

# Normal Appearing White Matter Damage is Associated with Neuropsychiatric Symptoms in Systemic Lupus Erythematosus

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## Introduction

Diffusion tensor imaging (DTI) is a quantitative MRI technique that measures the structural integrity of brain tissue (1). We used DTI to investigate white matter damage in SLE patients with both mild and major neuropsychiatric involvement. Despite having normal conventional MRI scans we show that DTI provides evidence for structural damage in the normal appearing white matter of the brain in SLE. Patients with major neuropsychiatric involvement displayed the greatest changes in mean diffusivity (MD) and fractional anisotropy (FA) maps.

## Methods

SLE patients were recruited from routine clinics in three centres across London between October 2003 and March 2005. All patients fulfilled the American College of Rheumatology (ACR) criteria for the classification of SLE (1997) (2) and had at least one neuropsychiatric episode, as defined by the neuropsychiatric SLE (NPSLE) definitions of the ACR ad hoc committee (3). All conventional MRI scans of recruited patients were reviewed by two neuroradiologists and only normal scans (exclusion of significant cortical, subcortical lesions and cerebral atrophy) were included in the analysis. Of the 47 NPSLE patients recruited and scanned, 32 had normal MRI scans (1 male; 39 females, age range 19 to 47 years; mean age 37 years). 18 healthy age matched controls with normal MRI scans (1 male, 17 females, age range 21 to 41 years; mean age 38 years) were included in the analysis. NPSLE episodes ranged from intractable headache and cognitive dysfunction to psychosis. As this was a very heterogeneous group, NPSLE were further subdivided into two groups: mild (intractable headache, depression and mild cognitive dysfunction), and major (psychosis, seizures and severe cognitive dysfunction). All subjects were scanned on a 1.5T GE MRI system. T2-weighted, FLAIR and DTI data were acquired. DTI was achieved using a single shot echo planar sequence with 12 diffusion sensitised directions as described previously (4). Two interleaved acquisitions comprising 25 slices each provided whole brain coverage (resolution: in plane 2.5mm; through plane 2.8mm). MD and FA maps were calculated for each pixel of the image data as described previously (5). T2-weighted images were then used to segment tissue into white matter, grey matter and cerebrospinal fluid. A histogram of MD and FA values was then determined for the segmented white matter volume in each subject. Mean values for MD and FA across controls and the minor and major NPSLE groups were determined. An ANOVA was conducted using SPSS to compare the groups and an effect size calculated by eta squared using the equation  $t^2/(t^2+(N1+N2-2))$  for those with significant results.

## Results

A one way between-groups analysis of variance was conducted to explore the impact of NPSLE on measurements of mean MD and mean FA in normal appearing white matter in patients and normal white matter in controls. There was a statistically significant difference for FA ( $p<0.0001$ ) (fig 1) and MD ( $p<0.001$ ) (fig2) between the groups. Post hoc comparisons using the Tukey test indicated significant differences for both MD and FA when comparing healthy controls with major NPSLE (MD:  $p<0.001$ , FA  $p<0.002$ ). Post hoc tests also showed significant differences between minor NPSLE and major NPSLE for MD ( $p<0.005$ ) but no other between group analysis reached statistical significance. The effect size for healthy controls versus major NPSLE was large for both MD values and FA values (0.34 and 0.22 respectively).

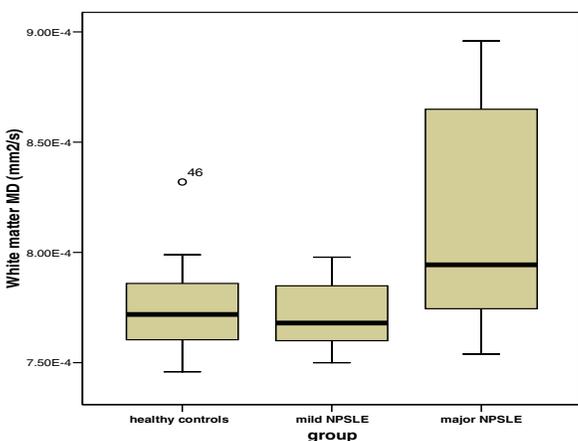


Fig 2. Boxplot of White matter MD in controls and NPSLE

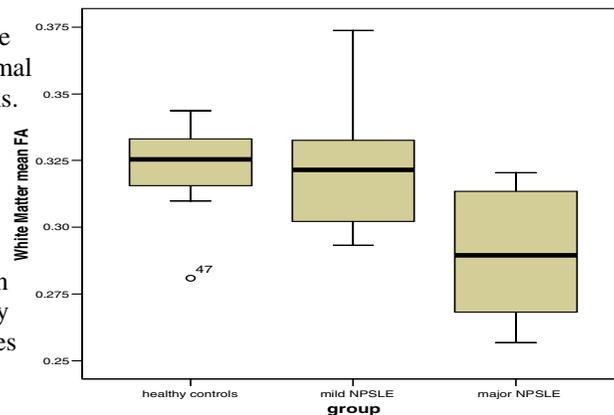


Fig 1. Boxplot of White matter FA in controls and NPSLE

## Conclusion

Patients with major neuropsychiatric symptoms frequently have normal conventional MRI scans. Using DTI we have shown, for the first time, that major neuropsychiatric symptoms are associated with decreased FA values in white matter. These FA reductions are accompanied by increased MD values suggesting damage to normal appearing white matter, in agreement with previous findings (6). DTI parameters were also abnormal in patients with minor neuropsychiatric symptoms but these did not reach statistical significance. Longitudinal studies are now required to determine the relationship between DTI parameters and the evolution of neuropsychiatric events over time.

## References

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