only, and normotensive only.
Effect sizes (r) for the t-test comparison for the SLE groups with controls

\* p<0.05; **p<0.01 (t-test comparison with healthy controls)
† SLE renal - no current or previous renal involvement
‡ SLE normotensive=normal blood pressure and not on anti-hypertensive drugs.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=28)</th>
<th>SLE all (n=37)</th>
<th>SLE renal-† (n=32)</th>
<th>SLE normotensive‡ (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>53.56</td>
<td>47.28* r=.24</td>
<td>47.45* r=.27</td>
<td>48.01 r=.18</td>
</tr>
<tr>
<td>SOP</td>
<td>53.75</td>
<td>46.84* r=.30</td>
<td>47.55** r=.40</td>
<td>46.95* r=.34</td>
</tr>
<tr>
<td>Executive control</td>
<td>53.93</td>
<td>46.81* r=.30</td>
<td>47.17* r=.37</td>
<td>46.37* r=.33</td>
</tr>
<tr>
<td>Compound RT</td>
<td>53.19</td>
<td>46.95* r=.26</td>
<td>47.76** r=.32</td>
<td>46.62* r=.36</td>
</tr>
</tbody>
</table>

7.5 Discussion

In the whole SLE group, there were significant correlations between cognitive performance and depression, anxiety, pain, fatigue and physical health. Significant correlations between cognitive function and depression and anxiety have previously been shown in SLE (Hay, 1994; Monastero, et al., 2001). Separating the SLE group into NPSLE and non-NPSLE subgroups revealed a different pattern of correlations, and therefore the subgroup relationships will be further discussed.

7.5.1 Mood, fatigue and pain

The relationships between cognitive performance and anxiety, fatigue, pain and physical health did not reach statistical significance in either the NPSLE or non-NPSLE group. However, the correlation coefficients suggested the correlations in the SLE group as a whole were driven by a relationship in the NPSLE group, and these relationships were significant with the removal of one outlying participant. Fatigue, pain and physical health also correlated with CII, and fatigue with the individual domains of SOP and memory, and pain with SOP and compound RT. Finally scores on the cognitive failures questionnaire (CFQ) also correlated with CII. Within the non-NPSLE the only significant correlations were between depression and SOP and compound RT.
These results partially support Kozora et al. (2006), who also found significant correlations between cognitive impairment and fatigue, pain and perceived cognitive failures in the NPSLE group, but not the non-NPSLE group. Kozora et al. (2006) suggest that there are multiple behavioural problems in NPSLE that may be associated. The authors do not speculate on how these may be linked, but one interpretation could be that they are driven by underlying changes in central nervous system integrity as these behavioural problems were only linked in NPSLE. The current data differs from Kozora et al. (2006) in two ways, firstly significant correlations were found in the NPSLE group between cognitive performance and anxiety, rather than depression. Kozora et al. (2006) did not measure anxiety, so it is uncertain whether they would also have found a relationship. It may be that the multiple linked behavioural problems in NPSLE relate to emotional disturbance rather than depression specifically.

A second discrepancy was the finding of a significant correlation between SOP and compound RT and depression in the current non-NPSLE sample. Although other studies have found this relationship in combined SLE groups, Kozora and colleagues (2006, 2008) suggest no such relationship in non-NPSLE, and this is also supported by other non significant findings (Sabbadini, et al., 1999). However, depression in general has been associated with poor cognitive function (Austin, Mitchell, & Goodwin, 2001). It could be that the relationship in the present thesis reflects a general link between depression and cognition in this non-NPSLE sample that may be separate from their SLE.

7.5.2 Correlation with disease activity

Within the NPSLE group, there were significant correlations between cognition and disease activity (SLEDAI score) and white matter FA, but not ADC. Although previous studies have identified disease activity as a predictor of later cognitive impairment (Gladman, et al., 2000; Mikdashi & Handwerger, 2004), studies have tended to find no relationship between current disease activity and cognitive function (Glanz, Schur, Lew, & Khoshbin, 2005; Hanly, Fisk, Sherwood, & Eastwood, 1994; Kozora, Arciniegas, et al., 2008; Kozora, et al., 2007; Maneeton, Maneeton, & Louthreno, 2010; Monastero, et al., 2001). One study has shown an association between cognitive impairment and SLEDAI scores (Kozora, et al., 2006). However, in this study both the NPSLE and non-NPSLE participants showed a relationship between these variables, whereas in the current study a relationship was only evident in the NPSLE group. In the imaging chapter of this thesis there was also a relationship between SLEDAI scores and imaging
parameters in the NPSLE group. This was interpreted as indicating low grade cerebral inflammation even outside of a significant disease flare. The relationship with cognitive impairment may be the clinical consequence of this.

7.5.3 The relationship with Diffusion Tensor Imaging

In the NPSLE group, white matter FA showed a significant correlation with cognitive function, with lower FA associated with worse cognitive performance. FA is a measure of brain structural integrity; in directional fibres, such as white matter, FA is high as diffusion is easier along the fibre (axial diffusion) rather than across it (radial diffusion). Destruction of biological barriers to diffusion may result in an increase in radial diffusion, and therefore a decrease in the FA value of the tissue. The correlation between white matter FA and cognitive function has not previously been revealed in SLE, but FA has been shown to correlate with cognitive function in patients with multiple sclerosis (MS) (Hecke, et al., 2010) and across the adult lifespan (Bendlin, et al., 2010; Kennedy & Raz, 2009). These, and other studies, have also found significant correlations between cognition and ADC, or the extent of diffusion, which did not correlate significantly in the current data. However, the relationship between ADC and compound RT and SOP approached significance, with correlation coefficients of around $r=-.50$, which is a large effect size. The non-NPSLE group did not show a relationship between cognitive function and either FA or ADC.

Correlations were evident between FA and SOP, executive control and compound RT but not the memory domain. Previous studies have shown an association between white matter DTI parameters and processing speed, executive functions and episodic memory (Bendlin, et al., 2010; Kennedy & Raz, 2009). However, although Bendlin et al. (2010) found associations between DTI parameters and some episodic memory tasks, they found no association with the Rey Auditory Verbal Learning Test – the test that is incorporated in the current memory domain. Additionally, Kennedy & Raz. (2009) only found correlations with memory in central white matter regions, whereas correlations with working memory and executive function tasks were more widespread. This suggests a relationship may have been evident with memory if regionally specific DTI measures had been used and that other tasks may involve more diffuse brain regions and therefore better relate to global measured of white matter integrity.
7.5.4 Cognitive function and brain volume

Several regions emerged that showed a correlation between grey and white matter volume and cognitive domains scores. These regions were generally overlapping for all domains, which probably reflects the high correlation between the domain t-scores and were spread across the temporal, frontal and parietal lobes. One previous study also correlated VBM with cognitive performance and showed attention, memory and the number of domains impaired all correlated with volume loss in the grey and white matter of the frontal, parietal and temporal lobes (Appenzeller, Bonilha, et al., 2007). These regions did generally overlap with those shown in the current study, but also extended beyond them. However, Appenzeller et al. (2007) also found more extensive atrophy in general in their SLE group, which could explain the greater correlation with cognition.

In the grey matter, significant correlations were found in the left the inferior temporal lobe for all domains, the left frontal lobe executive control, SOP and compound RT and the right parietal lobule and thalamus for memory. Many of the tasks included in the executive control domain can be considered “frontal” tasks which could explain the relationship. Memory models suggest a role for the anterior thalamus in episodic memory, with extensive links between the thalamus and hippocampal system (Aggleton & Brown, 1999). More extensive clusters were found in the white matter for the correlation with SOP and compound RT than memory or executive control. These clusters ran through the sub-gyral white matter from the frontal lobe to occipital lobe bilaterally. Investigating the relationship in the control group, and in the SLE subgroups suggests, (1) these were not general correlations as similar ones were not found in the control group (2) they were driven by a relationship in the NPSLE group.

7.5.5 Serology

The APS+ patients performed worse on all domains than the APS- participants and a greater proportion were classed as impaired, although these differences did not reach significance. There were still significant differences in cognitive function between the SLE participants and controls with the APS+ participants removed. Previous studies have indicated that APS is associated with cognitive deficits in SLE (Stojanovich, et al., 2007). The present data suggests there are also deficits in patients without any evidence of APS.
7.5.6 Corticosteroid use

The SLE participants who were currently on a high dose of corticosteroid (>10 mg per day) performed worse on all domains than those on a low dose or no steroids, and this was significant for the memory domain. This supports previous studies that indicate a link between corticosteroid use and memory deficits in animal models (McEwen, 2000) and humans (Brown, et al., 2004; de Quervain, et al., 2000; Keenan, et al., 1996; Young, et al., 1999). Current steroid use rather than previous use showed this association, which supports one study that suggested acute steroid use accounted for differences between patients and controls (Coluccia, et al., 2008). In SLE, cumulative steroid dose has been related to hippocampal atrophy (Appenzeller, et al., 2006) but current steroid dose has generally not been related to cognitive impairment (Carbotte, et al., 1986; Carломagno, et al., 2000; Kozora, Arciniegas, et al., 2008; Lapteva, et al., 2006; Maneeton, et al., 2010; Monastero, et al., 2001). One possibility for this discrepancy is that these studies looked at overall cognitive impairment rather than memory specifically. The difference did not appear to be titrated by dose, as the participants on a low dose of steroids (<10 mg per day) actually performed better on the memory domain than the patients not taking any steroids. This is supported by one study that showed no difference in memory performance between participants receiving a low dose of cortisol (40 mg/day – equivalent to 10 mg/day prednisone) or placebo, but large differences in the group receiving a high dose (160 mg/day – equivalent to 40 mg/day prednisone). However, caution should be used in interpreting this finding, as only five participants were on a high corticosteroid dose at the time of testing. Nonetheless of these, 80% had t-scores less than 40 on the memory domain.

7.5.7 Illness controls

The illness control group predominantly consisted of rheumatoid arthritis (RA) patients. These patient groups have not previously been compared on DTI parameters. However, differences in brain metabolism have been identified in RA patients using spectroscopy (Emmer, et al., 2009). There have been mixed results on previous studies comparing SLE and RA patients on cognitive measures, with some indicating no differences (Antonchak, Saoudian, Khan, Brunner, & Luggen, 2011; Hanly, et al., 2010) whilst others found greater impairment in the SLE group (Tomietto, et al., 2007). These have not directly compared patients with NPSLE and RA, which could explain the differences in findings.
The illness controls showed significantly higher depression score than healthy controls and lower quality of life. The three patient groups (NPSLE, non-NPSLE and illness controls) showed similar levels of depression, anxiety and perceived cognitive failures, and similar values on the SF-36 mental component score. The illness controls showed no evidence of differences from healthy controls on DTI parameters or cognitive function, with no participants classed as impaired. In contrast the NPSLE group had significantly lower scores than healthy controls on all cognitive domains, and increased ADC. This suggests that deficits identified in the NPSLE group are more than just a response to being ill, or of mood disturbances.

7.5.8 Confounding variables

7.5.8.1 Finger tapping test

The finger tapping test showed significant correlations with both SOP and compound RT in the SLE group, with slower mean tapping speed associated with worse performance. This effect was stronger in the non-NPSLE participants, but the correlation also had a medium effect size in the NPSLE group. The control group showed no relationship between these parameters. This suggests some of the difference in performance on these domains may relate to the motor components of making a manual response. However, finger tapping also showed a significant relationship with the memory and executive control domains, which did not have a manual response. This suggests there may be other factors that correlate with finger tapping and cognition, rather than motor speed having a direct causal effect.

7.5.8.2 Renal involvement

Removal of the renal+ patients increased the effect size for the comparison between SLE group and controls, indicating group differences were unlikely to be due to the presence of the renal+ participants.

7.5.8.3 Hypertension

The hypertensive participants performed worse than the normotensive participants on memory domain. Exclusion of these participants increased the effect size for the comparison with controls on SOP, executive control and compound RT, but removed the significant
difference for the memory domain. Hypertension typically contributes to cognitive decline through vascular changes/disease. The characteristic profile of vascular cognitive impairment involves deficits in attention and executive functions, with slowed information processing, whilst episodic memory is relatively spared (O’Brien, et al., 2003). Additionally, the hypertensive group were relatively young, with no evident of hypertensive disease, such as nephropathy, retinopathy or ischemic heart disease. Therefore, it appears unlikely that cognitive deficits in the SLE group were due to the presence of the hypertensive patients, although it can’t totally be excluded as a possibility for the memory domain.

7.6 Summary

(1) In the NPSLE group there were significant correlations between cognitive performance and white matter FA and disease activity. Correlations were also evident with state anxiety, pain, fatigue and physical health with one outlying participant removed.

(2) In the non-NPSLE group there was a significant correlation between speed of processing and compound RT and depression. No other correlations were evident with clinical, imaging or mood variables.

(3) Patients with antiphospholipid syndrome had worse performance on all cognitive domains, however there were still significant differences in cognitive function between the anti-phospholipid negative SLE patients and healthy controls.

(4) The patients with a high current corticosteroid dose performed worse than those on a low dose or no steroid on the memory domain.

(5) Comparisons with illness controls revealed similar scores on mental health and wellbeing for the patient groups. The illness controls showed no evidence of changes on DTI measures, or cognitive impairment.

(6) There was some evidence that confounding variables (finger tapping and hypertension) influenced cognitive performance. However, it is unlikely these factors account for all differences identified between NPSLE patients and controls.
NPSLE presents a diagnostic challenge as it is not clear to what extent subtle psychiatric manifestations, such as cognitive dysfunction, depression and anxiety are direct consequences of SLE disease activity or are secondary responses to chronic illness or treatment with corticosteroids. A second issue that arises is whether the NPSLE and non-NPSLE patients form two distinct groups, or whether they show a continuum of severity of CNS involvement with subclinical involvement in non-NPSLE.

There were three main aims of the study. The first was to identify differences between SLE patients and controls in terms of cognitive performance, psychology and imaging. This was addressed by recruiting a group of patients with a diagnosis of SLE and a group of age matched healthy controls and comparing them on measures of mental health and wellbeing, a broad cognitive test battery and on quantitative imaging measures. The second aim of the research was to investigate the extent to which the differences from controls were specific to those with neuropsychiatric manifestations of SLE (NPSLE). This was addressed by separating the SLE group into those who had a current or previous neuropsychiatric manifestation of SLE (as defined by the ACR (ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999a)) and those who had not (non-NPSLE). These two subgroups were then compared to each other and to controls on all the above measures. The third aim of the study was to investigate the relationship between cognitive performance and the clinical, emotional and imaging parameters. The correlation between these factors was considered for the NPSLE and non-NPSLE groups separately to see whether these groups showed different correlates of cognitive function. These were also assessed in the SLE group as a whole, along with the effect of possible confounds such as hypertension, renal involvement and motor speed. Additionally, to address the question of whether observed changes were specific to SLE or related to chronic illness in general, a group of illness controls were recruited and compared to the other groups on all measures.
8.1 The difference between the SLE patients and controls

The SLE group as a whole scored significantly higher than controls on measures of depression, anxiety and perceived cognitive failures, and lower on quality of life. The largest effect sizes were for physical health related quality of life and depression. On cognitive assessment, the SLE group performed worse than the healthy controls across multiple domains (memory, speed of processing, executive control and compound reaction time). These differences had small to medium effect sizes ($r=.24$ to $.30$) which were of similar magnitude to average effect sizes across previous studies (Benedict, et al., 2008). On quantitative imaging measures, group differences emerged on white matter Apparent Diffusion Coefficient (ADC - extent of diffusion) and whole brain ADC. There were no differences in the grey matter, no differences on Fractional Anisotropy (FA-directionality of diffusion) and no differences on Magnetisation Transfer Imaging. Voxel-based morphometry analysis of brain volume revealed a few diffuse areas of reduced grey and white matter volume. Overall this indicates the presence of mild cognitive impairment and mood disorders in SLE, and suggests there may be concurrent damage to brain parenchyma.

8.2 Differentiation between the NPSLE and non-NPSLE groups

In chapter 3, the NPSLE and non-NPSLE groups did not differ on depression, anxiety, overall perceived cognitive failures or mental health aspects of quality of life. The NPSLE group had significantly reduced quality of life on physical health aspects of quality of life and reported more cognitive failures relating to memory. Both the NPSLE and non-NPSLE groups had significantly higher depression scores that controls, and lower quality of life. This indicates that on measures of mental health and wellbeing there is not a significant differentiation between the groups.

In chapter 4, the NPSLE group had significantly lower scores than controls on all four domains of the test battery. They also had lower scores than the non-NPSLE participants on the memory and speed of processing domains. The non-NPSLE group did not differ from controls on any domain or on any individual task. In the categorical analysis the NPSLE group had significantly higher scores of global impairment and a significantly higher proportion were classed as showing cognitive impairment than both other groups. This suggests that on cognitive tasks there is a difference between the NPSLE and non-NPSLE patients. It is still
possible that performance represents a continuum, but the NPSLE group more like to fall at the impaired end. In support of this there was a slight increase in the percentage of non-NSPLE patients who were classed as having cognitive impairment compared to controls. On the other hand, inspection of figure 4.1 indicates the non-NPSLE and control group had very similar scores on most tasks, and a similar proportion of non-NPSLE and control participants were impaired on each individual task.

Chapter 5 investigated three tasks in greater detail. These tasks suggest deficits in retrieval and speed of processing underlie the performance on these tasks in NPSLE. Again the non-NPSLE group did not differ from controls on any task and on reaction time variability measures it was the non-NPSLE group that differed from the NPSLE group. It has previously been suggested that reaction time variability is a marker for central nervous system integrity. Using this argument it appears there is a reduction in integrity in the NPSLE group but not the non-NPSLE group.

Chapter 6 investigated differences on quantitative imaging. Separating the SLE group indicated it was the NPSLE group that differed from controls on white matter ADC. The non-NPSLE group differed from controls on whole brain mean ADC. Using DTI to detect pathology revealed a similar proportion of non-NPSLE and NPSLE patients had elevated white matter ADC if using a cut-off of one standard deviation above the control mean. But if a more stringent cut-off was used the proportion on non-NPSLE patients with elevated ADC dropped to zero. This suggests there may be subtle damage occurring in both NPSLE and non-NPSLE patients, but this was more widespread in a subset of NPSLE patients.

Chapter 7 discussed the correlations between the various parameters and cognitive performance. In the NPSLE group there were significant correlations between cognitive function and imaging parameters, (white matter FA correlated with SOP, compound RT and executive control) mental health and well being (state anxiety correlated with all domains, and trait anxiety with SOP and executive control) and clinical variables (the cognitive impairment index correlated with physical health, pain, fatigue and disease activity). In contrast, in the non-NSPLE group the only significant correlations were between SOP and compound RT and depression. This suggests the NPSLE and non-NPSLE groups are distinct in terms of the correlates of cognitive function. Although correlation does not imply causation, the fact there
are different correlates does imply there may be different causes of cognitive impairment in the two groups.

8.3 Theories behind cognitive dysfunction

8.3.1 Lupus specific damage to brain parenchyma

Whilst the research programme discussed in this thesis is not able to distinguish between the various proposed mechanisms for lupus mediated damage to brain parenchyma, it is able to provide evidence for a correlation between central nervous system integrity and cognitive function. This was addressed by the relationship between cognitive domain scores and quantitative imaging measures. In chapter 1 it was proposed that if cognitive dysfunction does result from the direct action of lupus disease on brain tissue, then three hypotheses could be made: (1) there would be a difference between patients and controls on brain imaging measures. In chapter 6 differences were identified between patients with SLE and controls on white matter ADC. (2) There would be a correlation between the imaging parameters and cognitive function. In chapter 7 relationships were found between white matter FA and cognitive function in the NPSLE group, and between cognitive performance and brain volume in the SLE group as a whole. (3) If damage to the nervous system only occurs in patients with NPSLE then this group would differentiate from healthy controls whereas the non-NPSLE patients would not. This was partially supported. It was the NPSLE group that differed from controls on white matter ADC, but the non-NPSLE group also had slightly raised ADC, and this difference from controls was significant if measured in the whole brain. The non-NPSLE group did not show a correlation between these parameters and cognitive function suggesting changes to brain parenchyma were not driving cognitive performance in this group. Although on VBM correlations were found with cognitive domain scores in the whole SLE group, the relationship between white matter volume and SOP and compound RT appeared to be driven by the NPSLE group.

8.3.2 The effect of emotional disturbance

The relationship between emotional disturbance and cognitive function was assessed by correlating scores on measures of depression and anxiety, and scores on cognitive domains. In chapter 1, it was proposed that if cognitive dysfunction is related to emotional disturbances
then two predictions can be made: (1) There would be a significant negative correlation between scores on measures of depression and anxiety and cognitive function. In the NPSLE group there were negative correlations between state anxiety and all four cognitive domain scores, and between trait anxiety (HADS-A) and SOP and executive control. In the non-NPSLE group depression scores correlated with the compound RT and SOP domain scores. (2) Differences between NPSLE and non-NPSLE patients would only be expected if there are also differences on measures of emotional disturbance. As previously mentioned, as far as measures of mental health and wellbeing go there was not a differentiation between the NPSLE and non-NPSLE groups. However, on measures of cognitive performance the groups did separate, with the NPSLE group performing significantly worse on the overall cognitive impairment index, and on the memory and SOP domains. This suggests that emotional disturbance per se did not explain the cognitive dysfunction evident in the NPSLE group.

8.3.3 Non-specific aspects of chronic illness

Cognitive dysfunction could be a response to non specific aspects of ill health, such as symptoms including fatigue, pain or generally feeling unwell, or the effect of treatment such as corticosteroids. In chapter 7, cognitive performance was assessed separating the SLE group into those on a high (>10mg/day), low (<10 mg/day) or no corticosteroid dose. The participants on a high current steroid dose had lower scores on the memory domain than the other two groups, with 80% showing a t-score less than 40. There were no differences on the other domains, or the cognitive impairment index. This supports previous studies that have linked memory deficits to corticosteroid use (Brown, et al., 2004; de Quervain, et al., 2000; Young, et al., 1999) and cumulative corticosteroid dose with hippocampal atrophy (Appenzeller, et al., 2006). It was not possible to separate this effect into the NPSLE and non-NPSLE subgroups, as only five participants were on the high current dose. The lack of difference on the other domains suggests that corticosteroid use did not explain all the cognitive performance differences in the present sample.

In chapter 1, it was proposed that if cognitive dysfunction in SLE is related to non specific aspects of chronic illness then two predictions can be made: (1) There would be a correlation between cognitive function and systemic disease activity or measures of physical health, pain or fatigue. In the NPSLE group the cognitive impairment index score correlated with all of the above measures. These correlations were not evident in the non-NPSLE group. Similar
correlations between cognitive impairment, fatigue, pain and SLEDAI scores have previously been shown in NPSLE (Kozora, et al., 2006).  

2. No difference in cognitive performance would be expected between NPSLE and non-NPSLE patients, or other chronic illness controls assuming the groups have similar levels of systemic disease activity. The NPSLE and non-NPSLE groups had similar levels of systemic disease activity measured by the SLEDAI (3.0±2.4 for non-NPSLE group and 2.5±2.7 for NPSLE group). On the other hand the NPSLE group had significantly lower scores on quality of life relating to physical health (SF-36 physical component score) than the non-NPSLE group, or the other disease controls. This suggests they did have more severe physical disability than the other patient groups. Additionally, the NPSLE participants had significantly lower scores than the non-NPSLE group on the physical health and pain subscales of the LupusQoL questionnaire, lower scores on the fatigue subscale, and significantly poorer motor performance as measured by the finger tapping test. This means that non-specific aspects of chronic illness cannot be ruled out as driving the group differences in cognitive function.

8.3.4 Summary of findings relating to theories of cognitive function

The above findings suggest that cognitive performance in NPSLE may be driven by damage to brain parenchyma, or by non-specific aspects of chronic illness. These options are not necessarily distinct from each other. It may be that health related symptoms are associated with the same disease process that leads to immune mediated damage to brain parenchyma. Cognitive performance in the non-NPSLE group did not appear to be related to any of the measured variables. This highlights the importance of further investigation of the cognitively impaired non-NPSLE group. Kozora and colleagues have found correlations between cognitive function and neurometabolites measured using H1-MRS in non-NPSLE (Filley, et al., 2009; Kozora, et al., 2005; Kozora, et al., 2011). They suggest that mild cognitive impairment in non-NPSLE may result from early myelinopathy, and this precedes the more severe cognitive dysfunction that is related to more obvious white matter and neuronal damage in NPSLE (Kozora & Filley, 2011). This raises the question of whether these patients are likely to progress into NPSLE, and whether spectroscopy is a more sensitive imaging technique to this early damage.
8.4 Clinical implications

Clinical implications of research may relate to either diagnosis or treatment of a particular condition. The imaging aspects of the research suggest that using measures of diffusion in white matter may provide information in the diagnosis of NPSLE, particularly as this measure had high specificity for NPSLE. This would be a relatively simple analysis that could be done using automated procedures. Pre-analysis of the imaging techniques suggested that ADC and FA measures were reliable, but they would need to be calibrated on different scanners in order for it to be clinically useful. Tofts and Collins (In Press) describe the normal range of white matter values as 690-930 $10^{-6} \text{m}^2 \text{s}^{-1}$, which is well beyond the group differences that have been identified between patients with NPSLE and controls. Steens et al. (2004) investigated the reproducibility of ADC histograms and found histograms were robust, but using different pulse sequences did give rise to different histogram shapes and mean ADC values. There have been multicentre studies using DTI measures suggesting these differences can be overcome e.g. (Welsh, et al., 2007).

This thesis has demonstrated increased depression scores and reduced quality of life in SLE patients. However, on the basis of this thesis it would not be appropriate to embark on more aggressive treatment in these patients. These mood disorders were also present in patients with rheumatoid arthritis, and in the SLE sample did not correlate with disease activity or duration. However, this does suggest the importance of psychological assessment and consideration of whether these patients could be better managed using antidepressants or psychological therapy. A relationship was found between appearance concerns and depression scores, and this is supports a previous study that found the same relationship in patients with SLE and rheumatoid arthritis (Monaghan, et al., 2007). The authors suggest that targeting appearance concerns may also improve mood, and this could be done using cognitive behavioural therapy.

Thirdly, subjective cognitive complaints were present in 40% of NPSLE participants, and all of these were classified as showing cognitive impairment using neuropsychological assessment. There was also a significant correlation between the cognitive impairment index and scores on the cognitive failure questionnaire in the NPSLE group. This highlights the importance of taking subjective complaints seriously, and looking for cognitive end points in drug trials. Studies have suggested beneficial effects of dehydroepiandrosterone (DHEA) on cognition in SLE (e.g. Van
Vollenhoven, et al., 2001). DHEA is an adrenal hormone that is usually produced endogenously, but may have low levels in patients with SLE (e.g. Kozora, Laudenslager, Lemieux, & West, 2001). Another drug trial looked at the effect of the stimulant Modafinil on cognitive function in SLE but the results are as yet unavailable (US National Institute of Health, 2009).

8.5 Limitations of the current research

The first limitation of this research is the sample size, particularly in the NPSLE group where there were only 15 participants, and 14 who completed the imaging session. On the other hand this does highlight the differences between the NPSLE and non-NPSLE groups, as when significant differences were evident it was always the NPSLE group that differed from the controls, despite the reduced power that accompanies fewer participants. The small number of participants in the NPSLE does affect the extent to which the findings can be generalised, especially as 73.3% of the group were impaired on a simple motor speed task. This is a greater proportion than has previously been suggested by studies such as Kozora et al. (2004). Finally small numbers prevented any subgroup analysis within the NPSLE group, according to specific neuropsychiatric manifestation for example. Expanding the numbers would have its downsides, as it is likely a multicentre study would be needed in order to get significantly more participants. It would then be more difficult to keep the clinical and neuropsychological assessment homogenous across participants. Additionally, multicentre imaging studies add challenges to the imaging protocol and analysis, although the sources of variation are well understood and it is possible to overcome them (Steens, Admiraal-Behloul, Schaap, et al., 2004; Tofts, et al., 2006).

A second limitation results from the location of the research programme. The ethnic mix of the patient population reflects that of the local population and the SLE group were predominantly Caucasian with only 4/37 exceptions (two of Asian descent, one African and one South American). There is evidence that there is a different clinical picture when race is taken into account. Lupus nephritis is more common in Afro-Caribbean, Chinese and Indo-Asian populations (Patel, et al., 2006) and although in the current study there was no link between kidney disease and cognitive function, this may reflect the ethnic mix of the participants. There are also studies suggesting greater neuropsychiatric involvement in Chinese and Asian SLE samples relative to Caucasian (Feng & Boey, 1982; Samanta, et al., 1991), which suggests that different results may be found if different populations were studied. On the other hand
Breitbach et al. (1998) compared African-American and white SLE patients and controls on cognitive function. Although the African-American SLE patients performed worse than their white counterparts, there was no interaction between race and disease and the remaining difference could be accounted for by socioeconomic factors. The location of the current research, meant the participants were recruited from a relatively affluent area. The above research suggests this could have impacted on the neuropsychological assessment and caution should be used in generalising to other populations. It is possible there were also group differences in socioeconomic factors, as some of the control participants were recruited from the University population. Although the groups were matched as far as possible, the control group had significantly lower NART error scores indicative of higher IQ and a larger proportion of patients left school at 16 or younger. The differences in NART scores were accounted for statistically in all analyses of cognitive performance, but there may be other psychosocial factors that had effect and could have been measured and controlled for.

A third limitation is the cross sectional design of the study rather than longitudinal. Although the present study has been able to identify correlates of cognitive performance, these do not necessarily imply causation. SLE is a disease that is characterised by flares and remissions in symptoms and longitudinal studies having also suggested a fluctuating course of cognitive impairment (Hay, 1994). Therefore repeated measurements, perhaps matched to changes in symptoms, would be useful in advancing our understanding of mechanisms and long term prognosis of cognitive dysfunction. Kozora and Filley (2011) suggest that mild cognitive impairment in non-NPSLE may be a precursor to the more significant cognitive dysfunction seen in NPSLE and longitudinal analysis is needed in order to see this progression. Longitudinal studies have other challenges, for example it is vital to ensure the reliability and reproducibility of the scanning protocol, and to account for practice effects on neuropsychological testing.

Three limitations relate to the classification of patients. Firstly classification into the NPSLE and non-NPSLE groups was done retrospectively using the patient’s medical notes, and the expertise of a Rheumatologist who knows the patients well. This method did have some advantages – it allowed classification of all patients to be made at the end of the study, which meant the neuropsychological assessment and imaging analysis was completed blind to the clinical status of the patient. It also meant equal weighting was given to past neuropsychological manifestations as present ones. Classification based on the current clinical picture would only detect current manifestations. Nonetheless, retrospective classification
may have missed some subtle neuropsychological manifestations if they were not recorded in
the medical notes. It is worth noting that the NPSLE group consistently differed from the
controls, whereas the non-NPSLE group did not. This suggests there were not a significant
number of NPSLE patients who had been misclassified in the non-NPSLE group. Secondly, the
antibody analysis matched to the neuropsychological and imaging assessment in not currently
available. The relationship between cognitive function and serological measures was
therefore based on results taken from routine clinical monitoring. These were matched in time
to the research assessment as far as possible, but in some cases the bloods were taken ±2-3
months before or after assessment. Where there was a time lag between these assessments,
serological measurements were collected from multiple occasions to ensure there did not
appear to be a change in clinical picture during the time of assessment. In the case of positive
anti-Cardiolipin antibodies, it was confirmed that these were raised on both sides of the
assessment time point. Thirdly, participants were classified according to steroid dose into high,
low and no steroid categories. There was no relationship between cognitive function and
previous steroid dose, but this could have been due to the use of a crude measurement.
Calculating cumulative steroid dose gives a better indication of the lifetime steroid burden of
the patient. This has previously been shown to correlate with cortical (Appenzeller, Bonilha, et
al., 2007) and hippocampal volume loss (Appenzeller, et al., 2006). Nevertheless, a selective
relationship was found between current high dose and memory suggesting this measure was
adequate for investigating the effects of current corticosteroid dose.

8.6 Future directions

Future directions can be divided into two categories – further analyses of the existing data and
possible expansions of the study. The in the first category is analysis of the serological data
collected at the time of the neuropsychological assessment. A collaboration has been arranged
with a group who recently reported three new antibodies associated with SLE using multiple
proteomic analyses; crystallin αB, esterase D and APEX nuclease 1. Of these, Apex nuclease 1
antibodies were associated with psychiatric manifestations (Katsumata, et al., 2011). This
group has also linked anti-NR2A antibodies to NPSLE (Gono, et al., 2011). The purpose of the
collaboration is to analyse these antibodies in the present SLE sample, and to correlate these
with cognitive function and imaging parameters.

We have arranged a collaboration with a team in Japan for antibody analysis of the serum samples, but
the results are not available in time for writing this thesis.
One future direction could include comparison of the findings in SLE with other immune mediated rheumatologic diseases. Approximately half of the patients in the current study had co-morbid Sjögren’s syndrome (SS), which makes this an obvious choice. SS is also a multisystem autoimmune disease, and is also complicated by central nervous system involvement (Soliotis, Mavragani, & Moutsopoulos, 2004) and cognitive dysfunction (e.g. Spezialetti, Bluestein, Peter, & Alexander, 1993). The neuropsychological manifestations of SLE and SS are similar, and there is a similar prevalence of cognitive dysfunction (Harboe, et al., 2009). However, there are differences between the conditions, such as the increased prevalence of hypertension, renal involvement and vascular disease in SLE. This suggests there may be some separation in the mechanisms behind neuropsychological involvement. Comparison of the profile of cognitive dysfunction or imaging analysis in SLE and SS may provide some insight into CNS damage, for example greater impairment in SLE may suggest vascular origins for damage. Secondly, comparison with a group of SS patients will allow analysis of whether the effects reported in this thesis are effects of SLE or effects of SS. There is an ongoing study into the neuropsychological profile of primary SS patients at the Brighton and Sussex Medical School, using equivalent measures which will allow these comparisons with this cohort.

A logical future direction for the current work would be to address the limitations in sample size and cross sectional design by expanding the study by testing a larger number of patients or asking participants to come back for a second testing session. Expanding the numbers could involve specifically recruiting NPSLE patients to match this group in size to the healthy controls, and seeing whether the significant results, and in particular the significant correlations between cognitive function and clinical or imaging variables remained. As previously commented, expansion of the study to include significantly more participants would require a multi-centre study. Nonetheless a larger group size would permit investigation of finer subgroup analyses. This could include investigation of genetic characterisation of patients, or a more detailed look at the role of different auto-antibodies, particularly ones that are relatively rare in the population. A larger group of NPSLE patients would also allow the division of the NPSLE group into those with and without cognitive dysfunction, by potential mechanisms, such as those with and without vascular abnormalities. Longitudinal analysis of the current patient cohort could be useful. If major cognitive decline is detected this could suggest there is untreated vascular or inflammatory disease that has not been treated. This may also correlate with imaging findings which would increase their diagnostic utility. Three
previous quantitative imaging studies have used a longitudinal design. Appenzeller and colleagues showed a progression in hippocampal (Appenzeller, et al., 2006) and grey and white matter (Appenzeller, Bonilha, et al., 2007) atrophy over a relatively short time period (mean follow up 19 months). Emmer et al. (2006) showed changes in MTR that corresponded to changes in clinical status. There have been no longitudinal studies using DTI, and none of these studies also used repeated measurements in a control group.

There are a number of ways the imaging aspects of this study could be extended. These also include further analysis of existing data, and new techniques that could be adopted. It was argued in chapter 6 that overlapping regions of damage across patients is not necessarily expected, and instead we should be looking for techniques that can detect ‘damage’. In the present study no differences were found in white matter FA, and I suggested this could be due to reduced sensitivity of measuring FA across the whole white matter. If this is correct regions that are more sensitive do need to be detected; one possible regions being the corpus callosum, which has been previously identified as showing atrophy (Appenzeller, Rondina, Li, Costallat, & Cendes, 2005) and reduced FA (Jung, Caprihan, et al., 2010; Zhang, et al., 2007). This could be assessed by directly comparing results directly across studies, for example looking for FA differences in the regions identified as showing group differences by Hughes et al. (2007) or Zhang et al. (2007), or repeating TBSS analysis and seeing if parallel regions are identified as previous studies (Emmer, et al., 2010; Jung, Caprihan, et al., 2010).

In the category of new imaging techniques, future studies could use arterial spin labelling (ASL), quantitative Magnetisation Transfer (qMT) or look at functional connectivity using resting state functional MRI. ASL is a technique that enables the measurement of cerebral blood flow without the need for contrast agents or ionising radiation, by using magnetically labelled endogenous blood water as a freely diffusible tracer (Deibler, et al., 2008). Functional studies using SPECT or PET to assess blood flow in SLE have identified areas of hypoperfusion (e.g. Appenzeller, Amorim, et al., 2007) and vascular abnormalities have been a proposed mechanism for cognitive dysfunction. This may be detected in SLE using ASL. Like MTI, qMT is also dependent on the magnetisation transfer (MT) effect. Instead of applying a singly RF pulse to saturate the bound fraction or protons, the MT pulse is applied at several offset frequencies. MT is a function of the MT pulse power and offset, as you move the pulse the MT effect will change and this is dependent on the local environment.
The MTR metric gained in the current study approximates the number of bound protons, but is also affected by other factors such as $T_1$. By taking multiple measurements you can remove the effect of $T_1$ and by applying a model to the acquired data you can fit a number of parameters including the bound proton fraction. This may be more sensitive to the effects of disease in SLE. Functional MRI is an imaging technique which relies on the differential magnetic properties of deoxyhaemoglobin and oxyhaemoglobin. As deoxyhaemoglobin is paramagnetic, it distorts the local $T_2^*$ weighted MRI signal. This is the source blood-oxygen-level-dependent (BOLD) effect. fMRI is usually measured during an external task where blood flow to a region is thought to reflect the increased metabolic demands of a region that is active. In resting state fMRI the low frequency fluctuations in BOLD signal are measured when the brain is at rest i.e. not during any particular task. A number of consistent networks have been identified, which are regions that show synchronous fluctuations in activity (Lowe, 2010; S. M. Smith, et al., 2009). Resting state fMRI gives an indication of the functional connectivity between brain regions, while DTI provides evidence on the structural connectivity. This has not previously been studied in SLE, but disruption of resting state networks has been identified in diseases, including MS (Lowe, et al., 2008). Evaluation of the same cohort of SLE patients may provide some insight into cognitive dysfunction in SLE.

8.7 Final remarks

When I sat down with the data for this thesis a year ago, my expectation was that I would not necessarily find a difference between the NPSLE and non-NPSLE groups on measures of cognition and mood. Having met the participants there did not seem to be much distinction between them, the groups had similar levels of systemic disease and few of the participants in the NPSLE group had significant neuropsychiatric manifestations at the time of testing. Once the SLE group was separated into NPSLE and non-NPSLE, this expectation was predominantly born out on the measures of mental health and wellbeing, but on the other measures there was a consistent pattern with the NPSLE group differing from healthy controls. This perhaps should not be surprising as it converges with previous research suggesting more widespread damage in NPSLE (Kozora & Filley, 2011). I sought to evaluate the distinction between the NPSLE and non-NPSLE groups, but this has raised more questions. Does subclinical involvement imply these patients will convert to NPSLE? Can we identify which patients will convert? and is having mild cognitive dysfunction or depression indicative of subclinical brain involvement or potential to experience further neuropsychiatric symptoms?
Having completed this body of work, I now feel I understand the challenges of medical research, including the consideration needed in selecting measures to answer the research questions, gaining ethical approval for a study and the particular challenges of participant recruitment. This thesis has demonstrated to me the power and limitations of modern imaging techniques and has made me enthusiastic about conducting similar research in the future.
REFERENCES


Hermosillo-Romo, D., & Brey, R. L. (2002). Diagnosis and management of patients with neuropsychiatric systemic lupus erythematosus (NPSLE). *Best Practice & Research in Clinical Rheumatology*, 16(2), 229-244.


APPENDICES

1. QUESTIONNAIRES

HOSPITAL ANXIETY AND DEPRESSION SCALE
SPEILBERGER STATE ANXIETY INVENTORY
COGNITIVE FAILURES QUESTIONNAIRE
MEDICAL OUTCOMES SURVEY SHORT FORM-36
LUPUSQOL©
1.1 HOSPITAL ANXIETY AND DEPRESSION SCALE

Questionnaire removed from e-thesis due to copyright material.

See Zigmond and Snaith (1982)
1.2 SPEILBERGER STATE ANXIETY INVENTORY

Questionnaire removed from e-thesis due to copyright material.

See Speilberger, Gorsuch and Lushene (1970)
1.3 COGNITIVE FAILURES QUESTIONNAIRE

Questionnaire removed from e-thesis due to copyright material.

See Broadbent, Cooper, Fitzgerald and Parkes (1982)
1.4  MEDICAL OUTCOMES SURVEY SHORT FORM-36

Questionnaire removed from e-thesis due to copyright material.

See Ware and Sherbourne (1992)
1.5 LUPUSQOL®

Questionnaire removed from e-thesis due to copyright material.

See McElhone et al. (2007)
2. QUESTIONNAIRE SUBSCALES

Questionnaire subscales removed from e-thesis due to copyright material.

See Zigmond and Snaith (1982) for HADS subscales

See Wallace, Kass and Stanny (2002) for CFQ subscales

See Ware and Sherbourne (1992) for SF-36 subscales

See McElhone et al. (2007) for LupusQol subscales
3. SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX

Questionnaire removed from e-thesis due to copyright material.

See Bombardier et al. (1992) for details of the questionnaire.
4. THE COGNITIVE TEST BATTERY

4.1 NATIONAL ADULT READING TEST

INSTRUCTIONS:

Please read each word out loud how you think it is pronounced in English.

Sample removed from e-thesis due to copyright material.
4.2 REY AUDITORY VERBAL LEARNING TEST

Sample removed from e-thesis due to copyright material.
WORDS FOR RAVLT RECOGNITION TEST

INSTRUCTIONS:

Here is a sheet with the words that were included on List A. Please circle the words you recognise as being from list A. There were 15 words in total so I’d like you to circle 15 words.

Sample removed from e-thesis due to copyright material.
4.3 REY-OSTERREITH COMPLEX FIGURE

INSTRUCTIONS:

Please copy the figure below in the space provided. I am going to time how long it takes you to complete it, but I would like you to copy it carefully and not worry about the time. The aim is to copy it accurately rather than doing it as quickly as you can.

INSTRUCTIONS FOR DELAYED RECALL

I got you to copy a figure at the beginning of the testing session. I would like to draw as much of the figure as you can remember without seeing it again.

Sample removed from e-thesis due to copyright material.

4.4 RAPID VISUAL INFORMATION PROCESSING

INSTRUCTIONS:

In this test random numbers will appear in the middle of the computer screen one after another at a fairly rapid pace. Your task is to watch the screen carefully and press the SPACEBAR each time you see either THREE ODD numbers in a row or THREE EVEN numbers in a row.

All are single digit numbers (1 – 9).

The target sequence of three odd or even numbers may be in any combination.

Example 1: 3, 1, 5
Example 2: 8, 2, 6

Press the SPACEBAR whenever you see a set of three, and try to avoid making too many incorrect presses.

If you have any questions about the instructions please ask the experimenter now.

PRESS SPACE BAR TO BEGIN
4.5 DIGIT SYMBOL COPYING

Sample removed from e-thesis due to copyright material.
4.6 DIGIT SYMBOL SUBSTITUTION TEST

Sample removed from e-thesis due to copyright material.
4.7 CARD SORTING TEST AND PROSPECTIVE MEMORY

INSTRUCTIONS:

Screen 1

This task involves a deck of playing cards. Each card will appear in the middle of the screen. Please sort the cards into their appropriate suits by pressing the corresponding button on the keyboard.

As you will notice only two suits are denoted on the keyboards, therefore please sort only the cards with SPADES or HEARTS into their appropriate suit.

Screen 2

Press the spade button when you see a SPADE and press the heart button when you see a HEART.

Do not respond if the card is either a CLUB or a DIAMOND.

Screen 3

There is one deck of cards. IT IS VERY IMPORTANT THAT YOU RESPOND AS **QUICKLY** AND AS **ACCURATELY** AS POSSIBLE.

Prospective memory instruction (given after completing the card sorting)

For the next section, in addition to sorting the cards into hearts and spades, when you come across the target card, which is ANY card with the number ‘7’ on it, I would like you to press SPACEBAR if you see a 7.

Do this instead of responding to the suits.
4.8 TRAIL MAKING TEST

PART A - INSTRUCTIONS:

On this page are some numbers. Begin at number one and draw a line from one to two, two to three, three to four and so on in order until you reach the end. Draw the lines as fast as you can, without lifting the pen from the paper.

Sample removed from e-thesis due to copyright material
TRAIL MAKING TEST

PART B - INSTRUCTIONS:

On this page are numbers and letters. Draw a line from one to A, A to two, two to B, B to three, three to C and so on, in order until you reach the end. Remember first you have a number, then a letter, then a number, then a letter and so on. Draw the lines as fast as you can without removing the pen from the paper.

Sample removed from e-thesis due to copyright material
4.9  CONTROLLED ORAL WORD ASSOCIATION TEST

INSTRUCTIONS:

I am going to give you a letter of the alphabet. Then I would like you to write down as many words as possible beginning with that letter, as quickly as possible. For instance if I say ‘B’, you might give me ‘bed’, ‘bottle’, ‘battle’.

Please do not do use proper names such as ‘Bob’ or ‘Birmingham’. Also do not use the same word again but with a different ending such as ‘bash’, ‘bashing’, ‘bashes’, and ‘bashed’.

LETTER USED:

F A S
4.10 LETTER NUMBER SEQUENCING

Sample removed from e-thesis due to copyright material
4.11 MENTAL ROTATION TEST

INSTRUCTIONS:

In this task you will see the same letter presented in eight different orientations. Some of the letters will be reversed, others will not – your task is to indicate for each presentation whether the letter is reversed or not.

Do this by pressing the “Z” and “M” buttons on the keyboard.

PRESS “Z” for REVERSED presentations
PRESS “M” for NORMAL – i.e. NON-REVERSED – presentation.
4.12 ALTERNATIVE USES TEST

INSTRUCTIONS:

You will be given a common object and your task is to find as many alternate uses for that object as possible. Each acceptable use must be different from each other and from the common use.

I am going to give you 2 objects in turn. Your task is to give me as many alternative uses as you can. You will have a minute for each item.

Item 1: A shoe (used as foot wear)  
Item 2: A button (used to fasten clothing)
4.13 STROOP TEST

INSTRUCTIONS:

You are going to be shown coloured words on the computer screen. Your last is to press the key corresponding to the colour ink the word is written in not what it says. Four keys have been labelled with coloured stickers (red, yellow, green and blue). Please press the key that corresponds to the colour ink the word it written in.

EXAMPLE:

Black
Congruent trial

Green
Incongruent trial
5. CODING RULES FOR CLUSTERING AND SWITCHING

Phonemic fluency

Taken from (Troyer, et al., 1997). Phonemic clusters consisted of successfully generated, consecutive words that shared any of the following phonemic characteristics:

1) *First letters:* Words that began with the same first two letters, such as ‘arm’, ‘art’
2) *Rhymes:* words that rhyme, such as ‘sun’ and ‘stun’
3) *First and last sounds:* words differencing only by a vowel sound, regardless of the actual spelling, such as ‘sat’ and ‘seat’ ‘soot’ ‘sight’ and ‘sought’
4) *Homonyms:* Words with two or more different spellings, such as ‘some’ and ‘sum’

Semantic fluency

Taken from (Lezak, et al., 2004). Semantic clusters consisted of successfully generated consecutive words that were semantically related:

1) They had shared meanings, such as ‘sun’ and ‘stars’
2) They had shared associates, such as ‘salt’ and ‘sugar’

General coding rules: (Troyer, et al., 1997)

1) Errors (repetitions, use of proper names or words with the same root) were included in the clusters, but were not scored in the total number of words generated.
2) When two clusters were embedded in each other the largest cluster was recorded only, such as ‘sly’, ‘slit’, ‘slim’, ‘slam’ all begin with ‘sl-’ but an additional cluster could be formed from ‘slim’ and ‘slam’.
3) When two clusters overlapped the overlapping items were assigned to both clusters, such as ‘son’ ‘sun’ ‘sunk’. ‘Sun’ is a homonym to ‘son’ and also begins with the same two letters as sunk. These would be classed as two separate clusters each with a cluster size of 1 (two words minus 1).
4) Clusters and switches were calculated separately for phonemic clusters and semantic clusters.

Scoring rules: (Troyer, et al., 1997)

1) Switches were calculated as the number of transitions to a new cluster, including single words.
2) Clusters size was measured starting with the second word (e.g. a cluster of one would score zero, a cluster of two would score one)
3) A second cluster size measure (cluster size 2) was also generated in accordance with Unsworth et al. (2011) using only the clusters with a size greater than 1.
6. ETHICAL APPROVAL

01 May 2008

Miss Rebecca Haynes
MPhil research student
The Brighton and Sussex Medical School
Medical Research Building,
University of Sussex,
BN1 9PS

Dear Miss Haynes

Full title of study: Quantitative Imaging and Psychological Assessment in Neuropsychiatric Systemic Lupus Erythematosus (NPSLE)

REC reference number: 08/H1103/28

Thank you for your letter of 18 April 2008, responding to the Committee’s request for further information on the above research and submitting revised documentation, subject to the conditions specified below.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites (“R&D approval”) should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.scforum.nhs.uk.

This Research Ethics Committee is an advisory committee to South East Coast Strategic Health Authority

The National Research Ethics Service (NRES) represents the NHS Directorates within

the National Patient Safety Agency and Research Ethics Committees in England
Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

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<th>Document</th>
<th>Version</th>
<th>Date</th>
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<tr>
<td>Application</td>
<td>2</td>
<td>18 April 2008</td>
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<td>Appendix II: Serological Markers</td>
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Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

An advisory committee to South East Coast Strategic Health Authority
The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

[08/H1103/29]

Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely,

Ray Godfrey
Chair

Enclosures: “After ethical review – guidance for researchers”
Site approval form

Copy to: Mr Scott Harfield
R&D office for NHS care organisation at lead site

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