The Spiritual Brain: Selective Cortical Lesions Modulate Human Self-Transcendence

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SUMMARY

The predisposition of human beings toward spiritual feeling, thinking, and behaviors is measured by a supposedly stable personality trait called self-transcendence. Although a few neuroimaging studies suggest that neural activation of a large fronto-parieto-temporal network may underpin a variety of spiritual experiences, information on the causative link between such a network and spirituality is lacking. Combining pre- and post-neurosurgery personality assessment with advanced brain-lesion mapping techniques, we found that selective damage to left and right inferior posterior parietal regions induced a specific increase of self-transcendence. Therefore, modifications of neural activity in temporoparietal areas may induce unusually fast modulations of a stable personality trait related to transcendental self-referential awareness. These results hint at the active, crucial role of left and right parietal systems in determining self-transcendence and cast new light on the neurobiological bases of altered spiritual and religious attitudes and behaviors in neurological and mental disorders.

INTRODUCTION

Spirituality, i.e., the complex of feelings, thoughts, and behaviors (James, 2008; Paloutzian and Park, 2005; Spilka et al., 2003) that reflect a view of the human condition in transcendent contexts and in relation to unseen realities/supernatural agents, has long been considered impenetrable to empirical investigation. However, recent advances in cognitive and affective neuroscience have started the neuroscientific exploration of the mental processes and the neural underpinnings underlying spiritual experiences. Spirituality is a multidimensional construct reflecting the ultimate concerns of people largely independently from specific faith traditions (Emmons and Paloutzian, 2003). In our study, we focused on an important component of spirituality, namely the tendency to project the self into mental dimensions that transcend perceptual and motor bodily contingencies (Paloutzian and Park, 2005). Changes in the complex self-awareness that accompany the spiritual epiphanies of human beings may range from a detachment from current body perceptions and actions to states of consciousness characterized by weak self-other boundaries and feelings of a strong connection of the self with the universe as a whole (Cahn and Polich, 2006; Lutz et al., 2008a; Newberg and Iversen, 2003; Paloutzian and Park, 2005). Electrophysiological and neuroimaging studies in people of faith such as Catholic nuns or Buddhist monks, expert in different forms of meditation, indicate that these phenomenological and introspective changes parallel neural changes in a cortical network that includes the prefrontal and cingulate cortex, temporal and parietal areas, and subcortical regions (Azari et al., 2001; Beauregard and Paquette, 2006; Brefczynski-Lewis et al., 2007; Cahn and Polich, 2006; Hölzel et al., 2007; Lazar et al., 2000; Lutz et al., 2004, 2008b; Newberg and Iversen, 2003; Newberg et al., 2001; Schjoedt et al., 2009). Studies indicate that spiritual experiences linked to meditation are underpinned by a large brain network. At least two explanations for this seeming lack of specificity can be offered. On the one hand, different aspects of spirituality may be mapped in different neural regions, the activity of which is best highlighted by specific techniques (e.g., neuroimaging versus neurophysiology). On the other hand, different forms of meditation, as well as the degree of the meditators' expertise, influence differentially the complex patterns of activations at play during spiritual experiences (Cahn and Polich, 2006; Lutz et al., 2008a; Newberg and Iversen, 2003; Rubia, 2009).

Crucially, continuing meditation practice may induce changes of cognitive functioning (Brown and Ryan, 2003; Jha et al., 2007) and neural activity (Brefczynski-Lewis et al., 2007; Cahn and Polich, 2006; Hölzel et al., 2007; Lutz et al., 2004, 2008a, 2008b) associated not only to the achievement of spiritual states but also to long-lasting attitudes that accompany expert meditators beyond a given state. Furthermore, differences in cortical thickness have been reported between expert meditators and individuals with no experience in meditation (Hölzel et al., 2008; Lazar et al., 2005), suggesting that the differences in cognitive and emotional styles of expert meditators may correlate with differences in brain anatomy. This pattern of results carries out the important implication that practices able to modify higher-order self-awareness may dynamically shape personality traits (Cahn and Polich, 2006), i.e., the enduring dispositions associated with the consistent patterns of behavior, thoughts, and feelings that make each individual unique. While most of the previous studies are concerned with short-term, spiritual-states-related neural changes (Cahn and Polich, 2006; Lutz et al., 2008a; Newberg and Iversen, 2003), information about the neural underpinnings of stable individual differences in spirituality is meager. Indeed, people differ in their predispositions to spiritual feeling, thinking, and behavior independently of their meditation expertise and state. According to a widely known psychobiological model of personality, interindividual differences in spiritual feeling and thinking are detected by the Temperament and Character Inventory (TCI) (Cloninger et al., 1994; Cloninger, 1994) and cluster into a supposedly stable personality dimension called self-transcendence (ST). ST reflects the enduring tendency to transcend contingent sensorimotor representations and to identify the self as an integral part of the universe as a whole. Twin studies have shown that additive genetic effects influence ST, with a heritability estimate of 0.37 and 0.41 for male and female individuals, respectively (Kirk et al., 1999). Furthermore, molecular neuroscience studies have shown that the ST profiles seem related to the functioning of the serotoninergic system and may be partially determined by genetic variations (Borg et al., 2003; Comings et al., 2000; Ham et al., 2004; Lorenzi et al., 2005; Nilsson et al., 2007). Correlations between ST and metabolic activity (Turner et al., 2003) or gray matter density (Kaasinen et al., 2005) in cortical networks encompassing frontal, temporal, and parietal lobes have been reported in a few systems neuroscience studies. Such correlation approaches, however, cannot establish whether functional and structural brain markers associated to the spiritual feeling and thinking indexed by changes of ST actively determine interindividual differences in cognitive and emotional styles or are epiphenomenal to them.

Here we addressed this fundamental issue by combining the analysis of ST scores obtained before and after surgery in patients undergoing removal of brain glioma, i.e., cancer types affecting the neural brain tissue, with advanced lesion-mapping procedures (Bates et al., 2003; Rorden et al., 2007a). This approach allowed us to explore the possible changes of ST induced by specific brain lesions and the causative role played by frontal and temporoparietal structures in supporting interindividual differences in ST. The design offers an ideal model for exploring the neural foundations of personality because its different dimensions can be measured in the same patient before and soon after surgical ablation of tissue in specific brain regions. Based on the notion that ST is modulated by changes of neural activity in specific cortical areas, we predicted that selective damage to frontal and temporoparietal areas decreased and increased ST, respectively.

RESULTS

We tested 24 patients with high-grade glioma (HgG), 24 patients with low-grade glioma (LgG), 20 patients with recurrent gliomas, and 20 patients with brain meningiomas. The four groups of patients with different types of tumors were analyzed separately to take into account the different neuropsychological consequences of tumors with different histological malignancy and growth rates (Desmurget et al., 2007). Within each patient group, half of the patients had lesions involving the frontotemporal cortex (anterior patients) and the other half had lesions involving the occipitotemporoparietal cortex (posterior patients; Table 1 and Figure 1). The analysis of the patients' age revealed no significant effect of lesion site and damaged hemisphere or interaction for the HgG (all $Fs_{1,20} < 3.18$, $Ps > 0.09$), LgG (all $Fs_{1,20} < 2.24$, $Ps > 0.15$), recurrent glioma (all $Fs_{1,16} < 2.8$, $Ps > 0.11$), or meningioma patients (all $Fs_{1,16} < 1$). In a similar vein, we found nonsignificant main effects or interaction for education in the HgG (all $Fs_{1,20} < 2.42$, $Ps > 0.13$), LgG (all $Fs_{1,20} < 1.34$, $Ps > 0.26$), recurrent glioma (all $Fs_{1,16} < 2.6$, $Ps > 0.13$), or meningioma patients (all $Fs_{1,16} < 1$). The analysis of the interval between the first episode (e.g., seizure) and testing failed to show any main effects or interactions in any of the groups (HgG all $Fs_{1,20} < 1.87$, $Ps > 0.18$; LgG all $Fs_{1,20} < 1$; recurrent glioma all $Fs_{1,16} < 3.62$, $Ps > 0.07$; meningioma patients all $Fs_{1,16} < 3.1$ $Ps > 0.2$). General cognitive abilities were measured before surgery with the Raven Colored Matrices (Raven, 1954) for all participants except one left and one right posterior recurrent glioma patient. No main effect or interaction reached the significance threshold for the HgG (all $Fs_{1,20} < 4.23$, $Ps > 0.05$), LgG (all $Fs_{1,20} < 1.57$, $Ps > 0.22$), recurrent glioma (all $Fs_{1,14} < 3.21$, $Ps > 0.09$), and meningioma patients (all $Fs_{1,16} < 1.11$, $Ps > 0.3$). The absence of any significant difference between the demographical and clinical variables in the different subgroups was also confirmed by an overall analysis collapsing across the histological types of tumors (age: all $Fs_{1,84} < 1.29$, $Ps > 0.25$; education: all $Fs_{1,84} < 1.15$, $Ps > 0.28$; illness duration: all $Fs_{1,84} < 1$; and general cognitive abilities: all $Fs_{1,82} < 1.39$, $Ps > 0.24$).

Modulation of ST after Brain Surgery

Comparing the ST T scores obtained before and after surgery in HgG patients revealed a site-specific modification of ST after surgery (interaction between lesion site and time: $F_{1,20} = 8.73$, $p = 0.008$; Figure 2A). Indeed, ST of posterior patients was significantly higher after surgery (60.74) than before (55.75; $p = 0.009$; Cohen's $d = 0.499$). By contrast, a nonsignificant reduction of ST after surgery was observed in anterior patients (before: 50.21; after: 47.98; $p = 0.211$; Cohen's $d = -0.223$). Posterior patients had higher ST scores than anterior patients both before ($p = 0.005$; Cohen's $d = 0.554$) and after surgery ($p < 0.001$; Cohen's $d = 1.276$; main effect of lesion site: $F_{1,20} = 5.79$, $p = 0.026$). No other effect proved to be significant ($F_{1,20} < 1.6$, $p > 0.2$).

A partially similar pattern of results was obtained in the LgG patients (Figure 2B). A significant main effect of time ($F_{1,20} = 10.11$, $p = 0.005$) suggested an ST increase after surgery, which, however, was specific for damage to the posterior cortex (interaction lesion site by time: $F_{1,20} = 4.49$, $p = 0.047$). Indeed, the ST T scores of posterior patients significantly increased after surgery (before, 51.02; after, 57.49; $p = 0.002$; Cohen's $d = 0.647$). In contrast, no modification was observed for anterior patients (before, 50.57; after, 51.86; $p = 0.487$; Cohen's $d = 0.129$). Unlike the HgG patients, no difference was observed between anterior and posterior LgG patients before surgery ($p = 0.797$; Cohen's

Table 1. Composition of the Patient Groups and Their Demographic and Clinical Information (Mean ± SD)

Group	N	Gender (N Females)	Age (Years)	Education (Years)	Duration of Illness (Months)	Lesion Volume (cc)	Raven Colored Matrices (/36)
High-Grade Gliomas							
Left anterior	6	2	40.2 ± 12.6	14 ± 4.8	4.3 ± 6.3	61.6 ± 71.1	29.8 ± 4.0
Left posterior	6	3	55.8 ± 4.2	10.3 ± 2.9	13.7 ± 9.1	73.9 ± 124.4	24.8 ± 5.6
Right anterior	6	2	47.5 ± 14.9	11.8 ± 3.2	7 ± 7.5	47.8 ± 55.5	26.0 ± 3.5
Right posterior	6	3	50.8 ± 16.8	10.3 ± 5	10.3 ± 18.6	52.6 ± 18.8	23.5 ± 4.4
Low-Grade Gliomas							
Left anterior	6	5	49.5 ± 10.9	10.7 ± 6	6.5 ± 7.5	55.7 ± 31.8	27.2 ± 5.5
Left posterior	6	1	41.5 ± 9.1	11.7 ± 3.1	7.7 ± 10.7	49.5 ± 36.8	30.0 ± 3.3
Right anterior	6	2	40.8 ± 10.5	14.3 ± 5.1	6.1 ± 4	74.7 ± 79.3	28.8 ± 6.9
Right posterior	6	1	44.8 ± 8.7	12.3 ± 3.7	3.5 ± 4.2	33.1 ± 28.1	26.2 ± 5.3
Recurrent Gliomas							
Left anterior	5	3	43 ± 10.3	10 ± 3.5	23.8 ± 21.4	67.8 ± 54	24.8 ± 7.2
Left posterior	5	0	51.2 ± 9	12.2 ± 4.8	6 ± 5.5	102.4 ± 79	28.5 ± 7.3
Right anterior	5	1	42.2 ± 12.4	12.8 ± 1.6	22.4 ± 12.4	63.7 ± 50.6	30.8 ± .8
Right posterior	5	2	48.2 ± 4.7	9.4 ± 4.9	14.4 ± 7.4	68.8 ± 48.7	25.0 ± 4.8
Meningiomas							
Left anterior	5	4	52.6 ± 6.8	10.4 ± 2.8	18.6 ± 18	30.6 ± 17.8	28.8 ± 3.0
Left posterior	5	4	49.4 ± 19.2	9.6 ± 3.9	5.4 ± 3.2	54.1 ± 57.4	28.2 ± 6.0
Right anterior	5	4	52.8 ± 13.3	10 ± 5.2	4.2 ± 1.9	64.1 ± 56.2	25.4 ± 5.6
Right posterior	5	4	49.2 ± 15.6	10.8 ± 6.7	5.2 ± 0.8	39.1 ± 25.7	26.0 ± 8.0

Data are reported according to the histological nature of the tumor, the damaged hemisphere, and the lesion site. Note that the duration of illness refers to the time interval between testing and the first clinical manifestation (e.g., epileptic seizures).

d = 0.045). By contrast, ST after surgery was higher in posterior than in anterior patients (p = 0.004; Cohen's d = 0.563). No other effect proved to be significant ($F_{1,20} < 2.1$, $p > 0.16$). Thus, the removal of HgG and LgG affecting posterior brain areas induced a selective increase of ST independently from the affected hemisphere. While the HgG patients had higher ST scores even before surgery, the LgG patients presented an increase of ST solely after surgical removal of neural brain tissue. The influence of

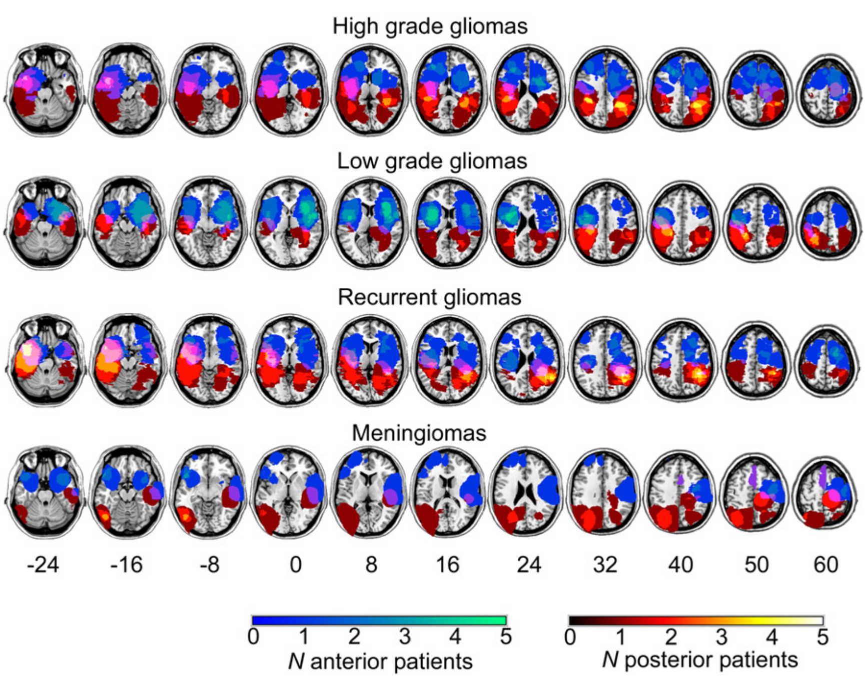

Figure 1. Overlap of the Patients' Lesions
The preoperative patient anatomical MRI scans and the lesion drawings were normalized to the Montreal Neurological Institute (MNI) template by using cost function masking procedures. The number of overlapping lesions in the anterior damage and posterior damage subgroup is illustrated by different colors that code for increasing frequencies.

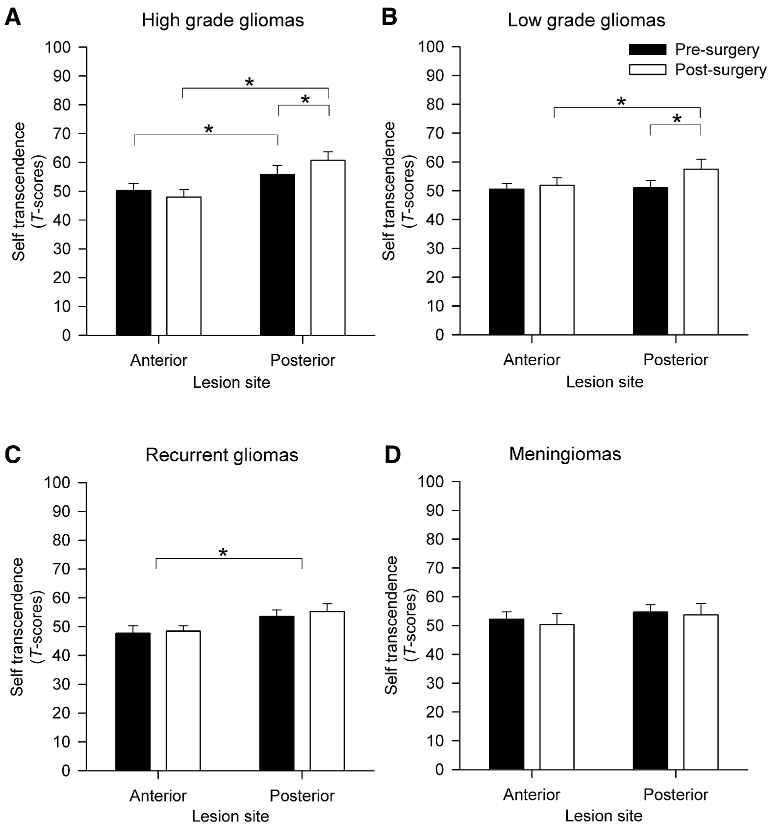

Figure 2. Self Transcendence Scores of Patients before and after Surgery

Mean (±SEM) ST T scores obtained by patients soon before (range 1–7 days) and soon after (range 3–7 days) the operation are reported according to the lesion site (anterior, posterior). Patients with posterior (A) high-grade gliomas (HgG) and (B) low-grade gliomas (LgG) presented a significant ST increase after surgery. (C) Posterior recurrent glioma patients had higher ST scores as compared with anterior patients both before and after surgery. (D) No difference was observed in meningioma patients. *p < 0.05. See also Tables S1–S3.

histological malignancy and growth rate of the tumors (Desmurget et al., 2007) on the ST modulation further corroborates the specificity of the anatomo-clinical relationship between damage to posterior areas of the brain and the ST increase.

Importantly, the fast effect of cortical ablations on ST change was long lasting as indicated by the TCI scores obtained in a different group of 20 patients (16 HgG and 4 LgG patients) who had been operated on the first time 2–48 months before testing. Analysis of ST scores soon before and soon after the second intervention for removal of recurrent gliomas (Figure 2C) showed only a significant main effect of lesion site ($F_{1,16} = 4.51$, $p = 0.049$). This effect was due to higher ST T scores in posterior patients (54.42) than anterior patients (48.05; Cohen's d = 0.592) both before and after the second surgery. No other effect was significant ($F_{1,16} < 2.2$, $p > 0.15$).

To rule out any nonspecific effect of craniotomy on the ST modulation observed in patients with gliomas, TCI was delivered, again before and after surgery, to 20 patients with meningiomas. This type of tumor does not imply removal of neural brain tissue, and therefore no effect of surgery was expected in these patients. Indeed, comparing ST scores in patients with meningioma involving the anterior or posterior areas (Figure 2D) revealed no significant effect (all $Fs_{1,16} < 1$).

Lesion-Mapping Analysis

To determine the lesion correlates of ST modulation, we entered the difference between ST T scores obtained before and after surgery in the 48 HgG and LgG patients as predictors in a Voxel-based Lesion-symptom Mapping (VLSM) analysis (Bates et al., 2003; Rorden et al., 2007a). The t test statistic analysis, with permutation thresholding, was used to compare ST changes in relation to lesioned and nonlesioned voxels (Bates et al., 2003; Rorden et al., 2007a). The regions associated with ST increase along with the coordinates of the center of mass based on the Montreal Neurological Institute (MNI) probabilistic brain atlas, are shown in Figure 3. We found two clusters of voxels located in the left inferior parietal lobe (L-IPL; BA 40; Figure 3A) and in the right angular gyrus (R-AG; BA 40; Figure 3B) whose damage was associated with a significant ST increase. To further investigate the effects of lesions of these bilateral parietal clusters, we entered the difference between the ST T scores obtained before and after surgery by the left and right hemisphere patients into two separate analyses of covariance (ANCOVAs), with lesion group (lesion or intact patients) as between-subjects variable and education and lesion volume as covariates of interest. The analysis on the left hemisphere patients revealed nonsignificant effects of education and lesion volume (all $Fs_{1,20} < 1$), while the effect of having or not having a lesion involving the L-IPL cluster was still significant ($F_{1,20} = 19.57$, $p < 0.001$) after controlling for the main effect of the covariates. In a similar vein, the analysis on right hemisphere patients revealed a significant effect of lesion group ($F_{1,20} = 11.27$, $p = 0.003$), but nonsignificant effects of the covariates (all $Fs_{1,20} < 1$). Thus, we show a specific causative relationship between lesions of the left and right posterior parietal cortex and ST changes.

Results of the Formal Interview with Patients

To investigate how ST was correlated with religion-related behavior and experiences in daily life, we recorded the patients' reports during the formal interview conducted at the time of the first evaluation (Table 2). The interview focused on three main aspects: (1) the patients' evaluation of their religiosity, including questions on whether or not they did pray or attend church services regularly; (2) the patients' report of mystic experiences, including peak experiences, extrasensorial perceptions, or experiencing the presence of God; (3) the patients' acceptance of their illness. The interview focused on daily life experiences and was conducted only at the time of the first evaluation before surgery. Analyzing together the four groups of patients revealed

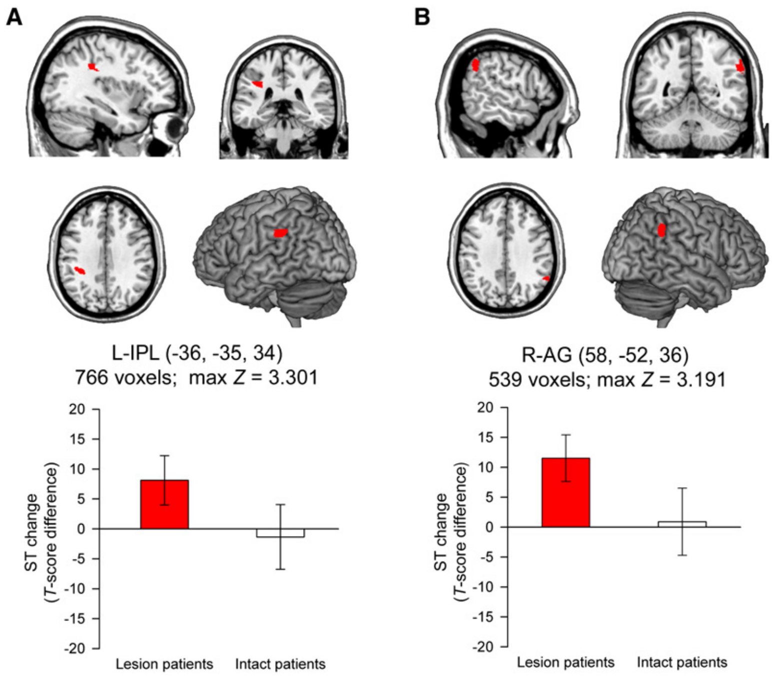

Figure 3. Lesion Correlates of Increased and Decreased Self Transcendence

Clusters selectively associated with an increase of ST scores after surgery were overlaid on the Montreal Neurological Institute (MNI) template. We found two clusters of voxels located in the left inferior parietal lobe (L-IPL; A) and in the right angular gyrus (R-AG; B) whose damage was associated with a significant ST increase. The MNI coordinates (x, y, z) of the center of mass, the maximum t test Z statistic obtained in each cluster, and the number (N) of clustering voxels that survived the significance threshold of $p < 0.05$ (permutation thresholding corrected) are reported for each cluster. The ST post-pre surgery differences (T scores, mean ± SEM) in patients with and without lesions to the left and right parietal clusters are plotted in the left and right lower panel, respectively.

that a greater number of patients with posterior than anterior lesions judged themselves as being religious persons. The 59 patients who judged themselves as religious also showed higher ST T scores before surgery (53.82 ± 7.94 versus 48.13 ± 8.27; $t_{86} = 3.12$, $p = 0.002$), suggesting that self-judgments of religiosity and ST measures are strongly associated (Kirk et al., 1999). On the other hand, no difference was obtained between anterior and posterior patients in the number of patients reporting mystic experiences or illness acceptance. Nevertheless, the 19 patients reporting mystical experiences had higher ST scores than the remaining patients (56.2 ± 7.13 versus 47.62 ± 8.44; $t_{86} = 2.56$, $p = 0.012$), while no ST modulation of illness acceptance was observed (52.97 ± 7.94 versus 50.87 ± 8.9; $t_{86} = 1.517$, $p = 0.245$).

Considering separately the four groups of patients with different types of brain tumors (Table 2), we found an increased probability of religiosity self-judgments among posterior HgG and recurrent glioma patients, who presented also higher ST scores before surgery as compared to anterior patients. Furthermore, the posterior recurrent glioma patients, who underwent surgery several months before, also reported mystic experiences more frequently than the anterior patients. These consisted mostly in experiencing the presence of God or visions during prayer, while one patient reported a single-event feeling of a presence. No patient reported frank out-of-body experiences, although some patients reported undefined illusory bodily sensations before the occurrence of epileptic seizures. Recurrent glioma patients with posterior lesions and high ST scores seemed to accept their illness better. In contrast, anterior patients with low ST scores seemed to be in despair about their situation and could hardly be comforted. The different attitude of high versus low ST patients was independent of their awareness of illness. In the formal interview with the patients, we did not include any question directly concerning their brain tumor, in order to avoid providing inappropriate information. However, written records of the spontaneous reports of each patient provided the following information: all but three HgG (one with right anterior, one with left anterior, and one with right posterior lesion) and three LgG patients (one with left anterior and two with right posterior lesion) explicitly referred to their illness as a brain tumor. We had been asked by the relatives of the other six patients not to provide any detail concerning the disease, to avoid unwanted emotional reactions. Also for these patients, however, we noticed during testing that they seemed to know the nature of their disease but preferred not to talk explicitly about it.

Analysis of the Other TCI Scales

The extended analysis of all the TCI scales (see Supplemental Information and Table S2) revealed no specific change of personality dimensions other than ST after surgical removal of tumors affecting the anterior or posterior brain areas. Among the temperament scales, we found a significant association, which was present both before and after surgery, between right posterior lesions and increased novelty seeking (NS) scores in the HgG and recurrent glioma patient groups. Furthermore, anterior HgG patients had higher harm avoidance (HA) scores than posterior patients, an effect which was not found, however, in the LgG or recurrent glioma patients. Among the character dimensions other than ST, only self-directedness (SD) was consistently higher in the right hemisphere than in the left hemisphere patients, mainly when lesions involved posterior areas. Such effects, however, were not modulated by glioma surgery, thus ruling out the hypothesis that the ST increase found in posterior patients of the present study was epiphenomenal to other personality changes.

Neuropsychological Functions

Cognitive abilities were measured with a series of neuropsychological tests administered before surgery (for all patient groups) and also after surgery for HgG and LgG patients (Tables 3 and 4; see Supplemental Information for extensive description of these results). No effect of surgery and no modulation according to the lesion site was obtained for the patients' cognitive

Table 2. Results of the Formal Interview with Patients before Surgery

	N Posterior Patients	N Anterior Patients	χ^2 Analysis
All Patient Groups (N = 88)			
Religiosity	35/44	24/44	χ^2 = 6.22, p = 0.013
Mystic experiences	12/44	7/44	χ^2 = 1.68, p = 0.195
Illness acceptance	25/44	20/44	χ^2 = 1.14, p = 0.286
High-Grade Gliomas (N = 24)			
Religiosity	12/12	3/12	χ^2 = 14.4, p < 0.001
Mystic experiences	2/12	2/12	χ^2 = 0, p = 1
Illness acceptance	6/12	7/12	χ^2 = 0.168, p = 0.682
Low-Grade Gliomas (N = 24)			
Religiosity	7/12	9/12	χ^2 = 0.75, p = 0.386
Mystic experiences	2/12	3/12	χ^2 = 0.25, p = 0.615
Illness acceptance	7/12	8/12	χ^2 = 0.18, p = 0.673
Recurrent Gliomas (N = 20)			
Religiosity	9/10	5/10	χ^2 = 3.81, p = 0.05
Mystic experiences	5/10	0/10	χ^2 = 6.67, p = 0.01
Illness acceptance	8/10	3/10	χ^2 = 5.05, p = 0.025
Meningiomas (N = 20)			
Religiosity	7/10	7/10	χ^2 = 0, p = 1
Mystic experiences	3/10	2/10	χ^2 = 0.267, p = 0.606
Illness acceptance	4/10	2/10	χ^2 = 0.952, p = 0.329

The number of patients with anterior and posterior lesions reporting to be religious persons, to have had mystic experiences, and to accept with acquiescence their illness were compared in the whole sample as well as in each lesion type group.

general abilities measured with the Mini Mental State Examination (MMSE) (Folstein et al., 1975; Measso et al., 1993), suggesting that the differential reduction of general cognitive abilities in the four subgroups of patients cannot explain the ST changes after surgery. On the other hand, although patients with language comprehension disorders were not included in the research, patients with left hemisphere damage had lower token (Spinnler and Tognoni, 1987) and naming test (Riddoch and Humphreys, 1993) scores than patients with right hemisphere damage. Such subclinical deficits of the language comprehension and production abilities of the left hemisphere patients, however, cannot explain the selective ST changes, which occurred after the removal of posterior lesions in both the left and the right hemisphere. Furthermore, naming deficits are not likely to affect ST scores, because evaluation of personality dimensions does not require any type of verbal production, except for the true/false or yes/no response when the items of the TCI are presented orally by the experimenter. Moreover, any purported linguistic difficulty is likely to be identical for the different temperament and character scales. Nonsignificant effects of surgery, lesion site, damaged hemisphere, and interactions were found in the verbal (digit span) (Orsini et al., 1987) and visuospatial (Corsi test) (Spinnler and Tognoni, 1987) immediate memory abilities of the four patient groups. In a similar vein, no effect was found for the visual attention (attentional matrices) (Spinnler and Tognoni, 1987) and executive functions abilities (trail-making test) (Giovagnoli et al., 1996). On the other hand, right posterior HgG and recurrent glioma and right meningioma patients exhibited impaired constructional abilities as measured with a drawing on copy test (constructional apraxia) (Spinnler and Tognoni, 1987). Thus, the marginal effects of the site and side of the lesion on cognitive functions were in keeping with the relative roles of the left and right hemispheres in verbal or visuospatial functions, but no neuropsychological deficit was specifically associated to the ST increase in posterior glioma patients. In a similar vein, nonsignificant differences were obtained between the percent score changes of patients with or without a lesion involving the L-IPL (for all neuropsychological tests, $-1.13 <$ all $ts_{22} < 1.89$, $p > 0.073$) and the R-AG clusters (for all neuropsychological tests, $-0.79 <$ all $ts_{22} < 0.75$, $p > 0.443$) associated to increased ST after surgery.

DISCUSSION

The present study was aimed at investigating the active role played by anterior and posterior brain lesions in determining interindividual differences in spiritual feeling and thinking. We explored any possible modulation of ST after brain damage by assessing ST in patients undergoing removal of brain tumors affecting the anterior, frontotemporal cortex or the posterior, occipitotemporoparietal cortex. We found that removal of HgG and LgG affecting the posterior areas of the brain induced a specific, significant, and reliable increase of ST (higher than 0.5 SD). These changes were observed soon after cortical ablation, thus hinting at a specific role of the involved structures rather than at a slow adaptation process. Although we could not perform long-term follow-up tests of patients with HgG and LgG, the analysis of recurrent glioma patients who had previously undergone operations several months before testing may suggest that the fast changes of ST induced by posterior cortical ablation were long lasting. Indeed, posterior recurrent glioma patients presented increased ST scores with respect to anterior patients both before and after the second operation. No ST modulation was observed after removal of meningiomas that spare the nervous tissue, thus ruling out any nonspecific effect of craniotomy per se. Furthermore, the different effect of anterior and posterior lesions rules out the possibility that the ST increase may be ascribed to nonspecific changes of self-conceptions and life perspectives in reaction to the presence of a brain tumor. In a similar vein, the ST changes are not likely due to mood change induced by brain lesions. Indeed, while several studies (Cloninger et al., 2006; Farmer et al., 2003; Halvorsen et al., 2009) have shown that high harm avoidance (HA) and low self-directedness (SD) scores are associated with depression, no specific HA increase or SD decrease was consistently associated with posterior versus anterior lesions in our patient groups (see Supplemental Information and Table S2).

The changes of ST after surgery in HgG and LgG patients involved equally the three subscales of which ST is made, namely creative self-forgetfulness, transpersonal identification, and spiritual acceptance (see Supplemental Information and Table S1). The three ST subscales describe different aspects of transcendental self-awareness, namely subjective experience

Table 3. Results (Mean ± SD) of the Neuropsychological Tests Conducted before (pre) and after (post) Surgery on Patients with High- and Low-Grade Gliomas

Group	Time	MMSE (/30)	Token (/36)	Naming (/40)	Digit Span	Corsi Span	CA (/14)	AM (/60)	Trail B-A (s)
High-Grade Glioma									
Left anterior	Pre	27.3 ± 1.2	31.1 ± 2.3	39.5* ± 0.8	4.7 ± 0.8	4.3 ± 1.5	12.7 ± 0.5	47 ± 3.6	86.8 ± 17.4
	Post	26.7 ± 1.7	30.4* ± 2.7	32.8* ± 16.1	5.5 ± 1.2	4 ± 1.6	12.7 ± 0.5	47.9 ± 6.1	107.3 ± 62.9
Left posterior	Pre	26.7 ± 2.4	30.5 ± 3	30.8* ± 10.8	4.2 ± 1.5	4.3 ± 0.5	13.1 ± 0.3	46.9 ± 2.3	88 ± 75.3
	Post	25.8 ± 2.5	30.3* ± 2.9	28.2* ± 13.1	4.2 ± 1.5	4.2 ± 0.5	13.1 ± 0.3	46.8 ± 1.9	90.5 ± 74.9
Right anterior	Pre	25.4 ± 0.7	32.1 ± 2.5	39.2 ± 1	4.7 ± 0.9	3.9 ± 1.2	12.6 ± 2	44 ± 9.7	118.3 ± 143
	Post	25.6 ± 1.4	32.5 ± 2.4	39.3 ± 1	4.5 ± 0.8	3.6 ± 1.2	12.6 ± 2	36.2 ± 19.8	115.3 ± 145.2
Right posterior	Pre	26.2 ± 1.5	31.7 ± 1.4	39 ± 1.7	4.1 ± 0.5	3.6 ± 0.3	10* ± 2.6	44.4 ± 3.6	101.2 ± 137.2
	Post	25.5 ± 1.1	32.5 ± 1.4	38.7 ± 2	4.1 ± 0.5	3.3 ± 0.8	11* ± 2.1	44.4 ± 3.9	85 ± 143.6
Low-Grade Glioma									
Left anterior	Pre	28.1 ± 1.7	32.8 ± 2.4	37.7 ± 4.3	4.5 ± 1.2	4 ± 0.9	12.5 ± 1.2	47.6 ± 4.8	38 ± 44.8
	Post	27.1 ± 2.4	31.8 ± 3.3	33.7 ± 9.6	4.4 ± 1	4 ± 0.9	12.5 ± 1.2	44.8 ± 10	78 ± 89.7
Left posterior	Pre	26.3 ± 1.7	28.9* ± 2.7	39.8 ± 0.4	4 ± 1	4.4 ± 0.8	12.6 ± 0.4	46.2 ± 3	69.2 ± 32.2
	Post	25.8 ± 1.9	29.3* ± 2.8	33.3 ± 15.8	3.3 ± 1.5	3.9 ± 1.3	11.6 ± 2.6	46.2 ± 3.2	68.2 ± 31
Right anterior	Pre	27.1 ± 2.5	31.5 ± 2.4	38.5 ± 1.8	4.2 ± 1.3	4 ± 0.7	11.4 ± 1.9	46.5 ± 3.3	94.8 ± 135.2
	Post	26.6 ± 2.2	31.5 ± 3	39 ± 0.9	4.7 ± 1.6	3.5 ± 0.7	11.4 ± 1.3	46 ± 1.8	100.8 ± 70.1
Right posterior	Pre	27.4 ± 1.9	33 ± 1.3	39 ± 1.1	5.3 ± 1.6	4 ± 0.8	12 ± 2.2	43.6 ± 6.1	96.7 ± 100.4
	Post	27.6 ± 2.1	33.8 ± 0.9	39.3 ± 1	5.3 ± 1.6	4 ± 0.4	11.7 ± 2.3	42 ± 10.5	88.8 ± 105.6

MMSE, Mini Mental State Examination; CA Constructional Apraxia; AM, Attentional Matrices test. Scores from subgroups showing significant reduction of performance as compared to the other subgroups are highlighted with an asterisk (see also Supplemental Information).

of spatiotemporal dimensions, individual worldview, and acceptance of spiritual phenomena. However, these subscales tend to be associated, and individuals with high scores on a subscale tend to have high scores on the other two. The present finding that the association between damage to the posterior areas of the left and right hemispheres and ST increase involved all the three ST subscales may provide neurobiological support to the factorial structure of the ST scale in the TCI model (Cloninger et al., 1994).

The lack of specific short-term changes of the other TCI scales according to the lesion site may be explained by the fact that the interindividual differences in the activation, maintenance, and inhibition of response behavior tapped by the temperament scales may reflect activity of large cortical and subcortical neural systems (Cohen et al., 2009; Gusnard et al., 2003; Kaasinen et al., 2005) rather than of specific cortical regions. The lack of changes in the other character scales may be due to the fact that ST items tap online evaluation of self-referential awareness. In contrast, the other scales may rely more on the memory of how the individual behaved in previous life events. Therefore, the ST may be more amenable to changes after brain damage than other personality traits, as suggested by the evidence of an association between ST and brain modifications in elderly people (Turner et al., 2003).

Table 4. Results (Mean ± SD) of the Neuropsychological Tests Conducted before Surgery on Patients with Recurrent High-Grade Gliomas and with Meningiomas

Group	MMSE (/30)	Token (/36)	Naming (/40)	Digit Span	Corsi Span	CA (/14)	AM (/60)	Trail B-A (s)
Recurrent Gliomas								
Left anterior	27.6 ± 1.8	31.1* ± 2	38.2 ± 3	4.6 ± 0.9	4.7 ± 1.2	12.3 ± 0.6	43.3 ± 3.8	104 ± 116.4
Left posterior	26.4 ± 1.6	29.3* ± 2.9	30.4* ± 5.9	4.5 ± 1	4.2 ± 0.5	12.1* ± 0.9	44.6 ± 6.6	97.2 ± 52.7
Right anterior	26.1 ± 1.9	33.4 ± 0.7	40 ± 0	4.2 ± 0.9	3.4 ± 0.5	12.3 ± 0.9	46.4 ± 2.2	86.8 ± 34.8
Right posterior	26.6 ± 1.7	33.3 ± 1.2	36* ± 7.9	5 ± 1.4	4.3 ± 0.6	10.2* ± 2.2	47.8 ± 2.4	129 ± 150.1
Meningiomas								
Left anterior	28.4 ± 1.7	33.3 ± 1	39.8 ± 0.4	4.4 ± 0.5	4.3 ± 0.6	13 ± 0.4	48.6 ± 7.6	32.8 ± 33.8
Left posterior	25.4 ± 2.3	30.8 ± 3.7	36* ± 2.8	5.2 ± 1.1	4.3 ± 1	12.8 ± 0.8	44.3 ± 10.1	119.4 ± 72.9
Right anterior	28.1 ± 2	33.3 ± 2.6	39 ± 2.2	5.4 ± 1.5	4.1 ± 0.5	11.5* ± 1.8	45.5 ± 7.8	59 ± 33.1
Right posterior	27.2 ± 2.7	32.3 ± 3	39.6 ± 0.9	5 ± 1.1	3.5 ± 0.7	11.2* ± 1.3	42.8 ± 8.5	66.2 ± 55

MMSE, Mini Mental State Examination; CA. Constructional Apraxia; AM, Attentional Matrices test. Scores from subgroups showing significant reduction of performance as compared to the other subgroups are highlighted with an asterisk (see also Supplemental Information).

The results of the present study expand the correlational evidence in healthy subjects that meditation (Cahn and Polich, 2006) and ST profiles (Kaasinen et al., 2005; Turner et al., 2003) may be associated with neural activity in frontoparietal areas. Evidence for changes in religious beliefs and behaviors has been reported in patients with frontotemporal dementia or temporal-lobe epilepsy (Devinsky and Lai, 2008; Miller et al., 2001). However, although very interesting, these studies were mainly anecdotic, were conducted on small groups of patients, and did not provide any direct information about the prelesional personality profiles of the patients. Furthermore, changes in religious beliefs, like conceptions on the existence of God, and behaviors, like participation in institutional religious activities, were not disentangled from the subjective spiritual feelings and thinking that allow projecting the self into a transcendental dimension. However, religious beliefs and spirituality are at least partially independent phenomena, as documented by people that report to be ''spiritual'' but not ''religious'' (Paloutzian and Park, 2005; Shahabi et al., 2002). Interestingly, a recent functional neuroimaging study (Kapogiannis et al., 2009) has shown that religious beliefs correlate with neural activity of the frontotemporal networks that are also associated to the embodied and conceptual representations of others' behaviors and emotions. In a similar vein, having confident religious beliefs was associated with changes in the neural activation of dorsal and ventromedial prefrontal cortex during self-referential processing (Han et al., 2008). In particular, neural activity of ventromedial prefrontal cortex in Christian participants did not differentiate between self and other-related judgments of personality traits (Han et al., 2008). Furthermore, people of faith as compared to nonbelievers showed less activation of the anterior cingulate cortex, a region implicated in monitoring self-performances (Inzlicht et al., 2009). Thus, previous studies have suggested that religious beliefs may be associated with altered self-representations.

Our study significantly expands current knowledge by revealing the neural basis of the cognitive and emotional styles that characterize the spirituality of each individual. Our results indicate that damage to the left and right posterior parietal cortex may increase ST. This figure suggests that the extended self-referential awareness, which characterizes high ST individuals, is supported by a lower activity of the left and right posterior-parietal cortex. It is worth noting that, although different techniques and patient samples may disclose the role of different brain regions in mapping various aspects of spirituality (e.g., the medial prefrontal cortex) (Cahn and Polich, 2006; Lutz et al., 2008a; Newberg and Iversen, 2003), our VLSM procedure highlighted the crucial role played by the posterior parietal cortex in determining ST profiles. It is relevant that the posterior parietal cortex is involved in the representation of different aspects of bodily knowledge (Berlucchi and Aglioti, 1997; Schwoebel and Coslett, 2005). Lesions of the left posterior parietal cortex induce selective deficits in the representation of the spatial relationships between body segments (Felician and Romaiguère, 2008). Disownership (Aglioti et al., 1996) and delusions regarding body parts (Halligan et al., 1995) occur after lesions centered on the right temporoparietal cortex. Furthermore, illusory localization of the self into the extrapersonal space has been reported in patients with left (heautoscopic phenomena) (Blanke et al., 2004; Brugger et al., 2006) and right temporoparietal damage (out-of-body experiences) (Blanke et al., 2004). Thus, we posit that the reduction of neural activity in the temporoparietal cortex during spiritual experiences may reflect an altered sense of one's own body in space (Cahn and Polich, 2006; Newberg and Iversen, 2003). Indeed, focusing attention toward one's own inner world requires transcendence from current body perceptions and actions and the ability to project self-image into past or future scenarios (Morin, 2006). Our results suggest that interindividual differences in spirituality may reflect differences in the ability to transcend the spatiotemporal constraints of the physical body (Fuller, 2008; Newberg and Iversen, 2003).

In conclusion, our symptom-lesion mapping study demonstrates a causative link between brain functioning and ST. In particular, the study shows that damage to posterior parietal areas may induce unusually fast changes of a stable personality dimension related to transcendental self-referential awareness. Thus, dysfunctional parietal neural activity may underpin altered spiritual and religious attitudes and behaviors. It is relevant that ST profiles seem to be influenced by genetic variations (Borg et al., 2003; Kirk et al., 1999; Lorenzi et al., 2005) and are altered in patients with schizophrenia (Boeker et al., 2006) and personality disorders (Svrakic et al., 2002). Thus, exploring the effects of brain lesions on complex personality dimensions, like ST, may cast light on the interaction of genetic and environmental factors in shaping our spirituality profiles and may help to understand the role of interindividual differences in mental disorders (Davidson, 2003). Finally, that a stable personality trait like ST may undergo fast changes as consequence of brain lesions would indicate that at least some personality dimensions may be modified by influencing neural activity in specific areas. This would carry out the fundamental implication that novel approaches aimed at modulating neural activity, e.g., repetitive transcranial magnetic stimulation, may up- or downregulate brain plasticity and ultimately pave the way to new treatments of personality disorders.

EXPERIMENTAL PROCEDURES

Patients

Patients suffering from HgG, LgG, recurrent gliomas, or meningiomas were recruited for the exclusive purpose of the present study at the Neurosurgery Unit of the University Hospital ''Santa Maria della Misericordia'' (Udine) over a 27 month period. All the participants provided written informed consent, and the procedures were approved by the Ethics Committee of the University of Udine. The study was carried out in accordance with the guidelines of the Declaration of Helsinki. The main inclusion criterion was the presence of tumors involving the prerolandic (anterior subgroup) or the temporoparietaloccipital structures (posterior subgroup). Patients with large anterior and posterior hemispheric lesions and with involvement of subcortical structures were therefore excluded from the study. For the recruitment process, we weekly screened the list of patients planned for surgery at the Neurosurgery Unit, viewed the MRI scans and classified each patient according to the histological nature of the tumor (HgG, LgG, recurrent gliomas, meningiomas) and to the lesion site (left anterior, left posterior, right anterior, right posterior). If the corresponding subgroup had not reached the planned size, we contacted the patient at the time of admission to the hospital for a preliminary neuropsychological evaluation. Patients fulfilling the inclusion-exclusion criteria were then tested for the study. If a patient had to be excluded from the study for the subsequent occurrence of exclusion-criteria conditions, e.g., presence of deep language comprehension disorders after surgery, she/he was discarded and replaced with a similar-characteristic patient until the corresponding subgroup reached the planned size. The sequential recruitment procedure used in the study allowed us to exclude any bias in patient selection. All the patients were native Italian speakers and were right handed. None had a history of psychiatric diseases or previous neurological disorders. All the patients received antiepileptic medication that was maintained constant both before and after surgery. Furthermore, no HgG, LgG, or meningioma patient underwent radiotherapy or chemotherapy for cancer treatment before surgery or at the time of the postsurgery evaluation.

Neuropsychological Screening

Individual scores for the different neurological and neuropsychological tests were corrected for age, sex, and education as appropriate. Patients who presented before or after surgery cognitive deterioration as indexed by the MMSE test (corrected score below 23.8) (Measso et al., 1993) or noncontextual language comprehension deficits at the token test (score below 24.5) (Spinnler and Tognoni, 1987) were not included in the study.

Personality Assessment

The Italian translation of the TCI self-report questionnaire (Italian translation available at https://psychobiology.wustl.edu/research.html) was used. The TCI consists of 240 items (226 scale items and 14 validity items) and covers the four temperament dimensions of NS (40 items), HA (35 items), reward dependence (RD; 24 items), and persistence (P; 8 items) and the three character dimensions of SD (44 items), cooperativeness (C; 42 items), and ST (33 items). The test-retest reliability of the 240 item version of the TCI, as estimated in the US norms (Cloninger et al., 1994), is high for all seven scales (NS, 0.78; HA, 0.87; RD, 0.76; P, 0.65; SD, 0.86; C, 0.89; ST, 0.84). The items were presented preferentially in written form where possible. Three anterior and four posterior HgG patients, one anterior and three posterior LgG patients, four anterior and five posterior recurrent glioma patients, and three anterior and three posterior meningioma patients had difficulty in reading the questions and were presented with the items orally. The same item presentation format was used before and after surgery for all patients. Scores were expressed as T scores relative to the distribution by age and gender of the scores obtained by a group of 320 Italian healthy individuals aged 18–80 years (Table S3). This allowed us to control for any spurious effect of age and gender. Supplementary analysis was conducted also on the individual partial T scores for each of the three ST subscales.

Lesion Drawing

Lesion extent and location was documented by using a 3D T1-weighted MRI scan acquired, after contrast-injection, 1–7 days before surgery. The preoperative MRI scans were used to draw lesions in order to avoid any confusion in analyzing postoperative MRI scans due to the replacement of neural brain tissue that occurs after surgical removal. The surgeon's reports and postoperative CT scans documented complete tumor resection in all patients.

By using the MRIcro software (available at http://www.mricro.com/mricro), each patient lesion was drawn on the T1-weighted MRI scan while also looking at the T2-weighted MRI scan, which allows better identification of the lesion extension. The patient anatomical MRI scans and the lesion drawings were normalized to the Montreal Neurological Institute template by using SPM2 (Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB 7 (Mathworks Inc., Sherborn, MA, USA). Damaged areas were masked to reduce their influence on the normalization process (Brett et al., 2001). Superimposing the patient normalized lesion onto the standard brain allowed us to estimate the total brain lesion volume (in cc). An ANOVA on the HgG patients' lesion volume revealed no significant main effect of lesion site ($F_{1,20} < 1$) or damaged hemisphere ($F_{1,20} < 1$) or their interaction ($F_{1,20} < 1$). In a similar vein, no main effect of lesion site ($F_{1,20} = 1.45$, $p = 0.243$), damaged hemisphere ($F_{1,20} < 1$), or their interaction ($F_{1,20} < 1$) was obtained from the analysis on the LgG patients' lesion volume. We also estimated the lesion volume in the recurrent glioma patients by including both the resection cavity and the recurrent tumor. No significant effect was obtained from the analysis of lesion volume in the recurrent glioma (all $Fs_{1,16} < 1$) and meningioma patients (all $Fs_{1,16} < 1.6$, $Ps > 0.11$).

VLSM Analysis

To determine the neural correlates of ST increase and decrease, we used VLSM methods implemented in MRIcron and nonparametric mapping (NPM, version 2 July 2009) software (Rorden et al., 2007a, 2007b). Normalized lesion drawings were converted into MRIcron format. The differences between ST T scores obtained before and after surgery in the 48 HgG and LgG patients were entered as predictors in two separate VLSM analyses, one for the left and one for the right hemisphere lesion patients. The t test statistic analysis for each voxel of the brain was used (Rorden et al., 2007a) for the voxel-wise comparisons between the ST changes of lesioned and nonlesioned patients. Colored VLSM maps were then produced that represent the z statistics of the voxel-wise comparisons between lesioned and nonlesioned patients. The maps indicate the voxels at which patients with a lesion in a given voxel had a significantly higher ST increase or decrease than patients without a lesion in that voxel. A permutation generated family-wise error threshold at $p < 0.05$ was used to correct for multiple comparisons (Rorden et al., 2007b), and only voxels that survived the above threshold were overlaid to the standard brain. Moreover, only voxels lesioned in more than three patients were tested. We used this criterion to balance between the need to increase the statistical power by testing only voxels that were injured in a significant number of individuals and to detect the effect of regions that are reliable predictors of deficits but were lesioned in just a few patients. The same analysis was also conducted by using the nonparametric permutation-derived BM rank-order statistic (Rorden et al., 2007a, 2007b), which yielded the same results (data are not reported here to avoid any redundancy).

Behavioral Data Analysis

Analyses were performed by means of the Statistica 7 software (StatSoft, Inc., Tulsa, USA). The patients' T scores before and after surgery were entered in different mixed-model ANOVAs with the lesion site (anterior, posterior) and damaged hemisphere (left, right) as between-subjects variables and time (before surgery, after surgery) as within-subjects variable. All post hoc pairwise comparisons were carried out by means of the Duncan test. For each patient, presence and absence of personal religiosity, mystic experiences, and illness acceptance in the formal presurgery interview were scored 1 and 0, respectively. The number of anterior and posterior patients reporting personal religiosity, mystic experiences, and illness acceptance were compared using the χ^2 analysis. The demographic and clinical variables of the different patient groups were entered into separate two-way ANOVAs with lesion site and damaged hemisphere as between-subjects variable.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Text and three tables and can be found with this article online at doi:10.1016/j.neuron.2010.01.026.

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