Recovering and Worsening at Design Fluency in 22 Neurosurgical Patients: Pre-immediately Post-surgery and Follow-up Testing

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Abstract

The five-point test (FPT) measures the ability to voluntarily generate non-verbal novel patterns. We investigated how this ability can be impaired or improved before immediately after brain surgery, and at follow-up. Twenty-two patients undergoing neurosurgery in the right hemisphere performed the FPT at T0 (pre-), T1 (1 week post-), and T2 (follow-up at 5 months after surgery). Significant improvements at T1 (in patients who had a deficit at T0) measured recovering (N=3/22); in addition there were patients who become pathological (8/22) and subjects who presented with the same degree of impairment as observed at T0 (stable, 1/22). Similarly, at T2 (4-5 months after surgery) we measured the effect of post-op reorganization: there were patients (5/22) who had been pathological at T1 and recovered at T2. Lesions overlapped in the right body of the corpus callosum/anterior cingulum reflecting the overcome of the deficit. Amelioration can be an effect of edema reduction. In addition, there were those who become pathological (4/22). Lesions overlapped in the right supramarginal gyrus. Lastly, there were subjects who presented with the same degree of impairment as observed at T1 (stable, 4/22) and those who remained spared (9/22). Multiple regression analysis was used to test if the number of strategies (CSs) used to solve the task or the perseverative behaviour (ErrI) significantly predicted participants' stratification, namely patients who worsened those who improved and patients who remained spared. It was found that the use of strategies significantly predicted participants' stratification, whereas perseverative behaviour was not a significant predictor.

Keywords: Design fluency; Strategy; Functional recovery; Disability; MRI; Neurosurgical patients; Plasticity

Introduction

The five-point test (FPT) is a measure of non-verbal fluency, namely the ability to generate non-verbal, non-overlearned responses [1]. Participants are required to invent novel designs starting from a matrix of five points in a limited amount of time. It is known that a deficit in design fluency can emerge in neurosurgical patients as an effect of lesion, thus detected prior to surgery, or can arise post-surgery, as an effect of tumor resection. For instance, Tucha et al. [2] studied 161 pre-surgical patients and found impaired design fluency in 74 of them. Unfortunately, no data about their post-surgical performance is available. Contradictory results emerge from another study [3] in which 95 patients with mass lesions of very different types (55 meningiomas, 4 astrocytomas, 5 oligodendrogliomas, 9 glioblastomas, 7 metastases, 5 cavernomas, 5 aracnoidal cysts, and 1 arterio-venous malformations) were studied prior to surgery and showed spared design fluency. Similarly, it has been show that deficits in design fluency can be a post-surgical effect of resection combined with the lesion effect. For instance, Ruff et al. [4] studied 30 patients (27 trauma-related lesions and 1 cardiovascular accident, 1 tumor, 1 seizure) and found that patients with right anterior dysfunction had a deficit in design fluency. Unfortunately, no data about their pre-surgical performance was reported, thus it is not possible to determine whether the deficit occurred as an effect of resection or was already present prior to surgery. Similarly, Baldo et al. [5] reported impairments in design fluency. They studied patients post-event, namely post-stroke (in 7 cases) and post-surgery (1 meningioma, 1 aneurysm, 1 arterio-venous malformation and 1 cyst). In another study (Robinson et al. [6] design fluency was found impaired in right frontal patients post-surgery, with a very high variability in time of assessment: testing occurred 0.07 to 181 months post-surgery.

Taken together, these studies indicate that impairments in non-verbal fluency can emerge both pre- and post-surgery. Since no study reported data collected pre- and post- surgery and at follow-up in the same patient sample, it is unclear whether an impaired ability in generating novel responses, can be subjected to an effect of re-organization/adaptation. As fluency refers to the ability to use one or more strategies to achieve the maximum number of new responses and avoiding repetitions [4], it is reasonable to assume that the use of strategies in design fluency tasks can be characterized by flexibility. In a recent meta-analysis [7] the need of more studies with longer post-op cognitive follow-up testing to better understand the conclusive effects of glioma surgery on cognition has been highlighted.

We investigated how brain surgery can impact on the abilities needed to succeed this task by asking 40 neurosurgical patients with right hemisphere glioma to perform the FPT at T0 (pre-surgery) and at T1 (1 week post-surgery). Half of them (22/40) were also examined at T2 (follow-up at 5 months after surgery). A deficit at T0 was the effect of the lesion on design fluency, a deficit at T1 (but not at T0) reflects the effect of surgery. Similarly, a significantly better performance at T1 (in patients with a deficit at T0) reflects recovery, and an improvement at follow-up entails a stable amelioration reflecting a reorganization of

the ability. In an exploratory analysis, we also addressed structural changes related to such behavioral adaptations.

We expected to observe decrements in the immediate post-surgery assessment and recover/adaptation in time. This hypothesis is indeed in line with clinical indications showing improvements at follow-up. For instance, Habets et al. [8] found significant improvements in information processing speed and visuo-construction at follow-up. Similarly, Correa et al. [9] studied twenty-five low-grade glioma patients pre-surgery and at 6 and 12 months and found a mild decline 12-month after surgery, and a mild improvement slightly at an additional follow-up (before the 18th month). In their meta-analysis of studies on glioma patients undergoing neuropsychological tests pre- and post-surgery, Satoer et al. [7] found a highly frequent deterioration in one or more cognitive domains in the immediate post-surgery period, whereas at 3-6/6-12 months postoperatively some patients recovered at some tasks, i.e., language and executive functions.

Materials and Methods

Participants

Study participants were 22 patients with a low- or high-grade glioma involving the right hemisphere.

The patients' lesion overlap map showed that the most frequently damaged voxels (see the bar code in Supplementary Figure 1) were found in the insula/inferior frontal lobe/dorsolateral and superior temporal cortex, and in the postcentral gyrus/inferior parietal lobule (mean volume, 67.62 ± standard deviation 50.11 cc). Patients with a history of psychiatric disease or drug abuse and with reported family history of developmental language problems or learning disabilities were excluded. Patients (5 F, 17 M) were native Italian speakers, had normal or corrected-to-normal vision and were all right-handed [10], with a mean age of 47.36 ± 14.75 years and mean education of 12.95 ± 4.13 years.

All the patients were tested before, after (at 1 week) surgery and at follow-up (at 4/6 moths). The neuropsychological assessment included tasks testing spatio-temporal orientation [11], non-verbal intelligence (Raven's Coloured Pictures Matrices-RCPM) [12], visuo-spatial working memory [13], visuo-spatial planning (clock test) [14], constructional apraxia [11], spatial attention (Star cancellation, Letter cancellation, Line cancellation, Line bisection) [15,16], psychomotor speed (Trail making test-A; TMT-A), attention shifting (Trail making test-B TMT-B) [16] and speed of processing (Digit symbol substitution test) [17]. They performed the neuropsychological screening tests successfully (See Supplementary Table 1).

The study was approved by the Ethics Committee of the Azienda Sanitaria Universitaria Integrata S. Maria della Misericordia and carried out in accordance with the 2013 Fortaleza version of the Declaration of Helsinki and subsequent amendments. The subjects' written informed consent was obtained.

The five-point test (FPT)

The FPT was administered following Cattellani et al. [18]. The stimulus material consists of a sheet with 40 matrices (eight rows and five columns, 3 × 2 cm), with each matrix formed by a fixed pattern of five symmetrically organized dots [18]. Participants were asked to draw, within each matrix, as many unique designs as possible by connecting two or more dots with straight lines, without replicating

any drawings. Before starting, the examiner provided two resolutions, one connecting only two dots and the other connecting all dots, and subjects were instructed to avoid repeating these sample designs. Participants had 3 min to complete the task.

The performance of a sample of healthy controls involving a total of 332 adults ranging from 16 to 60 years has been reported in Cattelani et al. [18]. Healthy controls were able to complete in 3 min of time a mean of 23.83 unique designs, by adopting a mean of 1.9 strategies and their perseveration index was 0.2246.

Data analysis

Behavioral data: Accordingly to the norms reported by Cattelani et al. [18] we calculated the number of unique designs generated (UDs) under a strategy defined as three or more consecutive unique designs). Patients' scores were corrected for age and education, closely following the norms reported for the Italian normative sample presented by Cattelani et al. [18]. The equivalent score=0 (i.e., the cut-off score) for the Italian population [18] for UDs was 23.83. Patients were classified as pathological if the adjusted number was equal or lower than 23.83.

The Italian normative study reports two other independent measures with respect to the UDs: Cumulative Strategies (CSs), corresponding to the number of UDs produced under strategy (strategy is defined as three or more consecutive unique designs that are organized following enumerative or rotational strategy). A cluster was considered strategic if it had three or more consecutive designs organized in a logical sequence.

Error Index (ErrI), corresponding to the percentage of failed designs meaning an interruption in the strategic cluster. It was calculated by adding the number of perseverative errors to the number of rule-breaking errors.

Behavioral data were analyzed by means of multiple regression analysis to test if the delta calculated on the number of strategies (CSs) used to solve the task or on the perseverative behavior (ErrI) between T1 and T2 significantly predict participants' performance, using SPSS 21.0 (SPSS, Inc., Chicago, IL).

Structural MR data: We retrospectively analyzed high-resolution T2-weighted (T2W_3D_TFE SENSE, TR=2500 ms, TE=368.328 ms, FOV=240.000 mm, 190 sagittal slices of 1 mm thickness, flip angle=90°, voxel size: 1 × 1 × 1) and post-gadolinium contrast T1-weighted (T1W_3D_TFE SENSE, TR=8.1007 ms, TE=3.707 ms, FOV=240.000 mm, 190 sagittal slices of 1 mm thickness, flip angle=8°, voxel size: 1 × 1 × 1) anatomical MR images, which were routinely acquired during pre-surgery investigations using a 3-T Philips Achieva whole-body scanner and a SENSE-Head-8 channel head coil. VOIs on the patients' lesions were drawn on their T2 MRI scans by using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/index.html). The ROIs were then normalized to the MNI (Montréal Neurological Institute) space using the "Clinical Tool box" (http://www.mccauslandcenter.sc.edu/CRNL/clinical-toolbox) for SPM8 (Statistical Parametric Mapping software. SPM; Wellcome Department of Imaging Neuroscience. London. UK http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) and MATLAB r2007b (The Mathworks Inc. Natick. MA/USA). The VOIs were used in a subtractive analysis carried out by using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/index.html). Following the procedure reported by Karnath et al. [19] we used a subtractive approach.

Results

Effect of surgery: T1 (post-surgery evaluation at 1 week)

Aside verifying that at T1 (immediate post-surgery evaluation) the number of pathological patients (9/22, 40.9%) significantly increased as compared to T0 (pre-surgery testing, N=4/22, t(21)=2.485, p<.05), we were interested in measuring the evolution in patient's performance from To to T1. There was indeed a stratification of the type of performance. There were patients (3/22) who had been pathological at T0 and recovered at T1, those who become pathological (8/22) and subjects who presented with the same degree of impairment as observed at T0 (stable patients, 1/22). Multiple regression analysis was used to test if the number of strategies (CSs) used to solve the task or the perseverative behavior (ErrI) significantly predicted participants' stratification, namely patients who worsened, those who improved and patients who remained spared. The results of the regression indicated the two predictors explained 25.2% of the variance (R^2=0.57, $F_{(2,20)}$=4.368, p<0.05). It was found that the use of strategies (CSs) significantly predicted participants' stratification (β=0.52, p<0.05),

whereas perseverative behavior (ErrI) was not a significant predictor (β= -0.24, p>0.05, n.s.).

Effect of long-term post-op changes: T2 (follow-up examination)

We measured what changes occurred at T2 (4-5 months after surgery). These changes measured by comparing T1 *vs.* T2 performance-reflect the effect of post-op reorganization as the mere effect of surgery alone was already detected by T0 *vs.* T1 comparisons.

At T2 (follow-up evaluation) aside considering the number of pathological patients (9/22, 40.9%) that remained comparable to T1 (p>0.05, n.s.), there was a stratification of the type of performance. There were patients (5/22) who had been pathological at T1 and recovered at T2, those who become pathological (4/22) and subjects who presented with the same degree of impairment as observed at T1 (stable patients, 4/22) and those who were spared (9/22) (Figure 1A and Table 1).

		T0 (mean ± S.D.)	T1 (mean ± S.D.)	T2 (mean ± S.D.)
Patients worsened	UDs	25.93 ± 5.36	31.19 ± 3.71	18.44 ± 6.11
	CSs	1.87 ± 1.47	1.25 ± 0.79	2.63 ± 1.79
	ErrI	0.22 ± 0.20	0.22 ± 0.13	0.35 ± 0.3
Patients improved	UDs	30.65 ± 3.47	22.00 ± 2.12	32.25 ± 5.95
	CSs	2.1 ± 1.72	0.85 ± 1.72	1.6 ± 1.35
	ErrI	0.076 ± 0.122	0.14 ± 0.3	0.04 ± 0.05
Patients stable	UDs	25.63 ± 9.76	18.69 ± 3.47	17.69 ± 5.23
	CSs	2 ± 1.59	1.56 ± 1.39	1.81± 1.82
	ErrI	0.15 ± 0.04	0.46 ± 0.49	0.34 ± 0.23
Patients spared	UDs	31.30 ± 6.19	31.3 ± 5.81	33.8 ± 4.13
	CSs	2.38 ± 1.35	3 ± 2.22	1.81 ± 2.33
	ErrI	0.122 ± 0.205	0.08 ± 0.11	0.04 ± 0.02

Table 1: Mean performance of patients at pre-surgery (T0), immediately post- (T1) and at follow-up (T2). Patients are stratified according to their T2 outcome with respect to T1, as those who worsened, those who improved and those who were stable and those who remained spared. UDs= Unique designs; ErrI=Error Index; CSs=Cumulative strategies. S.D.=standard deviation.

The results of the regression indicated the two predictors [the number of strategies (CSs) used to solve the task or the perseverative behavior (ErrI)] explained 31% of the variance (R^2=0.38, $F_{(2,21)}$=5.86, p<0.05). It was found that the use of strategies (CSs) significantly predicted participants' stratification (β=-0.57, p<0.005), whereas perseverative behavior (ErrI) was not a significant predictor (β=-0.29, p>0.05, n.s.). In particular patients who worsened at T2 tended to use

more strategies at T2 (2.63 ± 1.799 at T2 vs. 1.25 ± 0.79 at T1) but this was not sufficient to overcome the decrease in productivity (31.19 ± 3.71 at T1 vs. 18.44 ± 6.11 at T2); patients who improved at T2 tended to use more strategies at T2 (1.6 ± 1.35 at T2 vs. 0.85 ± 1.72 at T1) and strategic behaviour increased their productivity (22.00 ± 2.12 at T1 vs. 32.25 ± 5.95 at T2) (Figure 1B).
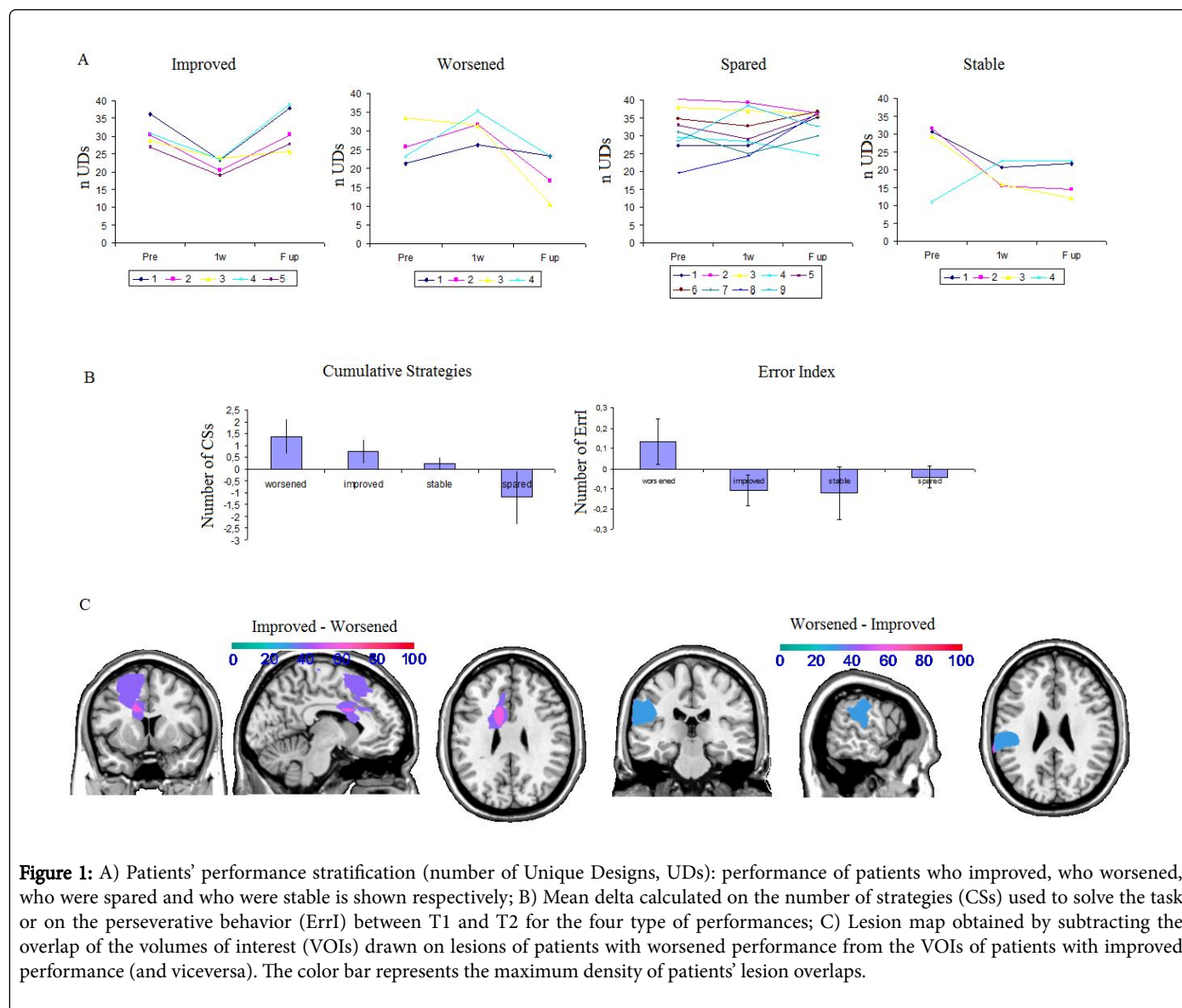
Figure 1: A) Patients' performance stratification (number of Unique Designs, UDs): performance of patients who improved, who worsened, who were spared and who were stable is shown respectively; B) Mean delta calculated on the number of strategies (CSs) used to solve the task or on the perseverative behavior (ErrI) between T1 and T2 for the four type of performances; C) Lesion map obtained by subtracting the overlap of the volumes of interest (VOIs) drawn on lesions of patients with worsened performance from the VOIs of patients with improved performance (and viceversa). The color bar represents the maximum density of patients' lesion overlaps.

Structural MR data

We investigated the neuroanatomical bases of such changes in patients with worsened performance and patients with improved performance at T2. We overlapped the lesion masks (VOIs) of patients who worsened, VOIs of patients who improved by using the MRIcron procedure (http://www.mccauslandcenter.sc.edu/mricro/mricron/index.html). The output is a percentage overlay plot showing on a color scale the rate of overlapping lesions for the two subgroups. We then subtracted the overlap lesion mask of the improved patients from the overlap lesion mask of the worsened patients. The output is a percentage overlay plot showing on a color scale the percentage of overlapping lesions of the patients. This analysis allows controlling for differences in sample size (by using proportional values. The maximum overlap for regions specific to patients with worsened performance (%patients with worsened performance>% patients with improved performance) occurred in the right supramarginal gyrus gyrus (Figure 1C), whereas the maximum lesion density for regions specific to patients with improved performance (%patients with improved

performance >% patients with worsened performance) occurred in the right body of the corpus callosum/anterior cingulum (Figure 1C).

Discussion

In the present study, we investigated how non-verbal fluency ability evolves as an effect of lesion/surgery and possible post-surgery changes. We hypothesized that, since fluency refers to the ability to use one or more strategies to achieve the maximum number of new responses and avoiding repetitions [4], the use of strategies for solving the task can be subject to adaptation in time and can be characterized by flexible mechanisms.

We found a significant increase in the number of pathological patients in the T1 testing as compared to T0. This is consistent with previous studies showing a frequent deterioration in one or more cognitive domains in patients with glioma. For a meta-analysis of studies comparing neuropsychological test scores pre- and post-surgery [7]. This is also in line with previous studies showing a deficit in design fluency after surgery [5,6,20]). Interestingly, different sub-

groups of patients emerged at T1. There were patients who became pathological, expressing the effect of resection; patients who remained as impaired as they had been at T0 (stable), expressing the effect of lesion, in line with, Tucha et al. [2] study showing that a deficit in design fluency can be detected pre-surgery. There were also patients who had been pathological at T0 and recovered at T1, possibly expressing the effect of flexible adaptation/amelioration.

This pattern of patients' performance was further addressed by analyzing their long-term post-operative changes (T2). Changes occurring at T2 *vs.* the T1 period reflect the effect of post-op adaptation as the mere effect of surgery alone was already detected by T0- *vs.* T1 comparisons. We found that some of the patients who showed a pathological performance on unique designs at T1 recovered. Other patients worsened. Multiple regression analysis was used to test if the number of strategies (CSs) used to solve the task or the perseverative behavior (ErrI) significantly predicted participants' stratification, namely patients who worsened those who improved and patients who remained spared. It was found that the use of strategies significantly predicted participants' stratification, whereas perseverative behavior was not a significant predictor.

In patients who recovered, the maximum lesion density was localized in the right body of the corpus callosum/anterior cingulum. Our results complement previous results [21], documenting deficits in visual memory, dysexecutive cognitive syndrome, and deficits in verbal fluency among the neuropsychological consequences of a resection of the anterior part of the body of the corpus callosum. We can speculate that the amelioration can reflect the effect of long-term reorganization. It is possible that a lesion affecting the anterior part of the body of the corpus callosum, known to be relevant to the executive network [21], might have led executive areas to overcome the deficit detected in the T1 period. Mechanical effects such as decompression or edema reduction cannot be responsible alone for such changes as 5 months elapsed in between. Patients improved because they better used strategies.

Patients who become pathological (as compared to T1). Their lesion analysis showed that the maximum lesion density was localized in the right posterior parietal cortex namely the supramarginal gyrus. This confirms what we found when we compared T1 and T0 performance showing a role of the parietal cortex in non-verbal design fluency as those patients undergoing surgery in that area significantly worsened, i.e., made significantly more errors, post-surgery. Results indicate a preponderant role of the posterior parietal cortex in visual fluency tasks that clearly supports spared visuo-spatial abilities.

The right posterior parietal cortex is involved in visuo-spatial tasks, orientation, visuo-spatial transformations. For instance it is required in mentally transforming spatial configurations through mental rotation; for a meta-analysis [22]. Interestingly, the incidence of broken rules in a visuo-spatial task such as the maze-learning test was also related to the right parieto-temporal cortex [23]. Thus, the right posterior parietal cortex is part of a network of areas required to produce well-organized new visual constructions.

It is known that a deficit in design fluency can emerge in neurosurgical patients as an effect of lesion, thus detected prior to surgery [2], or can arise post-surgery [4-6], as an effect of tumor resection. In a recent meta-analysis [7] the need of more studies with longer post-op cognitive follow-up testing to better understand the conclusive effects of glioma surgery on cognition has been highlighted. This is the first preliminary report on data collected pre- and post-

surgery and at follow-up in the same patient sample, indicating that an impaired ability in generating novel responses can be subjected to an effect of re-organization/adaptation. This group includes few patients and these data deserves further investigation. Nonetheless data are in line with other studies showing improvements at follow-up in information processing speed and visuo-construction [8]. In addition data evidence oscillatory evolution of patients' performance, with immediate post-surgery worsening and improvements at follow-up, in line with other studies showing a mild decline 12-month after surgery, and a mild improvement slightly at an additional follow-up (before the 18th month) [9].

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