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Preserved time but altered numerosity processing in epileptic patients with postoperative lesion in the inferior frontal gyrus

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Abstract

Previous researches have shown that the inferior frontal gyrus (IFG) is involved in time and numerosity processing. This study aimed at examining (i) interval timing and (ii) interaction between duration and numerosity processing in four drug-resistant epileptic patients with postoperative lesions in the IFG in comparison with thirteen healthy controls. The duration reproduction and discrimination tasks performed in the sub- and supra-second ranges did not reveal any significant differences between patients and controls. The duration discrimination task of stimuli varying in numerosity (DurN) and the numerosity discrimination task of stimuli varying in duration (NumD) revealed that only numerosity judgment was altered in IFG patients. A time-order effect was notably observed in the NumD task but in opposite directions for the two groups: The second patch was perceived as more numerous than the first patch in controls and conversely as less numerous in patients. Finally in the DurN task, we observed a congruency effect which was dependent on numerical distance in patients but not in controls. These converging results suggest that the IFG would be more specifically involved in numerosity than in duration processing, possibly playing a role in numerical decision.

Keywords: Inferior frontal gyrus, Interval timing, Numerosity processing, Time-order effect, Drug-resistant epilepsy

1. Introduction

Time perception allows detecting temporal regularities, anticipating future events and optimizing their processing and thus contributes to adaptation in a dynamic environment. It is unclear whether this ability to judge time intervals depends on dedicated timing networks in the brain or whether time intervals are estimated indirectly from the dynamic of neural processes (Goel & Buonomano, 2014; Merchant et al., 2013). Functional neuroimaging, lesion or stimulation studies conducted to investigate the neural substrates of time processing have revealed the participation of numerous brain regions including sub-cortical (basal ganglia and cerebellum) and cortical (frontal, parietal and temporal) areas (Coull et al., 2011; Merchant et al., 2013). Whether these different regions are involved in a dedicated timing network, in more general cognitive processes involved in timing tasks such as sustained attention (Casini & Ivry, 1999; Coull et al., 1998) and working memory (Mangels et al., 1998; Owen et al., 1999) or in a context-dependent fashion (Merchant et al., 2013) remains matter of debate. Interestingly, a main core timing network that consists of the supplementary motor area (SMA), the right inferior frontal gyrus (IFG) and the basal ganglia is found when performance levels on the temporal and controls tasks are carefully matched (Coull et al., 2008, 2004; Morillon et al., 2009; Nenadic et al., 2003). In addition, meta-analyses of fMRI studies on time processing (Teghil et al., 2019; Wiener et al., 2010) have found that two frontal regions, the SMA and the right inferior frontal gyrus (IFG), are involved whatever the duration range (sub-second and supra-second) and the type of task (perceptual or motor). Because the SMA activity has been shown to increase linearly with the objective or subjective duration of a stimulus (Coull et al., 2015, 2004; Macar et al., 1999), it has been assumed that this region located in the mesial part of the premotor cortex, in connection with the basal

ganglia could play a major role in the pacemaker-accumulator process. By contrast, the role of the IFG in timing remains largely to be clarified.

1.1. IFG and duration processing

The IFG consists in three sub-regions which are, on the rostro-caudal axis, the orbital, triangular and opercular parts, the later being in proximity with the anterior insular cortex (AIC). Numerous fMRI studies on time processing (Ferrandez et al., 2003; Kosillo & Smith, 2010; Lewis & Miall, 2006, 2003a, 2003b; Livesey et al., 2007; Pouthas et al., 2005; Rao et al., 2001; Stevens et al., 2007; Wittmann et al., 2010) have shown activity within a region located at the junction between the opercular part of the IFG and the AIC and it is not clear whether the IFG and the AIC have a common or a distinct role in timing. Craig (2009) proposed that the IFG/AIC region integrate internal and external environmental information to produce ‘global emotional moments’ which would be at the basis of our perception of time. When ‘global emotional moments’ are filled rapidly, due, for example, to the presentation of a highly-arousing negative event, their rate of accumulation would increase leading to a subjective lengthening of time, as it has been reported by Droit-Volet and Meck (2007). In line with this model, the right IFG/AIC region has been shown to be involved in the alteration of time processing by emotional arousal (Dirnberger et al., 2012; Pfeuty et al., 2015; Tipples et al., 2015). However, other roles have also been attributed to the IFG in timing. Conjointly with the SMA, the IFG has been shown to be involved in inhibitory control (Rae et al., 2014) and, interestingly, both regions are directly connected via the frontal aslant tract (Catani et al., 2012). Through its contribution to action inhibition, it has been proposed that, at the offset of the to-be-timed interval, the IFG could inhibit the accumulation process underpinned by the SMA during time processing (Harrington et al., 2010). Furthermore, Transcranial Magnetic Stimulation (TMS) over the right IFG have been shown to affect the performance in a

duration discrimination task but not in a temporal reproduction task, suggesting that this region could be involved in the categorical decision at play during a discrimination task (Hayashi et al., 2013).

Although the IFG involvement in interval timing is supported by numerous fMRI studies, only few neuropsychological studies showed the impact of lesion within this region on temporal performance. Using voxel-based lesion-symptom mapping (VLSM) in stroke patients with unilateral hemispheric lesions, lesions in the right IFG have been shown to be associated with a lower performance (i.e. a higher variability) in a duration discrimination task with sub- and supra-second intervals (Gooch et al., 2011) or in a reproduction task involving an irregular context (Teghil et al., 2020). In another study using emotional stimuli in patients with a stroke affecting the left or the right insula the temporal sensitivity was shown to be reduced in right insular patients while the effects of emotion on timing were similar between control participants and patients (Mella et al., 2019). However, in this study, the lesions were located in the whole insula and not specifically in the anterior insula. In another study (Monfort et al., 2014), a drug-resistant epileptic patient with a focal lesion in the right junction of the IFG and the AIC has been shown to importantly over-reproduce time intervals of 3, 5 and 7 seconds despite normal temporal variability. However, in this study, time processing investigation included a motor component and was limited to the supra-second intervals which have been shown to involve different timing mechanisms than sub-second intervals (Lewis & Miall, 2003b). Thus, we wonder whether a similar impairment in the accuracy of duration judgment would have been observed using perceptive (i.e. discrimination) and motor (i.e. reproduction) timing tasks with sub-second or supra-second intervals. Furthermore, the neuropsychological assessment of the patient revealed specific impairment in the arithmetic test of the WAIS III. As the ability in time perception has been shown to be related to mathematical skills (Tobia et al., 2018) and the IFG has been shown to

be involved in the processing of both time and numerosity (Hayashi et al., 2013), we also wonder whether the bias observed for duration judgment would have been also observed for numerosity judgment.

1.2. IFG and duration - numerosity interaction

In the ATOM (A Theory Of Magnitude), Walsh (2003) posits that the processing of time and numerosity in the brain depends on a generalized magnitude system, which suggests that these two magnitude dimensions shared a common neural code. From this idea of a common magnitude system in the brain derives the assumption of a reciprocal interaction of duration and numerosity. In line with this assumption, numerous behavioral studies reported interaction between these two dimensions, although the effect of numerosity on duration judgment has been more systematically observed than the effect of duration on numerosity judgment. Several studies using both duration and numerosity tasks actually revealed that stimuli with larger numerosities were perceived as longer in duration judgment while stimuli with longer duration were not reciprocally perceived as more numerous in numerosity judgment (Dormal et al., 2006; Droit-Volet et al., 2003; Hayashi et al., 2013; but see Javadi & Aichelburg, 2012; Lambrechts et al., 2013; Martin et al., 2017).

Several neuroimaging and TMS studies suggest that the common magnitude system would mainly involve the parietal cortices (Buetti & Walsh, 2009; Dormal et al., 2012; Riemer et al., 2016). However, neuroimaging studies have also revealed the contribution of IFG both in interval timing (Ferrandez et al., 2003; Kosillo & Smith, 2010; Lewis & Miall, 2006, 2003a, 2003b; Livesey et al., 2007; Pouthas et al., 2005; Rao et al., 2001; Stevens et al., 2007; Wittmann et al., 2010) and numerosity processing (Hayashi et al., 2013; Rusconi et al., 2013, 2011; Skagerlund et al., 2016; Wilkey & Price, 2019). In addition, several studies suggested that IFG lesions are associated with deficits in time perception (Gooch et al., 2011; Mella et

al., 2019; Monfort et al., 2014) and numerosity processing (Aiello et al., 2012; Doricchi et al., 2005; Pflugshaupt et al., 2020; Revkin et al., 2008). Interestingly, a study by Hayashi and colleagues (2013) investigated duration and numerosity discrimination with stimuli varying in both dimensions. They found that, among the regions commonly activated in duration and numerosity discrimination tasks, the right IFG was the only one whose activity was higher in congruent (shorter-less or longer-more) than in incongruent (shorter-more or longer-less) conditions. Considering that IFG activation was higher when the categorical judgment for one dimension was facilitated by the other dimension category but also because TMS over this region influenced temporal performance in discrimination but not in reproduction, the authors proposed that IFG was involved at the categorical decision stage in duration and numerosity processing.

1.3. Objective of the current study

The first objective of the present study was to determine whether IFG lesions in four epileptic patients were associated with impairment in the accuracy of the reproduction of supra-second intervals, as reported in the single-case study by Monfort et al. (2014). In order to determine whether time perception impairment following IFG lesions was not dependent on the motor component of the task and the duration range, performances of the patient group were compared to those of a healthy control group in reproduction and discrimination tasks performed separately in supra-second (2700 to 6300ms) and sub-second (400 to 900ms) ranges. Based on previous neuroimaging studies suggesting that the involvement of the IFG region in time processing is not context-dependent (Teghil et al., 2019; Wiener et al., 2010), we expected that temporal performance of the patient group would be impaired whatever the duration range (sub-second and supra-second) and the type of the task (perceptual or motor).

Because the IFG could be involved not specifically in time processing but more generally in magnitude processing, we also tested whether patients with IFG lesions were impaired similarly in a duration and a numerosity discrimination tasks of stimuli varying in both dimensions and whether the interactions between the two dimensions were modulated by the lesions. If temporal and numerosity processing depend on a common magnitude system involving the IFG (Hayashi et al., 2013), we expected that performance of the patient group would be impaired both in the duration and the numerosity tasks. Furthermore, larger numerosities should be associated with longer duration judgments and this congruency effect could be modulated by IFG lesions.

2. Materials and methods

2.1. Participants

Seventeen individuals (four drug-resistant epileptic patients with postoperative lesions in the IFG) participated in the study. All participants were fully informed about the aim of investigation before providing written consent for this study.

2.1.1. Patients

Four male patients (Mean age: 29.8 ± 7.4 years – Mean educational level: 14 ± 2.2 years – one right-handed: patient 3 and three left-handed: patients 1, 2 & 4) suffering from drug-resistant epilepsy were recruited through the Functional Exploration Department of Nancy University Hospital to participate in this study. Each patient underwent presurgical intracerebral evaluation (*i.e.* stereo-electroencephalography) to delineate epileptic zones and to avoid resection of functionally relevant areas. Patients were included as they had post-surgical focal lesions located within the right (three patients: patients 1, 2 & 3) or left (one

patient: patient 4) inferior frontal gyrus (IFG). The localization of the lesion of each patient is presented in Figure 1. All patients had an IQ above 70 and speak French as their mother tongue. Neuropsychological evaluation of executive functioning, working memory, processing speed, arithmetic skills and language performed before and/or after surgery for each patient are presented in Table 1.

Patient 1 was 31 years old, with epileptic history beginning at the age of 5 and suffered from partial seizures with hyperactivity and absence periods. Seizures stopped at the age of 15 and restarted four years later. Seizures occurred 2 to 3 times a day during critical phases and were separated by free periods from one week to one month. Based on fMRI and video-EEG, right frontal-orbital cortectomy was performed on the 2013/10/21. The lesion included the frontal pole and was limited dorsally by the inferior frontal sulcus, caudally by the pars triangularis, and medially by the medial line. Anti-seizure medication at the time of the study was: Carbamazepine 400 mg / Lamotrigine 5 mg / Olanzapine 10 mg. No seizure has been reported between surgery and the participation in the present study which occurred the 2015/04/27.

Patient 2 was 19 years old. Generalized seizures appeared at the age of 15 and then, he suffered from partial seizures since the beginning of treatment. Seizures occurred during the day and were anticipated by the patient. Right frontal cortectomy was performed the 2014/11/25 involving the prefrontal operculum, the middle frontal gyrus and the bottom of the middle frontal sulcus until the deep insular extension of the right hemisphere. Anti-seizure medication at the time of the study was: Carbamazepine 600 mg. No seizure has been reported between surgery and the participation in the present study which occurred the 2015/05/27.

Patient 3 was 34 years old. First generalized tonic-clonic seizures appeared at the age of 22. Seizures occurred only during night or during falling asleep with a frequency of three

of four times per year. Right frontal-polar corticotomy was performed the 2014/12/02 including medial and lateral frontal orbital part and the right operculum with a superior limit at the level of the inferior frontal sulcus and a posterior limit at the level of premotor operculum. Anti-seizure medication at the time of the study was: Levetiracetam 500 mg / Clobazam 5 mg / Oxcarbazepine 450 mg. No seizure has been reported between surgery and the participation in the present study which occurred the 2015/06/03.

Patient 4 was 34 years old. First epileptic seizures appeared at the age of 8 leading to the diagnosis of a tuberous sclerosis complex. Seizure generalization started in 2003 with generalized morpheic and partial seizures, mostly occurring at the end of the day. Epileptic seizures could be complicated by a status epilepticus and psychosis were frequently observed during the post-ictal phase. Seizures were frequent, several a day, and probably underestimated by the patient. The origin was tubers localized in the left middle frontal gyrus (premotor region). Left frontal cortectomy with resection of the two tubers was performed the 2011/07/06. The resection of the tuber localized in the left middle frontal tuber was limited to the pre-central sulcus and the resection of the tuber localized in the inferior frontal gyrus was limited posteriorly by the Broca's area and by the pars triangularis. Anti-seizure medication at the time of the study was: Pregabalin 250 mg / Lacosamide 150 mg / Lamotrigine 200 mg / Clobazam 5 mg. No seizure has been reported between surgery and the participation in the present study which occurred the 2015/07/07.

2.1.2. Control group

Thirteen healthy control participants (eight males; 11 right-handed) were recruited, matched by age (25.1 ± 4.2 years) and educational level (14.2 ± 2.5 years). They were all native French speakers. None of the control participants had a history of neurological or psychiatric illness.

2.2. Behavioral tasks

Patients and control participants performed several tasks allowing to investigate, firstly, motor (reproduction) and perceptual (discrimination) timing in the sub-second and supra-second range and, secondly, interaction between duration and numerosity processing. Each task was computerized, stimulus presentation and response collection being controlled via E-prime 2 Software. For each task, a training phase was previously proposed for familiarization, during which the participant received a feedback based on his performance. Tasks order was identical for all participants and consisted of the following: duration discrimination task of stimuli varying in numerosity (DurN) - supra-second duration reproduction - supra-second duration discrimination - sub-second duration reproduction - numerosity discrimination task of stimuli varying in duration (NumD) - sub-second duration discrimination.

2.2.1. Motor and perceptual timing tasks

2.2.1.1. Duration reproduction

Two separated duration reproduction tasks were designed for the sub-second and the supra-second ranges. Each trial began with the presentation of a blue square for a target interval (TI) of 400, 600 or 900ms (in the sub-second range task) and of 2800, 4200 or 6300ms (in the supra-second range task) that the participants had to memorize. After a constant inter-stimulus interval (ISI) of 1500ms, the reproduction interval (RI) started with the onset of a grey square on the screen. The participants had to press the “space” key on the keyboard when they judged the duration of the grey square as equal to the memorized TI. If the participant did not press the key within a delay equal to 4 times the TI, the grey square disappeared and the trial was counted as a missed trial. There was a total of 45 trials (15 trials for each TI) per duration range, divided up into 3 blocks of 15 trials. Each TI was presented in a pseudo-random order.

2.2.1.2. Duration discrimination

Two separated duration discrimination tasks were designed for the sub-second and the supra-second duration ranges. Each trial began with the presentation of a blue square for a TI of 400, 600 or 900ms (in the sub-second range task) and of 2800, 4200 or 6300ms (in the supra-second range task) that the participants had to memorize. After a constant ISI of 1500 ms, the comparison interval (CI) started with the onset of a grey square on the screen. The duration of the CI was 16.7% shorter or longer than the previously memorized TI (333/467ms, 500/700ms and 750/1050ms for the sub-second range and 2333/3267ms, 3500/4900ms and 5250/7350ms for the supra-second range). At the end of the CI, participants used the keyboard to state whether they judged the CI to be shorter (“b” key), or longer (“n” key) than the TI. They were asked to respond as accurately as possible, without worrying about speed. There was a total of 54 trials (18 trials for each TI) per duration range, divided up into 3 blocks of 18 trials. Each TI was presented in a pseudo-random order.

2.2.2. Interaction between duration and numerosity

On each trial, two circular patches of white dots were presented sequentially. Each patch was generated using a program made from the MATLAB Software. The first and second patches were separated by a constant ISI of 1500ms. The duration of stimulus presentation and the number of dots were manipulated for each patch. The duration and the numerosity of the second patch changed in the same (increase/increase or decrease/ decrease) or opposite (increase/decrease or decrease/increase) directions in trials defined as congruent or incongruent, respectively.

In the duration (DurN) task, participants had to indicate whether the duration of the second patch (S2) presentation was shorter (“b” key) or longer (“n” key) than the duration of

the first patch (S1) presentation. Three pairs of duration were used: 417/500, 583/700 and 833/1000ms (longer/shorter = 1.20). We used sub-second intervals because most of the studies showing interaction between time and numerosity used sub-second stimuli. For each pair, S2 was either shorter or longer than S1 (S2-type was S2-shorter in half trials and S2-longer in the other half trials). Eight pairs of irrelevant numerosity were used with either close: 80/96, 144/172, 216/260 and 256/308 points (more/less ratio = 1.20) or far: 80/144, 96/172, 144/260 and 172/308 points (more/less = 1.80) distance. For each pair, the patch with the larger numerosity was presented either in first or second position. The different pairs of irrelevant numerosity were equiprobably distributed among the different pairs of duration. There was a total of 96 trials (32 trials for each pair of duration) divided up into 6 blocks of 16 trials. Each pair of duration was presented in a pseudo-random order. The number of trials for each congruency-distance condition (congruent-close Cc, incongruent-close Ic, congruent-far Cf and incongruent-far If) was equivalent.

In the numerosity (NumD) task, participants had to indicate whether the second patch (S2) contained less ("b" key) or more ("n" key) dots than the first patch (S1). Three pairs of numerosity were used: 120/144, 168/200 and 232/280 points (more/less = 1.20). For each pair, S2 contained either less or more dots than S1 (S2-type was S2-less in half trials and S2-more in the other half trials). Four pairs of irrelevant duration were used for the close: 333/400, 500/600, 750/900 and 1000/1200ms (longer/shorter = 1.20) and the far: 333/600, 417/750, 500/900 and 667/1200ms (longer/shorter = 1.80) conditions. For each pair, the patch with the longer duration was presented either in first or second position. The different pairs of irrelevant duration were equiprobably distributed among the different pairs of numerosity. There was a total of 96 trials (32 trials for each pair of numerosity) divided up into 6 blocks of 16 trials. Each pair of numerosity was presented in a pseudo-random order. The number of trials with each congruency-distance condition (Cc, Ic, Cf, If) was equivalent.

2.3. Statistical analyses

Linear or logistic mixed effect regression models were performed using JAMOVI 1.1.9 (The jamovi project (2019). jamovi. (Version 1.0) [Computer Software]. Retrieved from <https://www.jamovi.org> - Gallucci, M. (2019). GAMLj: General analyses for linear models. [jamovi module]. Retrieved from <https://gamlj.github.io/>) to investigate single trial performance in the different tasks. In each model, participant was included as a random factor on the intercept, the group factor (between-subject) was dummy-coded with the control group as reference category and the other factors (within-subject) were simple-coded. Whenever a fixed effect or interaction was significant, a d-like effect size was computed. For linear mixed effect models, the unstandardized regression coefficient was divided by the residual standard deviation ($d = \text{unstandardized regression coefficient} / \text{residual standard deviation}$; Rouder et al., 2012). For logistic mixed effect models, the log odds ratio was transformed into d ($d = \ln \text{Odds Ratio} / (\pi / \sqrt{3})$; Chinn, 2000).

For the time reproduction task, two indexes (accuracy and precision) were calculated. The accuracy of temporal reproduction was examined by computing the ratio between the reproduction interval and the target interval (RI/TI ratio; Monfort et al., 2014). A RI/TI ratio less than or greater than 1 indicates an under- or over-reproduction of the target interval. The precision of temporal reproduction was examined by computing the coefficient of variation (CV) with the following formula: *Standard Deviation of the RI/Mean RI*. Considering that CV cannot be computed on single trials, RI/TI ratio and CV were computed for each TI and each participant on 5 consecutive trials. Then, linear mixed effect models were computed to examine the effect of group (patients vs. healthy controls), duration range (supra-second vs. sub-second) and interaction term between the two factors (group x duration range) on RI/TI ratio and on CV. For each duration range, three different TI were used. Yet, it is well

established in this case that a central-tendency effect (Vierordt, 1890) is observed with a lower RI/TI ratio for shorter TI and longer RI/TI ratio for longer TI. However, the present study did not aim at investigating this central tendency effect and the three different TI were only used to generate variability in the task. Thus, the effects of TI were not investigated.

For the duration discrimination task, logistic mixed effect models were computed to examine the effect of group (patients vs. healthy controls), CI (longer vs. shorter than TI), duration range (supra-second vs. sub-second), first and second order interaction terms between the three factor (group x CI, group x duration range, CI x duration range, group x CI x duration range) on the correctness of the response (0: incorrect answer, 1: correct answer). The effects of CI and of interaction between CI and the two other factors were examined to determine whether there was a decision bias in the duration judgment and whether this decision bias differed between controls and patients or between sub-second and supra-second ranges and also whether the CI x group interaction effect differed between sub-second and supra-second range. As for the reproduction tasks, the effects of TI were not investigated.

Concerning the interaction between duration and numerosity, for each task (DurN/NumD), logistic mixed effect models were computed to examine the effect of group (patients vs. healthy controls), S2-type (DurN: S2-longer vs. S2-shorter, NumD: S2-more vs. S2-less), congruency (congruent vs. incongruent), distance (far vs. close), first order interaction terms between group and other factors (group x S2-type, group x congruency, group x distance), first order interaction term between congruency and distance (congruency x distance) and second order interaction term between group, congruency and distance (group x congruency x distance) on the correctness of the response (0: incorrect answer, 1: correct answer). The effects of S2-type and group x S2-type were examined to determine whether there were decision biases in duration and numerosity judgment and whether these biases differed between patients and controls. The effects of congruency, distance, group x

congruency, group x distance, congruency x distance and group x congruency x distance were examined to determine whether there were congruency effects (of numerosity variations on duration judgment and of duration variations on numerosity judgment) and whether these congruency effects differed between large and small variations and between patients and controls and also whether the congruency x distance interaction effect differed between patients and controls. For each task (DurN and NumD), three different pairs were used to generate variability in the task and thus, the effect of pair was not investigated.

2.4. Single-case analyses

In order to compare each individual patient to the control group, different scores were first computed individually for each task and then Crawford's modified t-tests (Crawford & Howell, 1998) were performed.

2.4.1. Duration reproduction and discrimination tasks

For the time reproduction task, two indexes (of accuracy and of precision) of temporal reproduction were calculated for each duration range. The accuracy of temporal reproduction was examined by computing for each TI the RI/TI ratio and then by averaging these RI/TI ratios across the three TI to obtain one global index of accuracy for each duration range. The precision of temporal reproduction was examined by computing for each TI the coefficient of variation (CV) with the following formula: *Standard Deviation of the RI/Mean RI* and then by averaging these CV across the three TI to obtain one global index of precision for each duration range.

For the duration discrimination task, analyses based on the signal detection theory (Green & Swets, 1966; Macmillan & Creelman, 2005, Pfeuty & Peretz, 2010) were performed separately for each duration range. Two indexes (of sensitivity and of decision bias) were

computed for each TI. The index of sensitivity (d') was calculated as the difference between the z -score transformation of the hit and false alarm rates according to the following formula: $d' = z(H) - z(FA)$. A correct answer to a trial in which the CI was shorter than the TI was considered as a hit and an incorrect answer to a trial in which the CI was longer than the TI was considered as a false alarm. The decision bias (c) was calculated according to the following formula: $c = -0.5 \times [z(H) + z(FA)]$. The c value indicates whether participants judged the CI as shorter or longer than the TI. A negative (or positive) c indicates that the CI is judged shorter (or longer) than the TI. Note that a log-linear rule was applied to account for extreme cases where participants had a hit or false alarm rate of 0 or 1, so that $Nh = (Nh + 0.5) / (N + 1)$ and $Nf = (Nf + 0.5) / (N + 1)$, where N is the maximum number of hits or false alarms, whereas Nh and Nf are the actual numbers of hits and false alarms, respectively. The d' and c values were averaged across the three TI to obtain one global index of sensitivity and one global index of decision bias for each duration range .

2.4.2. *DurN and NumD tasks*

Concerning the interaction between duration and numerosity, analyses based on the signal detection theory were performed separately for the duration and the numerosity task. In each task, the indexes of sensitivity (d') and of decision bias (c) described in the previous paragraph were computed for each participant, for each congruency-distance condition (congruent-close Cc , incongruent-close Ic , congruent-far Cf and incongruent-far If) and for the each pair of relevant dimension.

For each task, the d' and c values were first averaged across the three pairs of relevant dimension to obtain one d' and one c value for each congruency-distance condition (Cc , Ic , Cf , If). Then, the d' and c were averaged across the four congruency-distance conditions to obtain one global index of sensitivity and one global index of decision bias for each task.

3. Results

3.1. Timing tasks

3.1.1. Reproduction of sub- and supra-second time intervals

The linear mixed effects models investigating the effect of group, duration and group x duration range interaction on RI/TI ratio and on CV in the sub- and supra-second range did not reveal any significant fixed effect of group nor any significant group x duration range interaction effect. As observed in Figure 2, RI/TI ratios and CVs were not significantly different between controls and patients in both interval ranges. The fixed effect of duration range on RI/TI ratio (supra-second - sub-second: $\beta = -0.12$, $p < .001$, $d = -0.54$) and on CV (supra-second - sub-second: $\beta = -0.06$, $p < .001$, $d = -0.64$) were significant. The RI/TI ratio was higher for sub-second (mean = 1.14, 95% CI [1.07, 1.21]) than for supra-second intervals (mean = 0.99, 95% CI [0.92, 1.06]). This result is in line with a central-tendency effect (Vierordt, 1890) that would operate between the different duration ranges. The CV was also higher for sub-second (mean = 0.22, 95% CI [0.18, 0.26]) than for supra-second intervals (mean = 0.17, 95% CI [0.13, 0.21]). This would be due to motor variability which does not increase with time and would thus have a greater impact on CV in the sub-second than in the supra-second range.

3.1.2. Discrimination of sub- and supra-second time intervals

The logistic mixed effect models investigating the effect of group, CI, duration range, group x CI, group x duration range, CI x duration range and group x CI x duration range interaction on correctness did not reveal any significant fixed effect of group, CI and duration range. The CI

x duration range interaction effect was significant (longer - shorter CI x supra-second - sub-second: $\beta = 0.98$, $p < .001$, $d = 0.54$). The effect of CI was significantly negative for sub-second intervals (longer - shorter CI: $\beta = -0.69$, $p < .001$, $d = -0.38$) and significantly positive for supra-second intervals (longer - shorter CI: $\beta = 0.76$, $p < .001$, $d = 0.42$). The group x CI interaction effect and the group x CI x duration range interaction effect were not significant. As observed in Figure 3, the level of correctness was higher for shorter than for longer CI in the sub-second range and was conversely higher for longer than for shorter CI in the supra-second range and these effects of CI on correctness were not significantly different between controls and patients. As in the reproduction tasks, these opposite biases between the two duration ranges are in line with a central tendency effect. In the sub-second range, target intervals would regress towards higher values leading to a higher level of correctness for shorter comparison intervals. Conversely, in the supra-second range, target intervals would regress towards lower values leading to a higher level of correctness for longer comparison intervals.

3.2. Interaction between duration and numerosity processing

3.2.1. Duration discrimination of stimuli varying in numerosity (DurN task)

The logistic mixed effect model investigating the effect of group, S2-type, congruency, distance, group x S2-type, group x congruency, group x distance, congruency x distance and group x congruency x distance interaction on correctness did not show any fixed effect of group (Figure 4-a). There was a significant fixed effect of S2-type (S2-longer - S2-shorter: $\beta = -0.64$, $p < .001$, $d = -0.35$) and a significant group x S2-type interaction effect (patients - controls x S2-longer - S2-shorter: $\beta = 0.54$, $p = .042$, $d = 0.30$). As observed in Figure 5-a, the level of correctness was higher for S2-shorter than for S2-longer trials in controls (S2-longer -

S2-shorter: $\beta = -0.64$, $p < .001$, $d = -0.35$) while it did not significantly differ in function of S2-type in patients (S2-longer - S2-shorter: $\beta = -0.11$, ns).

For controls, there was a significant fixed effect of congruency (congruency - incongruent: $\beta = 0.28$, $p = .029$, $d = 0.16$), no significant effect of distance and no significant congruency x distance interaction effect. Group x congruency and group x distance interaction effects were not significant but a significant group x congruency x distance interaction effect was observed (patients - controls x congruent - incongruent x far - close: $\beta = 1.14$, $p = .033$, $d = 0.63$). In controls (Figure 5-b), the effect of congruency was positive but not significant for close (congruent - incongruent: $\beta = 0.25$, ns) and far (congruent - incongruent: $\beta = 0.31$, $p = .089$) distances. By contrast, in patients (Figure 5-c), the effect of congruency was negative and not significant for close distance (congruent - incongruent: $\beta = -0.39$, ns) and significantly positive for far distance (congruent - incongruent: $\beta = 0.81$, $p = .020$, $d = 0.45$).

3.2.2. Numerosity discrimination of stimuli varying in duration (NumD task)

The logistic mixed effect model investigating the effect of group, S2-type, congruency, distance, group x S2-type, group x congruency, group x distance, congruency x distance and group x congruency x distance interaction on correctness revealed a significant fixed effect of group (patients - controls: $\beta = -0.30$, $p = .031$, $d = -0.17$). As observed in Figure 4-b, the global level of correctness in the NumD task was lower in patients (mean = 0.71, 95% CI [0.66, 0.76]) than in controls (mean = 0.77, 95% CI [0.74, 0.79]). There was a significant fixed effect of S2-type (S2-more - S2-less: $\beta = 0.82$; $p < .001$, $d = 0.45$) and a significant group x S2-type interaction effect (patients - controls x S2-more - S2-less: $\beta = -1.61$, $p < .001$, $d = -0.89$). As observed in Figure 6-a, the level of correctness was significantly higher for S2-more (mean = 0.83, 95% CI [0.80, 0.86]) than for S2-less (mean = 0.69, 95% CI [0.65, 0.72]) trials in controls (S2-more - S2-less: $\beta = 0.82$; $p < .001$, $d = 0.45$) while it was significantly

higher for S2-less (mean = 0.79, 95% CI [0.72, 0.84]) than for S2-more (mean = 0.62, 95% CI [0.55, 0.69]) trials in patients (S2-more - S2-less: $\beta = -0.80$; $p < .001$, $d = -0.44$). This interaction effect can also be explained by the fact that, compared to the control group, the level of correctness in the patient group was lower for S2-more trials (patients - controls: $\beta = -1.10$, $p < .001$, $d = -0.61$) but higher for S2-less trials (patients - controls: $\beta = 0.51$, $p = .01$, $d = 0.28$). There were no significant fixed effects of congruency and distance and no significant congruency x distance interaction effect. Group x congruency, group x distance and group x congruency x distance interaction effects were also not significant (Figures 6-b and 6-c).

3.3. Complementary analysis

The fact that the congruency effect of numerosity on duration judgment observed in the DurN task was more importantly reduced between far and close numerical distance conditions in patients than in controls could be related to their lower global level of correctness in the NumD task. To determine whether the group x congruency x distance interaction effect observed in the DurN task remained significant after controlling for the global percentage of correct responses obtained in the NumD task (i.e. NumD-score), the variable NumD-score was added as covariate in the logistic mixed effect model performed in the DurN task. This model examined the effect of group, S2-type, congruency, distance, group x S2-type, group x congruency, group x distance, congruency x distance and group x congruency x distance interaction and also the effect of NumD-score as well as first and second order interaction terms between NumD-score and the three variables of the controlled interaction (NumD-score x group, NumD-score x congruency, NumD-score x distance, NumD-score x group x congruency, NumD-score x group x distance, NumD-score x congruency x distance, see Yzerbit, Muller, & Judd, 2004) on the level of correctness in the DurN task. In this model, the group x congruency x distance interaction effect was no longer significant ($\beta = 0.76$, $p = 0.20$)

suggesting that the group x congruency x distance interaction effect was partly explained by the global percentage of correct responses obtained in the NumD task.

An alternative logistic mixed effect model was also performed in which the group variable was replaced by the NumD-score covariate. This model examined the effect of NumD-score, S2-type, congruency, distance, NumD-score x S2-type, NumD-score x congruency, NumD-score x distance, congruency x distance and NumD-score x congruency x distance interaction on the level of correctness in the DurN task. A significant NumD-score x congruency x distance interaction effect was observed (NumD-score x congruent - incongruent x far - close: $\beta = -0.11$, $p = .024$, $d = -0.06$) suggesting that the congruency x distance interaction effect observed in the DurN task varied according to the global percentage of correct responses obtained by the participants in the NumD task. The lower was the ability to discriminate numerosity in the NumD task, the larger was the congruency x distance interaction effect in the DurN task.

3.4. Single-case analyses

3.4.1. Duration reproduction and discrimination tasks

Table 2-a presents the RI/TI ratio and CV obtained by the control group and each individual patient in the time reproduction task for each duration range. Crawford's t-tests did not reveal any significant difference between the control group and each individual patient for the RI/TI ratio in both duration ranges and for the CV in the sub-second range. The CV measured in the supra-second range was significantly higher in patient 2 than in the control group ($t = 2.61$, $p = 0.023$) and was significantly lower in patient 4 than in the control group ($t = -2.96$, $p = 0.012$).

Table 2-b presents the d' and the c values obtained by the control group and each individual patient in the duration discrimination task for each range of duration. Crawford t -test analyses did not reveal any significant difference between the control group and each individual patient for the d' and c values in both duration ranges.

3.4.2. *DurN and NumD tasks*

Table 3-a presents the d' and c values obtained by the control group and each individual patient in the duration discrimination task using stimuli varying in numerosity. Crawford's t -tests did not reveal any significant difference between the control group and each individual patient for the d' and c values.

Table 3-b presents the d' and the c values obtained by the control group and each individual patient in the numerosity discrimination task using stimuli varying in duration. Crawford's t -tests showed that the d' value was significantly lower in patient 2 ($t = -2.30$, $p = 0.040$) than in the control group and that the c value was significantly lower in patients 1 ($t = -2.57$, $p = 0.024$), 3 ($t = -3.36$, $p = 0.006$) and 4 ($t = -2.44$, $p = 0.031$) than in the control group.

4. Discussion

The present study aimed at examining (i) the processing of duration and (ii) the interaction between duration and numerosity processing in four drug-resistant epileptic patients with postoperative lesions in the inferior frontal gyrus (IFG) by comparing their performance to that of thirteen control participants. Duration processing was investigated by reproduction and discrimination tasks in the sub- and supra-second ranges. At odds with the hypothesis according to which the IFG would play a crucial role in time processing, the performance in all of these timing tasks did not differ between patients and controls. A duration discrimination task

of stimuli varying in numerosity (DurN) and a numerosity discrimination task of stimuli varying in duration (NumD) were used to investigate the interaction between duration and numerosity. The numerosity judgment was altered in IFG patients but not the duration judgment. A time-order effect was notably observed in the NumD task but in opposite directions for the two groups: the level of correctness was higher when the second patch contained more dots in controls and conversely when the second patch contained less dots in patients. Additionally, a congruency effect was observed in the DurN task which was dependent on numerical distance in patients but not in controls. These different results provide new insights on the role of the IFG in temporal and numerosity processing, as discussed now.

4.1. IFG and duration processing

In a study by Monfort et al. (2014), a drug-resistant epileptic patient with a right-sided pre-operative lesion at the junction of inferior frontal gyrus (IFG) and anterior insular cortex (AIC) was shown to be importantly impaired in duration reproduction of supra-second time intervals. A first goal of the present study was to determine whether this impairment in the reproduction of supra-second intervals could be observed in a group of epileptic patients with postoperative IFG lesion and also whether this impairment could be generalized to the sub-second range and be observed during a duration discrimination task. In the sub- and supra-second reproduction tasks, the precision (CV) and the accuracy (RI/TI ratio) were not different between controls and patients. Similarly, in the discrimination tasks, the level of correctness did not differ between controls and patients in both interval ranges. These results suggest that epileptic patients with postoperative lesions in the IFG have the same ability as control participants to reproduce and discriminate time intervals in the sub- and supra-second range. The IFG lesions observed in the present study were heterogeneous and globally more anterior than the operculo-insular lesions which have been associated with lower motor or perceptual

timing performance in previous neuropsychological studies (Gooch et al., 2011; Mella et al., 2019; Monfort et al., 2014; Teghil et al., 2020). Only two patients (patients 2 and 3) had lesion in the opercular part of the right IFG and only one (patient 2) in the right insula. Single-case analyses (Table 2) were performed to compare temporal performance of each patient with controls. Results did not reveal any significant effect except in reproduction of supra-second time intervals in which higher variability was observed in patient 2. Together, these results suggest that the IFG as a whole is not crucial for timing and the fact that temporal performance in patients 2 and 3 was broadly intact indicates that lesions in the operculo-insular region are not systematically associated with disturbances in interval timing.

4.2. IFG and duration - numerosity interaction

The second goal of the present study was to determine whether IFG lesions would affect performance in both duration and numerosity discrimination tasks and whether it would also affect the interaction effects between the two dimensions. In line with the results reported above, time processing was spared in patients as their level of correctness did not differ from controls in the DurN task. By contrast, the level of correctness in the NumD task was lower in the patient group than in the control group. However, this group effect was dependent on the type of trials. Compared to controls, performance in patients was lower on S2-more trials but higher on S2-less trials. Although this finding is hardly compatible with a general impairment of numerosity discrimination following IFG lesions, it indicates that the numerosity judgment was altered in the patient group but not the duration judgment. Within the IFG, neuroimaging and neuropsychological studies showed that time processing concerns primarily the IFG pars opercularis (BA44) at the junction with anterior insular cortex (Gooch et al., 2010; Kosillo & Smith, 2010; Monfort et al. 2014; Wiener et al., 2010). By contrast, IFG regions involved in numerosity processing would include the pars orbitalis (Skagerlund et al., 2016; Wilkey &

Price, 2019), pars triangularis (Rusconi et al., 2013, 2011; Skagerlund et al., 2016; Wilkey & Price, 2019) and pars opercularis (Hayashi et al., 2013; Skagerlund et al., 2016; Wilkey & Price, 2019). The fact that the location of lesions in the patient group extended from the pars orbitalis of the IFG to the insulo-opercular region could explain the selective alteration of numerosity judgment.

Few lesions' studies have investigated the cerebral bases of numerosity processing and most of them have shown impairment in patients with lesions in the intra-parietal sulcus (Cappelletti et al., 2011; Koss et al., 2010; Roitman et al., 2012 for review). The role of the IFG in numerosity is mainly based on neuroimaging data and, to our knowledge, there are few study revealing deficits in numerosity processing following damage located in this region. It has notably been observed that corticobasal syndrome patients with atrophy in parietal and inferior frontal regions were impaired in numerosities judgment (Koss et al., 2010). Furthermore, inferior frontal lesions have been associated with deviation in numeric interval bisection (Aiello et al., 2012; Doricchi et al., 2005) and disturbances in estimation of numerical magnitude (Pflugshaupt et al., 2020; Revkin et al., 2008). None of these studies did, however, investigate the impact of IFG lesion in numerosity discrimination tasks and the present findings provide the first evidence that damage to this brain region alters performance in that type of tasks.

More specifically, the results of the NumD task revealed a time-order effect which was in opposite directions for the two groups. In controls, performance was better for S2-more than for S2-less trials in line with the "recent is more" effect reported by van den Berg and colleagues (2017) during numerosity comparison tasks. According to the authors, when two non-symbolic numerical stimuli are presented successively, both stimuli are overestimated but the second one more strongly than the first one. By contrast in patients, performance was better for S2-less than for S2-more trials which would correspond to a « recent is less ». Because

most of patients were left-handed, it could be argued that the opposite time-order effects observed for controls and patients would actually result from handedness differences between groups. However, single-case analyses performed to compare NumD task performance of each individual patient to the patient group (Table 3-b) revealed that the “recent is less” effect was significant in two left-handed patients (patients 1 and 4) as well as in the only right-handed patient (patient 3), which would exclude handedness as possible confounding factor.

Electrophysiological recordings in primate suggested a complementary role for frontal and posterior parietal cortices in the processing of numerosity (Jacob et al., 2018; Jacob & Nieder, 2014). On the one hand, the intraparietal sulcus would be the first cortical region where numerical quantities are extracted from sensory input (Bongard & Nieder, 2010; Nieder, 2016) and could thus serve as a storage area for relevant target information (Jacob & Nieder, 2014). On the other hand, further processing on a higher hierarchical level, such as implementing abstract responses strategies would depend on prefrontal cortex (PFC) and dorsal premotor area (PMd) activity (Bongard & Nieder, 2010; Nieder, 2017; Ott et al., 2014; Vallentin et al., 2012). It has notably been shown that in relative numerical judgment tasks where monkeys have to indicate whether a test stimulus contains more or less items than a target stimulus, activity related to the encoding or the working memory storage of the target is almost absent in lateral PFC and PMd areas (Bongard & Nieder, 2010; Vallentin et al., 2012). By contrast, lateral PFC neurons appear to be selectively tuned to a specific “greater-than” or “less-than” mathematical rule and to process numerical information in a goal-directed way (Bongard & Nieder, 2010; Nieder, 2016). In line with these findings, the present results suggest that IFG lesions would not impair the memory representation of S1 numerosity but would more specifically impair the comparison of S1 and S2 numerosities. This is in agreement with the involvement of the IFG in categorical and explicit decision reported in a similar numerical comparison task (Hayashi et al., 2013). Furthermore, it has been suggested that in relative

numerical judgment tasks, such comparison between two numerosities would rely on an accumulation process supported by summation units (Nieder, 2016; Verguts & Fias, 2004). We propose that the "recent is less" effect observed in patients with IFG lesions would result from an alteration of this accumulation process leading to an underestimation of S2 numerosity compared to S1.

To determine whether the influence of numerosity on duration processing and the influence of duration on numerosity processing differ following IFG lesions, we tested a congruency effect (shorter-less or longer-more) on the level correctness with two different distance (close and far) between S1 and S2. In line with previous studies (Dormal et al., 2006; Droit-Volet et al., 2003; Oliveri et al., 2008; Xuan et al. 2007), numerosity was shown to interfere with duration judgment in the DurN task, the duration of the patch containing more dots being perceived as longer. By contrast, no effect of duration on numerosity judgment was observed during the NumD task. This pattern of results is coherent with several studies showing an influence of numerical information on temporal judgment but no reciprocal influence of temporal information on numerical judgment (Dormal et al., 2006; Droit-Volet et al., 2003; Hayashi et al., 2013, but see Javadi & Aichelburg, 2012; Lambrechts et al., 2013; Martin et al., 2017). This non-reciprocity in the interference effects may reflect the mandatory (i.e. automatic) nature of the numerosity processing contrasting with duration processing which would not be automatic, or not in a way which interferes with numerosity judgment (Dormal et al., 2006). Inhibition processes would thus be more importantly required in the DurN task than in the NumD task. This would exclude the hypothesis that the lower general performance in the patient compared to the control group observed in the NumD task might result from impairment in domain-general inhibition mechanisms.

In the control group, in line with the study by Hayashi and colleagues (2013), the congruency effect observed in the DurN task was independent on the numerical distance. By con-

trast, in the patient group, the congruency effect in the DurN task was observed for the far but not for the close numerical distance. This result seems at odds with the findings from the study by Hayashi and colleagues (2013) showing that the size of the congruency effects was not influenced by rTMS of the right IFG in a duration discrimination task. In this rTMS experiment, the authors did however, not examine the effects of numerical distance. Interestingly, the fact that the congruency effect measured in the DurN task was dependent on the numerical distance in patients but not in controls was partly explained by the global percentage of correct responses obtained in the NumD task. The decrease in the effect of numerosity on temporal judgment observed between far and close numerical distance conditions in the patient group could thus be explained by their lower ability to explicitly discriminate numerosity.

4.3. Conclusion

Time and number are essential information for optimal decision making. By examining the relative contribution of the IFG to the processing of these two dimensions, the present study contributes to delineate the clinical consequences of lesions within this brain region. We first showed that drug-resistant epileptic patients with postoperative lesions within the IFG were not impaired in interval timing. Furthermore, by means of discrimination tasks with stimuli varying both in duration and in numerosity, we observed that IFG lesions selectively altered numerosity judgment. Patients were not directly impaired in numerosity discrimination but were importantly biased in their judgment of relative numerosity of two successive stimuli. These results are consistent with IFG involvement in categorical and explicit decision in numerosity comparison tasks (Hayashi et al., 2013). In line with a previous research conducted by van den Berg and colleagues (2017) in healthy participants, our study emphasizes the interest to investigate the decision bias depending on the order in which numerical stimuli are

presented. The present findings have enabled us to see in what way IFG lesions dramatically affect this bias and has shown the need to identify the brain regions behind this bias.

The present results need to be confirmed with a higher number of IFG patients, which should allow to control for handedness as well as to investigate the respective contribution of right and left hemispheric lesions. Because the focus of this study was aimed to investigate time processing, a larger number of numerosity tasks would be of interest to better understand the mechanisms behind the effect of IFG lesions on numerosity processing. In particular, numerical estimation tasks could help to determine whether the bias we observed in the relative estimation of two successive stimulation could also be observed in the absolute estimation of numerical stimulation. Comparison between discrimination and estimation tasks has already provided further information about the nature of this decision bias, which may reflect a misjudgment concerning S1 and S2 or which may be specific to the comparison process (van den Berg et al., 2017).

Credit authorship contribution statement

Vincent Monfort: Conceptualization, Data Curation, Formal analysis, Investigation, Methodology, Writing – original draft. Micha Pfeuty: Conceptualization, Data Curation, Formal analysis, Investigation, Methodology, Writing – original draft. Inès Masson: Data Curation, Formal analysis, Investigation, Writing – original draft. Jean-Luc Kop: Formal analysis, Methodology. Hélène Brissart: Resources, Supervision, Validation. Louis Maillard: Resources, Supervision, Validation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Figure Captions

Fig. 1 Sagittal T1-weighted images of the four drug-resistant epileptic patients showing post-operative lesions located in the right (patients 1, 2 and 3) or left (patient 4) inferior frontal gyrus. For each patient, from the top to the bottom of the figure are presented four sagittal views from the lateral to the medial part of the lesion.

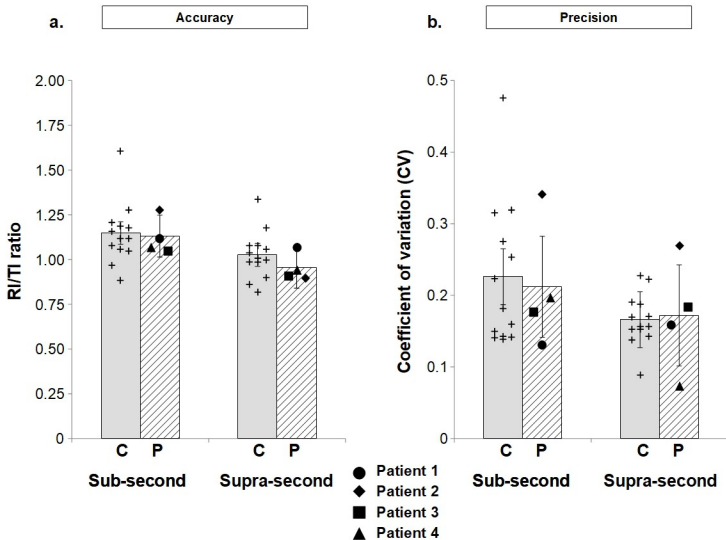
Fig. 2 Mean, confidence interval (95%) and individual data of the RI/TI ratio (**a**) and the coefficient of variation (**b**) obtained in control (C) and patient (P) groups in the time reproduction tasks performed in the sub-second and supra-second ranges.

Fig. 3 Mean, confidence interval (95%) and individual data of the level of correctness obtained in control (C) and patient (P) groups in function of the type of comparison interval (CI-longer vs. CI-shorter) in the duration discrimination task performed in the sub-second (**a**) and supra-second (**b**) ranges.

Fig. 4 Mean, confidence interval (95%) and individual data of the level of correctness obtained in control (C) and patient (P) groups in DurN (a) and NumD (b) tasks.

Fig. 5 Mean, confidence interval (95%) and individual data of the level of correctness obtained in control (C) and patient (P) groups in function of the S2-type (S2-longer vs. S2-shorter) in the DurN task (**a**). Mean, confidence interval (95%) and individual data of the level of correctness obtained in congruent and incongruent trials for close and far distances in control (**b**) and patient (**c**) groups in the DurN task.

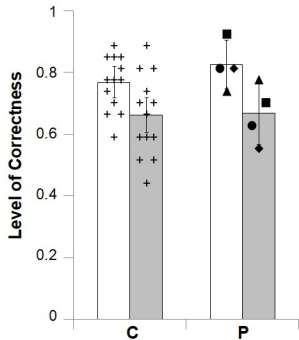
Fig. 6 Mean, confidence intervals (95%) and individual data of the level of correctness obtained control (C) and patient (P) groups in function of the S2-type (S2-more vs. S2-less) in the NumD task **(a)**. Mean, confidence interval (95%) and individual data of the level of correctness obtained in congruent and incongruent trials for close and far distances in control **(b)** and patient **(c)** groups in the NumD task.



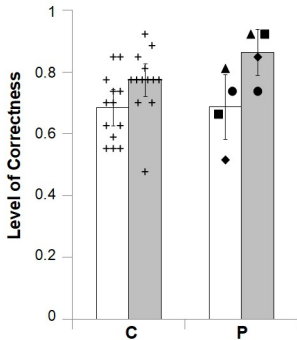
Sub-second

Supra-second

a.



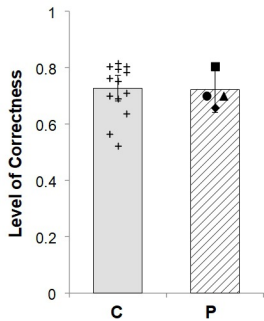
b.



- Patient 1
- ◆ Patient 2
- Patient 3
- ▲ Patient 4

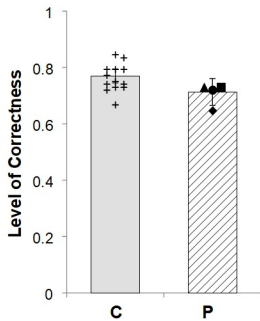
a.

DurN task

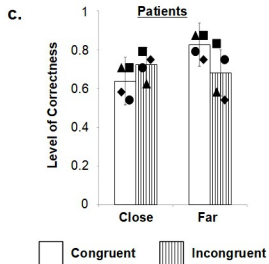
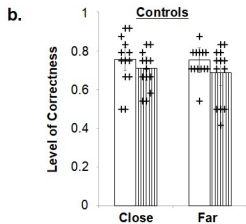
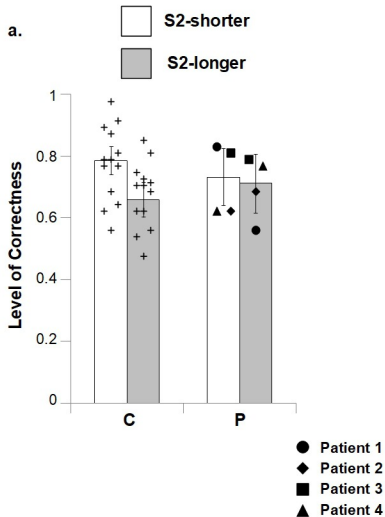


b.

NumD task



- Patient 1
- ◆ Patient 2
- Patient 3
- ▲ Patient 4



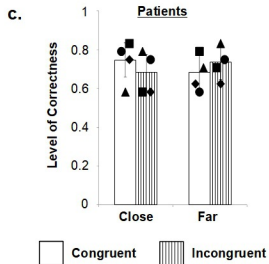
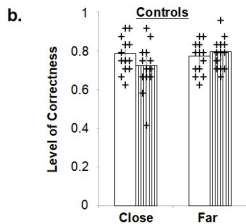
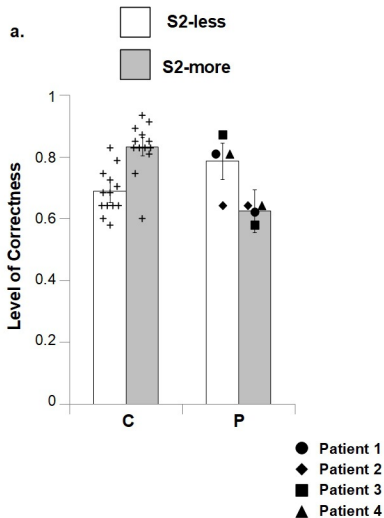


Table 1. Characteristics of the four patients and their scores obtained in neuropsychological tests.

	Patient 1		Patient 2		Patient 3		Patient 4	
Characteristics								
Sex	M		M		M		M	
Age (years)	31		19		34		34	
Education level (years)	12		13		17		14	
Edinburgh Handedness Inventory (EHI)	-90 (LH)		-100 (LH)		100 (RH)		-100 (LH)	
Hemisphere of the IFG lesion	Right		Right		Right		Left	
Neuropsychological tests								
	<i>pre</i>	<i>post</i>	<i>pre</i>	<i>post</i>	<i>pre</i>	<i>post</i>	<i>pre</i>	<i>post</i>
Global cognitive efficiency								
WAIS Full Scale IQ	101	NC	79	NC	130	137	96	NC
Executive functions								
Stroop Color (time)	NC	52	72	74	71	62	NC	NC
Word (time)	NC	40	60	51	53	40	NC	NC
Color Word (time)	NC	66	132*	120	95	90	NC	NC
Trail Making Test B (time)	NC	49	73	72	NC	NC	NC	NC
Semantic fluency	23	16	23	16*	33	26	NC	NC
Phonemic fluency	29	21	10*	10*	30	28	NC	NC
Working memory								
Digit-Span forward	5	5	5	4*	9	8	6	NC
Digit-Span backward	5	5	4	3*	7	8	5	NC
Processing speed								
Trail Making Test A (time)	NC	24	28	31	NC	NC	NC	NC
Coding WAIS /19	14	NC	7	10	8	11	NC	NC
Arithmetic skills								
Arithmetic WAIS /19	7	NC	6	NC	16	17	NC	NC
Language								
Oral denomination test DO80	77*	79	72*	72*	78	79	NC	NC

M: Male, LH: Left-handed, RH: Right-handed, IFG: Inferior frontal gyrus

pre: Preoperative, post: Postoperative, *: Impaired, NC: Not completed

Global cognitive efficiency was investigated with the Ward's seven subtests version of the WAIS-R in patient 1, the WAIS IV in patients 2 and 3, the WAIS III in patient 4.

The phonemic [R words] and the semantic [fruits] fluency tests were administered to patient 1 and the phonemic [P words] and the semantic [animals] fluency tests were administered to patients 2 and 3.

Table 2. Results of the single-case analyses performed in the duration reproduction (a) and discrimination (b) tasks with sub- and supra-second intervals.

	Controls mean (SD)	Patient 1	Patient 2	Patient 3	Patient 4
(a) Duration reproduction					
Sub-second range					
RI/TI ratio	1.15 (0.17)	1.12	1.29	1.05	1.07
<i>Crawford t-test</i>		<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>
CV	0.24 (0.10)	0.17	0.42	0.17	0.24
<i>Crawford t-test</i>		<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>
Supra-second range					
RI/TI ratio	1.03 (0.13)	1.07	0.90	0.91	0.94
<i>Crawford t-test</i>		<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>
CV	0.18 (0.04)	0.18	0.28	0.22	0.07
<i>Crawford t-test</i>		<i>ns</i>	<i>t = 2.61</i> <i>p = .023</i>	<i>ns</i>	<i>t = -2.96</i> <i>p = .012</i>
(b) Duration discrimination					
Sub-second range					
d'	1.32 (0.54)	1.28	0.92	1.85	1.35
<i>Crawford t-test</i>		<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>
c	-0.14 (0.23)	-0.30	-0.33	-0.40	-0.02
<i>Crawford t-test</i>		<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>
Supra-second range					
d'	1.28 (0.54)	1.34	1.08	1.63	2.26
<i>Crawford t-test</i>		<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>
c	0.13 (0.18)	0.06	0.48	0.42	0.19
<i>Crawford t-test</i>		<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>

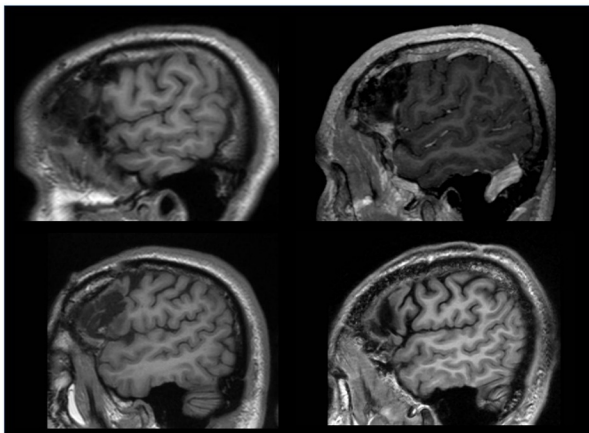
CV: Coefficient of variation, d': Index of sensitivity, c: Decision bias
Significant results are in bold.

Table 3. Results of the single-case analyses performed in the DurN (a) and NumD (b) tasks.

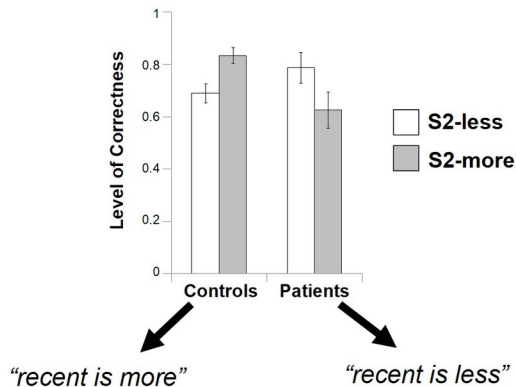
	Controls mean (SD)	Patient 1	Patient 2	Patient 3	Patient 4
(a) DurN task					
d'	1.23 (0.59)	1.09	0.79	1.66	1.04
<i>Crawford t-test</i>		<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>
c	-0.21 (0.29)	-0.39	0.08	-0.04	0.21
<i>Crawford t-test</i>		<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>
(b) NumD task					
d'	1.47 (0.33)	1.18	0.73	1.32	1.23
<i>Crawford t-test</i>		<i>ns</i>	<i>t = -2.30</i> <i>p = 0.040</i>	<i>ns</i>	<i>ns</i>
c	0.24 (0.20)	-0.28	0.00	-0.45	-0.25
<i>Crawford t-test</i>		<i>t = -2.57</i> <i>p = 0.024</i>	<i>ns</i>	<i>t = -3.36</i> <i>p = 0.006</i>	<i>t = -2.44</i> <i>p = 0.031</i>

d': Index of sensitivity, c: Decision bias
 Significant results are in bold.

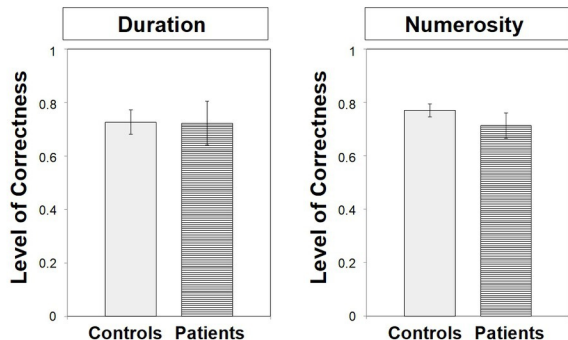
Four epileptic patients with postoperative lesions within the inferior frontal gyrus (IFG)



Time-order effect during numerosity comparison in opposite directions for controls and patients



Patients altered in numerosity judgment but not in time judgment



Congruency effect of numerosity on perceived duration depend on numerical distance (Close vs. Far) for patients but not for controls

