This is the unedited, author's version of a paper which was published in Neuropsychologia. Please cite this paper as follows: Vallesi A., Mussoni A., Mondani M., Budai R., Skrap M., Shallice T. (2007). The neural basis of temporal preparation: insights from brain tumor patients. Neuropsychologia, Vol. 45(12), pp. 2755-63. DOI:10.1016/j.neuropsychologia.2007.04.017.

I DEDICATE THIS WORK TO ALESSANDRO MUSSONI (SECOND AUTHOR), A DEAR FRIEND AND COLLEAGUE WHO ISN'T AMONG US ANYMORE.

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THE NEURAL BASIS OF TEMPORAL PREPARATION: INSIGHTS FROM BRAIN TUMOR PATIENTS

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Abstract

When foreperiods (FPs) of different duration vary on a trial-by-trial basis equiprobably but randomly, the RT is faster as the FP increases (variable FP effect), and becomes slower as the FP on the preceding trial gets longer (sequential effects). It is unclear whether the two effects are due to a common mechanism or to two different ones. Patients with lesions on the right lateral prefrontal cortex do not show the typical FP effect, suggesting a deficit in monitoring the FP adequately [Stuss et al. (2005), *Neuropsychologia, 43,* 396-417]. The aim of this study was twofold: 1) to replicate this neuropsychological result testing cerebral tumor patients before and after surgical removal of the tumor located unilaterally in the prefrontal, premotor or parietal cortex, respectively; 2) to investigate whether the sequential effects would change together with the FP effect (supporting single-process accounts) or the two effects can be dissociated across tumor locations (suggesting dual-process views). The results of an experiment with a variable FP paradigm show a significant reduction of the FP effect selectively after excision of tumors on right prefrontal cortex. On the other hand, the sequential effects were reliably reduced especially after surgical removal of tumors located in the left premotor region, despite a normal FP effect. The latter dissociation between the two effects supports a dual-process account of the variable FP phenomena. This study demonstrates that testing acute cerebral tumor patients represents a viable neuropsychological approach for the fractionation and localisation of cognitive processes.

Keywords: Foreperiod Effect; Frontal Lobe; Non-Specific Preparation; Prefrontal Cortex; Sequential Effects; Temporal Processing.

In cognitive terms, preparation is the ability to prepare an optimized response to forthcoming stimuli. It can take advantage of human capacity of anticipating future events, reducing uncertainty about them, and thus optimizing processes necessary for responding to them (Brunia & Van Boxtel, 2000). In particular, unspecific preparation over time usually implies the reduction of uncertainty about 'when' a response (regardless of 'what' specific response) should be executed. This capacity is used in everyday life. In soccer, for instance, a goalkeeper does not know in advance when an opponent will kick the ball towards the goal; as time elapses, however, the probability that the other player will decide to kick the ball increases and the goalkeeper has to increase his readiness consequently. In a more common situation, when a driver waits for the traffic light to turn green, especially if she/he is in a hurry, her/his right foot is more and more prepared to push the accelerator as time goes on with the traffic light still displaying red.

Experimentally, temporal preparation has been extensively investigated in studies manipulating the foreperiod (FP) duration, that is, the waiting time between a warning stimulus and an imperative stimulus requiring a response. Since the seminal study by Woodrow (1914), it has been consistently shown that, when a range of FPs is randomly drawn from a rectangular distribution, so that every FP has the same a priori probability of occurring on any trial, RTs are slower for shorter FPs and faster for longer ones. This is the so-called variable FP effect (Drazin, 1961; Karlin, 1959; Woodrow, 1914; see Niemi & Näätänen, 1981, for a review).

When each FP in the range occurs equally often across trials, it is impossible to predict the exact moment at which the imperative stimulus will occur on each trial. However, the elapsing time itself provides information about the next occurrence of the stimulus (Elithorn & Lawrence, 1955). Indeed, as time flows during the FP without the imperative stimulus occurring, the conditional probability of the imperative stimulus being presented in the next time-interval increases. The cognitive system presumably monitors this changing conditional probability in order endogenously increase response preparation (e.g., Elithorn & Lawrence, 1955; Näätänen, 1970).

However, despite its simplicity, this account has a limitation, in that it does not explain the pattern of sequential FP effects usually obtained in this paradigm (Karlin, 1959; Woodrow, 1914): RTs on the current trial (FP_n) are slower when preceded by a longer FP on the previous trial (FP_{n-1}) than when preceded by an equally long or shorter one. Such effects are usually asymmetric, being mainly present on the shortest FP_n in a block of trials, and so producing a typical FP_n x FP_{n-1} interaction in the RT data. Notably, the asymmetry in the sequential effects may contribute to the negative slope of the FP-RT function. If this would be the case, any account explaining the asymmetric sequential effects, explains in fact also the FP effect.

Recently, a non strategic account has been proposed by Los and colleagues explaining both the FP and the asymmetric sequential effects by means of common conditioning laws (Los, Knol, & Boers, 2001; Los & van den Heuvel, 2001; but see Alegria, 1975; Drazin, 1961; Karlin, 1959, for alternative strategic accounts). On this account, a conditioned level of activation corresponds to each possible FP. On any trial, this activation level is increased for the FP that actually occurs (reinforcement), unchanged for longer FPs, and decreased for shorter ones (extinction). This final assumption is motivated by a supposed need to avoid to respond before the onset of the imperative stimulus. This need is supposedly strong when the current FP is longer than the preceding one (Los & van den Heuvel, 2001, p. 372; Näätänen, 1971). It follows that the conditioned strength of activation corresponding to the longest FPs can never decrease, since no even longer FP can occur. Hence, the sequential effects, if present, should be asymmetrically biased towards the shortest FP. This single-process view has the advantage of making the FP effect a direct consequence of the asymmetric sequential effects, because the RT on the current trial is influenced by the conditioning mechanisms occurred on the previous trial.

Besides of this enduring interest of cognitive psychology in investigating the nature of the processes underlying preparation over time (e.g., Correa, Lupianez, & Tudela, 2006; Los & van den Heuvel, 2001; Los & Agter, 2005; Niemi & Näätänen, 1981), there is a renewed interest in elucidating which brain areas may be responsible for such processes (e.g., Coull & Nobre, 1998;

Janssen & Shadlen, 2005; Lewis & Miall, 2003; Stuss et al., 2005; Vallesi, Shallice, & Walsh, 2007).

In a recent neuropsychological study, Stuss and colleagues (Stuss et al., 2005) found that right lateral prefrontal patients were selectively impaired in a variable FP task, as they did not show the classical FP effect. Worth mentioning, these patients were not impaired in a similar RT task with a fixed FP presentation. According to the traditional account concerning conditional probability monitoring (e.g., Näätänen, 1970; Niemi & Näätänen, 1981), right prefrontal patients fail to check whether a stimulus has occurred over a few seconds, and are not able to increase their readiness to respond as time goes on (Stuss et al., 2005). This account fits a range of neuropsychological (e.g., Picton, Stuss, Shallice, Alexander, & Gillingham, 2006; Rueckert & Grafman, 1996; Wilkins, Shallice, & McCarthy, 1987) and functional imaging studies (e.g., Coull, Frith, Buchel, & Nobre, 2000; Henson, Shallice, & Dolan, 1999), which assign a monitoring role to the right dorsolateral prefrontal cortex (hereafter DLPFC; see Fletcher & Henson, 2001; Shallice, 2002; 2004 for reviews; cf. Posner & Peterson, 1990).

Another possible explanation for the deficit of right frontal patients, however, may be that the FP effect vanishes as a consequence of reduced or absent sequential effects. The conditioning single-process account, indeed, would predict this possibility (Los & van den Heuvel, 2001). On this view, the FP effect is entirely a side effect of the conditioning mechanisms operating on the preceding trial and generating the asymmetric sequential effects. Unfortunately, sequential effects were not investigated in Stuss and colleagues' study (Stuss et al., 2005). Therefore, it is not possible to disentangle this possibility directly from the data reported in that study.

A recent TMS study (Vallesi et al., 2007) replicated the neuropsychological finding (Stuss et al., 2005) on healthy participants. As results showed, when right DLPFC was temporarily inhibited by the TMS, a reduction in the FP effect was observed with respect to a pre-TMS baseline and with the stimulation of other control areas, such as the left DLPFC and the right angular gyrus. That study also checked the sequential effects, which were however not influenced in magnitude by the

TMS of any of the three areas under study. In other words, the FP effect was reduced in the presence of normal size sequential effects. To our knowledge, no study has found the opposite dissociation, namely reduced or absent sequential effects in the presence of an unchanged FP effect. Thus, it is not possible to know from that study whether the two effects derive from entirely independent processes, as the possibility exists that the asymmetric sequential effects are a necessary but not sufficient condition for the occurrence of a normal-size FP effect. In other words, the FP effect may have been reduced because of the impairment of an unknown process, whose contribution to the FP effect may be additional to that made by the sequential effects. On the other hand, the presence of a normal FP effect in the absence of asymmetric sequential effects, if found, could be taken as evidence for an independence of the processes underlying the two effects, according to the logic of double dissociations (Shallice, 1988).

In this study, an approach similar to that developed by Stuss and colleagues (e.g., Stuss, Shallice, Alexander, & Picton, 1995; Stuss et al, 2005) was adopted to analyse attentional deficits derived from lesions in different cortical areas. On this approach, a careful task analysis may provide valuable insights about the fractionation of cognitive functions (Stuss, 2006). This approach was specifically employed here on a cohort of patients with unilateral brain tumors performing a variable FP task. An anatomically-driven analysis was performed on patients grouped into different anatomical regions, according to the tumor location. As it arises from the brief review above, an open issue, which still remains to be investigated, is the neural locus of the sequential effects. For this reason, investigation of the neural bases of the FP phenomena has been extended, in this study, to lesions outside the prefrontal cortex. Therefore, the six tumor locations of patients tested here were: right and left prefrontal, right and left premotor, right and left parietal. Prefrontal patients have been tested with the specific purpose of replicating previous neuropsychological and TMS studies on the role of lateral prefrontal cortex in the variable FP effect (Stuss et al., 2005; Vallesi et al., 2007). The investigation of patients with tumors in premotor and parietal regions was justified by the fact that several imaging studies on temporal preparation or temporal processing have

consistently shown activations of areas within these regions (e.g., Basso, Nichelli, Wharton, Peterson, & Grafman, 2003; Coull et al., 2000; Lewis & Miall, 2003; Macar et al., 2002).

A clear advantage of the study of tumor patients with respect to other categories of neuropsychological patients is that baseline performance may be measured within-subject before tumor resection. As it is still unclear whether and to what extent tumors, especially high-grade ones, have deleterious effects on the cognitive system, we also investigated whether the baseline performance of tumor patients on the variable FP paradigm was already defective, due to the tumor per se, by comparing it with the performance of a control group of hospitalized (orthopaedic) patients without any cerebral disease.

Method

Assignment to Patient Group

The pre-operative location of the tumor was determined using a digital format T1-weighted MRI scan obtained 1-2 days before surgery. The post-operative MR scans were available 3-4 months after surgery, about one month from the end of the radiotherapy. As by this time the area of removed brain tissue was partially replaced by healthy brain, pre-operative MR scans have been used for localisation purposes. Each patient's lesion was referred to an anatomical template image AAL (Automated Anatomical Labeling; Tzourio-Mazoyer et al., 2002), that is a macroscopic anatomical partition of Montreal Neurological Institute (MNI) volume (Collins et al., 1998). MRIcro software was used to extrapolate a 3D representation of the lesion from digital MR scans (Rorden & Brett, 2000). The tumor contour was drawn as a region of interest (ROI) on each sagittal slide. Afterwards, the scans and ROIs were normalised using Statistical Parametric Mapping (SPM2, Wellcome Department of Cognitive Neurology, London, UK) with a human-assisted process. In collaboration with the neurosurgeon and, for low grade tumors, also with the neuroradiologist, who did not know the behavioral results, the tumor boundary was limited to the brain tissue effectively removed during the surgical operation, therefore excluding the oedema.

Patients were assigned to the parietal group if the tumor involved the parietal and occipito-parietal cortices or posterior temporal cortex (posterior to BA 4). Patients with tumors in either or both the motor and premotor areas (BA 4 and 6) have been included in the premotor group. Patients with tumors involving areas anterior to BA 6 have been included in the prefrontal group. Patients with tumors located in the anterior portion of Sylvian fissure, fronto-insular and fronto-temporal areas have been excluded.

Patient selection

One-hundred and eleven patients had initially been tested with tumors of the following types: gliomas, mav, meningiomas and metastases. Fifty-three patients have been excluded from the analysis reported in the current study for the following reasons: they were left-handed (2 cases), the operation was for a recurrence of the tumor (4 cases), they were only available for testing in one of the two sessions (11 cases), they had multiple metastatic lesions (2 cases), the lesions involved white matter almost entirely (2 cases) or were intra-ventricular (2 case), bilateral (8 cases), predominantly insular with frontal-temporal involvement (11 cases), involved roughly equally two of the three brain regions under study (7 cases), because of marked diffused cognitive deficits (1 case), because of the absence of a 3D scan (1 case), because the patient suffered from alcoholism (1 case) or mental retardation (1 case).

The remaining 58 patients were divided into 6 groups with the following sample sizes: 6 left prefrontal, 14 right prefrontal, 8 left premotor, 7 right premotor, 9 left parietal, 14 right parietal (see Figure 1). The histological examination of the tumors of the included patients were: 20 high grade gliomas, 20 low grade gliomas, 15 meningiomas, 3 metastasis. Mean tumor volume was 36.4 ml (on a total of 1352 ml), SD 29.8 ml.

Patients having tumors which show pronounced involvement of a defined region but a small involvement of other critical regions have been included in the study. This was the case for the 8 following patients: tumors of 3 right prefrontal patients extended to right premotor regions; tumor

of another right prefrontal patient extended to the anterior portion of Sylvian fissure; one left prefrontal patient had an involvement of the anterior portion of Sylvian fissure; tumor of another left prefrontal patient had compressive effects on a small portion of the right hemisphere (however, only the tumor in the left hemisphere was surgically removed); tumors of 2 premotor patients, one left and one right, involved a small amount of left and right prefrontal cortex, respectively. Occasionally patients had oedema involving other critical brain regions under study: two right parietal patients had oedema in the premotor and motor areas; one right premotor patient had an involvement of parietal and prefrontal cortex; two right prefrontal patients had oedema involving premotor areas.

Insert Figure 1 about here

A control group of 12 hospitalized orthopedic patients without neurological problems or cognitive impairment (Corrected Mini-Mental State Examination > 24) was also tested in order to check for learning effects, and for the baseline performance of tumor patients on the pre-surgery session. The demographic characteristics of each patient group are reported in Table 1.

When the 7 groups were compared in one-way ANOVAs, there was no significant differences between the groups with respect to age [$F(6, 63) = 1.38$, $p = .23$] and to years of education [$F(6, 63) = 1$, $p = .4$]. Among the 6 groups of tumor patients, there was a tendency towards significance for location on lesion volume [$F(5, 52) = 2.19$, $p = .07$]. The lesion volume for the premotor groups tended to be smaller than that for the parietal and prefrontal groups. Specific t-tests showed that left and right premotor patients had a significantly smaller lesion with respect to the right prefrontal patients (for both contrasts, $p < .05$). For all the other contrasts between each premotor group and each other group, the p value ranged between .052 and .12. There was no effect of hemisphere (left vs. right) in the lesion volume (t-test for independent samples, $p = .44$). Forty participants underwent surgery under general anesthesia, whereas the other 18 were awake during operation.

Preliminary analyses did not reveal any effect of interaction between gender, volume size or anesthesia, on the one side, and the variable FP phenomena and the testing session, on the other side. Therefore, data were collapsed with respect to these factors. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and was previously approved by SISSA ethical committee.

Insert Table 1 about here

Stimuli and Procedure

Each patient was tested individually with her/his gaze ~55 cm from the screen. Patients were tested twice: 1-3 days before operation and 2-6 days after it. The control participants were also tested twice with a comparable time-range between the two testing sessions (i.e., 4-8 days) but without any surgical intervention in between. In addition to the test reported here, tumor patients carried out 20 other neuropsychological tests: 5 on perception, 5 on praxis and 8 on executive functions and working memory, 1 on optic ataxia, and 1 on neglect. For the variable FP task, participants are required to fixate a cross in the centre of a 15” VGA monitor (composed by 2 black lines, 4 cm each). The onset of the fixation cross served as a warning signal. The cross was displayed on the screen until the FP expired. The imperative stimulus was a central yellow rectangle (width: 5.5, height: 4 cm). Participants were instructed to press the spacebar as soon as they would see the rectangle. The imperative stimulus disappeared when the response was detected. The FPs between the cross onset and the rectangle onset were: 3, 4, 6 and 7 sec, respectively. These relatively long FPs were chosen in order to use similar experimental conditions as those used by Stuss and colleagues (Stuss et al., 2005), who administered a very similar FP range to the frontal patients. The 4 FPs were administered randomly and equiprobably across trials. The inter-trial interval between the response detection and the next fixation onset was 1 sec. All the stimuli were presented against a white background. During each session, the experiment consisted of 36 trials (9

per each FP) presented in a different pseudo-random order for each patient. A familiarization phase with 4 trials (one per each FP) preceded the test phase. The recorded variable was the RT.

Data Analysis

RTs outside the 100-3000 ms range, the first trial of the test block and data from the initial familiarization phase were excluded from analyses. Initial analyses comprehend all the 7 groups, typically using a 7x2x2x2 mixed ANOVA. This ANOVA involved patient group as the only between-subject factor (left and right prefrontal, left and right premotor, left and right parietal, and controls), and 3 within-subject factors: FP_n (short vs. long, i.e., 3-4 vs. 6-7 sec), FP_{n-1} (3-4 sec vs. 6-7 sec), and testing session (first and second session, which means pre- vs. post-surgery for tumor patients). A mixed ANOVA with tumor type (high grade, low grade, meningioma, methastasis) and lesion area as the between-subjects factors, and testing session, FP_n, and FP_{n-1} as the within-subject factors did not give any effect of tumor type. Therefore we collapsed this factor in the following analyses.

Results

Excluded trials. Less than 0.6% of trials were discarded because of RTs being outside the 100-3000 ms range. This percentage tended to be significantly different across patient groups, as demonstrated by a non-parametric Kruskal-Wallis test [$H(6, N: 70) = 12.4$, $p = .054$]. This could be due to the fact that virtually no trial was excluded for the controls and the premotor groups. However, the percentage of excluded trials was low also in the other 4 groups (0.7, 0.6, 1.3 and 1.5%, for the left and right parietal, and left and right prefrontal groups, respectively).

Reaction Times. The results are presented in Figures 2 and 3. The overall ANOVA produced the following significant effects. The main effect of FP_n was significant [$F(1, 63) = 87.2$, $p < .001$], indicating that RTs were slower on the short FP_n than on the long one (i.e., the classical FP effect).

The main effect of FP_{n-1}, concerning basic sequential effects, was also significant [$F(1, 63) = 47.5$, $p < .001$]: RTs were slower after a long FP_{n-1} than after a short one. The effect of FP_{n-1} was modulated by the testing session [$F(1, 63) = 6.9$, $p = .01$], being stronger in the first testing session than in the second one. In agreement with the standard findings in the area (e.g., Drazin, 1961), the sequential effects were asymmetric as indicated by a significant FP_n x FP_{n-1} interaction [$F(1, 63) = 5$, $p < .05$]. However, the latter two interactions were better qualified by a tendency toward significance of the testing session x FP_n x FP_{n-1} interaction [$F(1, 63) = 3.7$, $p < .056$]. This tendency suggested that asymmetric sequential effects were present in the first session, but absent in the second session, a pattern mainly observed on the short FP_n.

More critically, the patient group x testing session x FP_n interaction was also significant [$F(6, 63) = 2.5$, $p < .05$]. Visual inspection of Figure 2 suggests that this interaction was due to a reduction of the FP effect selectively after removal of tumoral tissue in right lateral PFC. In order to corroborate this observation statistically, separate ANOVAs were conducted for each group with testing session, FP_n and FP_{n-1}, as repeated measures. As predicted (cf. Stuss et al., 2005), the testing session x FP_n interaction was significant for the right prefrontal patients [$F(1, 13) = 8.2$, $p = .01$], due to a reduction of the FP effect after surgery (12 ms) with respect to the pre-surgery effect (57 ms). We further checked if there was a correlation between this effect and lesion size. Neither the pre- nor the post-surgery FP effect in right prefrontal patients correlated with lesion size[1]. It should be noted that the testing session x FP_n interaction was not significant for all the other five tumor patient groups ($p = .73, .36, .44, .88, .12$, for the left prefrontal, left and right premotor, left and right parietal groups, respectively).

Insert Footnote 1 about here

Insert Figure 2 about here

These separate ANOVAs had also been carried out to find the source of the testing session x FP_{n-1} and, more relevant, of the testing session x FP_n x FP_{n-1} interactions in the overall ANOVA. Although these interactions are not significantly modulated by the patient group in the overall ANOVA, visual inspection of Figure 3 suggests that the premotor and prefrontal groups are principally responsible for these effects. This was only partially confirmed as the testing session x FP_{n-1} interaction was a tendency for the right prefrontal group ($p = .06$) and for the left premotor group ($p = .08$).

Insert Figure 3 about here

To find the source of the testing session x FP_n x FP_{n-1} interaction, which is critical for determining the locus of the asymmetric sequential effects, we chose a Bonferroni correction of a critical significance level of .0083 (i.e., .05 divided by the 6 tumor patient groups). The motivation for the use of a Bonferroni correction was twofold: first, the 3-way interaction was only a trend in the overall ANOVA; second, we did not have a precise a priori prediction as far as the locus of the asymmetric sequential effects was concerned. The only individual patient group which showed a significant testing session x FP_n x FP_{n-1} interaction, when analyzed separately from the other groups, was the left premotor one [session x FP_n x FP_{n-1} 3-way interaction: $F(1, 7) = 22.1$, $p = .002$]: the asymmetric sequential effects, which were present before surgery mainly on the short FP_n, had disappeared after it. This was observed in this patient group despite the standard FP effect being present with the same magnitude before and after the operation, as shown by a significant main effect of FP_n [$F(1, 7) = 55.4$, $p < .001$], which was not modulated by the testing session (session x FP_n interaction, $p = .36$). The main effect of testing session was also reliable in this group [$F(1, 7) = 31.7$, $p < .001$], due to RTs being slower after the operation than before, which could conceivably arise from a motor effect, given that these patients were all right-handed.

It should be noted that this 3-way testing session x FP_n x FP_{n-1} interaction was far from significant in all the other five tumor patient groups, the *p* values being .27, .94, .72, .38, .79, for the left and right prefrontal, right premotor, left and right parietal groups, respectively. However, when the post-surgery performance of each tumor patient group was contrasted to that of the same second session in the control group in a 2x2x2 mixed ANOVA (between-subjects factor: patient group; within-subject factors: FP_n, FP_{n-1}), the 2-way group x FP_{n-1} interaction (concerning basic sequential effects) was significant not only for the left premotor group ($p = .007$), but also for the left and right prefrontal groups ($p = .04, .03$, respectively; not significant if Bonferroni corrected), and there was a strong trend for the right premotor group ($p = .055$). However, the interaction was not significant for the left and right parietal groups ($p = .12$ and .40, respectively). This interaction shows that, the basic post-surgery sequential effects, when evaluated separately from the asymmetry of the effects (as revealed by the FP_n x FP_{n-1} interaction), were in fact smaller in all the frontal groups as compared to the controls. Critically, the left premotor patients were the only group differing in the asymmetric aspect of the sequential effects as compared to the controls, as indicated by the significant 3-way interaction [group x FP_n x FP_{n-1} interaction, $F(1, 18) = 8.9$, $p = .008$][2].

Insert Footnote 2 about here

Discussion

In this study, we aimed to investigate the variable FP phenomena in tumor patients, when tested before and after surgical removal of tumors which were located in different cortical areas. The most important finding was a reduction in the FP effect after surgical removal of tumors of the right prefrontal cortex. This finding corroborates recent studies on FP phenomena obtained in chronic patients with predominantly other etiologies such as stroke (Stuss et al., 2005; see also Picton et al., 2006), and in healthy participants undergoing inhibitory TMS over right DLPFC (Vallesi et al., 2007).

Although obtained in such a simple experimental task, the FP effect is generally considered as a marker of high-level monitoring processes (e.g., Näätänen, 1970; Niemi & Näätänen, 1981; Stuss et al., 2005; but see Los & van den Heuvel, 2001). On this view, this result supports the hypothesis that right lateral prefrontal cortex is the seat of the critical process producing the FP effect, that is monitoring of the increasing conditional probability of stimulus occurrence along the FP (e.g., Näätänen, 1970). The neuropsychological work by Stuss and colleagues (Stuss et al., 2005) helps clarifying that monitoring of the conditional probability of the stimulus occurrence is the process impaired in right prefrontal patients, and not keeping track of elapsing time per se. When the conditional probability of stimulus occurrence was kept constant by using an interval fixed within a block instead of a variable FP paradigm, the performance of the right prefrontal group was comparable to that of the controls. In contrast, with this fixed FP paradigm, the superior medial frontal group was the only group who was impaired. Monitoring of conditional probability was not relevant with a fixed FP paradigm, where time intervals are constant within a block. Moreover, as simple and choice RT tasks were used, monitoring of elapsing time was also not required. On the other hand, when the task demands require monitoring of temporal information, either implicitly (as in the current study) or explicitly, as it is the case for time estimation and reproduction tasks, evidence for an involvement of right lateral prefrontal cortex (usually dorsolateral) has been found in neuropsychological (e.g., Harrington, Haaland, & Knight, 1998; Koch, Oliveri, Carlesimo, & Caltagirone, 2002), TMS (Jones, Rosenkranz, Rothwell, & Jahanshahi, 2004; Koch, Oliveri, Torriero, & Caltagirone, 2003), and imaging studies (Lewis & Miall, 2003; Rao, Mayer, & Harrington, 2001), also when working memory demands were controlled (Smith, Taylor, Lidzba, & Rubia, 2003), although these studies generally involved different ranges of time intervals from that used in the current one.

Unlike the previous neuropsychological work (Stuss et al., 2005), the current study additionally investigated the effect of the preceding FP, which is known to give rise to sequential effects: RTs are slower for long FP_{n-1} than for short ones; these effects are typically asymmetric in that they

occur specifically only when the current FP is a short one. In the overall ANOVA, there was a reduced effect of the FP occurring on the preceding trial (i.e., basic sequential effects), when performance in the second session was compared to that in the first session. This effect is difficult to interpret from the localisational point of view, as we did not find clear statistical evidence for the specificity of the tumor site in the overall ANOVA or in more specific analyses. These analyses, indeed, showed that the basic post-surgery sequential effects were reduced (significantly or as a tendency) in the four frontal groups, even if not in the two parietal groups.

More critically, examining the behavior of the left premotor group provides additional information about the localisation of the asymmetric sequential effects and their underlying cognitive mechanisms. Despite the presence of an unchanged FP effect, the asymmetric sequential effects disappeared after operation; this was supported statistically when performance was compared within-group with the pre-surgery performance (i.e., a significant session x FP_n x FP_{n-1} interaction) and between-groups with the second session of the controls (i.e., significant group x FP_n x FP_{n-1} interaction). In particular, there was no RT reduction after a short FP_{n-1} in the post-surgery session of the left premotor patients. This result may be interpreted as suggesting a pre-motoric/motoric locus of a facilitatory effect when a short FP had occurred in the previous trial. Left premotor areas are indeed directly involved in the preparation of the manual key-press, which is the response required in the task. Supporting this hypothesis, an electrophysiological study on monkey premotor and motor cortex (Riehle & Requin, 1993) revealed that activity of neurons within this region correlate with performance speed in tasks with a preparation period. During the delay period of a delayed-reach task, moreover, micro-stimulation of neurons within premotor cortex lead to a highly-specific lengthening in reach RT (Churchland & Shenoy, 2006). Nevertheless, one cannot draw firm conclusions about the localisational of sequential effects because of the lack of interaction with the other patient groups in the overall ANOVA. Indeed, there are suggestions from the findings that reduced basic sequential effects may be present in all the

frontal groups. Therefore, these findings concerning the left premotor localisation of sequential effects should be seen as a suggestion for further studies.

However, functional conclusions can be drawn even in the absence of strong anatomical localisation. Indeed, this finding represents the second component of a double dissociation between FP and sequential effects. On the one hand, Vallesi and colleagues (Vallesi et al., 2007) found a reduction in the FP effect as a result of inhibitory TMS on the right DLPFC in the absence of a modulation in the sequential effects. On the other hand, here it has been shown that sequential effects disappear after surgery in left premotor patients despite an intact FP effect. This pattern supports dual-process accounts of the FP phenomena (e.g., Vallesi et al., 2007; Vallesi & Shallice, in press; see also Los & Agter, 2005), and is much difficult to account for in a single-process account (Los & van den Heuvel, 2001).

The functional meaning of the sequential effects, therefore, needs to be revised. According to the dual-process account put forward by Vallesi and colleagues (Vallesi et al., 2007; Vallesi & Shallice, in press), the sequential effects may be due to a tonic arousal modulation by the FP_{n-1}. As maintaining a high level of preparation for a long FP is effortful, a long FP_{n-1} decreases arousal (refractoriness) and lengthens RTs on trial n, whereas a short FP_{n-1} increases arousal (facilitation) and produces relatively faster RTs on trial n (see Los & Heslenfeld, 2005, for electrophysiological evidence). This arousal modulation is especially detectable on the shortest current FP (i.e., asymmetric sequential effects), when the compensatory effect of the monitoring the conditional probability of stimulus occurrence cannot take place. After tumor removal in frontal patients here, and especially left premotor patients, the second process (facilitation) seems to be impaired, so that RTs on a short FP_n do not benefit from a short FP_{n-1}, conceivably because the brain area where this arousal modulation should produce its effects (i.e., left premotor cortex) is not working properly due to the surgical lesion.

The effects of tumor per se on cerebral functionality are still almost unknown. However, there are a few studies investigating cognitive functioning of brain tumor patients before any treatment

and surgical intervention, which found cognitive deficits caused by the presence of tumor (e.g., Rabbit & Page, 1998; Tucha, Smely, Preier, & Lange, 2000). Therefore, a baseline evaluation of cognitive abilities before surgery is methodologically desirable in any study of tumor patients undergoing surgery. To that purpose, the use of a matched control group of orthopedic patients allowed us to exclude, at least before surgery, any particular deficit of our sample of tumor patients in performing the variable FP paradigm.

A critical aspect of the present results is that the effects found are selective and are generally robust across etiologies. Indeed, resection of a right prefrontal tumour gives the same reduction in the FP effect as in a cohort of patients primarily suffering from stroke in the same region (Stuss et al., 2005). From a methodological point of view, this study supports the one by Shallice and colleagues on optic ataxia (Shallice, Mussoni, D'Agostini, & Skrap, submitted), demonstrating that the effects of operation for resection of tumors can be a valuable method for localizing cognitive processes.

In conclusion, the present findings confirm the studies on the anatomical basis of the FP effect (Stuss et al., 2005; Vallesi et al., 2007), suggesting that this effect can be used as a measure of the functionality of right lateral prefrontal cortex, and additionally provide surprising new neuropsychological insights on the sequential effects. The latter are best explained by a dual-process account of the FP phenomena. Finally the findings strongly support the utility of using acute brain tumor patients as a source of evidence about the localisation and fractionation of cognitive functions.

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Footnotes

[1]When lesion size and FP effects in the post-surgery session are compared across patient groups, a significant negative correlation is observed (r = -.94), indicating that the FP effect decreases as the lesion volume increases at the group level. However, when the Pearson correlation analysis is carried out within each tumor group, that is between post-surgery FP effect of each patient within each group and her/his lesion size, no significant correlation is observed for any group. The r (and *p*) values were: .11 (*p* =.7), -.42, (*p* = .4) etc. , .17 (*p* = .72), .01 (*p* =.98), -.33 (*p* = .25), -.37 (*p* = .33), for the right and left prefrontal, left and right premotor, left and right parietal groups, respectively. These results suggest that lesion size alone cannot account for the reduction of the FP effect.

[2]Each tumor patient group was also contrasted with each other in a 2x2x2 mixed ANOVA for the post-surgery session, with region as the between-subjects factor, and FP_n and FP_{n-1} as the within-subject factors. The 3-way interaction was significant when the left premotor group was contrasted with the right parietal one [$F(1, 20) = 6.56$, $p = .018$], and there was a similar tendency when the left premotor group was contrasted with the left parietal one ($p = .07$). This interaction was not significant for any other pair of groups.

Acknowledgements

This research was partially supported by a grant from PRIN to TS and Raffaella Rumiati. AM was supported by a grant from Regione Friuli Venezia Giulia to SISSA, 2005/2006 "Neuropsicologia clinica delle funzioni esecutive e prassiche". The authors are also thankful to the members of the Neurosurgical Department, Ospedale S.M. Misericordia, Udine, for their helpfulness throughout the study.

Table 1

Main Demographical Characteristics of the seven Patient Groups included in the study.

	Mean Age[a]	Mean Education[a]	Gender		Anaesthesia		Tumor Volume[b]	Tumor Type				Sample size
Group	(min-max)	(SD)	F	M	G	L	(SD)	HG	LG	Mng	Mt	
Left Prefrontal	45 (33-62)	11 (4)	3	3	5	1	3.3 (1.5)	0	2	4	0	6
Right Prefrontal	45 (23-72)	12 (4)	5	9	12	2	3.6 (2.2)	4	6	4	0	14
Left Premotor	45 (31-60)	11 (3)	5	3	2	6	1.1 (0.8)	4	3	1	0	8
Right Premotor	39 (18-58)	12 (3)	2	5	2	5	1.3 (1)	2	4	1	0	7
Left Parietal	53 (31-70)	9 (3)	3	6	6	3	3 (2.4)	5	2	1	1	9
Right Parietal	54 (30-70)	10 (4)	6	8	13	1	3 (2.7)	5	3	4	2	14
Controls	47 (23-73)	11 (4)	6	6	---	---	---	---	---	---	---	12

Notes. [a]In years. [b]In percentage of the total volume. SD = standard deviation; F = female; M = male; G = general; L = local. HG = high grade glioma; LG = low grade glioma; Mng = meningioma; Mt = metastasis.

Figure Captions

Figure 1. Display of the tumor overlap for the 6 groups of tumor patients. The percentage of overlapping tumors in each voxel is illustrated using a grey-scale within the region of interest: the lighter is a point on that scale, the higher the percentage of patients within that group with that voxel damaged. The white colour indicates voxels with maximal percentage of tumors within each patient group. Maximal percentage of overlap was 67, 43, 63, 43, 56, 36, for the left and right prefrontal, left and right premotor and left and right parietal groups, respectively. The z-coordinates of each transversal section in Montreal Neurological Institute space are -8, 0, 8, 16, 24, 32, 40, 50, 60, 70. LPF = left prefrontal; RPF = right prefrontal; LPM = left premotor; RPM = right premotor; LP = left parietal; RP = right parietal. See supplementary Figure 1, for a color version of the Figure.

Figure 2. The foreperiod effect (reaction time difference between foreperiods of 3-4 and 6-7 seconds) as a function of patient group and testing session. FP = foreperiod. Tumor group labels as for figure 1.

Figure 3. The sequential effects as a function of patient group and testing session. Short = 3-4 seconds. Long = 6-7 seconds. FP = foreperiod. Error bars indicate the standard error of the mean.

Fig 1

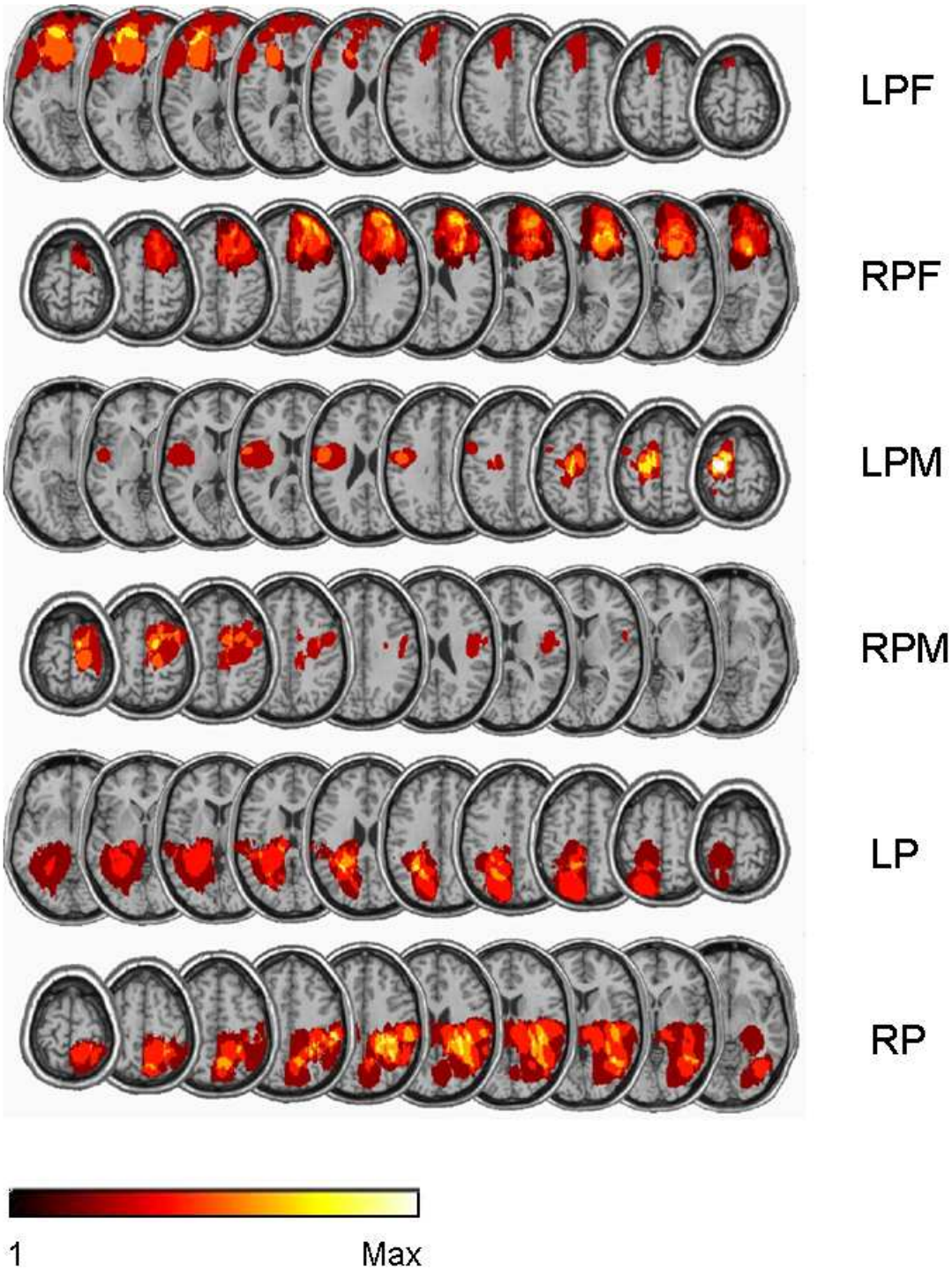


Fig 2

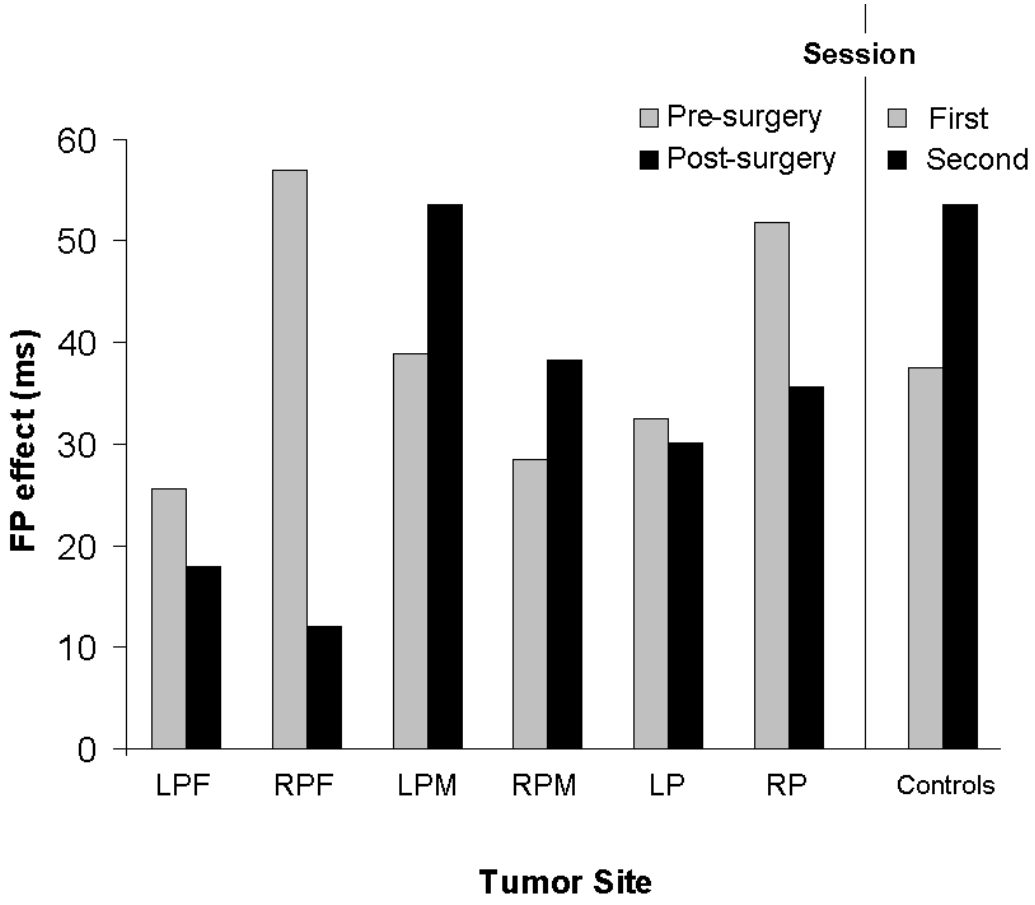
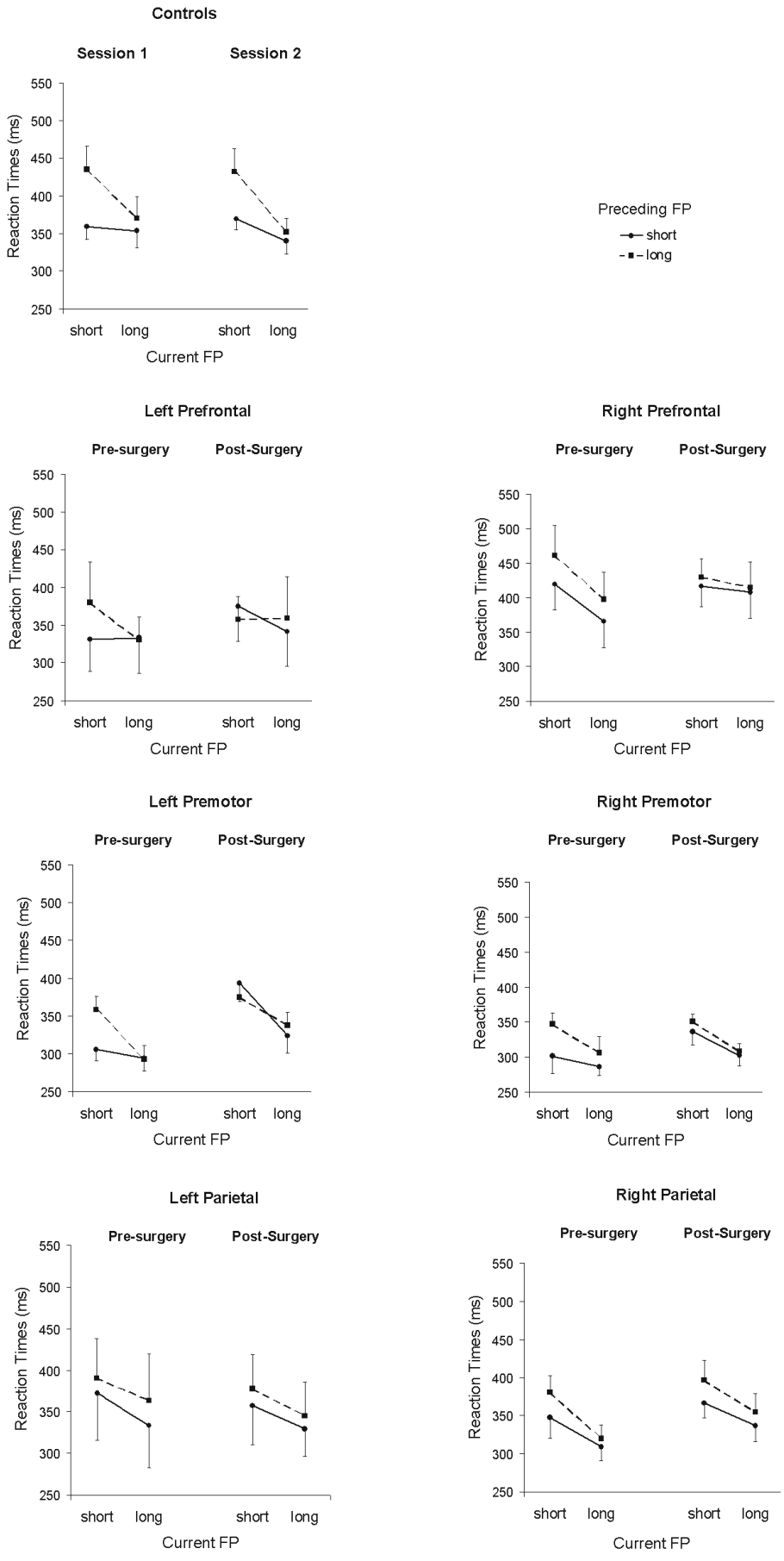

Session
Pre-surgery
Post-surgery
First
Second
60
50
40
30
20
10
0
FP effect (ms)
LPF
RPF
LPM
RPM
LP
RP
Controls
Tumor Site

Fig 3


Controls
Session 1
Session 2
Reaction Times (ms)
550
500
450
400
350
300
250
short
long
Current FP
Preceding FP
short
long
Left Prefrontal
Pre-surgery
Post-Surgery
Right Prefrontal
Left Premotor
Right Premotor
Left Parietal
Right Parietal