MAGNETOENCEPHALOGRAPHY (MEG) AND DIFFUSION TENSOR MAGNETIC RESONANCE IMAGING (DTI) OF FUNCTIONAL AND EFFECTIVE BRAIN CONNECTIVITY IN TRAUMATIC BRAIN INJURY

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1. Resume

The present study used an integrated multimodal neuroimaging approach involving MEG and DTI to assess their utility in functional and effective connectivity evaluation in TBI. The study population consisted of TBI patients and a group of healthy subjects. All patients in the sample were examined twice (before and after rehabilitation). All study patients completed a neurorehabilitation programme adapted to each individual's requirements. Patients and controls underwent a neuropsychological assessment in order to establish their cognitive status in multiple cognitive functions. Traumatic white matter injury has been measured with diffusion tensor imaging (DTI), impaired cortical activation has been detected with magnetoencephalography (MEG).

Brain networks connectivity analysis showed: TBI patients exhibit functional connectivity alteration as compared to the control subjects; overall significant reduction of MEG connectivity activity in TBI patients compared with control subjects, significant decrease in the long-distance connectivity and significant increase in the short-distance connectivity as a result of TBI. Extent of functional disconnection was associated with injury severity. Reduction of MEG connectivity originates from grey matter neurons that experience deafferentation due to axonal injury to the underlying white matter fibre tracts, which was manifested on diffusion tensor imaging (DTI) as reduced fractional anisotropy. Neuronal reorganization, as measured by brain connectivity, due to comprehensive rehabilitation process correlated with cognitive recovery as indicated by neuropsychological assessment.

This study demonstrates that TBI disturbances in functional connectivity are associated with network-specific neurological deficits and helps understanding of how the brain reorganizes itself in response to behavioural training and rehabilitation interventions. This longitudinal study has several advantages, most importantly enabling the investigation of dynamic evolution of MEG and DTI parameters and the correlation to neuropsychological outcome. Longitudinal studies like ours allow the investigation of the pattern of neural response over time and may provide insight into the mechanisms underlying recovery after brain injury. In addition, an important question in functional imaging is whether the reorganization found is also responsible for patients' functional improvement. Changes observed on psychometric test of cognitive function after rehabilitation is commonly interpreted as a sign of effectiveness of the rehabilitation

process. Our results provided by MEG and DTI neuroimaging studies principally show spatially localized physiological changes and confirm improvement especially with MEG. Furthermore, this integrated bimodal neuroimaging may provide sensitive and objective pre-post rehabilitation assessment of the effectiveness of TBI patient's intervention with neuroimaging-based changes useful for the evaluation of the effectiveness of intervention.

Background

This project aimed to assess changes in brain connectivity patterns (functional and effective), using MEG and DTI, as a methods to estimate neuronal reorganization due to comprehensive rehabilitation process after severe TBI.

Methods

The study population consisted of TBI patients (25 subjects) and a group of healthy controls (25 subjects). All patients in the sample were examined twice: before and after rehabilitation (preR and postR respectively). The control subjects were examined once. All study patients completed a neurorehabilitation programme adapted to each individual's requirements. Patients and controls underwent a neuropsychological assessment in order to establish their cognitive status in multiple cognitive functions (attention, memory, language, executive functions and visuospatial abilities) as well as their functioning in daily life. Traumatic white matter injury was measured with diffusion tensor imaging (DTI), impaired cortical activation was detected with MEG. MEG Dipole Density Analysis: Analysis of the source distribution of the neuromagnetic slow waves was used. Functional connectivity measures: Weighted Phase Lag Index (WPLI) (Vinck et al. 2011) in delta and alpha frequency range was applied. DTI pre-processing and analysis**:** Post-processing of DTI data and group comparison were performed within the FSL suite (version 4.1.8) (Smith et al., 2004).

2. Main Results

This cross-sectional and longitudinal study presents multimodal neuroimaging with magnetoencephalography and diffusion tensor mapping evidences of brain changes after traumatic brain injury and recovery evidences by patients who have suffered TBI. We have found both cross-sectional and longitudinal differences in grey matter cortical activation measured with magnetoencephalography and white matter injury measured with diffusion tensor imaging between TBI patients and controls. In a cross-sectional study MEG and DTI measurements were particularly sensitive, showing large areas of difference between patients and controls.

In the current study, we are showing that injured brain tissues in TBI patients generate pathological slow- wave magnetic signal that can be measured and localized by MEG). Pre rehabilitation patients exhibited significantly more slow waves activity in all areas in both hemispheres than the control group, this enhancement was particularly pronounced in bilaterally frontal and parietal regions (Figure 1). Regarding MEG functional connectivity PreR patients exhibited significantly decrease in interhemispheric connectivity in the alpha band and significant increase in the intrahemispheric distance connectivity in delta band as compared to normal subjects.

- Using DTI method TBI patients showed decreased FA and increased MD in several major fibres. - - All patients exhibited abnormal slow waves in MEG and white matter abnormalities in DTI; interestingly areas of grey matter that generated slow waves of MEG DD changes were in remote localization to areas of white matter changes. Additionally, there was negative correlation between MEG DD and FA in PreR patients, and positive correlation between DD and MD in PreR patients.

- Regarding domains of cognitive functions as measured by neuropsychological battery TBI patients had lower all scores as compared to control subjects (Figure 2).

- All regions with MEG DD abnormalities have been directly covered by adjacent abnormalities in FA and MD DTI results (Figure 3).

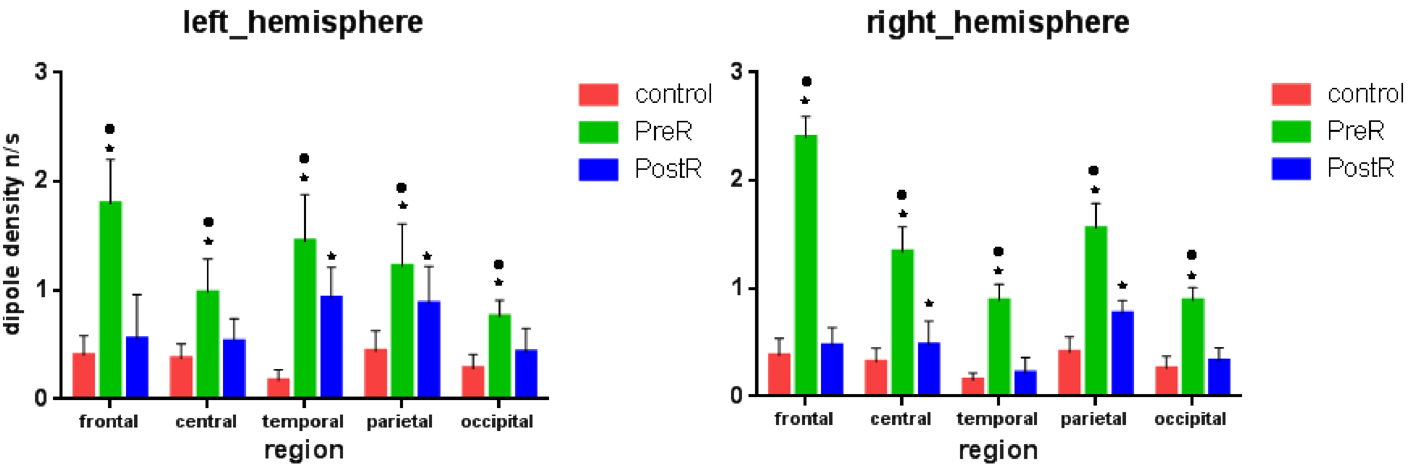

Figure 1. Distribution of MEG dipole densities in the delta frequency band, plotted separately for PreR, PostR and control groups showing the 10 regions of dipole density estimation in left and right hemisphere. Asterisk indicates statistical differences with control group and dot indicates statistical differences within PreR-PostR period.

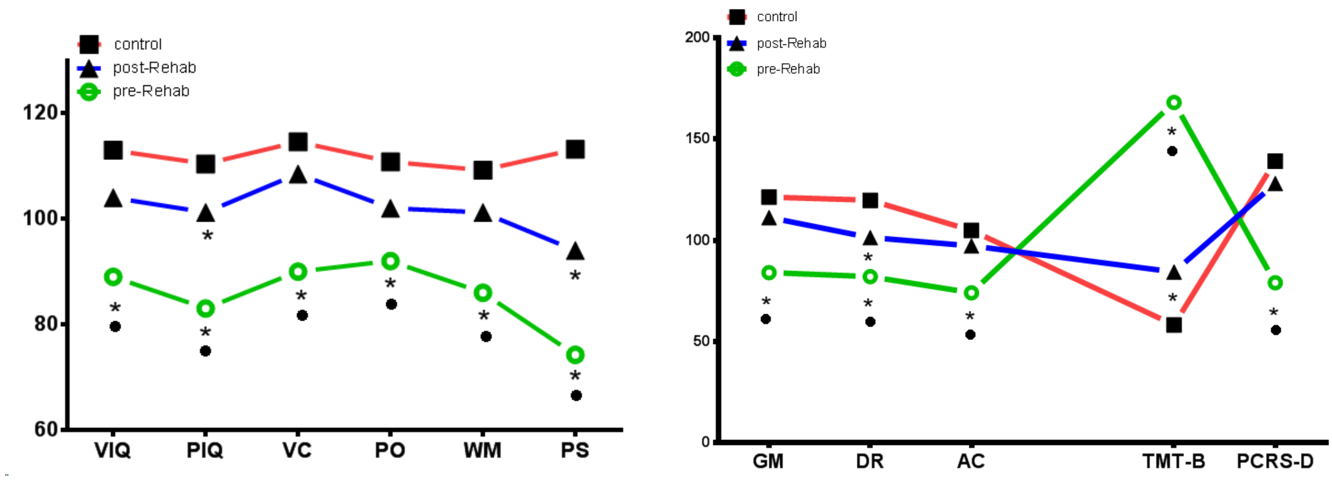

Figure 2. (A) General scores of WAIS III for PreR, PostR and control groups. (B) Some indexes of WMS-R and neuropsychological scores for PreR, PostR and control groups. VIQ-verbal IQ, PIC-Performance IQ, VC-verbal comprehension index, PO-perceptual organization index, WM-working memory index, PS-processing speed index; GM-general memory index, DR-delayed recall index, AC-Attention index, TMT-B-Trail Making test B, PCRS-D-patient competency rating scale (daily living). Asterisk indicates statistical differences with control group and dot indicates statistical differences within PreR-PostR period.

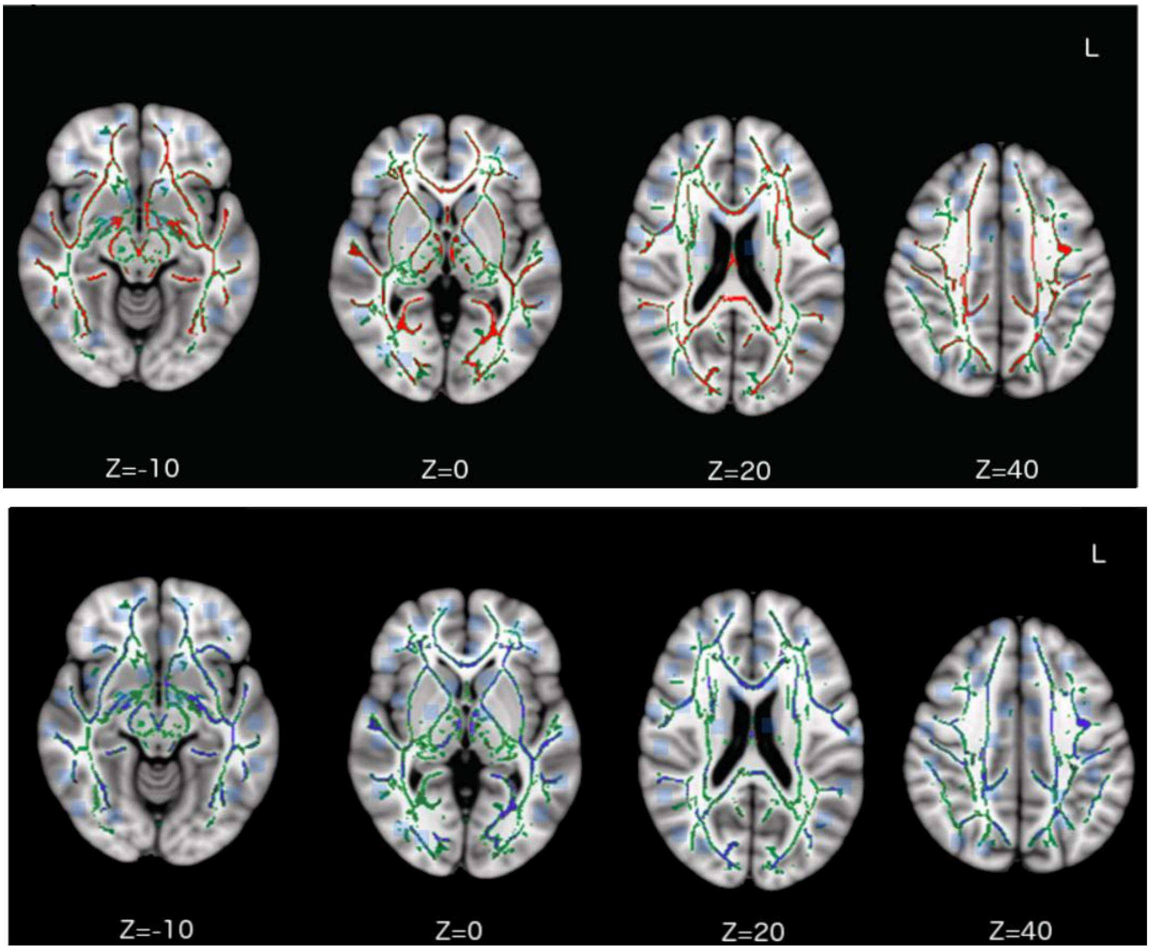

Figure 3. Linked MEG and DTI data on a cross-sectional comparison. TBSS fractional anisotropy (A) and mean diffusivity (B) with MEG DD slow waves generators overlaid on a standard MNI 152T1 brain. Regions of lower FA are shown in red, regions of higher MD are shown in blue. Violet voxels represents MEG delta waves generators. (radiological convention (right is left). Threshold $p<0.05$ corrected for multiple comparisons.

To our knowledge this is the first longitudinal multimodal imaging approach with MEG and DTI.

In a longitudinal evaluation TBI patients showed a general trend towards improvements related to number of slow waves generators in comparison with PreR in all brain areas reaching control values in all but 4 regions. In contrast, white matter probability maps were somewhat decreased to the PreR FA maps in all areas with exception for forceps major and splenium of the corpus callosum and fornix where TBSS analysis of the FA DTI measure on the follow-up scans showed significant FA reduction (Figure 4). MD DTI measures on the follow-up scans didn't show significant

MD changes but with clear tendency to increase. We have found an interesting paradox that even though the TBI brain appears to undergo several disadvantageous changes over time in a white matter (no change, or decreases in FA, increases in MD) grey matter cortical activation measured with MEG and neuropsychological function improves during the same time span. Especially, that after rehabilitation there was a general trend towards improvements in neuropsychological assessment observed in patients after therapy in comparison with PreR. All but 4 PostR results were close to scores obtained for control group (with negative correlation between WM, PIQ and TMT-B scores and MEG DD).

Moreover, TBI patients exhibited significant increase in the long-distance MEG connectivity in the alpha band and significant decrease in the short distance MEG connectivity (delta band) as compared to PreR measurement with general trend towards improvement (correlation was found between alpha band connectivity and WM index changes, and negative correlation between delta connectivity and VC, PO, VIQ and PCRS-D scores changes). Significant negative correlation has been found between PIQ scores changes and MEG DD changes in left frontal, right frontal, left temporal and right temporal regions. There was also significant negative correlation between WM index changes and left temporal and parietal, right temporal and parietal DD changes. Moreover, we found a negative correlation between TMT-B index changes and DD changes in frontal left and frontal right regions. WM index and GM index were found to be positively correlated with FA reduction in fornix. Changes in FA from PreR to PostR in fornix correlated with DD changes in right frontal and temporal DD changes. Interestingly, in a longitudinal linked MEG DTI comparison slow wave generating grey matter areas were adjacent to left and right posterior part of the brain adjacent to region with reduced DTI FA.

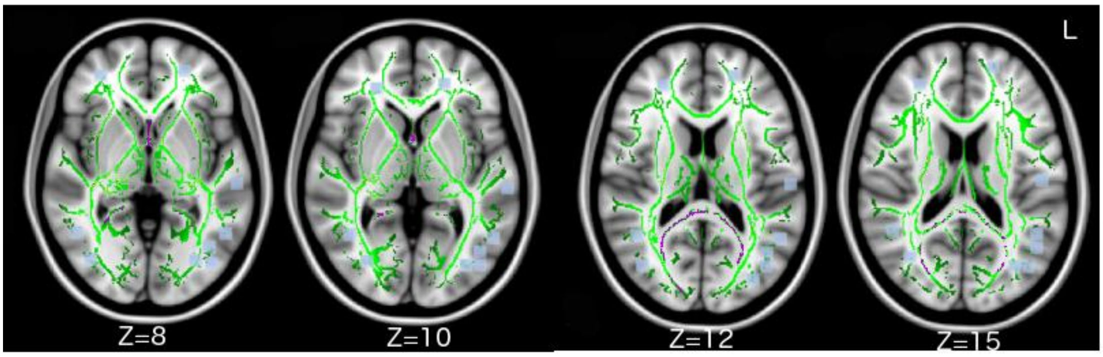

Figure 4. Linked MEG and FA DTI data on a follow-up comparison (PostR-PreR). TBSS fractional anisotropy with MEG DD slow waves generators overlaid on a standard MNI 152T1 brain. Regions of reduced FA are shown in purple. Violet voxels represents MEG delta waves generators. (radiological convention (right is left). Threshold $p<0.05$ corrected for multiple comparisons.

Considering follow-up improvement in MEG slow waves generators, MEG connectivity and the neuropsychological tests, without simultaneous general significant changes in DTI white matter FA and MD, we suggests that when recovery of brain function is facilitated by rehabilitation techniques, it may be accompanied by neuroplastic recovery via a reorganization of functional networks.

3. Relevance and possible clinical implications of the final results obtained

This longitudinal study has several advantages:

- Most importantly, enabling the investigation of dynamic evolution of MEG and DTI parameters and the correlation to neuropsychological outcome as pre-post rehabilitation assessment.

- Longitudinal studies like ours allow the investigation of the pattern of neural response over time and may provide insight into the mechanisms underlying recovery after brain injury.

- In addition, an important question in functional imaging is whether the reorganization found is also responsible for patients' functional improvement. Changes observed on psychometric test of cognitive function after rehabilitation is commonly interpreted as a sign of effectiveness of the rehabilitation process. Our results provided by MEG and DTI neuroimaging studies principally show spatially localized physiological changes and confirm improvement especially with MEG. Furthermore, this integrated bimodal neuroimaging may provide sensitive and objective pre-post rehabilitation assessment of the effectiveness of TBI patients intervention with neuroimaging based changes useful for the evaluation of the effectiveness of intervention.

4. Publications or communications derived from this research

Rafal Nowak; Magnetoencephalography and TBI. 4th Annual Meeting of the Catalan Neurophysiology Society (Barcelona, 10.04.2012).

Rafal Nowak; Magnetoencephalography; III Congreso de la Sociedad Española de Neurocirugía Funcional y Esteotáctica 14.15 de noviembre, 2013, Barcelona
Rafal Nowak, Sandra Giménez; Magnetoencephalography brain connectivity patterns in traumatic brain injury. Clinical Neurophysiology; abstracts of the 30th International Congress of Clinical Neurophysiology (ICCN) of the IFCN, March 20–23, 2014, Berlin, Germany and 58th Annual Meeting of the German Society for Clinical Neurophysiology and Functional Imaging (DGKN).

Rafal Nowak, Sandra Giménez; Brain connectivity patterns in traumatic brain injury - preliminary MEG results. 9th FENS Forum of Neuroscience, July 5-9, 2014, Milan Italy.

R.Nowak, S.Gimenez, A. Leist, A. Santana, A. Mora, G. Graetz; MEG and DTI evidences of brain changes after traumatic brain injury and recovery. International Society for the Advancement of Clinical Magnetoencephalography, 23-26 June 2015, Helsinki, Finland
R.Nowak, S.Gimenez, A. Leist, A. Santana, A. Mora, G. Graetz.

Magnetoencephalography (MEG) and Diffusion Tensor Magnetic Resonance Imaging (DTI) of functional and effective brain connectivity in Traumatic Brain Injury (TBI). The 15th European Congress on Clinical Neurophysiology, Brno, Czech Republic,
Carolina Migliorelli, Joan Alonso, Sergio Romero, Miguel Mananas, Rafal Nowak and Antonio Russi, Journal of Neural Engineering. Automatic BSS-based filtering of metallic interference in MEG recordings: definition and validation using simulated signals.

Journal of Neural Engineering (Impact Factor: 3.3). 05/2015; 12:046001.
DOI: 10.1088/1741-2560/12/4/046001

R.Nowak, S.Gimenez, A. Leist, A. Santana, A. Mora, G. Graetz; Diffusion tensor imaging and magnetoencephalography study in traumatic brain injury patients. Neurology (under revision 2016).

R.Nowak, A. Santana, A. Leist, S. Gimenez, A. Mora, G. Graetz; Neuroimaging with MEG and DTI during recovery from TBI. Journal of Neurotrauma (under revision 2016);