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Executive Summary of the Thesis

White matter changes in Episodic Migraine: a neurite orientation dispersion and density imaging (NODDI) study.

Laurea Magistrale in Biomedical Engineering - Ingegneria Biomedica

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1. Introduction

Migraine has been classified by the ICHD, 3rd edition [1], as a recurrent headache disorder with attacks that last 4 to 72 hours. In particular, the case of Episodic Migraine (EM) have been taken into account in this study, considering the particular case of Menstrual Migraine (MM). This type of patients show migraine episodes when the menstruation period is starting and, because of that, they were able to understand the period of time in which they will experience the seizure in order to perform the acquisition in the correct moment. Even if it is an extremely common disease, there are still not many effective therapeutic plans against it. This is partially due to the lack of knowledge of the cause of the disease itself and, for this reason, the investigations on the white-matter alterations are still considered a challenge by the whole scientific community. The focus on the in-vivo white matter could help to deepen our understanding of the disease.
In particular, the recent advances in Magnetic Resonance Imaging (MRI) have provided compelling evidence, which is why it's nowadays used to study the majority of brain pathologies. Diffusion MRI (dMRI) is one of the available MRI techniques that could provide in vivo microstructural information on biological tissues in a non-invasive way and, hence, it has been applied in several studies related to white-matter abnormalities in migraineurs.
White Matter (WM) could be defined as the structural basis of functional integrations between brain regions. It is essential to understand that detecting microstructural abnormalities in the white matter might benefit the understanding of abnormal functional activities.
Among the dMRI techniques, the NODDI model caught the attention of the author because of its feasibility and simplicity in clinical settings. Indeed, the NODDI model is capable to provide quantitative compartment-specific metrics that are biologically meaningful and interesting from a clinical point of view, including the Isotropic Volume Fraction (ISOVF), which quantifies the extent of contamination caused by Cerebrospinal Fluid (CSF); the Intracellular Volume Fraction (ICVF), which provides an estimate of axonal density in white matter; the Orientation Dispersion Index (ODI), which quantifies the extent of axonal dispersion in white matter. Also, this model had not been previ-

ously applied in Migraine research studies. One clear hypothesis has been made in this work: NODDI could detect white matter alterations when comparing between EM patients and control subjects.
Within the aim of testing this hypothesis, the data acquisition of 14 controls and 9 EM patients has been performed, using Tract-Based Spatial Statistics (TBSS) for quantitative analysis. In order to further test this hypothesis and to validate the results obtained with the previous TBSS analysis, a Region-of-interest (ROI) analysis has been used, considering a total number of 14 controls and 10 EM patients.

2. Methods

The data analysed throughout this thesis was previously acquired in the context of the Project MIG_N2Treat by the LASEEB research team. Both control and patient participants were scanned using a 3T Siemens Vida System scan. All the MRI and EEG data have been collected at Hospital da Luz of Lisbon. Indeed, the team performed the acquisition of a total of 24 subjects (all women), 14 controls and 10 Episodic Migraine patients. Regarding the control individuals, the brain activity was measured in two different conditions, which are Premenstrual (before the starting of the menstrual period) and Midcycle (in the menstrual period).
The brain activity of the EM patients, instead, was measured in four phases: Interictal (in between two different seizures), Preictal (before the start of the seizure), Ictal (during the seizur), Postictal (after the seizure). It is necessary to bear in mind that, in some cases, it has been hard to collect all the measures for all the phases. Indeed, some EM patients won't present the data for all 4 phases. Moreover the premenstrual session should control the variations derived from the cycle itself compared to the preictal, ictal, and postictal sessions. The midcycle session should control the variations inherent to the cycle compared to the interictal session.
The NODDI model has been applied to the aforementioned dataset. The aim of NODDI is the description of the water diffusion in each voxel considering three compartments, including intra-neurite, extra-neurite and free-water compartments. Mathematically, it is possible to define the diffusion weighted MR signal as a linear combination of the signals related to these three compartments:

$$S = [1 - f_{iso}][f_{ic}S_{ic} + (1 - f_{ic})S_{ec}] + f_{iso}S_{iso}, \quad (1)$$

where: S is the normalized diffusion weighted signal, S_{ic}, S_{ec} and S_{iso} are the normalized diffusion weighted signal decays contributed separately by the intra-neurite compartment, extra-neurite compartment and free water compartment, f_{ic} and f_{iso} are the volume fractions of the respective compartments.
In particular, the AMICO (Accelerate Microstructure Imaging via Convex Optimization) framework [2] has been applied to the dataset in order to reduce the time required by the fitting process (long fitting process time required by the NODDI matlab toolbox [3]).
Then, two different statistical analysis techniques have been applied in order to enlight the statistical differences among groups.
At first, a TBSS (Tract base spatial statistic) analysis has been applied, following the TBSS tutorial [4]. In this method, the white matter skeleton was created based on the mean Fractional Anisotropy (FA) map of the whole cohort. Then, in order to enlighten which FA skeleton voxels are significantly different between two groups of subjects, the voxelwise statistics on the skeletonized FA data were applied, using a t-test. Successively, the NODDI metrics maps were projected onto the skeleton. In particular, TBSS has been applied for ODI, ISOVF, and ICVF.
Based on the results that have been obtained from the TBSS analysis, the Region-of-Interest analysis have been applied to further validate the NODDI suitability in the case of EM. Specifically, 10 ROIs have been identified based on the significant results obtained with the TBSS analysis. Once the ROIs have been identified, the author proceeded with the extraction of the single ROIs, centered on the skeletonized maps of the mean FA values for each group of subjects. Then, a t-test was applied for all the comparisons for the parameters ISOVF, ICVF and OD (significant difference if p-value$<$0.05).

3. Results and Discussion

As mentioned before, not all the subjects in the patient group present the acquisition for all

phases, due to the fact that the acquisitions are still ongoing and due to the restricted available time that the author had during the research work. Indeed, for the phases connected to the migraine cycle itself, only the postictal and interictal phases have been chosen to perform the comparisons with the control subjects. This is due to the fact that the postictal and interictal phases acquisitions were the most abundant throughout all subjects in the patient group. Thus, this choice allows the author to have an higher number of subjects for the analysis (higher than the case of choosing just the ictal or preictal phase sessions). Ideally, it is better to consider all three phases connected to the premenstrual phase in order to have a solid statistical analysis. In order to highlight the differences between controls and EM patients for the parameters ODI, ICVF and ISOVF, two comparisons have been performed: premenstrual-postictal and midcycle-interictal.
Furthermore, in order to highlight the intra-phase differences in controls and EM patients for the aforementioned parameters, two other comparisons have been performed: interictal-postictal and midcycle-premenstrual. The age of all the subjects was inserted in the design matrix, and, hence, considered in the analysis.
In the performed TBSS analysis, no relevant results were found in the premenstrual-postictal, interictal-postictal, and midcycle-premenstrual comparisons.
Regarding the midcycle-interictal comparison, some significant results have been found only for the ISOVF parameter, as shown in Table 1. The whole-brain white matter analysis of NODDI metrics revealed a reduced value of ISOVF in the interictal phase compared to the midcycle phase in the left inferior fronto-occipital fasciculus, left forceps major, left superior longitudinal fasciculus, and left cingulum. In Figure 1, it is possible to visualize the areas in which significantly decreased ISOVF values in the interictal phase compared to the midcycle phase have been found for different values of z (Axial Plane representation).
The reduction of CSF (Cerebrospinal fluid) volume in the cingulum in migraineurs compared to controls (decreased ISOVF value) could suggest an increment of gray and white matter volume for those specific voxels that, according to Messina et al. [6], could lead to alterations related to the visual-spatial abilities of menstrual migraine patients. In the left superior longitudinal fasciculus, a decreased value of ISOVF (that could be associated with increased white matter and gray matter volumes) have been found in menstrual migraine patients. This should be assumed as an opposite result compared to what has been found by Masson et al [7]. In the left frontal major, the most significant differences in the ISOVF values between migraineurs and controls have been detected (smallest p-values in this tract). Even if several alterations in this area have been reported, the specific function of the tract is still unknown with the scientific community. The same could be stated for the decreased ISOVF values in the left inferior fronto-occipital fasciculus of menstrual migraine patients compared to controls.
Based on the TBSS results, the author tried to identify the ROIs that are included in those areas where this significant difference has been found by using the JHU atlases, with the purpose of deeply testing those areas and discovering other possible areas that could register significant differences among different groups and parameters present in the available database, using the high sensitivity offered by the ROI analysis.
Finally, Table 2 and 3 show the results that have been obtained at the end of the ROI analysis. It is important to specify that the multiple comparison correction for the p-values was not performed due to the fact that the obtained uncorrected p-values were too high to survive the correction and hence be classified as significant. From the ROI analysis results, it is possible to state that significant results have been found in the left splenium of corpus callosum, left anterior thalamic radiation (ATR), left posterior corona radiata (PCR), left inferior fronto-occipital fasciculus (IFOF) and left superior longitudinal fasciculus (SLF). In particular, in the left splenium of corpus callosum, a significant decrease of the ISOVF values of the EM patients under the interictal phase compared to the controls under the midcycle phase has been detected. The same result has been found in the left ATR and left IFOF. In the left PCR, significant differences in ISOVF values have been found for the midcycle-interictal comparison. Eventually, significant

Table 1: White Matter regions where significantly decreased ISOVF values were found in EM patients during the interictal phase compared to controls during midcycle phase. Only the regions with a p-value lower than 0.05 are included in this table. L Left, R Right, EM Episodic Migraineurs, CTRL controls.

Comparisons	White Matter tract	Averaged p-value (uncorrected)
EM<CTRL	Inferior Fronto-Occipital Fasciculus L	0.048
EM<CTRL	Forceps Major L	0.036
EM<CTRL	Superior Longitudinal Fasciculus L	0.044
EM<CTRL	Cingulum L	0.038

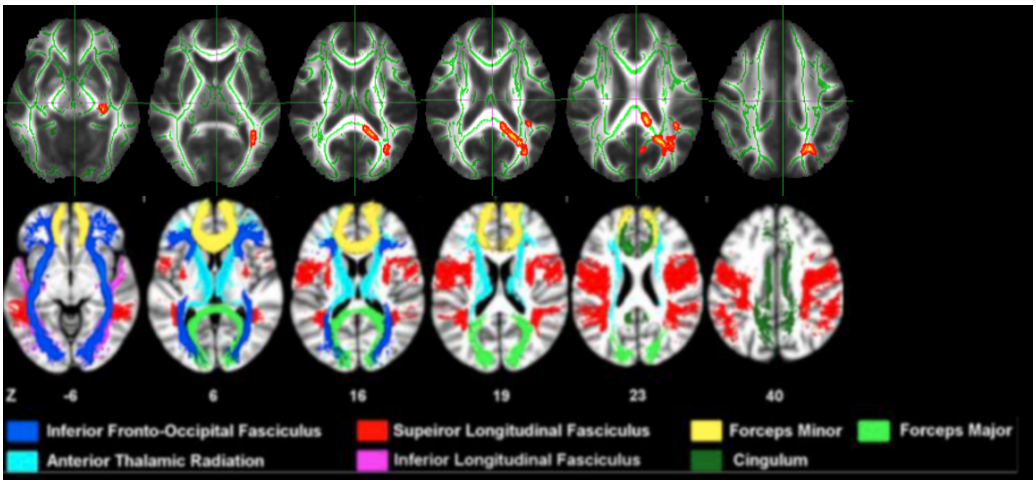

Figure 1: Up: White Matter regions where significantly decreased ISOVF values were found in the interictal phase compared to the midcycle phase for different z values (-6, 6, 16, 19, 23, 40). The white-matter skeleton is represented in green. Significantly decreased ISOVF values are represented with red-yellow clusters. L left hemisphere, R right hemisphere. Down: White-matter tracts using the Johns Hopkins University (JHU) white-matter tractography atlas. Color labels for the JHU tracts are displayed at the bottom. [5]

Table 2: Pair-wise comparisons of the uncorrected p-values of region-of-interest white matter tracts among different groups and parameters of interest (ISOVF, ICVF, OD).
L: left hemisphere. R: right hemisphere.
MID: Control subjects during midcycle phase. INT: MM patients during interictal phase.
*Significant differences ($p<0.05$) are marked with an asterisk.

WM tracts	Uncorrected p-values MID-INT		
	ISOVF	ICVF	OD
Splenium of corpus callosium L	**0.02***	0.18	0.30
Anterior thalamic radiation (ATR) L	**0.02***	0.25	0.65
Posterior thalamic radiation (PTR) L	0.08	0.17	0.34
Posterior corona radiata (PCR) L	**0.03***	0.50	0.80
Inferior fronto-occipital fasciculus (IFOF) L	**0.04***	0.29	0.52
Cingulum (hippocampus) L	0.29	0.97	0.85
Cingulum (cingulate gyrus) L	0.11	0.43	0.60
Inferior longitudinal fasciculus (ILF) L	0.56	0.15	0.18
Superior longitudinal fasciculus (SLF) L	0.12	0.42	0.85
Forceps major	0.11	0.06	0.19

Table 3: Pair-wise comparisons of the uncorrected p-values of region-of-interest white matter tracts among different groups and parameters of interest (ISOVF, ICVF, OD).
L: left hemisphere. R: right hemisphere.
POS: MM patients during postictal phase. PRE: Control subjects during premenstrual phase.
*Significant differences ($p<0.05$) are marked with an asterisk.

WM tracts	Uncorrected p-values		
	PRE-POS		
	ISOVF	ICVF	OD
Splenium of corpus callosium L	0.89	0.89	0.51
Anterior thalamic radiation (ATR) L	0.97	0.47	0.83
Posterior thalamic radiation (PTR) L	0.54	0.50	0.95
Posterior corona radiata (PCR) L	0.18	0.31	0.99
Inferior fronto-occipital fasciculus (IFOF) L	0.81	0.61	0.78
Cingulum (hippocampus) L	0.74	0.80	0.77
Cingulum (cingulate gyrus) L	0.40	0.23	0.44
Inferior longitudinal fasciculus (ILF) L	0.43	0.74	0.76
Superior longitudinal fasciculus (SLF) L	**0.03***	0.38	0.78
Forceps major	0.64	0.64	0.55

differences for the parameter ISOVF were found in premenstrual-posictal comparison in the left SLF.
A decrease of mean diffusivity (MD) could suggest a lower presence of water due to the fact that lower MD implies a lower average molecular motion. With that being said, it is possible to state that our results were consistent with the previous migraine studies [8, 9] in the cases of left IFOF and left splenium of corpus callosum. In these terms, we obtained opposite results in left SLF, considering Messina et al. migraine study [9]. Furthermore, we obtained significant differences in ATR and PCR for the ISOVF values even if no significant difference between migraineurs and controls had been found in previous studies [10, 11].
Comparing the ROI analysis results with the ones previously obtained with the TBSS analysis, it is possible to state that the obtained results were consistent just for the left IFOF. No significant results have been found in the Cingulum and Forceps major in the current case, while significant differences were detected in these tracts with the TBSS analysis. Furthermore, the ROI analysis revealed significant differences for ISOVF in the premenstrual-posictal comparisons for the SLF, while with the previous voxelwise approach this difference was found in the midcycle-interictal comparison for this tract. Also, it was possible to register significant differences in tracts that were not considered in the TBSS analysis, such as left ATR, left PCR and left splenium of corpus callosum.

4. Conclusions

To conclude, it is possible to state that generally the results that were found with the ROI analysis are inconsistent with respect to the ones obtained with the TBSS analysis. Although the TBSS definitely helped the author to understand what potential areas could be subjected to an alteration caused by migraine. Thus, it has been possible to limit our research to some specific ROIs, reducing the total number of performed statistical tests.
It is very important to consider that it is not fully certain that the NODDI model could be the most suitable one for the case of episodic migraine. Moreover, a large dataset should be required in order to investigate deeply the alteration of the whole-brain white-matter tracts in menstrual migraine. Hence, the limited sample size analyzed in this study could be seen as a strong limitation of the present study.

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