A multimodal approach to identify and localize complex pathological processes affecting tissue microstructure in Neuropsychiatric SLE

Ece Ercan[1], Carson Ingo[1], Cesar Magro Checa[2], Mark van Buchem[3], Andrew Webb[1], and Itamar Ronen[1]
[1]C. J. Gorter Center for High Field MRI, Department of Radiology, Leiden University Medical Center, Leiden, Netherlands, [2]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [3]Department of Radiology, Leiden University Medical Center, Leiden, Netherlands

Target Audience: Those interested in identifying pathomechanism-specific biomarkers for multiple mechanisms underlying neurological disorders.

Purpose: Systemic lupus erythematous (SLE) is a relapsing-remitting female-predominant autoimmune disease affecting multiple organs[1]. In about 40% of the patients, SLE adversely impacts the central nervous system, causing neurological and psychiatric (NP) symptoms[1]. NPSLE is divided into two phenotypes 1) *ischemic* NPSLE—identified by infarctions and thrombotic lesions in the brain arteries that are treated with antiaggregants and/or anti-coagulants; 2) *inflammatory* NPSLE—exhibited by rather diffuse symptoms that are treated with corticoids and immunosuppressant therapies[2]. In previous MTI studies, measurements in NPSLE patients showed lower peak heights in MT ratio (MTR) histograms compared to healthy controls (HC), suggesting either demyelination or an increase in free water resulting from cytotoxic or vasogenic edema[3-4]. In a separate DTI study, higher mean diffusivity (MD) and lower fractional anisotropy (FA) in white matter (WM) were reported for NPSLE patients compared to HCs, also suggesting a microstructural basis for the NP symptoms. In this study we applied a multi-modal approach to better characterize WM pathophysiology in NPSLE by co-analyzing FLAIR, DTI and MTI data from NPSLE patients, SLE (no NP) patients and healthy controls. Our results show significant differences in MTI and DTI measures between the groups. These differences, however, are only moderately co-localized to the same regions, suggesting that more than a single process affect tissue microstructure in the pathophysiology of NPSLE.

Methods: 9 inflammatory NPSLE patients (37 ± 13 years, all female), 9 SLE patients with no NP symptoms (44 ± 11 years, all female) and 14 healthy controls (HC) without known NP abnormalities or autoimmune diseases (40 ± 9 years, all female) were scanned on a 3T Philips Achieva equipped with an 8-channel receive coil. All NPSLE patients had at least one of the following active NP symptoms described by American College of Rheumatology: psychosis, headache, movement disorder, transverse myelitis, seizure, acute confusional state, anxiety, cognitive disorder or mood disorder[1]. *Data Acquisition:* The scan protocol consisted of 3D FLAIR (res=0.98x0.98x1.12mm^3, TR/TE=4800/279ms), DTI (res=2x2x2mm^3, TR/TE=8500/95ms, two b=0 images and 15 diffusion weighted images with a b-value of 1000 s/mm^2) and MTI (1.44x1.44x1.5mm^3, TR/TE=57/10ms, two image sets: with and without saturation via an RF pulse of 25ms duration). *Data Analysis:* WM lesions were manually delineated in FLAIR images by an expert reader using MIPAV software. FLAIR images were then affine registered to the MNI152 standard space using FSL FLIRT[5]. The same transformation matrices were applied to align individual lesion masks to the standard space. Lesions from all NPSLE and all SLE patients were added separately to generate NPSLE and SLE lesion maps. DTI images were denoised, and Rician noise and eddy current corrected by a custom MATLAB code. FA, MD, axial diffusivity (AD) and radial diffusivity (RD) maps were then generated by the dtifit function in FMRIB's Diffusion Toolbox (FDT) of FMRIB Software Library (FSL). FA maps were then used as an input to the tract-based spatial statistics (TBSS) tool in FSL where all individual FA maps were projected onto a common skeleton in MNI152 space. The same transformations and projections were applied to MD, AD and RD. A custom FSL script was then used to compute MTR maps. For each subject, the MTR maps were aligned with the b=0 image and then projected onto the FA skeleton by using the same transformations to MNI152 space[6]. Permutation tests were applied to 4D skeletonized FA, MD, AD, RD and MTR images to assess voxel-wise statistics between NPSLE patients, SLE patients and HC. 5000 permutations were used to correct for multiple comparisons.

Results and Discussion: Fig.1 shows the comparison of AD, RD, MD, FA and MTR between NPSLE patients vs. HC (top row) and SLE vs. NPSLE patients (bottom row) from one axial slice in MNI152 space. NPSLE patients showed significantly higher AD, RD and MD and lower FA than both HC and SLE patients. As in previous studies[7], there were no significant differences in any of the DTI or MTR measures for SLE vs. HC. MTR values were significantly lower in several regions in NPSLE vs. HC, strikingly, few regions were significantly lower in NPSLE compared to SLE. Moreover, the MTR differences for NPSLE vs. HC had only a moderate overlap with the DTI differences between the two groups in 44-49% of statistically-significant pixels. For example, extensive differences in RD, MD and FA were observed in the genu of the corpus callosum (yellow arrow), but were not accompanied by any MTR differences. All of this suggests that DTI and MTR give different weights to the tissue microstructural substrates of NPSLE. Cumulative WM lesion maps were computed for NPSLE patients (top right) and SLE patients (bottom right). These, taken with the TBSS results, indicate that the WM lesions are not exclusively responsible for the significant DTI and MTR changes. The large spatial extent of differences in RD compared to differences in AD suggests that most of the increase in MD (and decrease in FA) observed in the NPSLE patients is related to the increase in RD. Previous studies have attributed disease-related changes in both RD[8] and MTR[9] to changes in myelination. However, it also has been reported that MTR is sensitive to increased water content caused by edema in response to inflammation[10]. Furthermore, a recent study found that changes in Choline diffusivity may be a marker for inflammation-driven glial activation in NPSLE[11]. It is therefore premature to conclude that RD changes observed in NPSLE originate from demyelination, *particularly since changes in RD were not consistent with changes in MTR.*

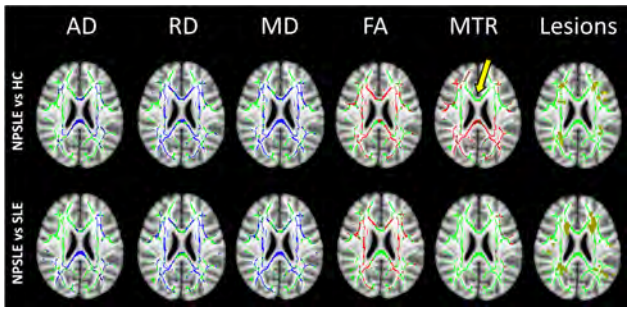

Fig.1 TBSS results showing statistically significant differences ($p<0.05$) in NPSLE patients compared to HC and SLE patients. Mean FA skeleton is shown in green, regions with higher values in the NPSLE patients compared to SLE or HC are shown in blue and regions with lower values in NPSLE patients compared to SLE and HC are shown in red. Lesions are shown in yellow.

Conclusion: This is the first study to offer spatial co-analysis of MTR and DTI metrics in NPSLE, with the additional information originating from FLAIR-based cumulative lesion maps. Our results suggest that only a multimodal approach has the potential to thoroughly characterize disease-related changes in the brain and that the information that pertains to the underlying pathological mechanisms can be inferred from both the overlap as well as from the mismatch between the different modalities. Current work is underway to acquire MTI and DTI data on NPSLE patients who no longer have active NP symptoms to further elucidate the biological basis for these microstructural measures in response to anti-inflammatory and anti-coagulant therapies.

References: 1. Jeltsch-David et al. Nature Reviews Neurology (2014) **2.** Zirkzee et al. J Rheumatol (2012) **3.** Bosma et al. Arth&Rheuma (2004) **4.** Emmer et al. JMRI (2006) **5.** Jenkinson, M et al. NeuroImage (2002) **6.** Bodoni et al. Hum Brain Mapp (2014) **7.** Jung et al. BMC Neurology (2010) **8.** Song et al. NeuroImage (2005) **9.** Schmierer et al. Ann Neurol (2004) **10.** Vavasour et al. JMRI (2011) **11.** Ercan et al. ISMRM 2014