Long-Term Cognitive Functioning and Psychological Well-Being in Surgically Treated Patients with Low-Grade Glioma

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■ OBJECTIVE: **The aim of this work is to provide an in-depth investigation of the impact of low-grade gliomas (LGG) and their surgery on patients' cognitive and emotional functioning and well-being, carried out via a comprehensive and multiple-measure psychological and neuropsychological assessment.**

■ PATIENTS AND METHODS: **Fifty surgically treated patients with LGG were evaluated 40 months after surgery on their functioning over 6 different cognitive domains, 3 core affective/emotional aspects, and 3 different psychological well-being measures to obtain a clearer picture of the long-term impact of illness and surgery on their psychological and relational world. Close relatives were also involved to obtain an independent measure of the psychological dimensions investigated.**

■ RESULTS: **Cognitive status was satisfactory, with only mild short-term memory difficulties. The affective and well-being profile was characterized by mild signs of depression, good satisfaction with life and psychological well-being, and good personality development, with patients perceiving themselves as stronger and better persons after illness. However, patients showed higher emotional reactivity, and psychological well-being measures were negatively affected by epileptic burden. Well-being was related to positive affective/emotional functioning and unrelated to cognitive functioning. Good agreement between patients and relatives was found.**

■ CONCLUSIONS: **In the long-term, patients operated on for LGG showed good cognitive functioning, with no significant long-term cognitive sequelae for the extensive surgical approach. Psychologically, patients appear to experience a deep psychological change and maturation, closely resembling that of so-called posttraumatic growth, which, to our knowledge, is for the first time described and quantified in patients with LGG.**

INTRODUCTION

A great challenge in neurosurgery is the preservation of patients' brain functions and quality of life. Over the past 15 years, the neuro-oncology and neurosurgery literature has shown a growing interest in low-grade gliomas (LGG),[1-4] which are slow-growing infiltrative brain tumors affecting younger individuals and often located close to or infiltrating eloquent brain areas (e.g., language). LGG patients typically do

Key words
- Cognitive functioning
- Low-grade glioma
- Posttraumatic growth
- Psychological well-being
- Quality of life

Abbreviations and Acronyms
ANOVA: Analysis of variance
ANCOVA: Analysis of covariance
BDI: Beck Depression Inventory
EOR: Extent of resection
HGG: High-grade glioma
LGG: Low-grade glioma
PANAS: Positive and Negative Affect Schedule
PTG: Posttraumatic growth
PWB: Psychological Well-Being
QoL: Quality of life
STAI-Y: State-Trait Anxiety Inventory Form Y
SWLS: Satisfaction With Life Scale
TCI: Temperament and Character Inventory

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not show cognitive deficits for many years and the presence of the lesion is mostly revealed by the onset of seizures.[5,6] In these tumors, survival is associated with the maximal extent of resection (EOR),[5,7] which, on the other hand, may affect neurologic/cognitive functioning and, consequently, patients' quality of life (QoL). In contrast, high-grade gliomas (HGG) are fast-growing, very aggressive, and destructive tumors affecting older people[6] and associated with reduced cognitive abilities.[8,9] They have a poorer prognosis, overall survival, cognitive functioning, and QoL with respect to LGG.

After surgical resection, patients with HGG have to immediately undergo adjuvant therapies (chemotherapy and radiotherapy) and their clinical picture is likely to change significantly in just a few months after diagnosis. Regarding QoL, in patients with HGG, poorer QoL was found to be linked to worse cognitive functioning, mood, and higher World Health Organization grading.[10] Also for patients with LGG, past studies tended to report a reduced QoL, with lower cognitive functioning (with respect to the healthy population), especially in patients receiving radiotherapy.[3,11] However, most studies have considered only general QoL measures[3,11] or, when deeper psychological aspects are considered, the studies tend to be more qualitative and descriptive,[12-14] often considering HGG and LGG together.[15-19] These studies seem to suggest that existential distress (i.e., the feeling of threat to one's own conception of meaning, purpose, and satisfaction with life) is common at different stages of illness progression,[17] with greater existential distress being linked to depression and poorer QoL.[20]

As a consequence, a comprehensive quantitative assessment of psychological functioning and well-being in patients with LGG seems particularly important, given that these patients may have a longer survival but the tumors may be potentially harmful for patients' cognitive and affective functioning and, more generally, for their well-being and QoL.

This study aims to provide an in-depth, comprehensive, and quantitative investigation of long-term cognitive and affective functioning and psychological well-being of surgically treated patients with LGG. This investigation is carried out by assessing patients' cognitive functioning with a series of neuropsychological cognitive tests, and their emotional state (including anxiety and depression) and psychological well-being with standardized quantitative measures.[21,22] This approach allows progression beyond the mere ascertainment of the absence of negative signs and symptoms, which is traditional in standard clinical practice.[23]

To this aim, all the cognitive and psychological well-being variables we measured were evaluated in relation to comparable segments of the healthy population by using standardized clinical, psychological, and neuropsychological measures and referring to the existing psychometric norms. In addition, because self-report measures are prone to potential self-presentation biases,[24,25] close relatives were also involved in the study to obtain an external point of view on the patients' functioning and experience.

METHODS

Participants

A consecutive series of 50 surgically treated patients with LGG, operated on at least 1 year previously (average, 3.35 years), participated in the study between May 2013 and June 2014 (further details on inclusion criteria are given in the **Supplementary Material**). Only patients showing radiologically stable LGG appearance at the time of evaluation were included (i.e., in a stable state of their illness). The study was approved by the local ethical committee and all patients gave written consent.

Table 1 summarizes demographic and clinical data (see **Supplementary Table 7** for a complete list of patients with specific anatomic location of lesions and lesion volume). All patients returned to work (or previous activity) on average 3.8 months after surgery (standard deviation, 3.71), with a single exception. Although 15 (30%) reported some work change, this was a consequence of the illness only for 7 (14%) (e.g., cognitive limitations because of the illness). All patients completed the neuropsychological evaluation and only 1 was unable to complete the well-being questionnaires because of reading and attention problems.

Research Protocol

Together with a complete neuropsychological evaluation, participants had to complete a series of self-report well-being measures. They also took part in an extensive semistructured interview investigating possible changes in quality of relations with spouse/partner, family, and friends after the illness and any relevant change in everyday life or life perspective/outlook. Patients also indicated a close relative, who took part in a parallel interview, during which they were asked to evaluate the patient's well-being by using some of the measures already used for the patient's self-evaluation. Forty-seven relatives participated. In the remaining 3 cases, the patient did not indicate anyone suitable. All scores from the cognitive and psychological tests used in the study were compared with the relative normative data, obtained from the standardization samples, by means of a series of one-sample *t* tests applying Bonferroni correction when needed.

Cognitive Status Evaluation

The neuropsychological profile was evaluated for each patient with a battery of 18 different tests tapping 6 main cognitive domains: overall cognitive functioning; language; attention and executive functions; short-term memory; long-term memory; and visuo-spatial skills. Neuropsychological tests were standard measures widely used and well established in neuropsychological assessment. The set of measures has been selected to cover all the main cognitive domains as well both the spatial and verbal aspects of performance (see **Supplementary Table 1** for further details). The observed number of cognitive deficits is summarized in **Table 1**. For group analysis, scores were transformed into *z* scores in relation to normative data (see **Supplementary Material** for details and references) and then averaged across tests within each domain to obtain 6 summary cognitive scores.

Comparison with Preoperatory/Postoperatory Cognitive Status. For the patients operated on after autumn 2011 ($n = 21/50$), a complete and comparable presurgery/postsurgery evaluation of cognitive functions was also available (but not for the patients operated on before; see **Supplementary Material**). A *z* score averaged across all tasks was computed for each patient in each of the 3 conditions (preoperatory, postoperatory and long-term follow-up), to obtain an overall cognitive score. Average scores were then compared

Table 1. Sociodemographic and Clinical Characteristics of Patient Population with Low-Grade Glioma

Sex (n)	
Male	23
Female	27
Age (years)	
Mean (SD)	40.02 (10.88)
Range	19—69
Education (years)	
Mean (SD)	14.16 (2.96)
Range	8—17
Months from surgery	
Mean (SD)	40.28 (36.28)
Range	12—181
Lesion volume (cm^3)	
Mean (SD)	41.95 (33.73)
Range	5—128
Extent of resection (%)	
Mean (SD)	90.19 (13.85)
Range	38—100
Surgical procedure (n)	
Awake	36
Asleep	14
Number of surgeries	
1	46
>1	4
Epileptic burden (n)	
Free	22
Mono AED	24
Poly AED	4
Adjuvant therapies (n)	
Free	38
Chemotherapy	5
Radiotherapy	5
Both	2
Number of cognitive deficits	
Free	25
1	17
>1	7
Hemisphere (n)	
Left	25
Right	25
Location	
Frontal	30
Nonfrontal (temporal+ parietal)	20 (15+5)

AED, antiepileptic drug; SD, standard deviation.

across conditions with a repeated measures analysis of variance (ANOVA) with "condition" as 3 level within subject variable.

Anatomic Analyses. The current performance of patients was also analyzed in further detail to detect potential differences in cognitive status of patients depending on lesion location or cognitive domain. Therefore to compare, for each domain separately, the performance of patients in the cognitive tasks, a series of analysis of covariance (ANCOVA) designs was adopted with "Hemisphere" (left vs. right) and "Lobe" (frontal vs. temporal vs. parietal) as between-subject variables. Preoperatory lesion volume, EOR (%), surgical protocol (awake vs. asleep), number of cognitive deficits shown, distance from surgery (months), epileptic burden (i.e., the number of antiepileptic drugs prescribed), presence of further adjuvant therapies (chemotherapy or radiotherapy), as well as sex, age, and education, were used as covariates to control for (and partial-out) their potential interfering effects on anatomic variables (see Table 3).

Affective/Psychological Well-Being

Affective/Emotional Functioning Evaluation. To measure affective/emotional functioning, 2 standard measures were selected to tap 2 affective aspects that are especially relevant in clinical conditions, such as anxiety and depression (State-Trait Anxiety Inventory [STAI-Y] and Beck Depression Inventory II [BDI-II]). In addition, a more general instrument was used to measure the general emotional status (Positive and Negative Affect Schedule [PANAS]). These measures are widely used in clinical and nonclinical settings and proved to be valid and reliable.[26-28] PANAS-20 measures experience of positive and negative affect.[29] Patients are asked to describe how intensely they generally experience 20 different feelings and emotions by using a 5-point scale. STAI-Y I-II[30] measures the levels of state anxiety (temporary discomfort derived from situations perceived as dangerous) and trait anxiety (an enduring disposition to stress/worry) on 20 items self-rated on a 4-point scale. BDI-II[31] is a 21-item self-report instrument measuring the intensity of depressive symptoms on a 4-point scale.

Psychological Well-Being Evaluation. Participants' well-being was assessed with 2 standard self-report measures (Satisfaction With Life Scale [SWLS] and Psychological Well-Being [PWB]),[21,22] again widely known and used in both clinical and nonclinical settings, plus a personality inventory (Temperament and Character Inventory [TCI]),[32] based on a neurobiologically grounded model of personality, which has been effectively used in the past to assess personality changes after brain damage.[33-35] From the TCI, the self-maturity measure was assessed, a dimension significantly

Table 2. Comparison of One-Sample *t* Tests Obtained by Patients in Each of the Cognitive and Psychological Well-Being Measures Collected, with Respect to That Expected from the Reference Population

Task/Domain	Measure	Mean	Standard Deviation	*P* Value
Cognitive functions*	General cognitive level	0.103	0.512	0.167
	Language	**0.319**	**0.418**	**<0.001**
	Attention/executive function	−0.086	0.436	0.169
	Long-term memory	−0.033	1.296	0.858
	Short-term memory	**−0.403**	**0.750**	**<0.001**
	Visuospatial skills	−0.265	1.219	0.131
Positive and Negative Affect Schedule 20†	Positive affect	**0.800**	**1.015**	**<0.001**
	Negative affect	**0.708**	**0.877**	**<0.001**
State-Trait Anxiety Inventory Y Form†	State anxiety	**0.627**	**1.290**	**0.001**
	Trait anxiety	−0.065	1.101	0.656
Beck Depression Inventory II	Average score	**61.428**	**25.146**	**<0.001**
Satisfaction With Life Scale	Average score	25.755	5.739	0.957
Psychological Well-Being Scale	Overall	0.168	0.791	0.143
Subscales*	Autonomy	−0.055	0.932	0.683
	Environmental mastery	**0.404**	**1.026**	**0.008**
	Personal growth	−0.014	0.894	0.910
	Positive relation	0.176	1.040	0.241
	Purpose in life	0.151	1.019	0.305
	Self-acceptance	0.348	0.919	0.011
Temperament and Character Inventory	Self-maturity	**67.346**	**10.608**	**0.032**
Subscales†	Self-directedness	**34.653**	**6.990**	**<0.001**
	Cooperativeness	32.694	5.269	0.686

All scores are standardized *z* scores, except for Satisfaction With Life Scale and Temperament and Character Inventory, for which raw scores are compared, and Beck Depression Inventory II, for which percentiles are compared (see **Supplementary Table 2** for an extended version of the table).
Bold values indicates significant differences.
*Bonferroni correction: $P = 0.05/6 = 0.008$.
†Bonferroni correction: $P = 0.05/2 = 0.025$.

related to well-being in clinical conditions.[36] SWLS[37] is a 5-item questionnaire assessing overall life satisfaction on a 7-point rating scale. PWB[21,23] is an 84-item questionnaire measuring psychological well-being through six 6-point subscales: autonomy, environmental mastery, personal growth, positive relations, purpose in life, and self-acceptance. TCI[32,38] is a 7-scale personality inventory: 2 of these scales were administered (self-directedness, measuring self-efficacy and self-esteem; and cooperativeness, linked to empathy) providing a self-maturity index (the sum of self-directedness and cooperativeness raw scores), which is a measure of efficient self-regulation, linked to the risk of personality disorder.[39]

Anatomic Analyses. With the same procedure used for the anatomic analyses in the cognitive functioning domain, each of the affective/psychological well-being measures underwent separate ANCOVA designs with hemisphere (left vs. right) and lobe (frontal vs. temporal vs. parietal) as between-subject variables. The same covariates (plus the number of cognitive deficits shown by patients) were used to control for (and partial-out) their potential interfering effects on anatomic variables (see **Table 4**).

Relatives' Evaluation and Semistructured Interviews

Three of the affective and well-being measures (PWB, BDI-II, and STAI-Y 1 and 2) were also administered in third person to close relatives, who had to evaluate the patient. The other measures were considered too personal to be assessed from an external viewpoint. Parts of the semistructured interview were also coded to obtain quantifiable information, both from patients and from relatives. Perceived changes in relationships with spouse/partner, family, and friends and in life perspective/outlook were coded on a 3-point scale (+1, positive, −1, negative; 0, no change). For all measures, for sporadically missing answers in the questionnaires, a mean substitution method was applied.

RESULTS

Cognitive Status

Patients' overall cognitive status was satisfactory. At an average of 3.5 years from surgery, 84% (42/50) were either free ($n = 25$) or with 1 ($n = 17$) detectable cognitive deficit (over 18 measures).

Comparison with Preoperatory/Postoperatory Cognitive Status. For the subset of patients (21/50) operated on after 2011, the ANOVA showed a significant effect of condition ($F_{2,40} = 4.107$; $P = 0.024$) showing that the cognitive status of patients changed in time (pre vs. post vs. follow-up). Immediately after surgery, patients' overall cognitive performance showed a declining trend ($P = 0.089$), whereas in the long-term follow-up, it significantly improved ($P = 0.009$), returning to preoperatory levels ($P = 0.278$). Further analyses (see **Supplementary Tables 5** and **6**) showed that preoperatory z scores of these patients were fully within the normality range in all cognitive domains.

Comparison of Current Cognitive Status with Reference Population. Current cognitive status of the full sample of patients ($n = 50$) was almost completely within the range of normality (see **Table 2**). Short-term memory was the only cognitive domain in which patients consistently scored lower than their corresponding norm ($P < 0.001$). For language skills, patients' results were even higher overall than the norm ($P < 0.001$), but they fell within the norm after the exclusion of the 3 easiest measures of the language battery ($t = 1.021$; $P = 0.312$).

Anatomic Analyses. As shown in **Table 3**, no consistent effects of lesion location were found in any of the cognitive domains considered, apart from long-term memory ($F_{2,33} = 4.165$; $P = 0.024$): patients who underwent temporal lobe surgery showed lower long-term memory scores than did parietal patients ($P = 0.016$) but did not differ from frontal patients ($P = 0.118$). Frontal and parietal patients did not differ either ($P = 0.189$). No other lesion location effect was found in any domain. Only sporadic significant influences of the covariates were reported. There was a negative effect of epileptic burden on short-term memory skills ($P = 0.023$).

Affective/Emotional Status

Comparison with Reference Population. The average patients' scores in each measure considered with respect to the reference population are shown in **Table 2**. Patients scored significantly above the reference in terms of both positive and negative affect (PANAS-20: $P < 0.001$), showing higher emotional reactivity. Most of the patients (38/49 [77.5%]) did not show clinically relevant signs of depression (BDI-II: scores $\leq$85 percentile). Still, at the group level, the average percentile score was significantly higher ($P = 0.001$) than the healthy population score. According to STAI-Y 1-2, patients' state anxiety was significantly higher than the norm ($P = 0.001$), whereas trait anxiety was comparable ($P = 0.656$).

Relatives' Evaluation of Patients. BDI-II ratings did not differ significantly between patients and relatives, although relatives tended to provide lower depression ratings of the patients (patients, $M = 8$; relatives, $M = 6.23$; $t(45) = 1.871$; $P = 0.068$).

Table 3. Cognitive Functioning: Analysis of Covariance Results (*P* Values)

	Anatomic Effects			Covariate Effects							
	Hemisphere	Lobe	Hemisphere + Lobe	Preoperatory Volume	Extent of Resection (%)	Surgery (Awake/Asleep)	Months from Surgery	Epileptic Burden	Adjuvant Therapy (Yes/No)	Sex (Male/Female)	Age	Education
General cognitive level	0.405	0.541	0.643	**0.010**	0.295	0.555	0.956	0.564	0.633	0.521	0.325	**0.016**
Language	0.315	0.506	0.832	0.285	0.421	0.349	0.249	0.919	0.225	0.899	0.113	0.939
Attention/executive functions	0.978	0.908	0.370	0.574	0.236	0.642	0.710	0.688	**0.028**	0.511	0.195	**0.004**
Short-term memory	0.364	0.095	0.442	0.570	0.627	0.658	0.889	**0.010**	0.804	0.774	0.411	0.095
Long-term memory	0.374	**0.024**	0.320	0.083	0.246	0.162	0.056	0.444	0.514	0.606	0.052	0.225
Visuospatial skills	0.396	0.993	0.930	0.370	0.223	0.112	0.867	0.532	0.168	0.074	0.348	0.638

Bold values indicates significant differences.
The table shows the effects of lesion location (by hemisphere, lobe, and the interaction of both) over each of the cognitive domains and also the influence of potential intervening variables (covariates) over anatomic effects. Lesion location effects were limited and restricted to the long-term memory domain.

A repeated measures ANOVA over the state and trait anxiety scales showed a significant effect of "rater" ($F_{1,45} = 7.153$; $P = 0.010$), meaning that patients reported higher state and trait anxiety scores than did relatives. Moreover, a main effect of scale showed that both patients and relatives agreed in reporting higher levels of state than trait anxiety ($F_{1,48} = 25.066$; $P < 0.001$), suggesting that patients live in a more aroused state.

Anatomic Analyses. No effect of lesion location (hemisphere, lobe, or interaction of both) was found for any of the emotional/affective measures considered (see **Table 4**). Epileptic burden was associated with 2/3 affective/emotional measures: patients with higher epileptic burden had higher depression (BDI-II: $P = 0.010$) and higher negative affect in everyday life (PANAS-20, negative affect: $P = 0.015$).

Psychological Well-Being

Comparison with Reference Population. Average patients' scores in each measure considered with respect to the reference population are shown in **Table 2**. Levels of satisfaction with life (SWLS) overlapped with those of the reference population ($P = 0.957$), as well as scores in all PWB scales (but patients showed higher scores in the environmental mastery scale). Patients also showed higher than expected self-maturity scores (TCI) ($P = 0.032$), in particular higher self-directedness scores ($P < 0.001$). Most patients indicated a positive change in life outlook/perspective after their illness (21/49 of the cases: 42%), whereas changes were negative for only 8/49 (16%).

Relatives' Evaluation of Patients. The ANOVA over 6 PWB subscales for both patients and relatives did not show any significant effect of rater ($F_{1,45} = 3.166$; $P = 0.082$). A significant effect of scale ($F_{2,225} = 10.324$; $P < 0.001$) and an interaction between rater and scale ($F_{5,225} = 5.474$; $P < 0.001$) were found. Post hoc tests showed that patients and relatives disagreed on only 1 scale: parents rated patients' autonomy levels higher ($P < 0.001$). The ANOVA analyzing potential changes over the quality of 3 relations considered (spouse/partner, family, friends) showed again a significant rater effect ($F_{1,27} = 5.052$; $P = 0.033$), with patients describing positive changes more frequently than did their relatives.

Anatomic Analyses. Again, no effect of lesion location (hemisphere, lobe, or interaction of both) was found for any of the psychological well-being measures considered (see **Table 4**). Again, epileptic burden was consistently associated also with the psychological well-being measures considered. Patients with higher epileptic burden showed a strong trend toward a lower satisfaction with life (SWLFS: $P = 0.043$) and reported lower psychological well-being (PWB: $P = 0.013$).

Relation Between Cognitive Status, Affective Status, and Psychological Well-Being

Further correlation analyses were performed to assess the degree with which affective, psychological, and cognitive measures correlated with each other. The analyses showed that cognitive measures were all unrelated to affective measures (all $P > 0.128$), as well as to well-being scores (with the exception of long-term memory related to PWB: $r = 0.315$; $P < 0.028$). Conversely, the affective measures were all significantly related with the 3 well-being measures (from $r = 0.353$, $P < 0.013$ to $r = -0.610$, $P < 0.001$, with the exception of 2 correlations involving STAI-Y1), specifically showing that a better affective status was always associated with higher well-being. Multiple regressions predicting well-being scores from the cognitive and the affective measures showed only significant or marginally significant effects of BDI-II. This finding held both for SWLS ($\beta = 0.40$; $P < 0.05$; $R^2 = 0.55$) and for TCI ($\beta = -0.35$; $P = 0.06$; $R^2 = 0.48$), but not for PWB. Including as predictors also demographic or clinical measures significantly related to some of the well-being measures (i.e., epileptic burden, preoperatory volume; see **Table 4**) confirmed the effects of BDI-II on SWLS ($\beta = -0.51$; $P < 0.05$; $R^2 = 0.60$) and on TCI ($\beta = -0.37$; $P = 0.06$; $R^2 = 0.60$) but also exposed a significant effect of PANAS (negative affect) on the PWB measure ($\beta = -038$; $P < 0.05$; $R^2 = 0.66$). Summarizing, well-being scores were predicted by affective but not by cognitive measures.

DISCUSSION

The present study provides a quantitative and comprehensive investigation of the long-term consequences of surgically treated patients with LGG, with an in-depth characterization of their cognitive and affective functioning and well-being.

Cognitive Profile

Patients' cognitive profile at 3.5 years from surgery was in line with the healthy population in all domains except short-term memory. Analysis of the covariates effects in ANCOVA designs further showed that short-term memory was not influenced by any of the clinical variables linked to surgery, such as lesion hemisphere or lobe location, or lesion volume, or EOR, but rather by epileptic burden (i.e., the number of antiepileptic drugs prescribed to the patient), an extrasurgical variable, the negative cognitive impact of which has been commonly reported (see Refs.[40,41]).

Anatomic analyses showed that cognitive picture of patients did not differ according to hemisphere or lobe location of the lesion in any of the considered 6 cognitive domains apart from long-term memory, which, consistently with anatomic predictions, was slightly lower in temporal lobe patients.

However, in line with previous reports,[33,42] our data support the observation of an immediate negative cognitive impact of the surgery in patients with LGG, but, importantly, they show no evident negative cognitive sequelae in the longer-term in any of the cognitive domains analyzed. The absence of any substantial anatomic correlation between lesion location and cognitive function at 3.5 years on average from surgery should not particularly surprise and should be interpreted in the light of the behavior of slow-growing lesions such as LGG: it has already been observed that, although an immediate cognitive impact of surgery is common in patients with LGG, these cognitive deficits tend to positively evolve within a few months.[33,42-44] This situation might be a result of particularly effective brain reorganization mechanisms, supporting the view of the brain as a complex system of many distributed networks, with a large plasticity potential (see the concept of "connectome"[44]) that may have also been already triggered before surgery itself.[42,44-46] On the other hand, the immediate cognitive impact of surgery is likely a result of the

Table 4. Affective Status and Psychological Well-Being: Analysis of Covariance Results (*P* Values)

	Anatomic Effects			Covariate Effects									
	Hemisphere	Lobe	Hemisphere. + Lobe	Preoperatory Volume	Extent of Resection (%)	Surgery (Awake/ Asleep)	Number of Cognitive Deficits	Months from Surgery	Epileptic Burden	Adjuvant Therapy (Yes/No)	Sex (Male/ Female)	Age	Education
PANAS-20: positive affect	0.960	0.189	0.763	0.257	0.224	0.205	0.366	0.972	0.171	0.729	0.422	0.881	0.956
PANAS-20: negative affect	0.459	0.905	0.383	0.473	0.457	0.220	0.895	0.930	**0.015**	0.830	0.588	0.757	0.666
STAI-Y1: state anxiety	0.221	0.124	0.099	0.244	**0.026**	0.718	0.810	0.964	0.534	0.428	0.839	0.790	0.444
STAI-Y2: trait anxiety	0.680	0.756	0.177	0.663	0.548	0.670	0.809	0.675	0.113	0.764	0.905	0.961	0.755
Beck Depression Inventory II: depression score	0.446	0.625	0.382	0.190	0.428	0.914	0.969	0.799	**0.010**	0.190	0.188	0.781	0.508
Satisfaction With Life Scale: life satisfaction	0.432	0.480	0.246	0.364	0.833	0.523	0.530	0.441	**0.066**	0.788	0.586	0.886	0.376
Psychological Well-Being	0.154	0.494	0.141	0.742	0.627	0.113	0.449	0.143	**0.040**	0.179	0.153	0.196	0.098
Temperament and Character Inventory: self-maturity	0.697	0.654	0.492	**0.036**	0.712	0.962	0.698	0.822	0.124	0.790	0.277	0.701	0.211

Bold values indicates significant differences.

The table shows the effects of lesion location (by hemisphere, lobe, and the interaction of both) over each of the affective status as well as psychological well-being measures and also the influence of potential intervening variables (covariates) over the anatomic effects. Lesion location effects absent. The most consistent effect is that of epileptic burden over many psychological and affective measures (see **Supplementary Table 4** for an extended version of the table).

PANAS, Positive and Negative Affect Schedule; STAI-Y, State-Trait Anxiety Inventory Form Y.

aggressive surgical strategy adopted with this type of lesions, aimed at the maximum EOR possible. This factor has as a consequence the removal of probably still functional, but infiltrated, tissue. Correlation analyses showed that cognitive variables did not predict psychological well-being in our sample of patients.

These observations seem to confirm that an extensive surgical approach to LGG, aimed at maximizing the EOR, is, in the long-term, safe overall from the cognitive and also the psychological viewpoint.

Affective Status and Psychological Well-Being

However, the most important finding comes from the psychological well-being profile. Patients seem satisfied with their lives and perceive greater maturity and solidity of self-representation than do the corresponding segments of the population (see **Table 2**). Patients' psychological well-being was in line with the healthy population, with high levels of environmental mastery, meaning that patients believe that they have full control of their life and environment. In addition, they described a positive change in life perspective and outlook, and frequently described themselves as having become a better person after the illness. Because they all know they will have to keep the illness under continuous monitoring, they often described themselves as "living more for the day" now, often describing as "futile" many of their previous activities, but they also reported that they "enjoy everyday experiences more than they did before". Therefore, also the well-being and QoL of patients were not harmed by illness and surgery.

The emotional side of the psychological world of patients seems to be mostly and specifically affected by the illness: patients became more reactive in terms of both positive and negative affects (PANAS) and state anxiety (STAI-Y). Although the average depression level was higher than in the healthy population, most patients did not show clinically relevant signs of depression. Different from grief reactions after loss events, characterized by high incidence of depression with limited anxiety, reactions to events constituting a continuous threat (such as LGG) seem to be typically characterized by a predominance of anxiety over depression.[47,48]

From an anatomic point of view, our data seem to show no consistent association between anatomic regions involved in the surgery and either emotional or psychological well-being. This finding seems to contrast with some previously reported data,[49,50] suggesting that right hemisphere tumors are linked for example with higher anxiety levels and poorer perceived QoL. However, both reported studies found the effects preoperatively, whereas our study assessed these issues in the very long-term postsurgical period (3.5 years). In this long period, reorganization mechanisms similar to those discussed in the previous paragraph regarding cognitive functions might have taken place. In further support of this observation, the study of Mainio et al,,[49] clearly shows that the higher levels of anxiety found preoperatively for right hemisphere patients progressively normalized at 3 months and 1 year after surgery.

Several affective and well-being measures were negatively influenced by epileptic burden (i.e., the number of antiepileptic drugs prescribed to the patient), in line with previous reports in patients with glioma and epilepsy.[1,2,51] However, multiple regressions predicting well-being scores from cognitive, affective, and clinical variables (epileptic burden included) showed that the only significant predictor was the level of depression, with no surviving effect of epileptic burden. This finding is in line with previous studies,[15,20] and it suggests that depression should be monitored carefully in these patients.

Posttraumatic Growth

Overall, the surprisingly positive psychological functioning reported by patients seems to meet the general criteria for the definition of the so-called posttraumatic growth (PTG), i.e. "the positive psychological change experienced as a result of the struggle with highly challenging life circumstances."[52] The psychological profile of the patients with LGG meet the typical PTG criteria, such as greater appreciation of life and changed sense of priorities, warmer and more intimate relationships with others, and a greater sense of personal strength. In these respects, our patients are not different from other oncologic populations, because PTG has already been described generally in patients with tumor.[53-55] However, generally, all studies of PTG have been qualitative (see Ref.[54] for review) and only one of these[56] dealt with LGG diagnosis. To our knowledge, this is the first time that PTG has been described and quantified in patients with LGG.

It may be argued that the high reported well-being of our patients with LGG in the face of a higher emotional reactivity and increased depression reflects a kind of reactive self-serving rationalization mechanism, aimed at making sense of the illness and at preserving personal identity,[57] and not a true PTG. If this was the case, then one would expect to find that higher rationalization (i.e., higher reported psychological well-being) would be found in those patients showing also higher emotional distress (i.e., lower emotional well-being). However, our findings show that better affective scores (i.e., better emotional status, e.g., lower depression) were related to higher levels of well-being in our sample and not the reverse, as a rationalization explanation would imply, showing that this potential alternative explanation is not empirically supported. As Ownsworth and Nash[17] suggest, the continuous life threat associated with some tumoral diseases pushes people to reconsider several aspects of their existence, such as meaning of life and the concept of finiteness and mortality (what they call existential well-being), and patients with tumor with higher existential well-being usually show lower emotional distress levels and better QoL.

External Evaluation from Relatives

The use of an external source of information such as relatives' evaluations, novel for LGG studies, was important in obtaining a reliable picture of patients' psychological well-being, because brain lesions may alter self-perception, thus introducing an additional bias in self-reports of well-being, beyond common social desirability biases and defensive mechanisms.[24,25] It is thus reassuring that patients' self-descriptions were largely confirmed by relatives, with the exceptions of parents' better evaluation of patients' autonomy levels and patients describing more positive changes in their relations than did their relatives.

Limitations and Conclusions

The first limitation of the present study is that it was not possible to involve patients who, for different reasons, dropped out from the regular neurosurgical follow-up. Although this factor was not necessarily a sign of poor health or psychological suffering (many patients simply lived far from the center and were followed by services closer to them), it may have harmed the representativeness of the sample. Moreover, patients with an initial diagnosis of LGG who progressed toward an HGG condition were not studied. Consequently, nothing can be said about the cognitive and psychological functioning of these patients who live intense emotional distress that could have led to a different psychological picture. However, illness progression implies adjuvant therapies (particularly radiotherapy), which have a significant cognitive impact on their own and, together with the progression of the illness, often lead to a severe cognitive decline, preventing a proper psychological evaluation.

Furthermore, a complete preoperatory and postoperatory cognitive assessment was not available for some of the patients, because the present study encompassed a long period and the cognitive assessment service underwent many organizational and content changes through the years. However, the comparison of newer and older groups of patients did not highlight major differences (see **Supplementary Material**).

Although the present evidence describes clearly a psychological picture close to the PTG phenomenon, a more direct measurement of the construct would have given a more unequivocal answer to this question. Thus, the use of instruments such as the Posttraumatic Growth Inventory[58] would have been beneficial. This factor will be of importance for future investigations dealing with a similar topic.

However, despite these limitations, we believe that the present findings highlight important aspects of the cognitive and affective functioning and of the psychological experience of patients struggling with a highly stressful and life-threatening diagnosis such as LGG. These findings might be important for neurosurgeons, neuropsychologists, and psycho-oncologists, and they might be useful for improving both their interventions and the relations with patients and their caregivers.

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Conflict of interest statement: F.C. was supported by a postdoctoral research fellowship from A.O.U.S. Maria della Misericordia "Regional basic and clinical research project for the use of High Field Magnetic Resonance Tomograph (3 Tesla)" and F.F. was supported by a grant from Fondazione Cassa di Risparmio di Udine e Pordenone (CRUP).

Accepted 1 April 2017

SUPPLEMENTARY MATERIAL

INCLUSION CRITERIA

A consecutive series of 50 surgically treated patients with low-grade glioma (LGG), operated on at least 1 year previously (average, 3.35 years), participated in the study between May 2013 and June 2014. Only patients showing radiologically stable LGG appearance at the time of evaluation were included (i.e., they had to be in a stable state of their illness). Therefore, patients with an initial diagnosis of (and operated for) LGG and who progressed toward a high-grade glioma (HGG) condition were not included. Patients had to be fluent in Italian and free from treatment for preceding psychiatric conditions. Eighteen patients who either withdrew from the regular follow-up or were followed from home by the unit with regular radiologic follow-up but were too far to visit the center to participate in the study were also excluded. Only 3 of the patients contacted refused to take part in the study.

COGNITIVE STATUS EVALUATION: STANDARDIZATION OF GROUP DATA

For group analysis, scores obtained from each patient in each cognitive task were transformed into z scores, calculated from the mean and standard deviations obtained from normative sample data. These standardization data were available for all but 3 of the tests. For these 3 tests, normative data provided only cutoff scores and it was therefore impossible to calculate z scores, in the absence of mean and standard deviation of the population. These tests were the stars cancellation, line bisection, and letter cancellation from the Behavioural Inattention Test battery,[10] and the data from these tests were therefore not included in the group analysis. However, they were not influential on the overall performance profile, because the performance of the patients was almost invariably at ceiling. Only 1 patient in the stars cancellation and 1 in the letter cancellation scored below the cutoff.

COMPARISON WITH PREOPERATORY/POSTOPERATORY COGNITIVE STATUS

It was not possible to obtain preoperatory data from all 50 patients who participated in the study with a complete preoperatory and postoperatory cognitive assessment, because the present study encompassed a long period, and the cognitive assessment service underwent many organizational and content changes through the years. However, for the patients operated on after autumn 2011 ($n = 21/50$), a complete presurgery–postsurgery evaluation of cognitive functions, comparable with the one used in the present work, was available. Therefore, a series of supplementary analyses were performed to ascertain, as far as possible, whether the data on the cognitive profile from the newer group of patients (21/50) for which preoperatory and postoperatory data were available, might be generalized also to the older group (29/50).

First, preoperatory z scores of the newer group from each of the 6 cognitive domains were compared with those expected from the healthy population, with a series of one-sample t tests, against a mean of 0 (no change) applying Bonferroni correction for multiple comparisons ($P = 0.05/6=0.008$). Results showed that in none of the 6 cognitive domains did patients show a defective performance before surgery (see **Supplementary Table 2**), thus showing that the current cognitive profile of patients is similar to the preoperative profile (apart from the short-term memory domain).

Second, we deemed it important to assess whether the current cognitive status of both the newer and older groups was comparable, to exclude that systematic differences existed between the 2 groups. Therefore, a series of paired samples t tests was performed on the z scores of each of the 6 cognitive domains (see **Supplementary Table 3**), applying Bonferroni correction for multiple comparisons ($P = 0.05/6=0.008$). The results showed that the cognitive profile of the 2 groups was comparable, because they did not differ in any of the 6 cognitive domains.

Supplementary Table 1. List of All Neuropsychological Tests in the Battery of Tests Administered to Participants, with Indication of the Cognitive Function and General Cognitive Domain Evaluated and References Listing the Main Characteristics of Standardization Samples

Cognitive Domain	Cognitive Function	Test
Overall cognitive level	Logical reasoning	Raven Coloured Matrices[1]
Language	Picture naming	Category-Specific Picture Naming[2]
	Verbal comprehension	Token Test[3]
	Verbal fluency	Letter Fluency[1]
	Auditory repetition	Aachen Aphasie Test (AAT): repetition[4]
	Writing	Aachen Aphasie Test (AAT): writing[4]
	Reading	Aachen Aphasie Test (AAT): reading[4]
Attention and executive functions	Sustained and divided attention	Visual Search[3]
	Attentional switching	Trail Making Test[5]
	Executive functions	Frontal Assessment Battery[6]

Continues

Supplementary Table 1. Continued

Cognitive Domain	Cognitive Function	Test
Short-term memory	Verbal short-term memory	Digit Span Forward[7]
	Verbal working memory	Digit Span Backward[7]
	Spatial short-term memory	Corsi Spatial Span[7]
Long-term memory	Verbal long-term memory	Short Story Recall[8]
	Visuospatial long-term memory	Rey-Osterrieth Complex Figure (Delayed recall)[9]
Visuospatial skills	Visuoconstructive skills	Rey-Osterrieth Complex Figure (Immediate copy)[9]
	Spatial attention (neglect)	Behavioural Inattention Test (BIT): stars cancellation[10]
		Behavioural Inattention Test (BIT): line bisection[10]
		Behavioural Inattention Test (BIT): letter cancellation[10]

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   Standardization population for the battery of tests is 340 Italian adults (age ranging between 20 and 89 years) and 134 patients affected by probable Alzheimer Disease.
2. Campanella, F., D'Agostini, S., Skrap, M., and Shallice, T. "Naming manipulable objects: anatomy of a category specific effect in left temporal tumours," Neuropsychologia 48, 1583 (2010).
   The version used is a shortened version with half (n=64) of the stimuli. It maintains the same characteristics and psychometric balancing. Reference scores and cutoffs for the current versions are calculated on a sample of 36 healthy Italian adults (age ranging between 19 and 75 years).
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   Standardization population for the test is 280 Italian adults (age ranging between 20 and 89 years).
10. Wilson, B., Cockburn, J., and Halligan, P. "Development of a behavioral test of visuospatial neglect," Archives of Physical Medicine and Rehabilitation, 68, 98 (1987).
    Standardization population for the test is 14 adults.

All tests are commonly used in Italy in everyday neuropsychological clinical practice and are standardized on large samples of the adult Italian population and have good psychometric characteristics, except tests at references 2 and 10. The picture naming[2] test we used was a shortened version of that published by Campanella et al. in 2010 and reference data are taken from a sample of 36 healthy Italian adults. No standard test for picture naming with good psychometric characteristics is available in Italy. Regarding the Behavioral Inattention Test (BIT),[10] although being standardized on a small sample of 14 patients, it is one of the most commonly used battery of tasks for the detection of unilateral neglect in Italy.

Supplementary Table 2. Extended Version of **Table 2** in the Main Text, Reporting Also *t* Values. One-Sample *t* Tests Comparing the Standardized Scores Obtained by Patients in Each of the Psychological Well-Being Measures Collected with Those of the Reference Population

Task/Domain	Measure	Mean	Standard Deviation	*t* Value*	*P* Value
Cognitive functions†	General cognitive level *z* score	0.103	0.512	$t(49) = 1.404$	0.167
	Language *z* score	**0.319**	**0.418**	**$t(49) = 5.392$**	**<0.001**
	Attention/executive functions *z* score	−0.086	0.436	$t(49) = -1.397$	0.169
	Long-term memory *z* score	−0.033	1.296	$t(49) = -0.180$	0.858
	Short-term memory *z* score	**−0.403**	**0.750**	**$t(49) = -3.799$**	**<0.001**
	Visuospatial skills *z* score	−0.265	1.219	$t(49) = -1.536$	0.131
Positive and Negative Affect Schedule 20‡	Positive affect *z* score	**0.800**	**1.015**	**$t(48) = 5.517$**	**<0.001**
	Negative affect *z* score	**0.708**	**0.877**	**$t(48) = 5.656$**	**<0.001**
State-Trait Anxiety Inventory Form Y‡	State anxiety *z* score	**0.627**	**1.290**	**$t(48) = 3.402$**	**0.001**
	Trait anxiety *z* score	−0.065	1.101	$t(48) = -0.448$	0.656
Beck Depression Inventory II	Percentile score	**61.428**	**25.146**	**$t(48) = 17.100$**	**<0.001**
Satisfaction With Life Scale	Average raw score	25.755	5.739	$t(48) = -0.055$	0.957
Psychological Well Being Scale	Overall *z* score	0.168	0.791	$t(48) = 1.488$	0.143
Subscales†	Autonomy *z* score	−0.055	0.932	$t(48) = -0.411$	0.683
	Environmental mastery *z* score	**0.404**	**1.026**	**$t(48) = 2.757$**	**0.008**
	Personal growth *z* score	−0.014	0.894	$t(48) = -0.114$	0.910
	Positive relation *z* score	0.176	1.040	$t(48) = 1.187$	0.241
	Purpose in life *z* score	0.151	1.019	$t(48) = 1.036$	0.305
	Self-acceptance *z* score	0.348	0.919	$t(48) = 2.652$	0.011
Temperament and Character Inventory	Self-maturity raw score	**67.346**	**10.608**	**$t(48) = 2.209$**	**0.032**
Subscales‡	Self-directedness raw score	**34.653**	**6.990**	**$t(48) = 3.658$**	**<0.001**
	Cooperativeness raw score	32.694	5.269	$t(48) = -0.407$	0.686

Bold values indicate significant differences.

*Degrees of freedom vary in function of the number of participants providing the measure.

†Bonferroni correction: $P = 0.05/6 = 0.008$.

‡Bonferroni correction: $P = 0.05/2 = 0.025$.

Supplementary Table 3. Extended Version of **Table 3** in the Main Text Reporting All Statistical Results. Cognitive Functioning: Analysis of Covariance Results (*P* Values)

	Anatomic Effects			Covariate Effects								
Cognitive Domain	**Hemisphere**	**Lobe**	**Hemisphere × Lobe**	**Preoperatory Volume**	**Extent of Resection (%)**	**Surgery (Awake/ Asleep)**	**Months from Surgery**	**Epileptic Burden**	**Adjuvant Therapy (Yes/No)**	**Sex (Male/ Female)**	**Age**	**Education**
General cognitive level												
F	0.711	0.626	0.447	**7.404**	1.131	0.356	0.003	0.340	0.232	0.422	0.997	**6.429**
P level	0.405	0.541	0.643	**0.010**	0.295	0.555	0.956	0.564	0.633	0.521	0.325	**0.016**
η^2	0.022	0.038	0.027	**0.188**	0.034	0.011	0.000	0.011	0.007	0.013	0.030	**0.167**
Language												
F	1.043	0.695	0.186	1.184	0.664	0.902	1.378	0.011	1.531	0.016	2.649	0.006
P level	0.315	0.506	0.832	0.285	0.421	0.349	0.249	0.919	0.225	0.899	0.113	0.939
η^2	0.031	0.040	0.011	0.035	0.020	0.027	0.040	0.000	0.044	0.000	0.074	0.000
Attention/executive functions												
F	0.001	0.097	1.024	0.322	1.456	0.220	0.141	0.165	**5.298**	0.441	1.751	**9.625**
P level	0.978	0.908	0.370	0.574	0.236	0.642	0.710	0.688	**0.028**	0.511	0.195	**0.004**
η^2	0.000	0.006	0.058	0.010	0.042	0.007	0.004	0.005	**0.138**	0.013	0.050	**0.226**
Short-term memory												
F	0.848	2.528	0.838	0.329	0.241	0.200	0.020	**7.551**	0.063	0.084	0.693	2.962
P level	0.364	0.095	0.442	0.570	0.627	0.658	0.889	**0.010**	0.804	0.774	0.411	0.095
η^2	0.025	0.133	0.048	0.010	0.007	0.006	0.001	**0.186**	0.002	0.003	0.021	0.082
Long-term memory												
F	0.813	**4.165**	1.179	3.200	1.393	2.049	3.913	0.600	0.436	0.270	4.062	1.531
P level	0.374	**0.024**	0.320	0.083	0.246	0.162	0.056	0.444	0.514	0.606	0.052	0.225
η^2	0.024	**0.202**	0.067	0.088	0.041	0.058	0.106	0.018	0.013	0.008	0.110	0.044
Visuospatial skills												
F	0.739	0.007	0.073	0.825	1.540	2.671	0.028	0.399	1.983	3.405	0.906	0.226
P level	0.396	0.993	0.930	0.370	0.223	0.112	0.867	0.532	0.168	0.074	0.348	0.638
η^2	0.022	0.000	0.004	0.024	0.045	0.075	0.001	0.012	0.057	0.094	0.027	0.007

Bold values indicate significant differences.

The table shows the effects of lesion location (by hemisphere, lobe, and the interaction of both) over each of the cognitive domains and also the influence of potential intervening variables (covariates) over anatomic effects. Lesion location effects were limited, and restricted to the long-term memory domain.

Supplementary Table 4. Extended Version of **Table 4** in the Main Text Reporting All Statistical Results: Affective Status and Psychological Well-Being: Analysis of Covariance Results (*P* Values)

	Anatomic Effects			Covariate Effects									
	Hemisphere	Lobe	Hemisphere + Lobe	Preoperatory Volume	Extent of Resection (%)	Surgery Awake/ Asleep	Number of Cognitive Deficits	Adjuvant Therapy (Yes/No)	Epileptic Burden	Months from Surgery	Sex (Male/ Female)	Age	Education
Positive and Negative Affect Schedule 20: positive affect													
F	0.002	1.758	0.273	1.333	1.540	1.672	0.840	0.001	1.964	0.122	0.662	0.023	0.003
P value	0.960	0.189	0.763	0.257	0.224	0.205	0.366	0.972	0.171	0.729	0.422	0.881	0.956
η^2	0.000	0.099	0.017	0.040	0.046	0.050	0.026	0.000	0.058	0.004	0.020	0.001	0.000
Positive and Negative Affect Schedule 20: negative affect													
F	0.561	0.100	0.990	0.526	0.567	1.567	0.018	0.008	**6.549**	0.047	0.300	0.098	0.190
P value	0.459	0.905	0.383	0.473	0.457	0.220	0.895	0.930	**0.015**	0.830	0.588	0.757	0.666
η^2	0.017	0.006	0.058	0.016	0.017	0.047	0.001	0.000	**0.170**	0.001	0.009	0.003	0.006
State-Trait Anxiety Inventory Form Y 1: state anxiety													
F	1.559	2.232	2.489	1.411	**5.476**	0.133	0.059	0.002	0.395	0.644	0.042	0.072	0.602
P value	0.221	0.124	0.099	0.244	**0.026**	0.718	0.810	0.964	0.534	0.428	0.839	0.790	0.444
η^2	0.046	0.122	0.135	0.042	**0.146**	0.004	0.002	0.000	0.012	0.020	0.001	0.002	0.018
State-Trait Anxiety Inventory Form Y 2: trait anxiety													
F	0.173	0.282	1.829	0.193	0.369	0.185	0.060	0.179	2.655	0.092	0.014	0.002	0.099
P value	0.680	0.756	0.177	0.663	0.548	0.670	0.809	0.675	0.113	0.764	0.905	0.961	0.755
η^2	0.005	0.017	0.103	0.006	0.011	0.006	0.002	0.006	0.077	0.003	0.000	0.000	0.003
Beck Depression Inventory II: depression score													
F	0.594	0.478	0.992	1.795	0.644	0.012	0.001	0.066	**7.579**	1.792	1.809	0.078	0.449
P value	0.446	0.625	0.382	0.190	0.428	0.914	0.969	0.799	**0.010**	0.190	0.188	0.781	0.508
η^2	0.018	0.029	0.058	0.053	0.020	0.000	0.000	0.002	**0.191**	0.053	0.054	0.002	0.014
Satisfaction with Life Scale: life satisfaction													
F	0.634	0.750	1.467	0.850	0.045	0.417	0.403	0.610	**3.615**	0.073	0.303	0.021	0.806
P value	0.432	0.480	0.246	0.364	0.833	0.523	0.530	0.441	**0.066**	0.788	0.586	0.886	0.376
η^2	0.019	0.045	0.084	0.026	0.001	0.013	0.012	0.019	**0.102**	0.002	0.009	0.001	0.025

Bold values indicate statistical significance.

The table shows the effects of lesion location (by hemisphere, lobe, and the interaction of both) over each of the affective status as well as psychological well-being measures and also the influence of potential intervening variables (covariates) over the anatomic effects. Lesion location effects absent. The most consistent effect is that of epileptic burden over many psychological and affective measures.

Continues

Supplementary Table 4. Continued

	Anatomic Effects			Covariate Effects									
	Hemisphere	Lobe	Hemisphere + Lobe	Preoperatory Volume	Extent of Resection (%)	Surgery Awake/ Asleep	Number of Cognitive Deficits	Adjuvant Therapy (Yes/No)	Epileptic Burden	Months from Surgery	Sex (Male/ Female)	Age	Education
Psychological Well-Being													
F	2.135	0.722	2.083	0.110	0.241	2.656	0.589	2.258	**4.591**	1.887	2.147	1.742	2.904
P value	0.154	0.494	0.141	0.742	0.627	0.113	0.449	0.143	**0.040**	0.179	0.153	0.196	0.098
η^2	0.063	0.043	0.115	0.003	0.007	0.077	0.018	0.066	**0.125**	0.056	0.063	0.052	0.083
Temperament and Character Inventory: self-maturity													
F	0.155	0.430	0.724	**4.785**	0.139	0.002	0.153	0.051	2.490	0.072	1.224	0.151	1.632
P value	0.697	0.654	0.492	**0.036**	0.712	0.962	0.698	0.822	0.124	0.790	0.277	0.701	0.211
η^2	0.005	0.026	0.043	**0.130**	0.004	0.000	0.005	0.002	0.072	0.002	0.037	0.005	0.049

Bold values indicate statistical significance.

The table shows the effects of lesion location (by hemisphere, lobe, and the interaction of both) over each of the affective status as well as psychological well-being measures and also the influence of potential intervening variables (covariates) over the anatomic effects. Lesion location effects absent. The most consistent effect is that of epileptic burden over many psychological and affective measures.

Supplementary Table 5. One-Sample *t* Tests Comparing the Averaged Standardized Preoperatory Scores Obtained by the Newer Subset of Patients (Operated on in 2011—2015) in Each of the Cognitive Domains Assessed, with Those of the Reference Population

Cognitive Domain	Mean	Standard Deviation	*t* Value*	*P* Value
General cognitive level *z* score	0.326	0.356	*t*(6)= 2.435	0.051
Language *z* score	0.131	0.659	*t*(20)= 0.909	0.374
Attention/executive functions *z* score	−0.060	0.400	*t*(20)= −0.683	0.502
Long-term memory *z* score	−0.379	1.121	*t*(16)= −1.393	0.183
Short-term memory *z* score	−0.078	0.734	*t*(20)= −0.490	0.629
Visuospatial skills *z* score	−0.436	1.128	*t*(15)= −1.546	0.143

*Degrees of freedom vary in function of the number of participants providing the measure. Bonferroni correction: $P = 0.05/6 = 0.008$.

Supplementary Table 6. Paired Samples *t* Test Comparing the Current Cognitive Profile of the Older (before 2011) and Newer (since 2011) Patients, Showing that There Were No Differences Among Them

	Older Group (Before 2011)			Newer Group (After 2011)				
Cognitive Domain	**Mean**	**Standard Deviation**	**n**	**Mean**	**Standard Deviation**	**n**	***T* Value**	***P***
General cognitive level *z* score	0.027	0.579	28	0.204	0.980	21	−1.203	0.235
Language *z* score	0.318	0.308	29	0.320	0.544	21	−0.016	0.987
Attention/executive functions *z* score	−0.123	0.405	29	−0.035	0.482	21	−0.702	0.480
Long-term memory *z* score	−0.008	1.075	29	−0.067	1.579	21	0.157	0.876
Short-term memory *z* score	−0.446	0.757	29	−0.343	0.755	21	−0.474	0.638
Visuospatial skills *z* score	−0.530	1.307	29	0.101	1.004	21	−1.847	0.071

Bonferroni correction: $P = 0.05/6 = 0.008$.

Supplementary Table 7. Complete List of Patients with Specific Anatomic Location of Lesions, Together with the Number of Neuropsychological Deficits Shown in the Cognitive Evaluation and the Volume of the Lesion

Patient	Sex	Age (years)	Education (years)	Hemisphere	Lobe	Number of Neuropsychological Deficit	Anatomic Location	Volume (cc)
LF01	F	39	11	Left	Frontal	1	Left premotor (ventral)	60
LF02	F	22	13	Left	Frontal	0	Left prefrontal (polar)	6
LF03	F	69	16	Left	Frontal	7	Left premotor (paramedian)	30
LF04	M	36	13	Left	Frontal	4	Left premotor (ventral)	82
LF05	M	41	13	Left	Frontal	0	Left premotor (ventral)	14
LF06	M	27	17	Left	Frontal	1	Left premotor (paramedian)	21
LF07	F	53	13	Left	Frontal	3	Left premotor (dorsal)	42
LF08	M	46	17	Left	Frontal	0	Left premotor (ventral)	56
LF09	F	43	15	Left	Frontal	1	Left premotor (ventral)	14
LF10	F	29	13	Left	Frontal	0	Left premotor (ventral)	5
LF11	M	20	14	Left	Frontal	0	Left premotor (ventral)	18
LF12	F	42	17	Left	Frontal	3	Left premotor (paramedian)	28
LF13	F	63	15	Left	Frontal	3	Left premotor (ventral)	76
LF14	F	33	17	Left	Frontal	3	Left premotor (ventral)	42
LP01	M	51	17	Left	Parietal	1	Left posterior parietal dorsal	10
LT01	M	24	17	Left	Temporal	3	Left temporal pole	22
LT02	M	46	13	Left	Temporal	2	Left temporal pole	30
LT03	M	34	17	Left	Temporal	0	Left temporal pole	86
LT04	M	39	13	Left	Temporal	0	Left temporal pole	65
LT05	F	24	16	Left	Temporal	0	Left posterior basal temporal	8
LT06	M	28	9	Left	Temporal	1	Left temporal medial	12
LT07	F	48	11	Left	Temporal	0	Left temporal pole	14
LT08	F	49	13	Left	Temporal	2	Left temporal pole	74
LT09	M	40	16	Left	Temporal	0	Left posterior temporal (Wernicke)	15
LT10	F	43	8	Left	Temporal	8	Left temporal medial	84
RF01	F	50	17	Right	Frontal	0	Right premotor (ventral + dorsal)	128
RF02	M	36	13	Right	Frontal	4	Right motor lateral	66
RF03	F	42	9	Right	Frontal	4	Right prefrontal basal	23
RF04	F	39	8	Right	Frontal	3	Right premotor (paramedian)	45
RF05	F	42	10	Right	Frontal	1	Right premotor (ventral + dorsal)	80
RF06	M	48	17	Right	Frontal	5	Right premotor (ventral + dorsal)	122
RF07	M	32	17	Right	Frontal	1	Right premotor (paramedian)	18
RF08	M	35	17	Right	Frontal	0	Right premotor (dorsal)	8
RF09	F	45	17	Right	Frontal	0	Right premotor (ventral)	69
RF10	M	45	14	Right	Frontal	1	Right premotor (dorsal)	18
RF11	F	19	13	Right	Frontal	1	Right prefrontal (polar)	8
RF12	M	39	14	Right	Frontal	1	Right premotor (dorsal)	16
RF13	F	36	17	Right	Frontal	0	Right prefrontal (polar)	22

Continues

Supplementary Table 7. Continued

Patient	Sex	Age (years)	Education (years)	Hemisphere	Lobe	Number of Neuropsychological Deficit	Anatomic Location	Volume (cc)
RF14	M	49	14	Right	Frontal	2	Right prefrontal basal	98
RF15	F	32	17	Right	Frontal	1	Right prefrontal (ventral + dorsal)	87
RF16	F	57	10	Right	Frontal	2	Right premotor (ventral)	103
RP01	F	37	17	Right	Parietal	2	Right posterior parietal paramedian	6
RP02	F	22	16	Right	Parietal	0	Right postcentral dorsal	14
RP03	M	48	8	Right	Parietal	2	Right posterior parietal paramedian	23
RP04	F	38	17	Right	Parietal	4	Right parietal lateral	65
RT01	M	41	11	Right	Temporal	0	Right temporal pole	78
RT02	M	36	17	Right	Temporal	1	Right posterior temporal	15
RT03	M	41	17	Right	Temporal	0	Right posterior temporal	20
RT04	F	62	10	Right	Temporal	1	Right temporal pole	16
RT05	F	41	17	Right	Temporal	4	Right posterior temporal	36

F, female; M, male.