

Simone Guerrieri<sup>1</sup>, Giovanni Di Maggio<sup>1</sup>, Marco Pisa<sup>1</sup>, Francesco Vitali<sup>1</sup>, Roberto Santangelo<sup>1</sup>, Stefania Medaglini<sup>1</sup>, Lucia Moiola<sup>1</sup>, Ubaldo Del Carro<sup>1</sup>, Vittorio Martinelli<sup>1</sup>, Alexander Klistorner<sup>2</sup>, Giancarlo Comi<sup>1</sup>, Letizia Leocani<sup>1</sup>

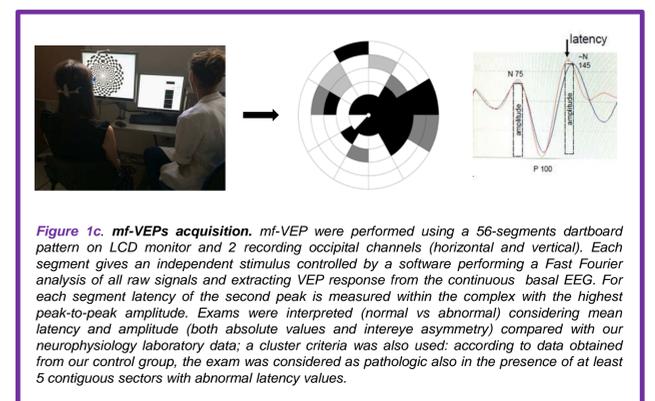
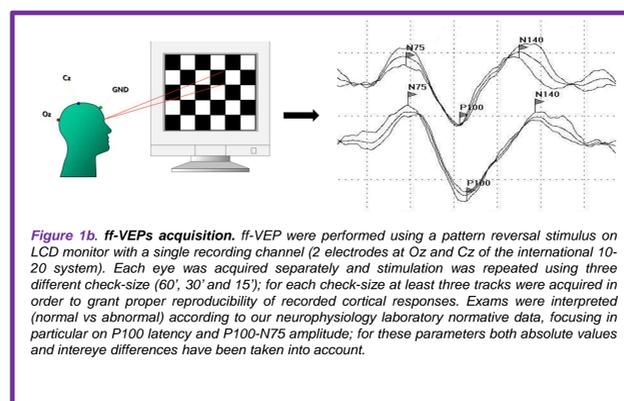
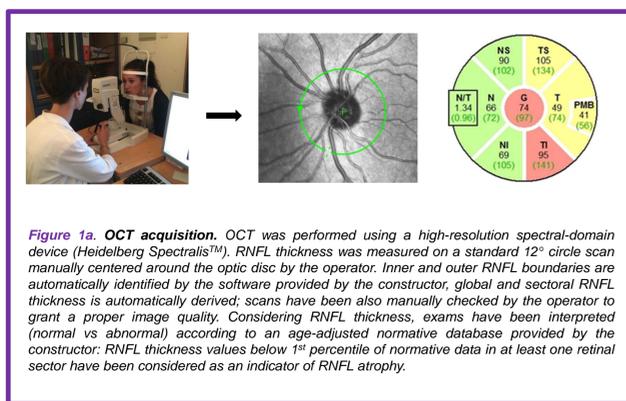
<sup>1</sup> Neurological Dep.t & INSPE - Institute of Experimental Neurology; University Hospital - IRCCS S.Raffaele, Milan – Italy  
<sup>2</sup> Faculty of Medicine and Human Science - Macquarie University; Save Sight Institute - Sydney University, Sydney – Australia

## Introduction

In the assessment of visual pathway in Multiple Sclerosis (MS), optical coherence tomography (OCT) is used, especially in the field of research, to measure retinal nerve fiber layer (RNFL) thickness as a marker of axonal loss [1-2] allowing to detect neurodegeneration in vivo and in a non-invasive way. On the other hand full-field visual evoked potentials (ff-VEPs) are commonly performed in neurological clinical practice as an indicator of demyelination [3], especially in the presence of optic neuritis. Multifocal visual evoked potentials (mf-VEPs) allows the electrophysiological assessment of conduction along the central visual pathways for separate portions of the visual field [4]; primarily developed for the assessment of glaucoma [5], this technique has proven to be useful in the investigation of other optic neuropathies and also MS [6]. In this perspective, starting from the experience of our neurophysiology lab, we explored whether a multimodal visual system evaluation, comprehensive of OCT, ff-VEPs and mf-VEPs, could be useful to assess MS patients in everyday clinical practice.

## Methods

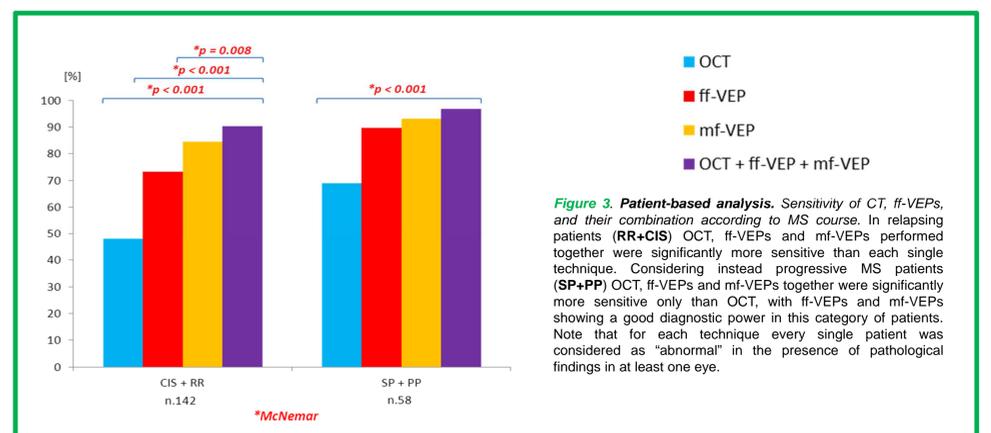
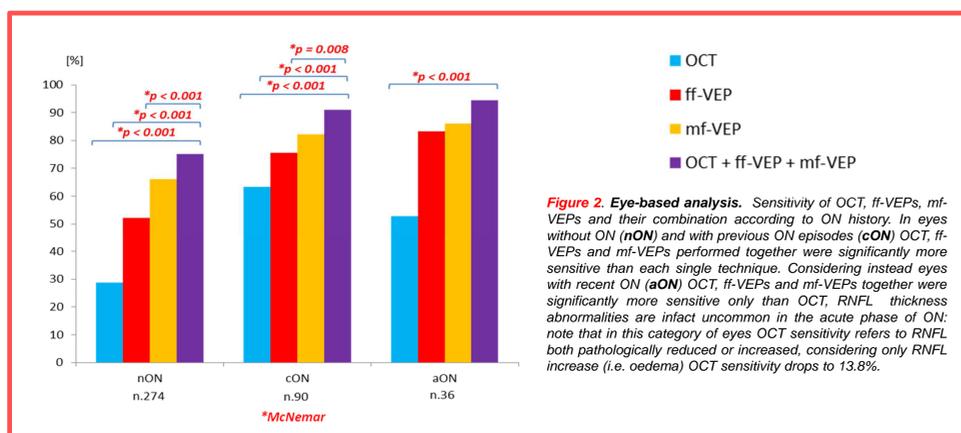
200 MS patients (16 Clinically Isolated Syndromes-CIS, 126 Relapsing Remitting-RRMS, 38 Secondary Progressive-SPMS, 20 Primary Progressive-PPMS, mean age 40.3 years, mean disease duration 8.19 years, median EDSS 2.0) underwent neurophysiological assessment (OCT, ff-VEPs and mf-VEPs) (figure 1a-c). OCT (global and sectoral RNFL thickness) was evaluated considering normative data provided by manufacturer; ff-VEPs and mf-VEPs (latency and amplitude) were interpreted according to our lab data; mf-VEPs cluster analysis was also performed. OCT, ff-VEPs and mf-VEPs sensitivities were analyzed according to ON history and disease course and compared using the McNemar Test.



## Results

**Eye-based analysis (figure 2):** in eyes without Optic Neuritis (nON, n=274), OCT, ff-VEPs and mf-VEPs combination was more sensitive than each single technique (75.2% vs 28.8%, 52.2% and 66.1% respectively, p<0.001). The same advantage (91.1% vs 63.3%, 75.6% and 82.2% respectively, p<0.001 for OCT and ff-VEP, p=0.008 for mf-VEP) was found considering eyes with previous ON (>3 months - cON, n=90). In eyes with recent ON (<3 months - aON, n=36) the combination of the three techniques was superior to OCT only (94.4% vs 58.8%, p<0.001); both ff-VEPs and mf-VEPs showed alone a good diagnostic power (83.3% and 86.1% respectively). When **comparing single techniques** both ff-VEPs and mf-VEPs were superior to OCT in nON eyes (28.8% vs 52.2% and 66.1% respectively, p<0.001), with mf-VEPs more sensitive than ff-VEPs (p<0.001). In cON eyes no statistical difference was found between OCT and ff-VEPs (63.3% vs 75.5%, p=0.071), with mf-VEPs more sensitive than OCT (82.2% vs 63.3%, p=0.002) but not than ff-VEPs. In aON eyes both ff-VEPs and mf-VEPs were superior to OCT (52.8% vs 83.4%, p=0.003 and 86.1%, p=0.008 respectively), with no difference among them. Including **cluster analysis** mf-VEPs were found more sensitive than ff-VEPs also in cON eyes (87.8% vs 75.2%, p=0.013), but not in aON eyes, although reaching 94.4% sensitivity in this category.

**Patient-based analysis (figure 3):** considering RRMS and CIS patients (RR+CIS, n=142) OCT, ff-VEPs and mf-VEPs combination was more sensitive than each single technique (90.1% vs 47.9%, 73.2% and 84.5% respectively, p<0.001 for OCT and ff-VEP, p=0.008 for mf-VEP). When considering progressive patients (SP+PP, n=58) the combination of the three techniques was superior to OCT only (96.6% vs 69.0%, p<0.001) but not than ff-VEPs and mf-VEPs (89.7% and 93.1% respectively). When **comparing single techniques** both ff-VEPs and mf-VEPs were superior to OCT in CIS+RR patients (47.9% vs 73.2% and 84.5% respectively, p<0.001), with mf-VEPs more sensitive than ff-VEPs (p=0.005). ff-VEPs and mf-VEPs were found to be more sensitive than OCT also when considering SP+PP patients (69.0% vs 89.7% and 93.1% respectively, p=0.001) with no statistical difference among them also after **cluster analysis** inclusion (98.3% vs 89.7%, p=0.063).



## Discussion and Conclusions

The present findings suggest the usefulness of a multimodal approach to the visual system in MS, combining morphological (OCT) with functional information (ff-VEPs and mf-VEPs). The latter techniques seem both useful although providing mutually complementary information. While ff-VEPs provide a global assessment of the visual pathway with robust diagnostic information, mf-VEPs allow to parcel out visual conduction, possibly identifying partial defects which may not influence standard VEPs results, as previously suggested [7] and, when detailed cluster analysis is used as in the present study, may provide higher sensitivity compared with ff-VEPs.

As expected, the advantage of a combined approach seems greater when considering the relatively **early phases of relapsing MS**, when EPs are less sensitive compared with the progressive phase [8] **particularly in eyes without previous ON**, where, consistently with what previously reported by our group [9], OCT is less sensitive than VEPs.

## Bibliography and Acknowledgements

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