NOVEL NEUROPSYCHOLOGICAL ASSESSMENT OF FRONTAL LOBE LESIONS BASED ON THE HYPOTHESIS OF DYNAMIC NEUROPLASTICITY AND COMPENSATION

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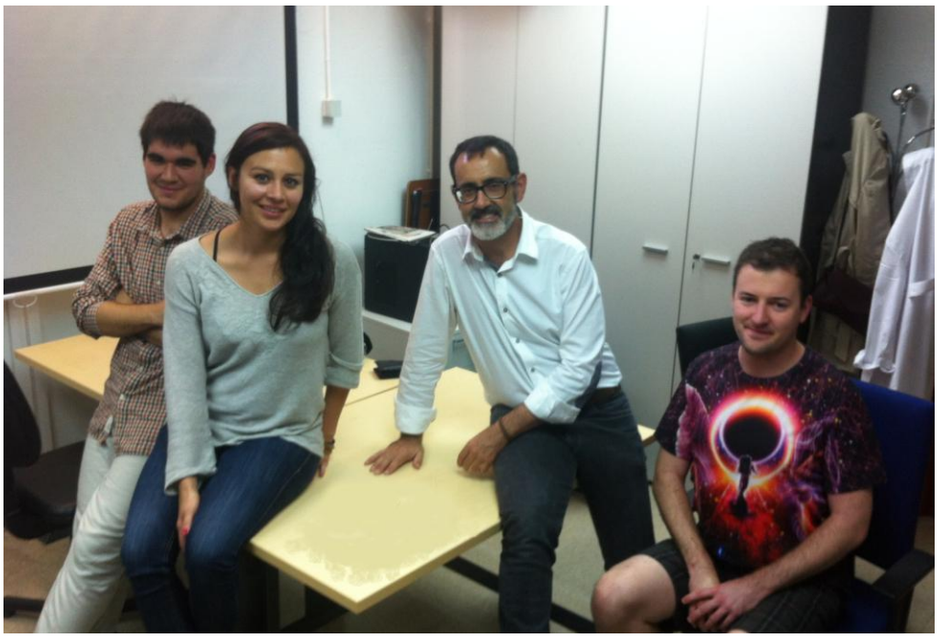

1. Summary of the project

Patients with brain lesions undergo enormous suffering and account for 35% of health care costs in Europe (Consensus Document on European Brain Research, EJN, 2011). Surprisingly, there currently are few scientifically informed ways to assist the recovery of cognitive dysfunctions suffered by these patients, particularly in the case of prefrontal lobe lesions. This research aimed to increase our insights into the neural mechanisms underlying recovery from prefrontal lobe damage, including a new neuropsychological assessment tool and advanced electrophysiological measures of human cognition for informing and guiding functional recovery of prefrontal lesion patients. In this context, the present project addressed two main questions: (a) whether the apparently normal cognitive performance often observed in unilateral prefrontal lesion patients could be explained by functional compensation by the intact homologous frontal cortex; and (b) whether recovery and compensation of prefrontal functions could be best explained from a dynamic (rather than static) model of neural plasticity. To meet these aims, we developed a new testing procedure that integrates state-of-the-art analyses of the electroencephalogram (EEG) with a computational model of human cognition based on a hierarchy of control processes in prefrontal cortex (Koechlin & Summerfield, 2007).

2. Results

To address our research questions, we examined 22 patients with cerebral lesions recruited from hospitals in Mallorca, plus an additional sample of 27 patients examined at the Cognition and Brain Sciences Unit of the Medical Research Council (MRC) in Cambridge. A normalization sample of healthy participants matched in age, gender, and education with the patients was also tested. All participants were administered a new bifield visuomotor procedure consisting of the same sequence of visual stimuli delivered under three different task contexts (Oddball, Go/NoGo, Switch) with increasing cognitive demands. Duration of each task: 20 min approx. (Figure 1).

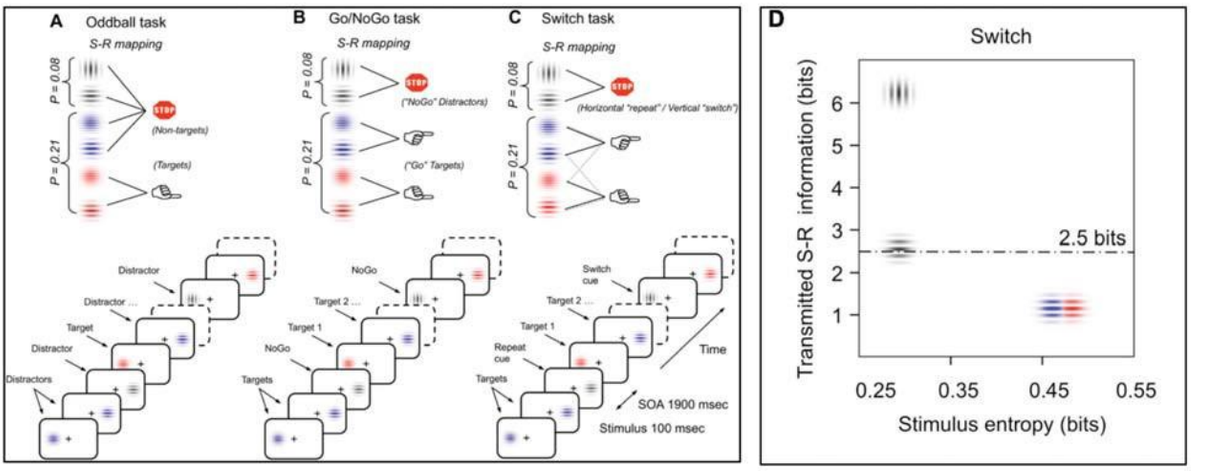

Figure 1. Novel neuropsychological assessment tool. All three tasks consisted of the same sequence of frequent colored Gabor stimuli with interspersed infrequent grey Gabor stimuli. (A) One-forced choice response task (i.e., "press a button for red Gabors"). (B) Two-forced response choice task ("press button 1 for red Gabors, and button 2 for blue Gabors". (C) Switch task with vertical and horizontal grey gratings instructing patients to switch and repeat the previous task rule, respectively. (D) A priori estimations of transmitted sensorimotor information in the most difficult Switch task.

The dotted line marks the human limit for holding information in working memory (cf., Cooper et al., 2016).

Using conventional *event-related potential (ERP) analyses* and *time-frequency decomposition* of EEG signals in the normalization sample of healthy controls, we demonstrated the utility of formal (i.e. information theoretic) descriptions of cognitive demands for an accurate, sensitive and cost- effective assessment of the cognitive deficits in neurological brain lesioned patients. Our novel neuropsychological assessment tool is highly sensitive to minor, often unnoticed, changes in cognitive demands and these correspond with scalp-recorded electrophysiological responses.

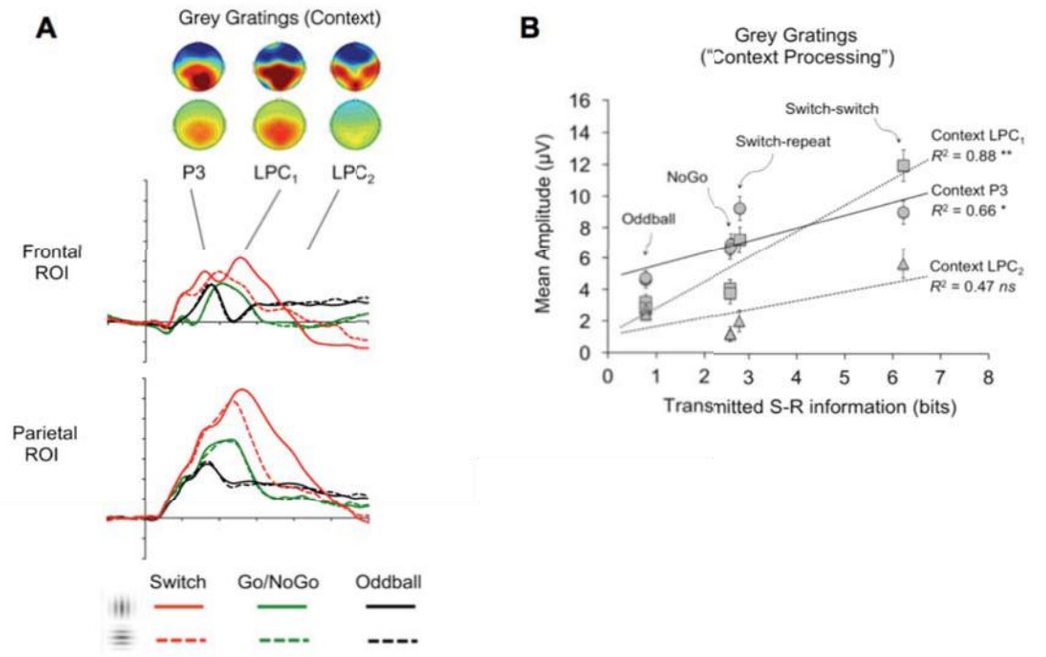

Figure 2. Analyses of brain responses in the normalization sample of healthy controls. (A) Mean brain responses from frontal and parietal scalp regions to the same grey Gabor stimuli delivered under three different task contexts. Gradual increases in cognitive demands produce gradually larger intensities of brain responses (B) Significant linear association between transmitted sensorimotor information (measured in bits) and the intensity of brain responses to the same stimuli under different task contexts, consistent with our computational model's predictions (Barceló & Cooper, in press).

Grey Gratings (Context)

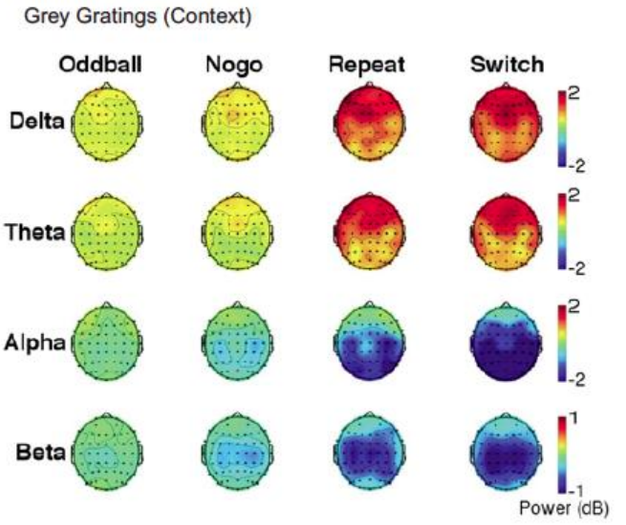

Figure 3. Topology plots depicting a rich frequency landscape in response to grey Gabor gratings. Whereas delta (2-4 Hz) and theta (4-7 Hz) oscillations were seen across all conditions, frontal regions showed larger intensities in response to more informative stimuli. Additionally, a broad, posterior decrease in alpha power was specifically associated to repeat and switch grey gratings that indexed anticipatory cognitive control (cf., Cooper et al., 2016).

We identified a dynamic and complex landscape of EEG oscillations related to the anticipation and execution of three simple cognitive tasks using our neuropsychological testing procedure. Specifically, frontoparietal delta (2-4 Hz) and central alpha (8-12 Hz) oscillations indexed task- rule execution and motor control respectively, whereas frontal theta (4-7 Hz) brainwaves were sensitive to increasing amounts of information, and parietal alpha desynchronization indexed anticipatory task control. Examples of this decomposition of EEG signals are shown for both healthy controls (Figure 3), and patients with cerebral lesions (Figure 4B).

Clinical sample

Some parts of the present project have not been completed yet (e.g. patient recruitment at MRC Cambridge, neuroimaging analysis, etc.) For that reason, here we present only achievements that have been already reported at international forums. We are currently finishing some clinical studies due to delays in recruiting patients that fulfill our very strict inclusion criteria (i.e. prefrontal lesions overlaying Brodmann areas 6, 9, 44, 45, 46 and temporoparietal lesions at Brodmann areas 39, 40). In the patients with frontal lesions studied in Mallorca (Figure 4A) and Cambridge (Figure 4B), abnormally enhanced electrophysiological responses from the intact contralesional frontal cortex were observed only (a) when stimuli were displayed to the contralesional visual field, and (b) only under those task conditions that caused information overload in the cognitive system as estimated with information theory measures. Advanced EEG analyses developed with the normalization sample are currently being applied to patients examined in Mallorca and Cambridge.

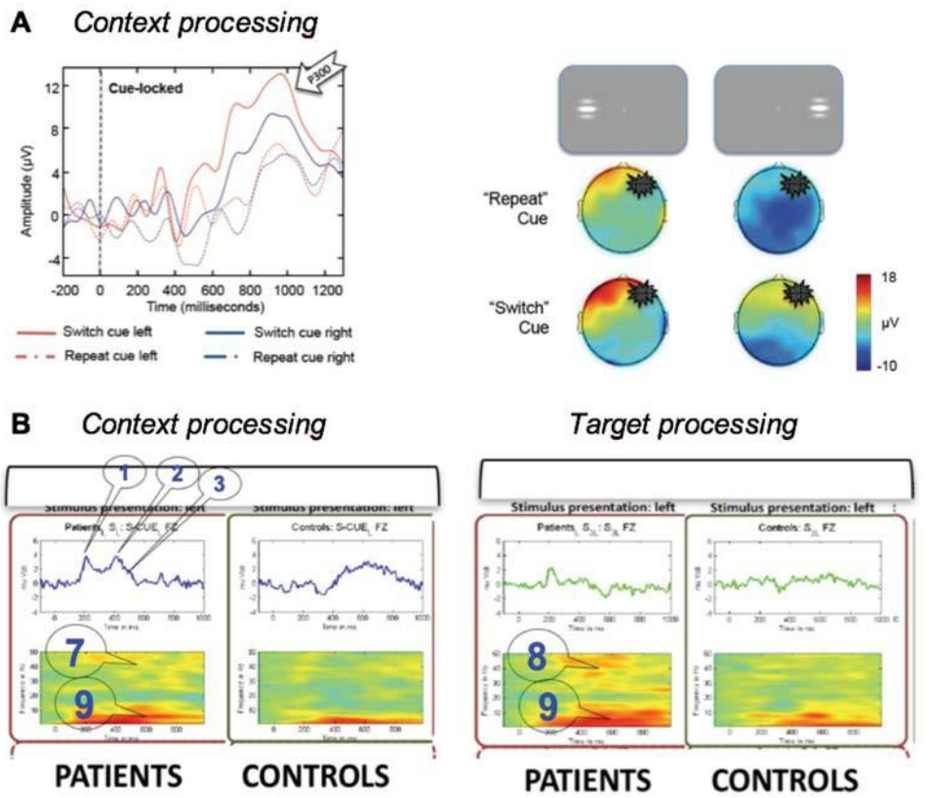

Figure 4. Dynamic Prefrontal Compensation. **(A)** *Left panel*: Frontal ERPs show the time course of activity over the intact PFC in response to high (continuous line) and low (dashed line) informative grey gratings displayed to ipsi- and contralesional visual fields of patients. These ERP signals were measured from the intact PFC. *Right panel:* Frontal load dependent compensation during visual attention under the difficult Switch task condition. Late frontal positivity (600-1000 ms) in patients is enhanced over the intact PFC compared to healthy controls in response to attended grey gratings presented contralateral to the side of lesion. No such compensatory enhancement is

observed for ipsilesional visual displays. The shaded star represents the relative scalp location of the patients' lesions. **(B)** Several signs of enhanced compensatory EEG oscillations in alpha (8-12 Hz) and gamma (30-40 Hz) bands are also observed in difficult switch task conditions (Barceló, Enriquez- Geppert, Chamielec, 2015).

3. Relevance and possible clinical implications

a) Conventional neuropsychological tests for the assessment of cognitive deficits in patients with frontal lesions often produce asymptomatic results. Our novel bifield task procedure, with fast displays to both visual hemifields, proves to be sensitive to subtle deficits in cognitive control that may go undetected with conventional neuropsychological tests.

b) The relatively normal cognitive performance observed in patients with unilateral frontal damage can be explained, at least in a proportion of the frontal patients examined, by functional compensation by their intact prefrontal cortex.

c) The compensation of cognitive deficits by the intact prefrontal cortex depends on dynamic factors that change rapidly from moment to moment with task demands (e.g. hemifield of visual display, amount and behavioral relevance of contextual information).

d) The mechanisms of neural compensation can be described as an enhancement of some brain responses to stimulus material. This neural compensation seems to depend on a rich landscape of EEG oscillations.

e) The assessment of cognitive deficits in patients with brain lesions can be much improved by using more formal (e.g. mathematical) estimates of intuitive concepts such as "mental load" or "task difficulty".

f) The conclusions of this project will contribute to the sensitive and cost-efficient detection of attention, memory and executive dysfunction associated to cerebral lesions.

3. Publications or Communications arising from this research

Scientific Articles

Laura Prada, Francisco Barceló, Christoph S. Herrmann, Carles Escera (2014). EEG delta oscillations index inhibitory control of contextual novelty to both irrelevant distracters and relevant task-switch cues. *Psychophysiology*, 51, 658-672. JCR Impact factor: 2.986.

Patrick S. Cooper, Álvaro Darriba, Frini Karayanidis, Francisco Barceló (2016). Contextually sensitive power changes across multiple frequency bands underpin cognitive control. *Neurolmage*, 132, 499-511. JCR lmpact factor: 6.357.

Francisco Barceló, Patrick S. Cooper (in press) An information theoretical account of late frontoparietal ERP positivities in cognitive control. *Psychophysiology*, Impact factor: 2.986.

Stefanie Enriquez-Geppert, Francisco Barceló (submitted). Multisubject decomposition of event- related positivities in cognitive control: tackling the age-related anterior shift.

Gema Díaz-Blancat, Juan García-Prieto, Fernando Maestú, Francisco Barceló (submitted). Fast neural dynamics of target detection versus proactive rule updating in a task-switching analogue of the Wisconsin card sorting test.

Miguel Sastre, Rosa Martorell, Maribel Adrover, Javier lbáñez, Francisco Barceló (submitted).

Relación de la hipótesis de la novedad-rutina con déficits neuropsicológicos disejecutivos en pacientes con daño cerebral frontal unilateral.

Marcelina Chamielec, Stefanie Enriquez-Geppert, Sharon Erzinclioglu, John Duncan, Francisco Barceló (in preparation). Novel assessment of dysexecutive deficits in patients with frontal lobe lesions based on the hypothesis of dynamic neuroplasticity and compensation.

Oral Communications

Francisco Barceló, Marcela Chamielec, Stefanie Enriquez-Geppert (2015). Novel assessment of dysexecutive deficits in patients with frontal lobe lesions. Invited talk at the MRC Cognition and Brain Sciences Lab (Cambridge, UK, January 19th 2015).

Francisco Barceló, Marcelina Chamielec, Álvaro Darriba (2015). Putting P300 in context: lts role in the updating of sensory versus sensorimotor representations during cognitive task-set switching. *Neuronus lBRO & lRUN Neuroscience Forum* (Krakow, Poland, 17-19 April, 2015).

Francisco Barceló (2014). Fast dynamics of a frontoparietal "multiple demand" system for cognitive control in cognitively impaired adults and neurological patients. Invited talk at the *VII Seminar on Clinical Neuropsychology* (Scinawa, Polonia, 21-22 May 2014).

Francisco Barceló, Marcelina Chamielec, Álvaro Darriba (2014). Fast dynamics of a frontoparietal "multiple demand" system for cognitive control in brain damaged patients. *lCON Satellite Symposium on Cognitive Control* (Newcastle, Australia, 21-22 July 2014).

Posters

Marcelina Chamielec, Álvaro Darriba, Javier Villacampa, Rosa Martorell, Francisco Barceló (2015). lnteraction between the executive control and orienting networks: Evidence from event- related potentials in a task-switching paradigm. *British Association for Cognitive Neuroscience Conference* (BACN 2015, Essex, UK, 10-11 September 2015).

Álvaro Darriba, Javier Villacampa, Rosa Martorell, Marcela Chamielec, Francisco Barceló (2014).

Fast dynamics of a frontoparietal "multiple demand" system for cognitive control. *International Conference on Cognitive Neuroscience* (lCON 2014, Brisbane, Australia, 27-31 July 2014). Frontiers Human Neuroscience, doi: 10.3389/conf.fnhum.2015.217.00043.

Laura Prada, Francisco Barceló (2013). Combined effects of aging and cognitive control on brain oscillations in a task-switching protocol. Invited talk at the *International Conference on Aging & Cognition*, Dortmund, 25-27 April 2013. *J. Psychophysiology*, 27, Suppl. 1, 35-35.

Alex Gálvez, Álvaro Darriba, Javier Villacampa, Rosa Martorell, Laura Prada, Francisco Barceló (2013). Effects of executive control on the flexible shifting of stimulus-response mappings in a bi-field visuomotor task with increasing cognitive demands. International Conference on Aging & Cognition, Dortmund, 25-27 April 2013. *J. Psychophysiology*, 27, Suppl. 1, 54-54.

Javier Villacampa, Álvaro Darriba, Alex Gálvez, Rosa Martorell, Laura Prada, Francisco Barceló (2013). Combined effects executive control on task-set inhibition and maintenance as indexed by task-switch unspecific restart and mixing costs. International Conference on Aging & Cognition, Dortmund, 25-27 April 2013. *J. Psychophysiology*, 27, Suppl. 1, 73-73.