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Research Report

Impaired creative cognition after surgery for an IDH-mutated glioma: A proof-of-concept study

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ABSTRACT

Assessment of high cognitive functions, such as creativity, is often overlooked in medical practice. However, it is crucial to understand the impact of brain tumors, specifically low-grade gliomas, on creative cognition, as these tumors predominantly affect brain regions associated with cognitive creativity. In this study, we investigated creative cognition using the Alternative Uses Task (AUT) and the Combination of Associates Task (CAT) in a cohort of 29 patients who underwent brain surgery for a low-grade glioma, along with 27 control participants. While the group of patients did not exhibit deficits in clinical neuropsychological assessments, our results revealed significant impairment in generating original and creative ideas compared to the control group. Furthermore, when analyzing the specific brain regions affected by the tumors, patients with lesions overlapping the left rostro-lateral prefrontal cortex, a critical region for creativity, displayed more pronounced impairments in the CAT compared to patients with lesions outside this region. These findings provide proof of concept that patients can experience impaired creative cognition following surgery for low-grade glioma, highlighting the importance of assessing higher-order cognitive functions, including creativity, in neurosurgical patients. Moreover, beyond its clinical relevance, our study contributes to advancing our understanding of the neuroscience of creativity.

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1. Introduction

Creativity is a multidimensional ability relevant to artistic productions, technological innovations, societal progress, or children's education (Lubart et al., 2013; Weisberg, 2006). It is defined as the ability to produce something (an idea, a work) that is both original and appropriate (Lubart et al., 2013; Sternberg, 1999). Creativity is popularly related to extraordinary discoveries. However, it is also relevant for everyday situations such as solving new problems, adapting to new events, overcoming constraints, or even coping with negative emotions (Lopez-Persem et al., 2022; Mastria et al., 2018; Weisberg, 2006; Wu et al., 2019). Research in the neuroscience of creativity has developed considerably in recent decades, leading to new frameworks for studying creative cognition and a better understanding of the underlying brain mechanisms. Although creativity is relevant in many everyday life aspects and has been related to activity in specific brain regions, studies investigating the consequences of brain lesions on creativity abilities are scarce (Abraham, 2019; Bieth et al., 2019; Bieth, Lopez-Persem, et al., 2021; Ovando-Tellez et al., 2019). Yet, exploring patients with brain lesions could lead to identifying critical brain regions involved in creative cognition. In return, investigating creativity impairments in neurological patients could help to monitor and plan therapeutic interventions.

Recent cognitive models of creativity suggested that creative thinking relates to an interaction between associative processes (i.e., the ability to generate spontaneously and freely associations of ideas) and control processes (i.e., the ability to evaluate and select an idea involving inhibition and goal-directed behavior) (Benedek & Jauk, 2018; Volle, 2017). Recently, functional connectivity studies revealed the importance of two brain networks during creativity tasks (Beaty et al., 2016, 2017): the default mode network, hypothetically associated with spontaneous associative processes (Christoff et al., 2016), and the executive control network likely supporting executive processes (Power & Petersen, 2013). This recent finding supports neurocognitive models of creativity in which associative and control processes are balanced during creative idea generation. In these models, the prefrontal cortex appears as a critical hub involved in both the executive control and the default mode networks. In agreement with this view, several meta-analyses of fMRI studies exploring brain correlates of creativity highlighted the prefrontal cortex as a consistently recruited region (Boccia et al., 2015; Cogdell-Brooke et al., 2020; Gonen-Yaacovi et al., 2013; Kuang et al., 2022; Pidgeon et al., 2016; Shen et al., 2016, 2018; Sprugnoli et al., 2017; Wu et al., 2015).

Although scarce, studies exploring creativity abilities in patients with brain lesions can help understand the brain critical regions and mechanisms of creativity. Most lesion studies showed that brain lesions were associated with deficits in various creativity tasks (Bieth et al., 2019; Bieth, Lopez-Persem, et al., 2021; Ovando-Tellez et al., 2019). However, they often compared patient groups according to their broad lesion locations at the regional level, leading to low anatomical resolution conclusions. Previous patient studies showed that patients with a focal lesion in the prefrontal cortex (Abraham et al., 2012; Bendetowicz et al., 2018; Reverberi et al., 2005; Shamay-Tsoory et al., 2011) or a neurological disease affecting the prefrontal cortex (Canesi et al., 2017; de Souza et al., 2010; Giovagnoli, 2020; Paulin et al., 2020; Rankin et al., 2007; Senf et al., 2016) were impaired in creativity tasks. This suggests that the frontal lobes are critical for creative thinking (Bieth et al., 2019; Bieth, Lopez-Persem, et al., 2021; Ovando-Tellez et al., 2019), consistent with findings from research on healthy participants (Boccia et al., 2015; Cogdell-Brooke et al., 2020; Gonen-Yaacovi et al., 2013; Kuang et al., 2022; Pidgeon et al., 2016; Shen et al., 2016, 2018; Sprugnoli et al., 2017; Wu et al., 2015). Only one study explored the consequences of a brain lesion on creative thinking using a lesion-deficit mapping approach at the voxel-based regional level and the brain network level (Bendetowicz et al., 2018). The authors found that a disconnection of the default mode network or the executive control network was associated with a deficit in a creativity task that relies on combining remote semantic associates. The findings highlighted two critical prefrontal regions within these networks: a left rostro-lateral region (included in the executive control network) and a medial region (included in the default mode network). These results emphasized the complexity of the prefrontal cortex organization involving subregions belonging to different functional systems (Thiebaut de Schotten et al., 2017) that play distinct roles in creativity. Although previous studies investigated the critical lesion location for creative thinking, little is known about creative abilities in patients suffering from a specific brain disease.

An intriguing group of patients to be studied in this regard is patients with low-grade IDH-mutated gliomas. Low-grade IDH-mutated gliomas are infiltrative brain tumors, occurring classically in young adults. They are characterized by an initial slow growth rate (Mandonnet et al., 2003), allowing efficient implementation of plasticity mechanisms. Hence, diagnosis is usually made after a first seizure, in an otherwise almost asymptomatic patient. However, these tumors may evolve towards higher-grade gliomas, then compromising patients' prognosis. This is why surgical resection is the first line of treatment (Weller et al., 2017). The challenge for the surgeon is to optimize the onco-functional balance in each patient, that is to resect brain tissue as much as needed (to cure the patient) without inducing cognitive deficits (to maintain a normal social-professional life) (Mandonnet & Duffau, 2018). Creativity in this pathology is important to study because the preferential locations of low-grade glioma largely overlap with brain regions or networks that support creative cognition in healthy subjects, such as the prefrontal cortex (in its medial or rostro-lateral parts), the insular, or the temporal lobe (Duffau & Capelle, 2004; Mithani et al., 2019; Parisot et al., 2016). Assessing lesion-related cognitive deficits in these patients – such as creative cognition measures – could be relevant not only to detect early high cognitive function deficits and provide early rehabilitation, but also, to design intraoperative tasks allowing to monitor these functions in an awake patient and to spare the critical areas (Mandonnet et al., 2020). Based on the brain regions known to be involved in creativity, we can hypothesize that frontal brain tumors and/or their resection will impair creative thinking tasks. Only two studies showed that such patients

were impaired in generating divergent thinking (Butler et al., 1993) or in insight problem-solving (Reverberi et al., 2005) after frontal tumor resection. However, several limitations should be considered. Butler et al. (1993) assessed patients' creativity by considering only fluency scores without paying attention to the originality or creativity of responses. In addition, they did not address the precise lesion location. Reverberi et al. (2005) used matchstick arithmetic insight problems with several levels of difficulty. Although creativity was assessed using a limited number of problems, the authors showed that compared to control, patients with a lateral lesion solved more problems whereas patients with a medial lesion were impaired in solving problems, leading to confusing conclusions. Finally, these two studies used patients with different types of brain tumors that showed distinct pathogenic profiles.

The present study aims to measure quantitatively and qualitatively the patients' creativity after surgery for a low-grade glioma. We chose this population because preferential low-grade glioma locations clearly overlap with the regions classically involved in creativity and because indirect evidence indicates that a tumor excision can affect patients' creative abilities. Creative abilities were assessed using two tasks exploring different aspects of creative cognition. First, the Alternative Uses Task (AUT) (Guilford, 1950) assesses divergent thinking, the ability to generate alternative and original ideas. It is considered the most used approach in neuroscience to study creativity. Second, the Combined Associates Task (CAT), a task adapted from the Remote Associate Test (Bendetowicz et al., 2018; Mednick, 1962), assesses associative combination, the ability to combine remote semantic associates to create a new one. This approach emphasizes the role of semantic associations in memory for creativity (Benedek & Neubauer, 2013; Kenett et al., 2014; Mednick, 1962; Mednick et al., 1964), supported by several studies (Benedek et al., 2017; Bernard et al., 2019; He et al., 2021; Kenett, 2019; Kenett et al., 2011, 2014; Kenett & Faust, 2019; Ovando-Tellez, Benedek, et al., 2022; Ovando-Tellez et al., 2023; Ovando-Tellez, Kenett, et al., 2022; Yan et al., 2021). Based on their preferential lesion location, we hypothesized that low-grade glioma patients would be impaired in creativity abilities compared to control and that our tasks could reveal specific deficits depending on lesion location.

2. Methods

2.1. Participants

The patient and control samples were included as part of a larger study that involved different lines of analysis and described in detail in Facque et al. (2022). In the current study, we focus on creativity tasks that were not assessed in this previous study.

2.1.1. Neurosurgical patients

We included patients retrospectively from a routine care cohort composed of patients suffering from IDH-mutated low-grade glioma followed in the neurosurgery department of Lariboisière Hospital (Paris, France). These patients underwent usual neuropsychological assessment by a speech therapist before and after surgery as well as a brain MRI. Starting from June 2018, a neuropsychologist also evaluated high-level cognition, including creativity, in the cohort of patients followed in our institute for a low-grade glioma. We did not include the rare patients who had creativity tests before surgery, to avoid a test-retest effect. Before their assessment, all patients were orally informed that these data could be used for clinical research. We retrospectively selected for our analysis native French speakers and right-handed patients who performed creativity tests after surgery between the 8th of January 2018 and the 5th of January 2021. We did not include patients with progressive disease or ongoing adjuvant therapy at the time of their evaluation, nor patients with non-IDH-mutated glioma, in order to have a group of patients as homogeneous as possible. As it was a retrospective study, the sample size was of convenience. A total of 29 patients suffering from IDH-mutated low-grade glioma (18 men and 11 women, mean age: 46 years old ± 2.11 (SEM)) were analyzed. The study was conducted following our institution's ethical standards for a retrospective study.

From the 29 patients included, 21 (72%) received antiepileptic medications (mainly Levetiracetam, except one patient had Levetiracetam combined with Carbamazepine, another one had Oxcarbazepine alone, and a last one had Oxcarbazepine combined with Lamotrigine), 15 (52%) had systematic adjuvant chemotherapy after the surgery, and 6 (21%) had external radiotherapy targeting the surgical site.

2.1.2. Control group

Twenty-seven native French speakers (13 men and 14 women, mean age: 48 years old ± 2.68 (SEM)) were included in the control group. They were healthy adults with normal or corrected-to-normal vision, with no color-blindness, no medical history of sleep disease, no psychiatry or medical history, no psychotropic substance abuse, no alcohol use 24 h before the assessment. They were matched one-to-one with patients' demographics (age, gender, and educational level). All participants gave a written informed consent to participate to this experiment, which had been approved by the ethics committee of Paris Sorbonne university. They received monetary compensation (30€) for their time.

2.1.3. A posteriori exclusion

Because of technical issues during the task completion, three patients and one control participant were excluded from analyses related to the AUT. Hence, 26 patients and 26 control were analyzed for the AUT, and 29 patients and 27 control were analyzed for the CAT.

2.2. Experimental procedure

The participants (patients and controls) underwent the same 4-h testing conducted by a neuropsychologist (VF). All tasks were computed using the Paradigm software running on individual computers. Task-related instructions were initially explained before the beginning of each task. Patients' tasks were administered in the neurosurgery department of Lariboisière Hospital (Paris, France). Controls' assessments were done in a classroom dedicated to cognitive experiments

(Prisme platform) in the Paris Brain Institute of La Pitié-Salpêtrière Hospital (Paris, France) (https://institutducerveau-icm.org/fr/plateforme-prisme/).

The overall assessment was aimed to also investigate fatigability induced by the various high-order cognitive tasks, including creativity tasks, on decision-making (Facque et al., 2022). Creativity tasks started right after the calibration of monetary choices. Before and in between creativity tasks, subjects were asked to perform series of monetary choices, which are not supposed to interfere with creative abilities. In the present study, we only report the results related to the impact of brain lesions on specific high-order cognitive tasks related to creative abilities, as well as on the clinical neuropsychological testing.

2.2.1. *Neuropsychological testing*

Patients performed usual neuropsychological tests assessing several cognitive functions. The average delay between the neuropsychological tests and the surgery day was 249 days (range = [60–1675], SD = 370).

First, we controlled patients' language abilities. Lexical abilities were assessed with DO80 (Metz et al., 1991), in which patients were asked to name as fast as possible 80 pictures. One patient did the picture naming task of the BECS (Merck et al., 2011) that included 40 trials instead of 80. Semantic abilities were assessed using the pyramid and palm tree test (Howard & Patterson, 1992) (PPTT), which requires patients to make semantic associations on a forced binary choice. Six patients did a semantic association test of the BECS (Merck et al., 2011) that included 40 trials instead of 52. In the categorical fluency task, patients were asked to provide as many animal names as possible in two minutes (Godefroy et al., 2010).

Then, executive functions and working memory abilities were tested. Cognitive inhibition was assessed with the Stroop test (Stroop, 1935), focusing on the difference between the completion times in the interference condition and the denomination condition. Mental flexibility was assessed with the trail-making test (Godefroy et al., 2010) (TMT), focusing on the difference between the completion times in part B and part A. Executive functions were also assessed with a lexical fluency task, in which patients were asked to give as many words starting with the letter "P" as possible in two minutes (Godefroy et al., 2010). Finally, patients did a forward and backward digit span (Grégoire & Van der Linden, 1997), testing their verbal working memory abilities.

All scores were z-scored compared to a standardized reference population, considering the age and the educational level of individuals. We reversed the sign of resulting z-scores for tests that used reaction time (i.e., TMT and Stroop test) in order to obtain homogeneous interpretation (the higher, the better). Although a few patients obtained pathological scores in one or several of these tests, none of these tests showed significant impairment at the group level (i.e., average normalized score minor than −1.68) (Table 1).

2.2.2. *Creativity tasks and behavioral measures*

Creative abilities were assessed using the AUT and the CAT. The delay between the creativity tests and the surgery day was on average 683 days (range = [78–1747], SD = 497).

2.2.2.1. The Alternative Uses Task (AUT).

The AUT is the most used task to explore divergent thinking abilities (Guilford, 1950), a component of creativity (Runco & Acar, 2012). In this open-ended task, we asked participants to find as many unusual and alternative uses as possible of a common object. Three objects (a car tire, a knife, and a bottle) were successively proposed to participants (Ovando-Tellez, Kenett, et al., 2022). They had 3 min per object and provided their responses verbally. The examiner wrote down the participants' responses and categorized them into three time periods, the first, second, and third minute on task. After each object, participants were asked to select among their own responses that were displayed to them, the three responses they judged as the most creative (Benedek et al., 2013). A short break was proposed after each object.

In this task, we assessed participants' responses based on several measures, including *fluency*, the *number of non-alternative uses*, *frequency*, and *creativity*. These measures were computed at the individual level for each object separately and were then averaged across the three objects for each individual.

Fluency corresponded to the number of responses generated during the 3-min period. We also measured *sub-fluency* for each time period of one minute (T1, T2, and T3). Propositions were counted as *non-alternative uses* when they were similar to the classical function of the object (e.g., a bottle is classically used to contain water, therefore this proposition was labeled as non-alternative). The *frequency* of a response was computed as the number of times this idea was given by the control group (the more frequently the response was given by other participants, the less original the response was). For patients, we assessed response *frequency* using the whole control group, while for each control participant, we used the control group with themselves removed. As for *fluency*, we provided *sub-frequency* scores for each time period of one minute. Finally, *creativity* corresponded to the creativity rating of the three most creative responses selected by the participant for each object. This creativity rating was obtained from an external panel of five experts in creativity neuroscience research (TB, SMR, ALP, VA, EV). They used a 5 points Likert scale from 1 ("not creative") to 5 ("highly creative"). All experts were asked to follow the scoring guidance for consensual creativity ratings, as proposed by expert researchers (https://osf.io/vie7s/). All participants' top-3 responses were shuffled so that judges were blinded to the participant group (patient or control). We observed good reliability across the five judges (intra-class coefficient = .82). Finally, the *creativity* variable corresponded to the average ratings across the three objects at the individual level.

2.2.2.2. The Combined Associates Task (CAT).

The CAT assessed another aspect of creative cognition, focusing on the ability to combine (remote) elements. The CAT is an adapted version of the Remote Associates Task (Mednick, 1962) in which participants were asked to find a word that connects three unrelated words (e.g., Bridge-Social-To tie, where the solution is Link). In the CAT, we controlled the semantic distance between the expected response and the three cue words (Bendetowicz et al., 2018). The semantic distance was approximated by the strength of association using a French associative norm available online (Debrenne, 2011). Based on

Table 1 – Classical neuropsychological assessment of patients.

		Average normalized score (SD)	Range normalized score	Number of pathological tests (z score < −1.68)
DO80[a]		.11 (1.55)	−6.90to 1.14	2
PPTT[b]		.02 (2.47)	−10.81 to 1.57	3
Digit span	Forward	−.74 (1.00)	−3.06 to 1.90	4
	Backward	−.67 (.95)	−3.37 to 1.30	4
Fluency	Animal	−.38 (.86)	−1.90 to 1.30	4
	Letter	−.10 (1.17)	−3.71 to 2.00	2
TMT[c]		−.28 (1.76)	−7.40 to 1.58	3
Stroop[d]		−.25 (1.91)	−7.21 to 1.57	3

[a] One patient was assessed with BECS picture naming task.
[b] Six patients were assessed with BECS semantic association task and four patients did not have specific semantic assessment.
[c] Two patients did not perform TMT.
[d] One patient did not perform Stroop test.

the semantic distance, we built close trials (in which the element to combine are semantically close) and distant trials (in which the element to combine are semantically remote).

The present version of the CAT includes 40 trials (20 trials in both close and distant conditions). Each trial was defined by a strength of association corresponding to the average strength of association of each of the three cue words with the expected response. We defined close and distant trials based on the median of the strength of association of all trials (median = 6.56, range = [.34–38.78]). Each trial followed the same procedure (Bendetowicz et al., 2017, 2018; Ovando-Tellez et al., 2023). First, the three cue words were displayed on the screen, and participants had up to 30 sec to respond. The response could be a noun, a verb, or an adjective but not a proper noun or a compound word. As soon as they thought they reached a correct answer, they pressed the space button on the keyboard and said their response aloud. The examiner wrote participants' responses down.

We measured the *accuracy* (i.e., the number of correct trials) for both close and distant trials. We computed a *CAT-index* reflecting the ability to solve distant trials (the more creative condition) when controlling for performance in close trials (the less creative condition). It was computed as the difference between accuracy on close and distant trials, divided by the average accuracy in both conditions (Bendetowicz et al., 2018). The lower the *CAT-index* was, the higher the creativity abilities were.

2.3. Behavioral analyses

AUT – We ran non-parametric two-tailed Wilcoxon tests (*wilcox.test* function) to compare the *number of non-alternative uses* and the *creativity* of responses in the AUT between the patient and control groups. The difference in *fluency* and *frequency* were explored using analyses of variance (ANOVAs, *aov* function) with *fluency* or *frequency* as dependent variables, and time (three levels: first, second, and third minute) and group (two levels: patient and control) as independent variables. We added the subject factor as a random effect in order to consider the repeated measures within participants and the variability between participants. Post-hoc analyses were performed to interpret significant effects in the model. Post-hoc analyses' *p* values were corrected by the number of analyses using a Bonferroni method.

CAT – We used ANOVAs to compare *accuracy* (dependent variable) across conditions (two levels independent variable: close and distant) and groups (two levels independent variable: patient and control). As in previous models, we added the subject factor as a random effect. Post-hoc analyses were performed to interpret significant effects in the model, and post-hoc analyses' *p* values were corrected for the number of analyses using a Bonferroni method. The *CAT-index* was compared between patient and control groups using a non-parametric two-tailed Wilcoxon test.

2.4. Lesion processing

We used individual patients' clinical T1-weighted MRIs performed systematically four months after surgery to delineate resection cavities. Post-surgical brain cavities were segmented manually using MI-Brain software (https://github.com/imeka/mi-brain), and were normalized into the Montreal Neurological Institute (MNI) space using the transformation between patient T1 and MNI template given by ANTs diffeomorphic registration (Avants et al., 2011). The overlap of individual cavities is displayed in Fig. 1. Most patients had a lesion in the frontal lobe (n = 23, 79%) and in the left hemisphere (n = 19, 66%).

2.5. Lesion location-based analyses

Whole-brain analyses were not conducted because the low number of overlapping lesions did not offer enough statistical power to conduct a whole-brain lesion-deficit mapping approach. Instead, we used a hypothesis-based approach to investigate the impact of brain lesion location on behavioral measures. We selected regions of interest (ROIs) based on previous patient studies on creativity using an exhaustive literature review (Bieth, Lopez-Persem, et al., 2021; Ovando-Tellez et al., 2019). For the CAT, we used the cluster reported in a previous study as a ROI (Bendetowicz et al., 2018). This study is the only one that provided a lesion-deficit mapping at the voxel level related to the CAT. This cluster was located in the left rostro-lateral prefrontal cortex (volume .23 cm^3;

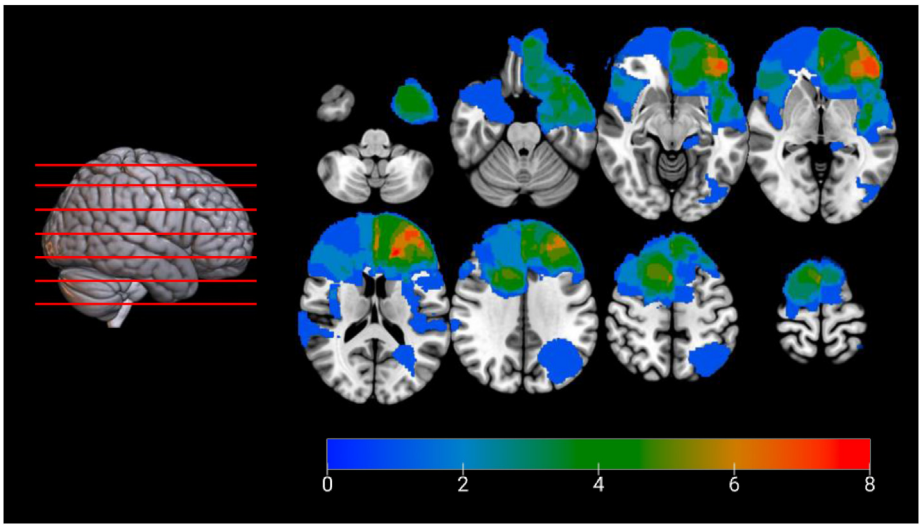

Fig. 1 – Overlap of brain lesions. Post-surgical brain cavities of the patients (n = 29) were normalized into the MNI space and overlapped on an MNI-normalized T1 MRI. Several axial slices are represented, corresponding to the red lines on the 3D brain representation. The radiological convention was used; hence left hemisphere is on the right side. The color bar indicates the number of patients with a lesion in this location (the warmer the color, the higher the number of patients).

Brodmann area 10; MNI coordinates $x = -30$, $y = 50$, $z = 2$ mm) and was associated with a deficit in solving CAT (i.e., *accuracy*), especially for distant trials (i.e., *CAT-index*). Among our 29 patients, seven (24%) had a lesion that overlapped with the ROI (ROI+), and 22 (76%) had a lesion that did not overlap (ROI−). It should be noted that Bendetowicz et al.'s study also reported a cluster located in the right rostro-medial prefrontal cortex (volume .38 cm^3, Brodmann area 10/11; MNI coordinates $x = 12$, $y = 43$, $z = -6$ mm) that was also associated with a deficit in solving CAT. However, only two patients had a lesion overlapping this rostro-medial prefrontal cluster, limiting the use of this brain region as a ROI. Nonetheless, we also tested the effect of this lesion indirectly by pooling patients who had a lesion in either the left rostro-lateral prefrontal or the right rostro-medial prefrontal clusters (ROI2+) and comparing them to the other patients (ROI2−).

Concerning the AUT, we did not find robust evidence in the literature of which ROI to use. Most of lesion studies exploring divergent thinking in patients used group-level analyses, pooling patients with similar anatomical locations. These studies did not provide an ROI with a sufficient spatial resolution. Only one study used a lesion-deficit mapping approach but with patients suffering from a neurodegenerative disease affecting mainly the temporal and frontal poles (Paulin et al., 2020). Although informative, studies conducted with healthy subjects cannot provide strong evidence for well-characterized brain regions that are critical for AUT. Hence, we did not run lesion location-based analyses for the AUT.

We used ANOVAs to compare the CAT *accuracy* across conditions (close and distant) and locations (patient ROI+ and patient ROI−). As in previous models used in behavioral analyses, we added the subject factor as a random effect. Post-hoc analyses were performed to interpret significant effects in the model using non-parametric two-tailed Wilcoxon test, and p values were corrected for the number of statistical tests performed using a Bonferroni method. The *CAT-index* was compared between patient ROI+ and patient ROI− groups using a non-parametric two-tailed Wilcoxon test.

We ran additional analyses to investigate the specificity of the relationship between brain lesion location and CAT performance. We used ANOVAs to compare performance in CAT and AUT (dependent variable) across locations (two levels independent variable: patient ROI+ and patient ROI−) and test (two levels independent variable: AUT and CAT), with the subject factor as a random effect. We ran four different ANOVAs to compare the CAT *accuracy* with successively the *fluency*, the *number of non-alternative uses*, the *frequency*, and the *creativity* variable of the AUT. In order to make the scores of the two tests comparable, we z-scored the scores across all patients for each test separately. We also reversed the sign of resulting z-scores for the *frequency* and the *number of non-alternative uses* (the higher, the better) to have all variables varying in the same direction. We expected to find a significant locations × test interaction effect if the ROI was specifically critical for performing the CAT task.

3. Results

3.1. *Divergent thinking but not associative combination abilities were impaired in neurosurgical patients at the group level*

3.1.1. *Divergent thinking in neurosurgical patients*

We found several results showing that patients (n = 26) were impaired in generating original and creative ideas compared to controls (n = 26), as assessed by the AUT (Fig. 2). First, we found that patients' ideas were, on average, rated by external judges as less creative (2.60 ± .10) than controls' ideas (2.99 ± .08, W = 521.5, $p = 8.08\ 10^{-4}$) (Fig. 2A).

Second, we found a significant main effect of the group [$F(1,46) = 5.04$, $\eta^2 = .62$, $p = .03$] and the time [$F(2,91) = 10.20$,

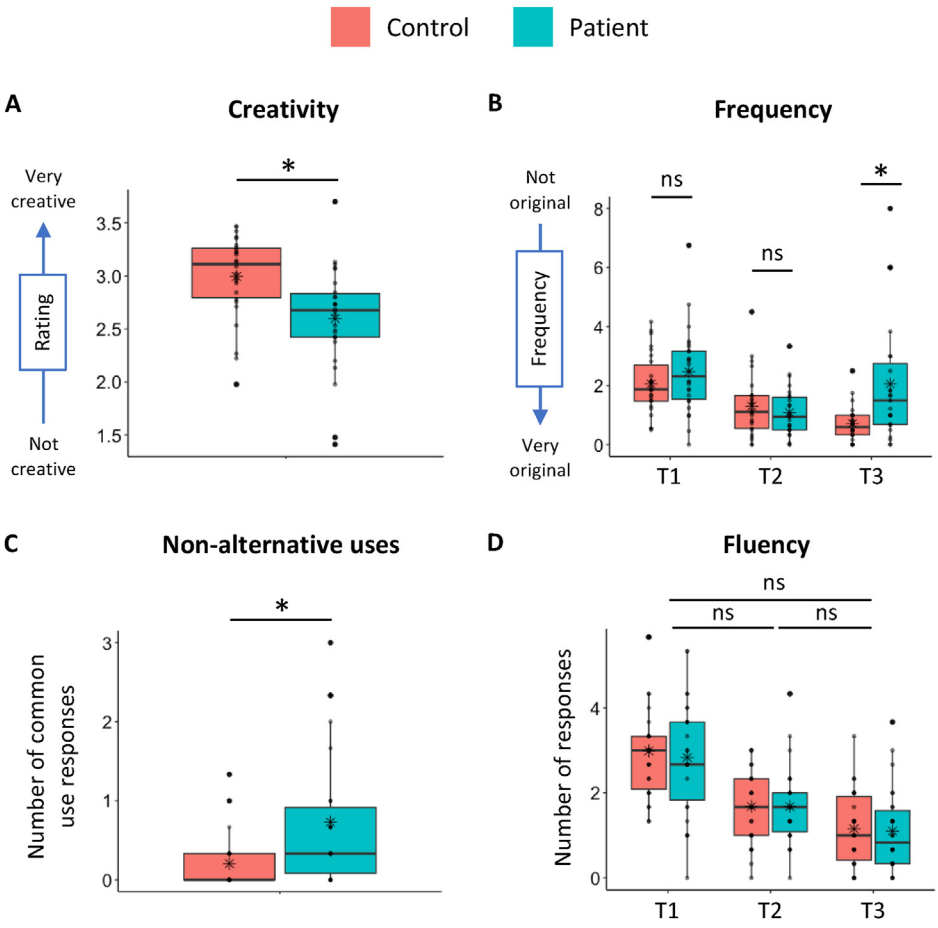

Fig. 2 – Patients' responses were qualitatively (not quantitatively) less creative than controls. *Frequency* (A), *creativity* (B), *number of non-alternative uses* (C), and *fluency* (D) scores for patients (in blue) and controls (in red). For *fluency* and *frequency*, scores are exposed for the first (T1), second (T2), and third (T3) minutes. Each dot represents a participant. Color boxes represent the upper and lower quartiles. Stars and black lines indicate, respectively, the mean and the median. *: $p < .05$, ns: non-significant differences.

$\eta^2 = .17$, $p = 1.01\ 10^{-4}$] on *frequency*, and a significant group × time interaction effect on *frequency* [$F(2,91) = 4.15$, $\eta^2 = .07$, $p = .02$]. The main effect of the group on *frequency* suggested that patients' responses were on average more common (average *frequency*: 1.88 ± .19) compared to controls (1.40 ± .13). Post-hoc analyses exploring the main effect of time on *frequency* revealed that, independently of the group, the *frequency* of responses decreased with time, in particular between the first minute (2.27 ± .17) and the second [1.20 ± .13, $F(1,49) = 27.01$, $\eta^2 = .36$, $p = 3.92\ 10^{-6}$] and the first and the last minute [1.40 ± .25, $F(1,44) = 9.39$, $\eta^2 = .18$, $p = 3.71\ 10^{-3}$]. These results suggested that the originality of responses increased with time for both patients and controls. We did not find a significant difference in *frequency* between the two last minutes [$F(1,44) = .32$, $p = .58$], probably because of the interaction effect. Whereas patients and controls seem to follow the same evolution of the *frequency* of responses during the two first minutes [T1: patient 2.47 ± .28 and control 2.06 ± .20; T2: patient 1.09 ± .17 and control 1.31 ± .21; $F(1,48) = 1.90$, $p = .17$], post-hoc analyses exploring the group × time interaction effect on *frequency* revealed that originality of responses increased more during the last minute of the task in controls than in patients [T3: patient 2.06 ± .41 and control .72 ± .13; $F(1,43) = 8.12$, $\eta^2 = .16$, $p = 6.69\ 10^{-3}$] (Fig. 2B). Of note, our results remained significant when removing the outlier patient with scores higher or lower than 2 standard deviations to the mean *frequency* score in T3.

In addition, as expected, we found a significant main effect of time on *fluency* [$F(2,100) = 88.52$, $\eta^2 = .64$, $p < 10^{-16}$]. Post-hoc analyses revealed that the participants' *fluency* decreased with time [T1: 2.91 ± .17, T2: 1.68 ± .12, T3: 1.13 ± .13; T1 *vs* T2: $F(1,51) = 85.06$, $\eta^2 = .62$, $p = 1.89\ 10^{-12}$; T2 *vs* T3: $F(1,51) = 28.36$, $\eta^2 = .36$, $p = 2.29\ 10^{-6}$; T1 *vs* T3: $F(1,51) = 117.7$, $\eta^2 = .70$, $p = 7.41\ 10^{-15}$]. However, the participants' *fluency* was not affected by the group [main effect of group on *fluency*: $F(1,50) = .19$, $p = .66$; group × time interaction effect on *fluency*: $F(2,100) = .45$, $p = .64$] (Fig. 2D).

Finally, we found that patients gave more responses considered as non-alternative uses (.73 ± .17) compared to control (.21 ± .07; $W = 187$, $p = 3.55\ 10^{-3}$) (Fig. 2C).

In summary, these results indicate that patients have difficulties in generating qualitatively original, alternative, and

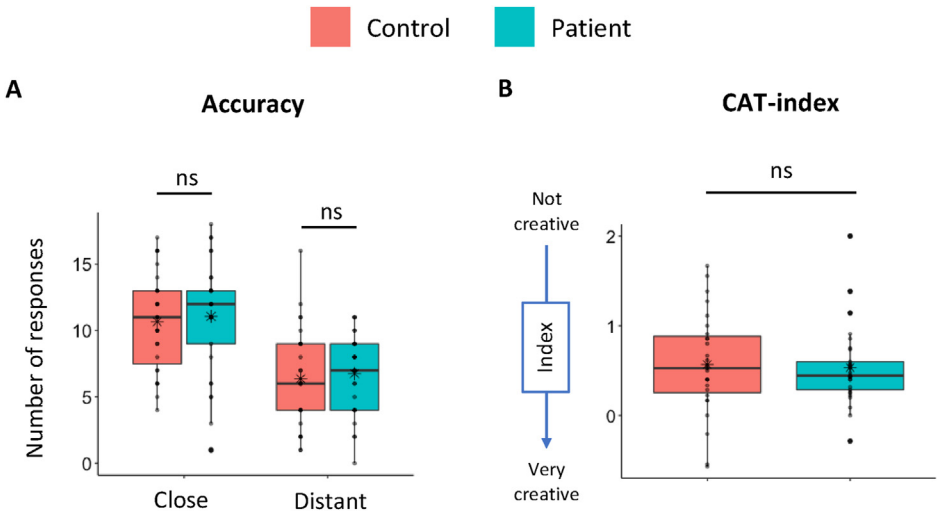

Fig. 3 – Associative combination abilities were not different between patients and controls (at the group level). *Accuracy* (A) and *CAT-index* (B) scores for patients (in blue) and controls (in red). Accuracy is presented for close and distant conditions. Each dot represents a participant. Color boxes represent the upper and lower quartiles. Stars and black lines indicate, respectively, the mean and the median. *: $p < .05$, ns: non-significant differences.

creative ideas compared to control but can provide an equivalent number of responses.

3.1.2. *Associative combination in neurosurgical patients*

At the group level, we did not find significant differences between patient (n = 29) and control (n = 27) in combining (remote) semantic elements, assessed by the CAT (Fig. 3).

As expected, we found a significant main effect of task condition on *accuracy* [F(1,54) = 92.14, $\eta^2 = .63$, $p = 2.85\ 10^{-13}$]. On average, participants were more accurate in close trials (average correct responses: 10.88 ± .53) compared to the distant trials (6.57 ± .44). However, we did not find a significant main effect of participant group on *accuracy* [patient 8.91 ± .63 and controls 8.52 ± .61; F(1,54) = .20, $p = .65$], nor a significant group × condition interaction effect on *accuracy* [F(1,54) = 0, $p = .99$]. In addition, we did not find a significant difference of *CAT-index* (i.e., the ability to solve distant CAT considering the ability to solve close ones) between patients (.53 ± .08) and controls (.57 ± .11; W = 417, $p = .68$).

In summary, patients showed no significant deficit in solving the CAT compared to controls (at the group level).

3.2. *Left rostro-lateral prefrontal cortex is critical in associative combination abilities*

To go further, we explored whether CAT performance could be related to the location of the lesion. We defined an ROI based on a previous focal lesion study showing the critical role of the left rostro-lateral prefrontal cortex for CAT performance (Bendetowicz et al., 2018) (Fig. 4A). Among our 29 patients, seven (24%) had a lesion that overlapped with the ROI (ROI+), and 22 (76%) had a lesion that did not overlap (ROI−). These two groups (ROI+ and ROI−) were not significantly different in the normalized scores of DO80 (ROI+: .03 ± .45; ROI−: −.20 ± .36; W = 81.5, $p = .84$), PPTT (ROI+: −.21 ± .83; ROI−: .02 ± .64; W = 31.5, $p = .22$), forward digit span (ROI+: −.42 ± .42; ROI−: −.94 ± .21; W = 97, $p = .32$), backward digit span (ROI+: −1.11 ± .55; ROI−: −.72 ± .19; W = 68, $p = .66$), animal fluency (ROI+: −.73 ± .34; ROI−: −.34 ± .19; W = 58, $p = .35$), letter fluency (ROI+: −.48 ± .68; ROI−: −.03 ± .21; W = 66, $p = .59$), TMT flexibility (ROI+: −1.11 ± 1.09; ROI−: .02 ± .28; W = 47, $p = .21$), and Stroop interference (ROI+: −1.27 ± 1.31; ROI−: .03 ± .31; W = 57.5, $p = .65$).

Regarding CAT performance, we found a significant main effect of condition on *accuracy* [F(1,27) = 70.06, $\eta^2 = .71$, $p = 5.57\ 10^{-9}$] suggesting that participants were more accurate in close trials (average correct responses: 11.07 ± .79) than distant trials (6.76 ± .54). Importantly, we found a significant main effect of group location on *accuracy* [F(1,27) = 7.69, $\eta^2 = .22$, $p = .01$]. A post-hoc non-parametric test confirmed this result, indicating that patients who had a lesion that overlapped with the ROI (ROI+ group, n = 7) were impaired in solving CAT (average correct responses: 6.14 ± 1.34) compared to the ROI− group (n = 22; average correct responses: 9.80 ± .55; W = 32, $p = .02$; Fig. 4B). We found similar results (and even more statistically robust) if we combined the two prefrontal clusters found in Bendetowicz et al. study (i.e., left rostro-lateral and right rostro-median) to define the ROI2. Two patients had a lesion that overlapped the right rostro-median cluster (average correct responses: 7 and 14, respectively). The ROI2+ group (n = 9) was significantly impaired in solving CAT (average correct responses: 5.94 ± 1.08) compared to the ROI2− group (n = 20, average correct responses: 10.25 ± .56; W = 25.5, $p = 2.47\ 10^{-3}$). The condition × location interaction effect [F(1,27) = 1.64, $p = .21$] was not significant. In addition, we did not find a significant difference in the *CAT-index* between the two groups (ROI+: .76 ± .27; ROI−: .46 ± .06; W = 86.5, $p = .65$; Fig. 4C).

In order to investigate the specificity of this result, we explored whether the location of the lesion and the type of creativity test (AUT or CAT) influenced the performance of patients. We removed one patient ROI+ (n = 6) and two patients ROI− (n = 20) because they did not undergo the AUT. We found a significant location × test interaction effect on patients' performance when we compared CAT *accuracy* with

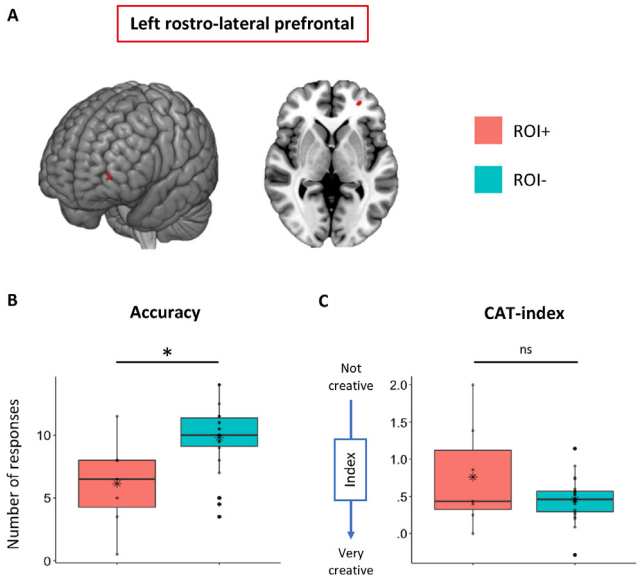

Fig. 4 – Left rostro-lateral prefrontal cortex is critical for combining unrelated elements. We extracted Bendetowicz et al.'s (2018) cluster associated with a deficit in CAT solving. This cluster is represented in red (A) on an axial and coronal slice of an MNI-normalized T1 (volume .23 cm^3; Brodmann area 10; MNI coordinates $x = -30$, $y = 50$, $z = 2$ mm). *Accuracy* (B) and *CAT-index* (C) scores for patients with a lesion that overlap the ROI (ROI+, in red) or not (ROI−, in blue). *Accuracy* is represented as an average of *accuracy* of close and distant conditions. Each dot represents a patient. Color boxes represent the upper and lower quartiles. Stars and black lines indicate, respectively, the mean and the median. *: $p < .05$, ns: non-significant differences.

AUT *fluency* [$F(1,24) = 5.06$, $\eta^2 = .17$, $p = .03$], CAT *accuracy* with AUT *frequency* [$F(1,24) = 7.93$, $\eta^2 = .25$, $p = 9.55\ 10^{-3}$], CAT *accuracy* with AUT *non-alternative uses number* [$F(1,24) = 6.06$, $\eta^2 = .20$, $p = .02$], and CAT *accuracy* with AUT *creativity* [$F(1,24) = 5.63$, $\eta^2 = .20$, $p = .03$] (Fig. 5). These results suggest that the lesion-related deficit in the CAT was specific to this task compared to AUT, supporting the critical and specific role of the rostro-lateral prefrontal cortex in combining unrelated semantic associates.

4. Discussion

The present study provides unique data showing how brain lesions related to low-grade glioma surgery impact creativity. Specifically, patients generated less original and creative ideas in a divergent thinking task. In addition, patients with a lesion that overlapped a critical node for creativity (i.e., the left rostro-lateral prefrontal cortex) showed a specific impairment in a creativity task that requires a combination of remote associates. These results provide proof of concept that patients with low-grade glioma may be impacted in their creative abilities after surgery, emphasizing the importance of assessing this high-order cognitive function in neurosurgical patients. Besides clinical relevance, these results also advance our knowledge on the neuroscience of creativity.

Although the preferential location of low-grade glioma largely overlaps with the regions and networks associated with creative cognition in healthy subjects (Bieth, Lopez-Persem, et al., 2021), only a few studies specifically focused on patients' creativity after brain tumor surgery. Reverberi et al. (2005) showed that patients suffering from various brain tumors (mainly meningioma) in the medial prefrontal cortex had poorer insight problem-solving rates, whereas the solving rate was higher if the lesion was in the lateral prefrontal cortex. Butler et al. (1993) found that patients with various brain tumors had difficulties in several divergent thinking tasks (including the AUT), but the authors only quantified fluency, not the originality of the ideas. In the present study, we extended these results by several means. First, we qualitatively assessed the originality and creativity of generated responses in the divergent thinking task, providing a more comprehensive assessment of creativity. We showed that patients generated less original and creative responses in a classical divergent thinking task (i.e., the AUT), compared to controls. This result was not due to a difference in *fluency* between the two groups. Second, we found that creativity of patients with rostral prefrontal lesions could be impaired in another aspect of creativity, that is the associative combination assessed by the CAT. Finally, our sample was exclusively composed of a homogeneous group of patients with low-grade IDH-muted glioma. It provides for the first-time evidence that these patients can have a deficit in creativity after surgery.

Remarkably, creativity deficit related to low-grade glioma contrasted with the preserved classical neuropsychological assessment of semantic and lexical abilities, working memory or executive functions. Considering the usual neuropsychological assessment alone, one could say that surgery did not impact individual cognition. This contrast suggests that routine medical care should assess high-order cognitive functions to plan therapeutic interventions or propose early specific cognitive rehabilitation in neurological patients. Ultimately, high-order cognitive assessment including creative thinking could be used in awake surgery to guide the surgeon in planning and/or monitoring the resection of the maximum of tissue without inducing cognitive deficits. However, adapting neuropsychological tests to the environmental constraints of the surgery room remains challenging (Bieth, Lopez-Persem, et al., 2021). Only one study adapted the AUT to match awake surgery condition to specifically investigate brain correlates of divergent thinking (Shofty et al., 2022). However, task performance was not assessed during the surgical procedure itself but rather analyzed off-line after the surgery. Additional work is needed to be able to provide useful and optimized on-line feedback about the patient's performance to guide the surgeon during the brain stimulations for cognitive mapping (Bieth, Lopez-Persem, et al., 2021). An alternative could be the use of other tasks that provide a straightforward scoring procedure, such as the CAT. It may help the surgeon remove the brain tumor as much as possible without inducing significant cognitive impairments. By observing creativity deficits after surgery, our study justifies initiating the adaptation of high-order cognitive tests in awake surgery, in particular for low-grade glioma.

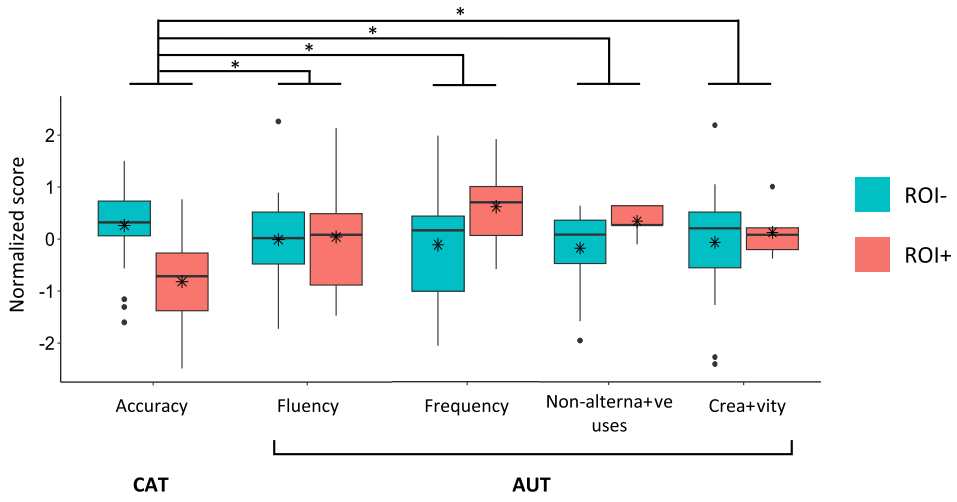

Fig. 5 – Lesion-related deficit in combining usual ideas is specific compared to divergent thinking abilities. Normalized scores (from left to right: CAT *accuracy*, AUT *fluency*, AUT *frequency*, AUT *non-alternative uses number*, and AUT *creativity*) for patients with a lesion that overlap the ROI (ROI+, in red) or not (ROI−, in blue). Normalized scores for AUT *frequency* and AUT *non-alternative uses number* were reversed to be comparable with CAT *accuracy* (the higher, the better). Each dot represents a patient. Color boxes represent the upper and lower quartiles. Stars and black lines indicate, respectively, the mean and the median. *: $p < .05$.

Our results also reinforced the critical role of the prefrontal cortex in creative cognition, as most of the lesion locations of our sample were in the prefrontal cortex (79%). This observation is in line with previous studies showing that focal (Abraham et al., 2012; Bendetowicz et al., 2018; Reverberi et al., 2005; Shamay-Tsoory et al., 2011) and non-focal lesions (Canesi et al., 2017; de Souza et al., 2010; Giovagnoli, 2020; Paulin et al., 2020; Rankin et al., 2007; Senf et al., 2016) affecting the prefrontal cortex were associated with deficits in various creativity tasks. It emphasizes that patients' creativity may be impaired due to neurological lesions affecting the frontal lobes. As the creativity of patients suffering from neurological or neurosurgical diseases is not assessed in medical practice, deficits in creativity may be underestimated.

Importantly, we replicated previous results showing the critical role of the rostro-lateral prefrontal cortex in associative combination (Bendetowicz et al., 2018) in a new sample of patients specifically suffering from resected low-grade gliomas. In our sample, we found that patients were impaired in the CAT in case of a lesion in the rostro-lateral prefrontal region, which was also found critical for the same task in the study by Bendetowicz and colleagues. In other fields, the rostro-lateral part of the prefrontal cortex has been associated with analogical reasoning (Hobeika et al., 2016; Holyoak & Monti, 2021; Urbanski et al., 2016), abstraction (Christoff et al., 2009), and multitasking (Koechlin et al., 1999). This brain region has also been associated with associative combinations in healthy participants using different neuroimaging methods (Bendetowicz et al., 2017; Bieth, Ovando-Tellez, et al., 2021; Gonen-Yaacovi et al., 2013; Ovando-Tellez et al., 2023). Our results reinforce the critical role of the left rostro-lateral prefrontal cortex in creativity, when a combination of ideas is needed to meet the constraints of the task. In our study, we did not find a significantly different effect of semantic remoteness on CAT solving rate (*CAT-index*) between patients and controls and between the lesion location within the patient group. It could be because we used a shorter version of the CAT, including 40 trials instead of 72 trials in the initial study (Bendetowicz et al., 2018).

Interestingly, we uniquely showed that this region was explicitly critical for associative combination but not divergent thinking. Associative combination may require additional cognitive processes than generating semantic associations, such as combining several new and unusual associations of ideas (Bendetowicz et al., 2018; Volle, 2017). It highlights the complex functional organization of the prefrontal cortex (Thiebaut de Schotten et al., 2017), and suggests that the prefrontal cortex is involved in several specific creativity processes. Of note, a minority of studies reported an exaltation of creativity after brain lesions (Reverberi et al., 2005; Shamay-Tsoory et al., 2011), or non-invasive transcranial stimulation (Chrysikou et al., 2013, 2021; Kleinmintz et al., 2018; Luft et al., 2017) targeting the prefrontal cortex. Brain stimulation findings have suggested a dissociation in the role of the left ventral and dorsolateral prefrontal cortex in divergent and convergent thinking and that inhibition of the inferolateral prefrontal region may improve divergent thinking specifically (Chen et al., 2022; Hertenstein et al., 2019; Li et al., 2023; Weinberger et al., 2017). Although these results need to be better understood (Bieth, Lopez-Persem, et al., 2021; Gonen-Yaacovi et al., 2013; Ovando-Tellez et al., 2019), they suggest that different prefrontal sub-regions, belonging to distinct networks, may support different creativity processes. In our study, we identified a brain region specifically

associated with CAT performance but not with AUT deficit, although the whole group of patients were impaired in several AUT scores. High anatomical resolution methodologies and brain connectivity approaches should be considered in further studies to clarify the functional organization of the prefrontal cortex for creativity. Cognitive mapping in awake surgery or intra-cranial EEG analyses may be a promising methodology to advance this question.

5. Limitation

Our study is not without limitations. First, we did not have enough power to run whole-brain analyses, our sample sizes remained small and asymmetrical, and brain lesion locations were majorly left-lateralized. In addition, in our ROI-based approach, we did not have a priori lesion locations to test a specific effect for the AUT performance. The current literature did not provide ROI with a high spatial resolution, or unbiased by the type of patients used. However, we found at the group level (independently of lesion location) that patients showed, on average, a deficit in producing original and creative ideas. It may suggest that divergent thinking requires a more extensive brain network, and that the rostro-lateral prefrontal cortex may be specifically involved in the combinatory processes allowing to solve a CAT. In Bendetowicz et al.'s study (2018), the authors also found the medial prefrontal cortex as a critical actor, specifically in generating distant associations of ideas. In the present study, only two patients had a lesion that overlapped the medial prefrontal cluster, preventing specifically testing the critical role of this brain region for solving CAT in our sample. However, these two patients showed poorer performance at the CAT. In addition, we found that patients with a lesion overlapping the rostro-lateral or rostro-medial prefrontal cortex were significantly impaired in solving CAT compared to patients with lesions elsewhere. Although we did not test the specific role of the medial prefrontal cortex in the CAT, these results suggest that this brain region may also be critical in solving the CAT.

Second, creativity assessment was conducted remotely after surgery, with delays between surgery and evaluation quite heterogeneous in our sample. Even if patients were still impaired in creative cognition, brain plasticity may have helped them recover their post-surgery acute impairments, minimizing deficits in the long term. However, we still observed remotely after the brain surgery a deficit in creative cognition whereas classical neuropsychological tests did not show any deficit. The real impact in daily life of patients of the deficits in creativity tasks were not specifically explored through targeted interviews. We will seriously consider this approach in future research.

Finally, by analyzing only post-surgical deficits, we investigated surgery-related cognitive impairment. Another approach could be to use a within-subject design, testing patients' creativity before and after the surgery. In such a design, each patient would be their own control. It could help disentangle the part of creativity deficits related to the lesion itself and the consequences of brain surgery, taking into account individual creativity level at baseline (i.e., before surgery). It may also better control potential confounding factors such as medications. However, it would require controlling the test-retest effect by developing alternative versions of our tasks for longitudinal testing.

6. Conclusion

The present study provides evidence that patients with a low-grade glioma surgically resected showed a creativity deficit. Specifically, these patients generated less original and creative ideas, and were impaired in combining (remote) concepts in semantic memory if the rostro-lateral prefrontal cortex was affected. In addition to shedding new light on the neuroscience of creativity, our study highlighted the relevance of assessing high-order cognitive function, such as creativity, in clinical practice. This could lead to a better monitoring of surgical interventions and guide early rehabilitation.

Credit author statement

Théophile Bieth: Methodology, Formal analysis, Writing original draft, Visualization. **Valentine Facque**: Conceptualization, Methodology, Investigation, Writing review and editing. **Victor Altmayer**: Formal analysis, Validation, Writing review and editing. **Isabelle Poisson**: Investigation, Writing review and editing. **Marcela Ovando-Tellez**: Methodology, Formal analysis, Writing review and editing. **Sarah Moreno-Rodriguez**: Methodology, Writing review and editing. **Alizée Lopez-Persem:** Methodology, Formal analysis, Writing review and editing. **Emmanuel Mandonnet**: Conceptualization, Methodology, Formal analysis, Supervision, Writing original draft. **Emmanuelle Volle**: Conceptualization, Methodology, Formal analysis, Supervision, Writing original draft.

Data availability

No part of the study procedures or analysis plans was preregistered prior to the research being conducted. The conditions of our ethics approval do not permit public archiving of anonymized patient data. Hence, the data sets generated processed in the current study are available on request to the authors. Readers seeking access to the data should contact the principal investigator Pr. Emmanuel Mandonnet. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data. Specifically, requestors must meet the following conditions to obtain the data: completion of a formal data sharing agreement. Study materials are archived and publicly accessible – when feasible – on OSF (https://osf.io/q58zf/?view_only=24bb3037314345f88c2da5e3c44b0f25). The CAT was programmed using MeyeParadigm [e(ye)Brain Inc., 2009], while all subsequent tasks (the AUT and usual neuropsychological tasks) used paper and pencil. Legal copyright restrictions prevent public archiving of usual neuropsychological tasks we used (i.e., other than creativity one) which can be obtained from the copyright holders in the cited references All tasks followed experimental procedure which are fully described in the manuscript and in the cited references. We used open software and toolboxes available online:

lesion preprocessing was done with MI-Brain software (https://github.com/imeka/mi-brain), and statistical analyses were done using Rstudio. We specified the statistical *r* functions that we used in the Methods section and the R codes used for analyses and data visualization are available in the OSF public repository.

Transparency statement

We report in the Method section how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

Declaration of competing interest

The authors declare that they have no competing conflicts of interest.

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