An Investigation of Microstructural Tissue Damage in Systemic Lupus Erythematosus (SLE) with Neurological and Psychiatric Symptoms using Diffusion Weighted Spectroscopy (DWS) at 7T

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Purpose: Systemic lupus erythematous (SLE) is an autoimmune disease with multi-organ involvement which results in neurological and psychiatric (NP) symptoms in up to 80% of the patients[1]. NP manifestations associated with the disease are widely heterogeneous among patients[1]. Conventional MRI of SLE patients with NP symptoms (SLEwNP) frequently appears normal and thus fails to explain the clinical symptoms, making the diagnostic procedure difficult and restricted to per exclusionem[2]. Previous studies showed correlation of the disease duration with atrophy in various brain regions including the corpus callosum[3]. Fractional anisotropy (FA) and mean diffusivity (MD) values obtained from diffusion tensor imaging (DTI) data of SLE, NPSLE and healthy controls showed significant differences in the corpus callosum (CC) of the patients compared to healthy controls[4]. Both DTI and morphometric studies are however non-specific as they reflect changes in tissue water which is abundant in both intracellular and extracellular compartments of the parenchymal cells. Diffusion weighted spectroscopy (DWS) can further elucidate the disease process since it provides metabolite-specific diffusion metrics, which can help identify cell-type- and compartment-specific microstructural damage in neuronal tissue[5]. Here, we utilize DWS of brain metabolites in normal appearing white matter in the CC to investigate the tissue microstructural correlate of SLEwNP. We focus on the analysis of the DWS results of N-acetylaspartate (NAA), a neuronal/axonal metabolite, and of soluble choline compounds (tCho), the concentration of which is significantly higher in astrocytes.

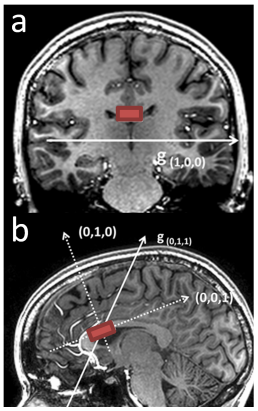

Fig.1. Planning of DWS with parallel (a) and perpendicular (b) gradient directions

Methods: 8 SLEwNP patients (all female, mean age: 39.2 ± 9.7 years) and 9 age-matched healthy controls (HC) (all female, mean age: 40.0 ± 11.2 years) with no neurological/psychiatric history were scanned on a 7 Tesla Achieva Philips MRI scanner equipped with a 32-channel head coil.

Data Acquisition: The scan protocol consisted of a 3D T_1-weighted image (0.85x0.85x1.00mm^3, TR/TE=4.05/1.81ms), DTI (1.75x1.75x2.2mm^3, TR/TE= 10,000/64 ms, one b=0 image and 15 encoding directions with b=1000 s/mm^2) followed by a single volume DWS scan planned on the body of the CC (Fig.1). DWS scan parameters: PRESS (Point Resolved Spectroscopy) with bipolar diffusion weighting gradients applied in 2 encoding directions, one along the RL direction of the VOI with 5 b-values of 252-3402 s/mm^2 and one applied perpendicular to the direction of the CC fibers with b-values 503-6805 s/mm^2, δ=34ms, Δ=60.5ms, VOI=25x15x8mm^3, TR/TE: 2 cardiac cycles /121ms, 1024 points.

Data Analysis: For each subject, DTI images were registered to the T_1 image and processed, generating FA, MD, radial diffusivity (RD) and axial diffusivity (AD) maps using MIPAV. In house MATLAB® code was used to calculate average FA, MD, AD and RD for the white matter within the DWS volume. DWS data were analyzed with in house MATLAB routines in which eddy current, phase and frequency-drift corrections were performed. Averaged spectra were subsequently analyzed with LCModel. NAA+NAAG (tNAA), total creatine (tCr) and tCho estimates at each diffusion condition were used to calculate parallel ($D_{||}$) and perpendicular ($D_{\perp}$) diffusivity (not shown) and ADC values for these metabolites.

Results: Table 1 shows the DTI results for the SLEwNP and HC groups. The only significant effect observed in the DTI data was an increase in AD (p=0.04) in the patient group. In Figure 2, the diffusion weighted data are shown for tNAA(left) and tCho(right) for both gradient orientations. The axonal anisotropy is clearly seen in the widely different slopes of the DWS NAA data in the two DW directions, while the slopes of DWS tCho data are much closer to each other, reflecting the more isotropic astrocytic content. ADC values for the 3 metabolites calculated based on the slopes of the DWS data are shown in Figure 3. The most significant disease-related effect was observed in the ADC (tCho) which was significantly higher in the SLEwNP group compared with the HC group (p=0.019). Interestingly, no significant difference was observed in ADC (tNAA) for the two groups, and the ADC (tCr) was slightly higher in the SLEwNP group without reaching significance.

Table 1. Water diffusion metrics from the patients and healthy controls

	Mean FA	Mean MD (10^{-3} mm^2/s)	Mean AD (10^{-3} mm^2/s)	Mean RD (10^{-3} mm^2/s)
SLE with NP	0.72±0.03	0.88±0.04	1.80+0.08*	0.43+0.003
HC	0.71+0.03	0.86±0.04	1.72+0.04*	0.43+0.004

Discussion and Conclusion: Both DTI and DWS measures indicate tissue microstructural damage in SLEwNP, reflected as an increase both in water AD and in ADC (tCho). The latter specifically suggests a disruption of astrocytic structure or physiology, which is in line with the inflammatory nature of the disease, as well as with the role of astrocytes in the re-uptake of glutamate, which is suspected to be involved in the etiology of NPSLE[6]. It is too early to postulate on the specific nature of the microstructural or physiological damage reflected in the measured changes, but our DTI and DWS findings support each other and when combined may provide a more specific explanation for the source of tissue damage in SLEwNP, which cannot be concluded based on DTI alone. Moreover, ADC(tCho) in itself may potentially become a biomarker for SLEwNP.

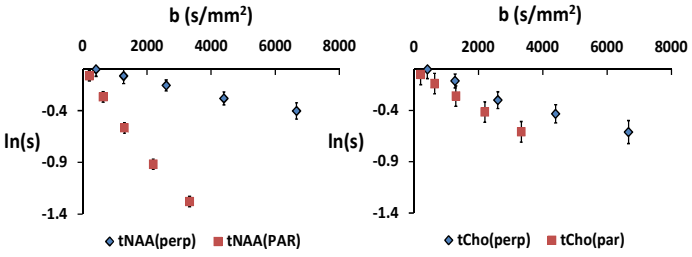

Fig. 2. DWS signal decay of tNAA (left) and tCho for the two diffusion directions.

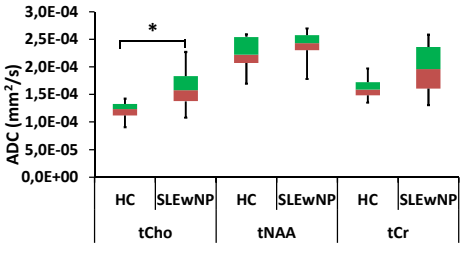

Fig 3. ADC values calculated for tCho, tNAA and tCr.

References: 1. Bertsias et al., Nat Rev Rheumatol, (2010). **2.** Emmer et al., Arthritis & Rheum. (2008). **3.** Appenzeller al., Arthritis & Rheum. (2005). **4.** Jung et al. BMC Neurology 2010. **5.** Wood et al., J Neuroscience (2012). **6.** DeGiorgio, L.A., et al., Nat. Med. (2001).