Final report of grant n° 122/14

INTERNAL AND EXTERNAL WORLD IN PARIETAL CORTEX

The present project lasted form the 01-02-2015 to the 31-07-2016. This project included two separated studies aiming to elucidate the causal role of different parietal and occipital cortices in specific cognitive domains.

First study: Task and regions specific top-down modulation of alpha rhythms in parietal cortex

Aim: The ability to anticipate predictable events is of great ecological importance. One robust electrophysiological correlate of anticipation is the modulation of posterior scalp electroencephalographic (EEG) alpha oscillations (8–12 Hz). Specifically, the pre-stimulus alpha power reduction (i.e. de-synchronization) is thought to reflect an attentional modulation of cortical excitability that relates to enhancement (suppression) of task relevant (irrelevant) information. The aim of the present project was to test the hypothesis of a causal role of left angular gyrus (AG) and left posterior intraparietal sulcus (IPS) (and by extension the role of the dorsal attention and default networks, i.e. DMN and DAN) in the regulation of cortical neural synchronization mechanisms (reflected by alpha rhythms) in two different cognitive domains.

Methods: A total of 19 right-handed (Oldfield RC 1971) volunteers (mean age ± SE= 28.5 ± 4.9 yrs old; 11 females), with no previous psychiatric or neurological history, participated in the experiment. One participant was excluded due to the presence of artifacts in the EEG recordings (see Electroencephalography recordings section). The study included two tasks: i) semantic memory, SM; and ii) visual spatial attention, VSA. Both tasks included three TMS conditions (see below), each with a different randomized list of stimuli. The order of tasks and TMS conditions was counterbalanced across subjects. Participants were allowed to take a break in the middle of each condition, each lasting approximately 6 minutes. The two tasks used the same stimuli and timing, and were carried out in a single experimental session. Stimuli were generated using E-Prime software v2.0 (Psychological Software Tools, Pittsburgh, PA), and included 150 four-letters Italian nouns, matched for frequency (mean frequency : 13.4), and were drawn from a linguistic database (Corpus e Lessico di Frequenza dell'Italiano Scritto (CoLFIS), Bertinetto and colleagues, 2005). Words were written in upper case. In both tasks subjects were instructed to maintain fixation on a central black cross (subtending 0.2° of visual angle), displayed on a white background at the center of the screen. In both tasks, participants performed two active rTMS (AG, IPS) and one inactive

TMS (i.e. Sham) conditions, applied in different blocks. In the "Sham" condition, a pseudo rTMS was delivered at scalp vertex; stimulation was ineffective due to the reversed position of the coil with respect to the scalp surface (i.e. the magnetic flux was dispersed to air). The rTMS train (i.e. 3 pulses) was delivered simultaneously to the central spot ~2 sec before the stimuli array with the following parameters: 150 ms duration, 20-Hz frequency, and intensity set at 100% of the individual motor threshold. To assess the physiological impact of rTMS on anticipatory neural activity we simultaneously recorded EEG activity from the scalp. Specifically, we measured the effect of magnetic stimulation delivered over different cortical sites on the mean amplitude as well as on the peak latency and amplitude of EEG alpha de-synchronization in parieto-occipital cortex. EEG data were recorded (BrainAmp; bandpass, 0.05-100Hz, sampling rate, 256 Hz; AC couple mode recording) from 32 EEG electrodes placed according to an augmented 10-20 system, and mounted on an elastic cap resistant to magnetic pulses. Electrode impedance was set below 5 KOhm. The artifact of rTMS on the EEG activity lasted about 10 ms and did not alter the EEG power spectrum. To compare the de-synchronization/synchronization (ERD/ERS) mean amplitude between the three TMS conditions in both tasks we carried out a stationary analysis, in which the frequency bands of interest were low and high alpha. With respect to the IAF, these frequency bands were defined as follows: (i) low alpha, IAF – 2 Hz to IAF, and (ii) high alpha, IAF to IAF + 2 Hz.

Results :

Behaviour: The main analysis tested the behavioral effect produced by rTMS stimulation over different parietal sites during the execution of the visuo-spatial attention (VSA) and semantic memory (SM) tasks. A clear double dissociation was observed with AG stimulation affecting the SM task, and IPS stimulation affecting the VSA task. This impression was supported by a significant interaction of TMS Condition (AG, IPS, Sham) by Task (SM, VSA) ($F_{2,34}=7.42$, $p=0.002$, statistical power=0.91), and relevant Duncan post-hoc tests ($p<0.05$). In particular, the speed of target discrimination during the SM task was significantly impaired following stimulation of AG (651 ms ± 16) as compared to IPS (620 ms ± 20; $p=0.02$) or Sham (612 ms ± 24; $p=0.005$). In contrast, the speed of target discrimination during the VSA task was significantly delayed following rTMS over IPS (596 ms ± 23) as compared to AG (559 ms ± 19; $p=0.01$) or Sham (567 ms ± 19; $p=0.035$). Importantly, there was no difference between Sham and IPS in the SM task ($p=0.5$), and between Sham and AG in the VSA task ($p=0.5$).

EEG: The mean amplitude of anticipatory low-frequency (~8-10 Hz) alpha ERD/ERS in parieto-occipital electrodes during the SM task was disrupted by AG, but not IPS, stimulation with a significant decrease of the de-synchronization observed in Sham. In contrast, during the VSA task stimulation of IPS, but not of AG, disrupted the characteristic de-synchronization observed in Sham. These observations were confirmed by a significant TMS Condition (AG, IPS, SHAM) by Task (SM, VSA) interaction ($F(2,34)=8.34$, $p=0.001$, statistical power=0.95). Duncan post-hoc test indicated that magnetic stimulation of AG disrupted the ERD during the SM task compared to both IPS ($p=0.03$) and Sham ($p=0.02$) conditions, and that rTMS over IPS affected the ERD during the VSA task compared to both AG ($p=0.005$) and Sham ($p=0.0005$) conditions.

An even more robust double dissociation was observed in the analysis of the anticipatory high-frequency (~10-12 Hz) alpha de-synchronization. There was a significant TMS Condition (AG, IPS, SHAM) by Task (SM, VSA) interaction ($F(2,34)=11.6$, $p=0.0001$, statistical power=0.99). Duncan post-hoc tested indicated that magnetic stimulation of AG disrupted the ERD during the SM task compared to both IPS ($p=0.007$) and Sham ($p=0.006$) conditions, and that rTMS over IPS affected the ERD during the VSA task compared to both AG ($p=0.001$) and Sham ($p=0.0008$) conditions. As observed for the behavioral results, no significant difference was observed between Sham and IPS in the SM task ($p=0.8$ for both low-and high alpha), and between Sham and AG in the VSA task ($p=0.3$ for low alpha and $p=0.9$ for high alpha), corroborating the specificity of the stimulated site in both tasks. Interestingly, for both low- and high- alpha sub-bands, TMS over AG and IPS induced a paradoxical alpha synchronization (ERS) during the SM and VSA task, respectively.

Discussion: By combining EEG recordings with rTMS, the present study examined whether pre-stimulus alpha de-synchronization in parieto-occipital cortex is specifically affected by suppression of two higher order regions in human posterior parietal cortex: posterior IPS part of the DAN, and AG part of the DMN. The results indicate a clear double dissociation of task by cortical location. In particular, stimulation of IPS, but not AG, impaired both the typical anticipatory alpha de-synchronization and the speed of target discrimination on a visuo-spatial attention task. Conversely, stimulation of AG, but not IPS, impaired both anticipatory alpha de-synchronization and the speed of semantic judgments during a semantic decision task. These findings suggest the existence of multiple dedicated parietal channels for the modulation of anticipatory alpha rhythms, and support the notion that alpha rhythms reflect task-specific modulation of excitability in occipito-parietal cortex.

Second study: Magnetic stimulation of visual cortex impairs perceptual learning

Aim: The ability to anticipate predictable events it is important as well as the capacity to learn and process visual stimuli more efficiently. Human visual perception can be improved through specific training, a phenomenon called Visual Perceptual Learning (VPL). VPL critically depends on attention and allows to answer more efficiently to the stimuli in the environment. Nevertheless, it was observed that after an intensive training fronto-parietal regions (i.e. intra parietal sulcus, pIPS) became less activated for trained as compared to untrained stimuli, while visual regions (i.e. V2d/V3 and LO) exhibited higher activation for familiar shape. With this point of view, during the project a second parallel rTMS study tested the hypothesis that the causal role of IPS observed in the visuo-spatial attention is less important when subjects perform the task after an intensive training.

Methods: 16 right-handed volunteers (age range: 20-30 yrs. old; 8 females) participated in this experiment. Subjects were trained with daily sessions to attend to the lower left visual quadrant and find the target shape among the distracters while maintaining central fixation. The stimulus array comprised 12 Ts arranged in an annulus of low eccentricity (i.e. 5° radius) and was displayed across the 4 visual quadrants. On each trial subjects fixated a central spot for 200 ms (fixation), after which the target shape (an inverted T) was presented at the centre of the screen for 2000 ms (target presentation); finally, an array of 12 stimuli, differently oriented Ts (distracters) with or without an inverted T (target), was briefly flashed for 150 ms (array presentation). The target shape appeared randomly in 1 of 3 locations in the left lower (trained) visual quadrant, and never in the three untrained-quadrants. The target shape appeared randomly in 1 of 3 locations in the left lower (trained) visual quadrant, and never in the other three untrained quadrants. Subjects attended to the lower left visual quadrant and indicated the presence or absence of the target shape visual quadrant by pressing a left/right mouse button with their right hand. Each block consisted of 45 trials, 36 (80%) that contained the target and 9 (20%) that did not. Training lasted one week, and an average of 100 practice blocks were necessary to reach a threshold of 80% accuracy in at least 12 consecutive blocks of trials. Of note, the accuracy of each block was weighted with the rate of false positive (Sigman and Gilbert, 2000) (Sigman et al., 2005) (Lewis et al., 2009). When subjects reached criterion, they were asked to perform three blocks of the same task during each TMS condition (i.e. V2d/V3, LO, pIPS, and Sham). Presentation timing was triggered by the TMS train, and the four TMS conditions were run in a counterbalanced order across subjects, who were instructed to respond as accurately and quickly as possible. The rTMS train (i.e. 3 pulses) was delivered simultaneously to the central spot ~2 sec before the stimuli array with the following parameters: 150 ms duration, 20-Hz frequency, and intensity set at 100% of the individual motor threshold.

Results Main experiment:

The results clearly indicated a slowing of response time (RT) during V2d/V3 and LO stimulation as compared to Sham and pIPS stimulation. This was confirmed by an ANOVA on RTs that showed a main effect of Condition ($F_{3,45}=7.23$ $p<0.0005$; ήpartial2=0.32; statistical power=0.97) with slower RTs after both V2d/V3 (580 ms ± 58 SD) and LO (577 ms ± 62 SD) as compared to pIPS (548 ms ± 52 SD; $p<0.001$) and Sham (560 ms ± 57 SD; $p<0.05$). Importantly, no difference were observed between RTs after the two visual regions (i.e. V2d/V3 and LO; p=0.71) and between RTs after the active (pIPS) and inactive (Sham) control conditions (p=0.12). Of note, in all TMS conditions the behavioral data were normally distributed (Lilliefors test> 0.15). Finally, the same statistical design using Accuracy did not provide any statistically significant difference across conditions. In Table 1 are reported the % of accuracy and the number of false positives (fp) for all TMS conditions with the relative statistical p values ($p>0.1$).

Interestingly, the behavioral impairment produced by V2d/V3 stimulation (measured as RTs [V2d/V3-Sham]) was positively correlated across subjects to the impairment produced by LO stimulation (RTs[LO-Sham]) (r=0.78; $p<0.001$). Conversely, the effect of rTMS over pIPS was not correlated neither with the interference over V2d/V3 (p=0.35) nor with LO (p=0.25).

Control experiment:

To test the causal specificity of the visual cortex only in the representation of perceptually learned visual stimuli, and not with simple visual processing of any object, a new group of subjects (N= 10, age range: 22-30 yrs. old; 5 females) were asked to perform a new simple visual task. To increase the low accuracy observed at the beginning of the training, in this control experiment no distracters were presented and only the target shape appeared randomly in 1 of 3 locations in the lower left visual quadrant. Subjects attended to this visual quadrant and discriminated the shape of the target (rotated "T", 80 % of total trials, and canonical "T", 20 % of total trials) by pressing a left/right mouse button with their right hand. The timing as well as the TMS protocol was the same of the main experiment. All subjects performed the task during the same four TMS conditions (i.e. V2/V3, LO, IPS and Sham), that were run in a counterbalanced order across subjects, who were instructed to respond as accurately and quickly as possible. Results clearly showed that interference with V2d/V3 and LO did not increase reaction times to simple visual stimuli as compared to pIPS and Sham control conditions. This was confirmed by an ANOVA on RTs that showed the lack of the main effect Condition ($F_{3,27}=0.13$ p=0.94, ήpartial2=0.01; statistical power=0.07) with similar RTs after both V2d/V3 (453 ms ± 39 SD) and LO (457 ms ± 52 SD) as compared to pIPS (452 ms ± 51

SD) and Sham (456 ms ± 36 SD). Notably the accuracy was high in all TMS conditions (V2dV3 96.3% ± 2.5 SD; LO 95.1% ± 3.5 SD; IPS 96.7% ± 2.3 SD; Sham 96.3% ± 3.1 SD), and no statistically significant difference was observed across conditions. These results support our main conclusion that V2/V3 and LO are causally engaged in the representation of perceptually learned visual stimuli and not in general simple visual processing.

Discussion: We used a causal approach to compare the role of two different visual regions (i.e. V2d/V3 and LO), within the right dorsal visual network, and an attention region (pIPS), in the identification of visual shapes learned through Visual Perceptual Learning (VPL). For the first time we show that, following VPL, only activity in topographically appropriate visual regions is causally involved in identifying learned shapes. These findings support the notion that the visual network has a causal role in the control of the perceptual learning.

Thanks to the BIAL foundation grant we published 2 papers on two important journal such as Cerebral Cortex and Neuroimage. Moreover, the results related to the project were presented at the International congress OHBM (Geneve 2016) with two posters. The BIAL Foundation was duly acknowledged in the papers and the events.

Overall I can declare that the project “internal and external world in parietal cortex”, funded by the BIAL foundation, is very productive and it is providing us with ground breaking knowledge.