Intensive Neurofeedback-based Training to Improve Impaired Attention and Executive Functions Secondary to Resection of Tuberculum Sellae Meningioma: A Case Study

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Abstract

Introduction. The present study aimed to evaluate the effectiveness of neurofeedback (NFB) for the treatment of acquired cognitive impairment after brain tumor surgery. **Methods.** The patient was a 49-year-old bilingual African woman who underwent surgical craniotomy after a tuberculum sellae meningioma was diagnosed. Cognitive deficits were evident following post-surgical recovery, and therefore intensive NFB training consisting of 15 sessions was carried out over a period of three weeks. Full neuropsychological testing and quantitative EEG analysis were performed before and after the training for outcome measurements. **Results.** The treatment resulted in improved attention and executive functions; specifically sustained, focused, and divided attentional abilities; cognitive flexibility, access to the lexical vocabulary, and a better processing speed. Analysis of the qEEG revealed an increased alpha peak frequency value and reduced delta/alpha ratio in frontal areas. The EEG examination revealed interhemispheric asymmetry after treatment. **Conclusion.** These findings suggest that a delta/alpha decrease might account for some clinical effects on cognitive abilities seen in a brain tumor resection survivor, reducing cognitive symptoms that can have a significant impact on daily life functions. Future studies on larger patients' samples should clarify the feasibility of NFB protocols for patients with brain tumors.

Keywords: EEG biofeedback; qEEG; neurorehabilitation; brain tumor; cognitive functions

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Introduction

Tuberculum sellae meningiomas (TSMs) are relatively common, accounting for 5 to 10% of all intracranial meningiomas (Goel et al., 2002; Nakamura et al., 2006). Located above the tuberculum sellae, suprasellar meningiomas occupy the posterior medial zone of the anterior cranial fissure and originate from the superior surface of the sphenoidal body, tuberculum or, possibly, the jugum.

Due to their origin location, the prognosis of TSMs poses a special challenge because of their proximity to major arteries, visual pathways, and the hypothalamus (Ehresman et al., 2019). TSMs are frequently associated with changes in cognition, personality, and behavior before surgery (Abel et al., 2016). Among others, the main clinical and cognitive features described in literature consist of sight deterioration or even blindness due to the compression of the optic nerve and chiasm,

impaired attention and executive functions (e.g., loss of concentration and generalized slowing of thought processes), as well as poor regulation of emotions and ensuing apathy, depression, and poor psychomotor speed secondary to frontal lobe compression (Abel et al., 2016; Bitter et al., 2013; Simoca et al., 1994; Tucha et al., 2000). Frontal lobes play an important role in the regulation of higher cognitive functions such as attention that can be classified as selective, divided, shifting; and executive functions encompassing a set of abilities serving to plan and evaluate effective strategies for problem solving (Battista et al., 2020, 2021). Attentional deficits can be completely or partially responsible for the observed impairment in working memory, learning, retention, perception, and problem solving; most of the cognitive disorders described in the TSM patients seem to be related to an increased reaction time. These cognitive symptoms can be present even after the surgical removal of the TSM and are one of the most vexing problems for survivors. If not addressed, they can evolve over time into cognitive phenotypes such as mild cognitive impairment (Cramer et al., 2019).

The above-described clinical manifestations experienced by TSM survivors are reflected in electroencephalographic (EEG) changes. Electrical brain activity may be depicted by quantified electroencephalography (qEEG) as different frequency bands, associated with different mental states (Sanei & Chambers, 2013). Five main EEG frequency bands are described according to different frequency ranges and associated with distinct levels of activity: Delta waves (0.1–3.0 Hz), related to deep sleep; theta waves (4–7 Hz) related to drowsiness and meditation; alpha waves (8–12 Hz) related to vigilance and relaxed wakefulness; sensorimotor rhythm (SMR; 12.5–15.5 Hz) which is active when sensory or motor areas are idle; beta waves (13–30 Hz) which range from focal attention and deep focus at low frequencies to emotional arousal and motor functions; and gamma waves (> 30 Hz) related to learning and higher cognitive processing (Sanei & Chambers, 2013). Variations of frequency rhythms such as increased focal slowing, a lower frequency, higher amplitude, greater persistence, wider distribution, beta asymmetry and epileptiform discharges can ensue after surgical TSM removal (Bartolomei et al., 2006; Beaumont & Whittle, 2000; Cobb et al., 1979; Derks et al., 2014; van Dellen et al., 2013). In particular, it has been shown that following a TSM resection, dramatic changes may occur in the EEG that can stabilize overall, leaving deficits that are difficult to define but usually consist

of excessive theta/lower alpha waves (Rothoerl et al., 2003; Telera et al., 2012).

After surgical meningioma resection, a regression of cognition and visual impairments can ensue (Di Cristofori et al., 2018; Zweckberger et al., 2017). According to Zweckberger et al. (2017), subjects with a diagnosis of TSM can spontaneously undergo a recovery from the cognitive deficits after 6–12 months from surgery. However, this scenario is infrequent and, in most patients, cognitive deficits may persist up to four years after surgery if not properly treated (Barrash et al., 2020; Di Cristofori et al., 2018; Rijnen et al., 2019) and in some cases become irreversible, with an impact on levels of functionality (Krupp et al., 2009).

Neurofeedback (NFB), or EEG-biofeedback, is a noninvasive intervention based on the principles of operant conditioning. It considers behavioral, cognitive, and subjective aspects as well as brain activity. In order to modulate the electrical activity of the brain, it provides real-time visual and auditory feedback to the patient, displaying moment-to-moment information on the state of an individual's physiological functioning. The goal of this technique is to encourage the subject to learn to operate self-regulation of the putative neural substrates underlying specific behaviors. It addresses several issues of brain dysregulation, involving training to reduce the excessive theta/lower alpha waves during attentional tasks that are responsible for reduced processing speeds, while enhancing beta activities (Hammond, 2011). Based on this feedback, various learning principles, and therapist guidance, changes in brain patterns can occur which are associated with positive changes in physical, emotional, and cognitive states. The patient is often not consciously aware of the mechanisms through which such changes are accomplished, although people routinely acquire the ability to sense these positive changes and are often able to access these states outside the feedback session. When provided with appropriate training by a professional, patients do not generally experience negative side effects. The studies conducted to date have promoted a better understanding of not only the efficacy of NFB but also of the underlying neural circuits related to the process of cerebral self-regulation. Reinforcing beta frequencies can increase attention and arousal in healthy subjects (Egner & Gruzelier, 2004). Research studies have demonstrated promising results of NFB intervention for epilepsy, psychogenic nonepileptic seizures, migraine, attention-deficit/hyperactivity disorder (ADHD), traumatic brain injury, and affective disorders (i.e., Shakibaei et al.,

2021; Sitaram et al., 2017). Few studies have yet investigated the effectiveness of NFB training in patients with cancer surgery sequelae (Hetkamp et al., 2019). The available records found improvements of cancer-related symptoms such as pain, fatigue, depression/anxiety, and sleep, ameliorating the quality of life (Benioudakis et al., 2016; Gorini et al., 2015; Luctkar-Flude & Groll, 2015; Patel et al., 2020; Prinsloo et al., 2017).

NFB has not yet been studied in depth in adults with acquired cognitive impairment after brain tumor resection. To the best of our knowledge, only one randomized clinical trial has been conducted on brain tumor patients to investigate the effects on NFB training on cognitive impairments. No specific NFB treatment effects were found, but the patients were pediatric brain tumor survivors and were treated with radiotherapy and chemotherapy that may have influenced the results (de Ruiter et al., 2016). Against this background of paucity of data about the application of NFB for cognitive impairment in adult brain tumor survivors, here we describe a case of an adult person with TSM postsurgery-acquired cognitive impairment, referred to our clinic for rehabilitation. We hypothesized that NFB training would improve objective measures of neurocognitive functioning as measured by neuropsychological testing.

Material and Methods

Clinical Case Presentation
The patient was a 49-year-old bilingual (French and Italian) African woman, with 13 years of formal education and right-handed (Oldfield, 1971), who worked as a supermarket cashier and had lived in Italy since she was 20 years old. The woman presented a history of 4 days of headache, resistant to common painkillers, and progressive visual loss in the lower right eye. Due to these symptoms, she attended the Accident and Emergency department on November 8, 2020, where she underwent computerized tomography (CT) scans showing the presence of a TSM in the right fronto-parietal areas (Figure 1). Laboratory tests were also performed, and she was diagnosed with hypothyroidism, hypogonadotropic hypogonadism, and hyperprolactinemia likely due to TSM compression of the peduncle.

The patient was hospitalized on November 11, 2020, at the Neurosurgery Unit of the Azienda Ospedaliera Policlinico of Bari with a diagnosis of hydrocephalus after the operation for meningotheliomatous meningioma of the tuberculum sellae,

hypopituitarism, and a recent state of nonconvulsive disease from viral encephalitis. On the following day, after the preoperative examinations were completed, the patient underwent neurosurgical intervention of the left peritoneal ventricle derivation with a Hakin-Cordis valve, calibrated at 170 mmH2O.

Figure 1. *CT scan of the patient showing a large tuberculum sellae brain tumor.*

The subject underwent craniotomy and resection of the TSM performed with a neuronavigation system and intraoperative neurophysiological monitoring. The awakening and postoperative course were unremarkable. On December 11, 2020, she was transferred to the intensive care unit of the Azienda Ospedaliera Policlinico of Bari, where she was monitored and underwent a percutaneous tracheostomy. When she woke up, she presented tetra hyposthenia. During this period, she suffered a critical episode followed by a comatose state and right cephalus-oculoversion. EEG was performed, suggestive of right focal nonconvulsive illness. She was then treated pharmacologically.

During the postintensive care hospital stay, she underwent a brain CT scan showing a progressive reduction of the valve opening pressure, at that time set at 130 mmH2O. On January 7, 2021, the woman was admitted to our neurorehabilitation unit of the Maugeri Institute in Bari for intensive postacute inpatient rehabilitation treatment. On admission, the patient was alert and cooperative. She had poor autobiographical memory and was disoriented in time and space. She presented with flaccid tetra-paresis, more severe on the right side; upper and lower limb osteotendinous reflexes were absent; and central palsy of the facial nerve was also present. Pupils were anisocoric for OD > OS with mydriasis in nonreactive OD.

Procedure

The Neurofeedback Training

The patient was treated in accordance with the ethical standards of the 1964 Helsinki declaration and its further amendments. At the beginning of the training protocol, the patient gave informed consent to the treatement after the nature and the goal of the NFB training had been explained.

Besides the physical therapy (1 hour, twice a day) and the pharmacological treatment (Cortisone 25 mg, Sodium Phenytoin 100 mg, and Escitalopram 10 mg), the patient underwent a qEEG recording in resting condition and at pretraining and posttraining neuropsychological testing.

A total of 15 sessions of NFB training were administered, each lasting 35 min, over a period of 3 weeks at five sessions per week (early afternoon at the same hour). The participant was seated in a comfortable armchair, eyes open, and electrodes were applied. A Gold electrode applied with gel on Cz localization on the scalp was used as an active guide (according to the international reference 10–20 system), grounded at the left and right earlobes. Impedance control for all channels was kept below 5 kΩ.

The NFB training consisted of the "beta/theta ratio" protocol, rewarding and encouraging 13–18 Hz brainwaves (low beta), while simultaneously discouraging 4–8 Hz brainwaves (theta) and 19–28 Hz brainwaves (high beta) in Cz for 15 half-hour NFB sessions. The protocol employed visual–auditory feedback to guide the patient to achieve an autonomous reduction of inattention and hypoarousal by inhibiting the theta (4–8 Hz) and high beta (19–28 Hz) frequencies and promoting (reward frequency) of low beta waves (13–18 Hz) as a feedback parameter, according to the existing protocol by Fuchs and colleagues (Fuchs et al., 2003). To this purpose, the "boat race game" available on the BioGraph Infiniti software (Thought Technology, Montreal, Canada) was adopted. In this task, the participant is shown three boats; each corresponds and moves forward according to the theta, high beta, and low beta wave activity threshold, respectively. Feedback thresholds were set automatically for all three amplitudes in order to maximize rewards, thereby encouraging training while at the same time making real-time adjustments as the level of difficulty was gradually increased.

The subject was instructed to make the low beta-associated boat move forward while preventing the theta and high beta-associated boats from moving forward. Pleasant sounds and a green light rewarded the subject when the low beta boat reached the finish line, whereas an unpleasant sound and red light ensued when the associated theta and high beta boats reached the end. For the baseline EEG recording, as well as the NFB sessions, ProComp2 hardware and the Biograph Infiniti Suite 360 software (Thought Technology, Montreal, Canada) were used.

Outcome Measures

Neuropsychological Testing

A neuropsychological evaluation was performed at the time of arrival (before the NFB training) and at the time of discharge (after the NFB training). Well-validated, reliable, and widely used neuropsychological tests were selected to provide a comprehensive assessment of neurocognitive functioning (see Supplementary Material, Neuropsychological Testing and Table S1 for a full description of the protocol). When available, we used their parallel forms for the posttraining assessment in order to decrease practice effects without losing the gestalt of the measures administered. The following cognitive domains were evaluated: global cognitive functioning, verbal and visual memory, attention and executive functions, visuo-constructive abilities, language, functional assessment. Specifically, the Trail Making Test (TMT A-B; Giovagnoli et al., 1996) and the Attentional Matrices (Spinnler & Tognoni, 1987) were applied to measure attentional abilities such as sustained, divided attention and shifting processes; and the Stroop Color and Word Test (Caffarra et al., 2002) and the Phonemic and Semantic fluency tests (Carlesimo et al., 1996) to measure cognitive flexibility, access to the lexical vocabulary, speed of processing, and inhibition components of executive functions.

EEG Recording

The pre- and posttraining EEG recordings were performed using a BE Plus PRO Standard (EB Neuro, Florence, Italy) device and EB Neuro Galileo software. A longitudinal 21 electrodes montage with bipolar derivation was used, in accordance with the international 10–20 system. Precabled EB Neuro headset channels of common reference EEG channels were recorded (Reference: Fz; Ground: Fz–Cz). Gold EEG electrodes fitted with 10 kΩ, 1-W current-limiting safety resistors were applied to Fp1, F7, T3, T5, O1, and the contralateral homologous channels. The sample rate of the signal was 256 Hz. The continuous EEG was processed with fast

Fourier transform (FFT). High frequency and notch filters were set at 50 Hz, while low frequencies were set at 1.6 Hz (TC: 0.1 sec). Trial conditions responses were tested with eyes open, eyes closed, and intermittent flashing light (SLI protocol 3–30 Hz).

Quantitative Electroencephalography (qEEG) Measures

Using a customized version of the method flt_clean_windows (BCIlab) to compute a moving windowed signal power, abnormal data with extreme magnitude from the continuous dataset were deleted to compute a moving windowed signal power. EEG 1s windows segments were removed if their power exceeded the 90% distribution quantile. Synchronous increases in signal amplitude were detected using the difference between the superior and inferior envelopes following the shape-preserving piecewise cubic interpolation (Butt & Brodlie, 1993), and EEG portions producing values greater than two standard deviations (in amplitude distribution) were removed.

Power spectral density was computed for each channel by averaging periodograms of windowed signal sections, using the pwelch function in MATLAB (The Math Works, Natick, MA). The window length was 2 s (512 time points), and 8 min of artifact-free EEG data of the patient were used for power analyses. The power spectral density was analyzed before and after the treatment using EEG records with the same temporal and quality features. The average power spectrum density (PSD) across all scalp electrodes was defined as the overall scalp power spectrum. We computed the average PSD for the following frequency bands: delta (1–4 Hz) and alpha (8.1–14 Hz). The "area's power spectrum" was defined as the mean PSD over adjacent electrodes within the following areas: frontal area (left side: Fp1, AF3, AF7, F1, F3, F5, F7; right side: Fp2, AF4, AF8, F2, F4, F6, F8), central area (left side: FC1, FC3, FC5, FT7, C1, C3, C5, T3, CP1, CP3, CP5; right side: FC2, FC4, FC6, FT8, C2, C4, C6, T4, CP2, CP4, CP6) and posterior area (left side: P1, P3, P5, T5, PO7, P03, O1; right side: P2, P4, P6, T6, PO8, P04, O2).

Signal processing and analyses were performed offline using MATLAB with custom scripts based on the EEGLAB toolbox (Delorme & Makeig, 2004). The average power values were subdivided into the four bands (alpha, beta, delta, and theta) qEEG metrics. Only alpha and delta showed a sufficient numerical consistency to compute the spectral power. In addition, the delta/theta ratio (DAR), i.e., the ratio of mean scalp delta to alpha power, was

calculated. Higher DAR scores indicate a higher EEG low-frequency activity (Finnigan et al., 2007). To assess specific cognitive functions, we separated, using digital postprocessing filters, the low beta waves or beta 1 (12.5–16 Hz, "beta 1 power") from the middle-high beta power or beta 2 (16.5–28 Hz). In addition, the power ratio index (PRI), consisting of the following equation PRI = (alpha + beta) / (delta + theta) was calculated to assess the shelving of the entire spectrum power. The total power was considered for each band as the arithmetic mean for the whole scalp.

Signals Elaboration and Statistical Analysis

The following formula was used to calculate the percentage of improvement during the neuropsychological tests: [(posttreatment − pretreatment) / pretreatment] * 100 (Benvenuti et al. 2011; Shakibaei et al., 2021). According to this formula, an improvement by 50% or more, without any increased medication, is considered a clinically significant improvement (Blanchard & Schwarz, 1988).

Mean amplitudes (μV) were calculated for each band: alpha, beta, delta, theta, and beta/theta ratio. To assess the differences of mean amplitude of each waveband, we subdivided the biofeedback treatments into three groups of lengths, per 5 days of treatment (group 1 = days 0–5; group 2 = days 6–10; group 3 = days 11–15). Normality of data was assessed and confirmed by Shapiro–Wilk test for the total distribution of alpha, beta, delta, theta, and theta/beta values for each day/treatment and across the lengths groups. Then we performed ANOVA analysis to assess any significant difference in amplitude trends across the three lengths groups and the 95% confidence intervals (CI). In addition, we built linear regression models to analyze whether the increase by day of treatment could predict the mean changes for every brainwave band, with 95% CI. All statistical analyses were performed using R software (Core Team 2013; R Foundation for Statistical Computing, Vienna, Austria). In addition, alpha, theta, delta, high/low beta DAR and PRI spectral power values (expressed as eigenvectors) were computed for the pretraining and posttraining EEG, to assess probable permanent quantitative permanent changes in the brainwaves before and after training, as described in the specific paragraph.

Results

EEG Measures

Eye and head movements or muscle artifacts were removed after a visual inspection of EEG data, for

artifact exclusion. The spectral power scores resulting from the pre- and posttreatment qEEG power analysis are reported in Table 1. Only alpha and delta bands showed sufficient numerical consistency to compute the spectral power using absolute numerical eigenvectors for magnitude. We report the results considering also the ratios of the different bands. We found an increase of frontal alpha power and reduced DAR power in the frontal and posterior areas. No significant changes were found in theta and beta bands in resting state EEG examinations, as these remained stable across the assessments.

Table 1

EEG Power Analysis and Quantitative Electroencephalography (qEEG) Measures Pre- and Posttreatment

Band	Frontal		Central		Posterior		Total	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Delta	24.17	28.6	23.46	23.17	26.49	26.31	24.7	26.02
Theta	1.42	1.49	1.65	1.78	1.14	1.42	1.40	1.56
Alpha	4.92	6.21	5.47	5.47	5.01	6.92	5.13	6.21
Beta	1.80	1.91	1.28	1.26	1.90	1.81	1.66	1.66
Beta 1	1.99	2.61	1.32	1.39	1.81	1.91	1.70	1.97
Beta 2	1.75	1.78	1.45	1.21	1.96	1.89	1.72	1.62
Delta/Alpha Ratio	4.91	4.60	4.28	4.23	5.28	3.80	4.82	4.21
Power Ratio Index	3.80	3.70	3.72	3.70	3.99	3.80	3.83	3.73

Table 2 shows the comparison of average amplitude (µV) for each band, among the three treatment length groups (group 1 = days 0–5; group 2 = days 6–10; group 3 = days 11–15). Beta amplitudes show a significantly increased trend across the lengths groups (p < .01), as in the linear model, for every day of treatment the beta amplitude increased on average by 0.46 µV (95% CI [0.41, 0.52]; Table 3).

Table 2

Description of the Whole Sample According to Treatment Length Groups

	Treatment Length			
	Days 1–5	Days 6–10	Days 11–15	*p* value
Alpha	8.55 ± 0.44	9.06 ± 0.87	9.00 ± 0.97	.38
Beta	3.03 ± 0.77	5.86 ± 1.06	7.75 ± 0.24	< .01
Delta	15.14 ± 2.31	11.98 ± 1.75	9.18 ± 0.58	< .01
Theta	16.24 ± 0.78	12.68 ± 1.68	9.83 ± 1.55	< .01
Theta/Beta	5.72 ± 1.75	2.27 ± 0.7	1.27 ± 0.22	< .01

One-way ANOVA

Table 3

Linear Regression Model on Collected Variables as Dependent Variable and Days of Treatment as Regressor

|	Coefficient	Std Err	95% CI	*p* value
Dependent Variable: Alpha				
Days of Treatment	0.04	0.05	[−0.05, 0.13]	.37
Dependent Variable: Beta				
Days of Treatment	0.46	0.03	[−0.41, 0.52]	< .01
Dependent Variable: Delta				
Days of Treatment	−0.59	0.08	[−0.76, 0.43]	< .01
Dependent Variable: Theta				
Days of Treatment	−0.66	0.04	[−0.73, −0.59]	< .01
Dependent Variable: Theta/Beta				
Days of Treatment	−0.46	0.05	[−0.56, −0.35]	< .01

Delta, theta, and theta over beta ratio (TBR) bands showed a marked decreased trend in amplitudes among ordinal treatments lengths groups, all values being statistically significant (p < .01). The results were confirmed by linear regression models that

showed respectively that, for every day of treatment increase: delta had a predicted decrease by -0.59 (95% CI [−0.76, −0.43]), theta by −0.66 (95% CI [−0.73, −0.59]), theta/beta by −0.46 (95% CI [−0.56, −0.35]) and SMR by −0.09 (95% CI [−0.11, −0.08]; Table 3).

At the pretraining EEG examination, we found an asymmetrical plot on the temporal regions. Throughout the right hemisphere, we also found an inconsistent representation of slow waves, of the theta or delta band. In the temporo-parieto-occipital regions, the appearance of synchronous epileptiform graph elements (especially sharp-waves followed by slow waves) was observed. The representation of

alpha sequences on the posterior regions was inconsistent. The posttraining EEG recording showed a basically symmetrical base path, with representations of alpha sequences on posterior regions. A scatter plot between days of treatment and collected variables displays the electrical activity changes in our patient over the 15 sessions (Figure 2), featuring widespread representation of rapid rhythms, a subcontinuous persisting presence on the right temporal regions of slow waves of theta band, with the constant and more widespread appearance, on the same hemisphere, of theta waves (4–7 Hz) sequences, showing little tendency to a contralateral diffusion.

Figure 2. *Scatter plot between days of treatment and collected variables.*
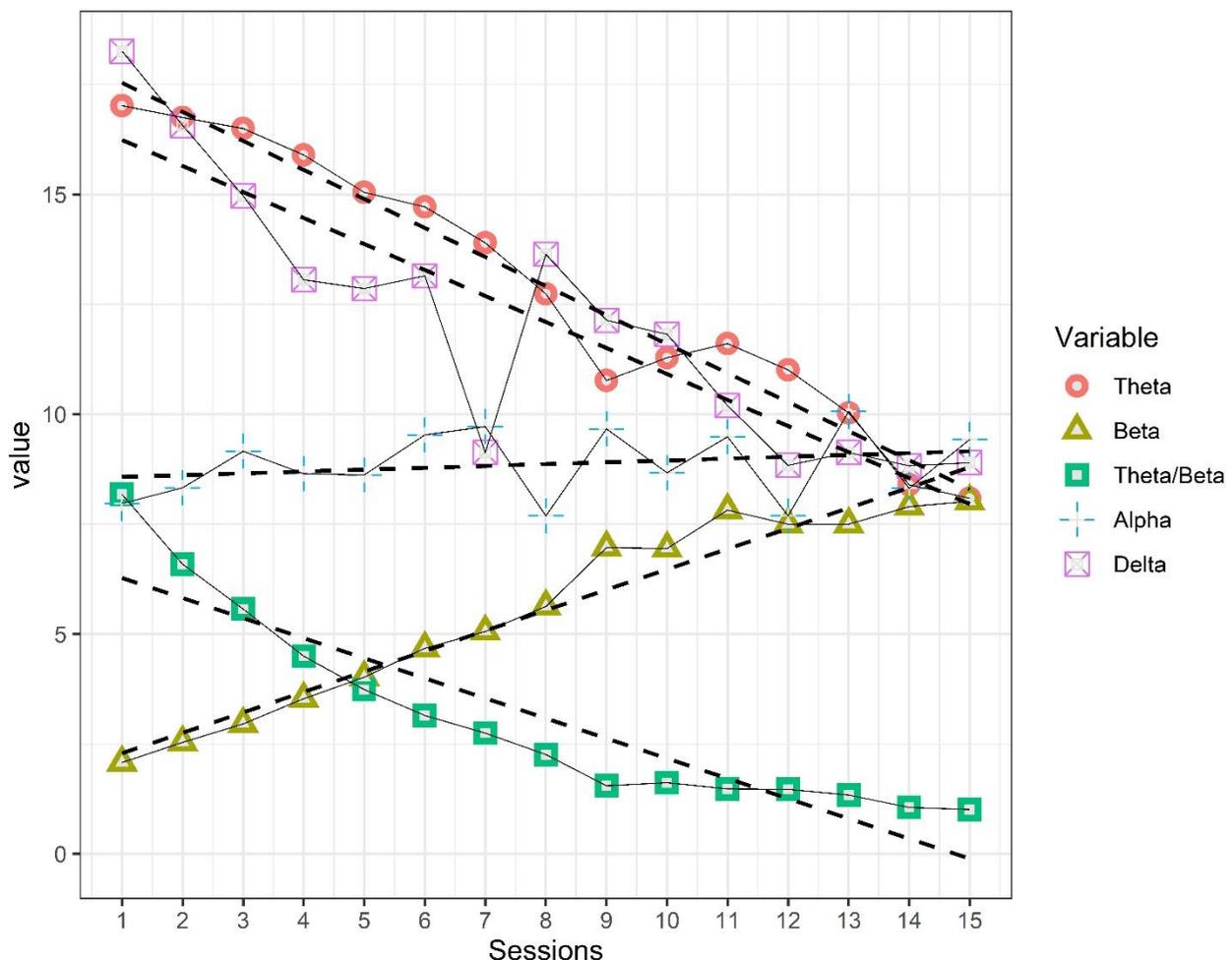
Note. Whole sessions mean (µV) of theta (4–7 Hz), beta std. (13–21 Hz) and theta/beta ratio during NFB training obtained from BioGraph software trend report after artifacts rejection over the 15 sessions.

The qEEG power analysis highlighted an increased delta activity in frontal regions (delta band pretreatment: 24.17 vs. posttreatment: 28.6), alpha activity in frontal regions (alpha band pretreatment: 4.92 vs. posttreatment: 6.21) and in posterior regions (alpha band pretreatment: 5.01 vs. posttreatment: 6.92), while theta and beta bands remained stable. DAR appeared significantly reduced in posterior regions (DAR pretreatment: 5.28 vs. posttreatment: 3.80) with a trend toward reduction in frontal areas but remained unchanged in central areas.

Neuropsychological Profile Pre- and Post-NFB Training

During the first neuropsychological examination, the patient appeared poorly oriented in regards to time, space, and autobiographical parameters. Her mood was apathetic and flat. On performance at the first-level battery, her general cognitive efficiency was impaired (MMSE = 22/30; Cut-off < 23.8). A poor performance emerged from the screening evaluation of global executive function (FAB = 10/18; Cut-off < 12.03), with a worse performance in the conceptualization and inhibitory control tests. The patient showed impairments in short-term and long-term visuospatial memory, due to her compromised spatial exploration ability and the presence of constructional apraxia. Spontaneous speech was characterized by fluent language characterized by short but well-structured sentences; she presented several anomia and semantic paraphasias to the confrontation naming task. No difficulties were recorded at episodic memory tests, nor learning and recognition of new verbal information. Attentional abilities were limited, with amplified reaction times and long latency in answering questions. Difficulties in attentional-executive function appeared to be severe and critical. The speed of information processing, selective attention in the focused and divided component, sensitivity to interference, inhibition of automatic responses, and conceptualization of time were all compromised. She also showed a lack of cognitive flexibility based on external feedback and choice of strategies in verbal fluency tasks, with several episodes of perseverations, and difficulties in learning functional strategies. The scores resulting from the first neuropsychological evaluation are reported in Supplementary Material, Table S1.

After 15 sessions of NFB training, the patient showed a reduction of the poor cognitive symptoms, with a qualitative improvement in the reaction times and attentional abilities. The posttraining neuropsychological assessment was administered after 3 weeks of NFB (Supplementary Material, Table S1). Compared to the performance at the pretraining assessment, her general cognitive efficiency had improved (MMSE = 26.89/30, Cut-off < 23.8), as well as global executive functionality (FAB = 14.20/18; Cut-off < 12.03), with worse performances registered in the conceptualization tests and mental flexibility. In addition, the results of pretreatment and posttreatment scores showed that the TMT A-B score decreased from 202 s to 88 s to complete the trial-A, decreased from 496 s to 212 s to complete the trial-B, and increased from 20.5 to 40.75 for the Attentional Matrices Test. These results indicate an increase of 56.43%, 57.25%, and 98.76%, respectively, in the attentional abilities after the training (Table 4). Moreover, we registered an improvement of her semantic fluency ability (the score increased from 10 to 25) and time to perform the Stroop Color and Word Test (the score decreased from 37.70 s to 20.72 s). These results indicate an increase by 81.22% and 98.9%, respectively, in two of the main components of the executive functions (access to the lexical vocabulary and speed of information processing) after the training (Table 4). At the behavioral level, perseverations appeared to a lesser extent and the patient showed much faster flexibility and reaction times. A latency in tasks that required more space exploration persisted. Concerning the other noncognitive areas, at the end of the rehabilitation cycle, the patient had successfully regained mobility, balance, and motor autonomy.

Table 4

Attention and Executive Functions Tests, Scores, and Percentage of Improvement of the Patient Pre- and Post-NFB Training

Neuropsychological Test	Pre-NFB	Post-NFB	% Improvement
Trail Making Test A	202	88	56.43
Trail Making Test B	496	212	57.25
Attentional Matrices	20.50	40.75	−98.78
Stroop Color and Word Test – Time	37.70	20.72	97.70
Semantic Fluency	10	25	60.00

Discussion

NFB is known to act through thalamocortical regulatory systems and increase cortical excitation thresholds (Mayer & Arns, 2016). The neurobiological underpinnings of NFB are based on the promotion of "long-term potentiation" (LTP; Sitaram et al., 2017), which constitutes a central element for associative learning, involving glutamate NMDA receptors and other neurotransmitters such as dopamine (event-dependent). Learning is the result of the concomitant occurrence of a strong presynaptic and postsynaptic activity conveyed by the release of dopamine. Based on contingent feedback, dopaminergic projections to the striatum can modify behavior in response to salient stimuli. In our patient, NFB contributed to systemically enhance LTP in the disrupted frontal and parietal areas involved in the fulfillment of attentional and executive tasks (Alvarez & Emory, 2006; Ball et al., 2011; Murray & Wojciulik, 2004), through their connections with the thalamus to regulate cortical arousal. Evidence regarding the positive effects on cognitive performance of NFB training is gradually emerging (Enriquez-Geppert et al., 2017). Recent studies testing NFB as a neurorehabilitation technique highlighted its efficacy on performance enhancement of several cognitive functions such as executive functions (Viviani & Vallesi, 2021), attention and memory (Yeh et al., 2020) in healthy individuals. Similarly, NFB seems to be effective in improving quality of life and as a nonpharmacological treatment for the relief of cognitive symptoms of many clinical conditions such as mild cognitive impairment (Trambaiolli et al., 2021), poststroke (Renton et al., 2017), and traumatic brain injury (Ali et al., 2020).

In the present case, the patient underwent a NFB training over 15 sessions. The results of this training, applied in a patient who had undergone right fronto-parietal craniotomy, were analyzed to investigate the efficacy of NFB in a brain tumor survivor. They reveal an improvement of attentional functions, selective, sustained, and divided attention and speed information processing, and improvements of executive functioning, specifically of cognitive flexibility and access to the lexical vocabulary, speed of information processing. These improvements were also mirrored in the functional autonomy of daily life, as the patient recovered her instrumental activities. Along with the clinical and neuropsychological outcomes, the neurophysiological brain activity changed across the sessions, as well as in comparison between before and after NFB training. In agreement with previous studies, the patient successfully learned to efficiently self-regulate her brain activity efficiently. In fact, statistical analyses revealed significant changes such as the augmented amplitude and percentage of beta bands across the sessions. On the contrary, slow wave activity, which was dominant in the first phase, as delta and theta bands, decreased significantly. No relevant differences in alpha activity were detected among the training sessions. The above-described neurophysiological changes support previous works which used the same protocol such as ADHD and demonstrated an improvement in attentional abilities (Van Doren et al., 2017). Importantly, the TBR amplitude dropped significantly over the weeks. The TBR was found to be negatively related to the executive control network but directly related to mind wandering and the default mode network (van Son et al., 2019).

After the training sessions, analyses revealed consistent changes in task accomplishment, and the qualitative pre–post resting state qEEG showed different but not contradictory results. The qualitative qEEG comparison between the pre- and posttraining showed an increase in alpha waves and particularly in the frontal alpha band activity post-NFB training. Similar results have been reported in the literature, associated with positive cognitive outcomes (e.g., inhibitory control and shifting, attention, executive functions, abstract reasoning, nonverbal intelligence). Alpha activity is linked to vigilance, information and cognitive processing such as attentional and executive functions, as well as maintaining an optimal cerebral arousal state (Klimesch, 2012; Schleiger et al., 2014). In our patient, we also observed a reduced DAR in the posterior cortices. Such a result is coherent with the negative correlation between the posterior DAR and cognitive outcomes found by Schleiger and colleagues (Schleiger et al., 2014). High DAR values indicate excess in delta power and lower alpha waves associated with poorer functional and cognitive outcomes (Aminov et al., 2017; Finnigan et al., 2007; Finnigan et al., 2016; Schleiger et al., 2014). No relevant changes were found in theta and beta bands in resting-state EEG examinations, as they remained stable across the assessments.

Notably, the qEEG signals elaborations of beta waves revealed a trend toward change. In particular, low beta waves, associated with thinking, focusing, sustained attention, alertness, and excitement showed a slight increase in frontal areas (beta 1 band pretreatment: 1.99 vs. posttreatment: 2.61) and a positive trend on global activity. On the contrary, high beta waves, linked to intensity,

hyperalertness and anxiety (Marzbani et al., 2016), showed a negative trend in global EEG measures. The limited increment of low beta waves could be explained by the fact that the waves appear when the subject is actively involved in a cognitive task and remains focused. For that reason, it is less likely to be detected during an EEG resting state. Moreover, as previously described by de Munck and colleagues, EEG wave bands are actively interdependent (de Munck et al., 2009). Consequently, the active training on low beta (13–18 Hz) produced an increase of lower hertz such as alpha bands (8–12 Hz) in resting state. Similar results were described in a study on healthy subjects conducted by Jurewicz and colleagues. The authors demonstrated that beta band upregulation resulted in alpha and beta increases, but the amplitude increment was greater for the alpha than the beta band (Jurewicz et al., 2018). As suggested by the authors, the alpha band activity could exercise a cortical inhibitory effect to balance global activity when beta oscillations rise in amplitude (Jurewicz et al., 2018).

To our knowledge, this is the first case report describing the efficacy of an intensive NFB training in a patient post-TSM resection. The data available on NFB training for cancer patients are scanty and mainly focused on pain, mood, and quality of life (Hetkamp et al., 2019). Few studies investigated the effects of NFB training on cognition in cancer patients, and most of these were survey self-reports (Alvarez et al., 2013; Luctkar-Flude & Groll, 2015; Sarvghadi et al., 2019). Above all, the high heterogeneity of clinical conditions and treatments, and the use of different outcome measurement tools, constitute a relevant limitation hampering the possibility of comparing the efficacy of protocols and approaches and making it difficult to compare the overall positive results. Furthermore, since cognitive impairment secondary to meningioma resections is the main clinical sequela (Cobb et al., 1979; Ehresman et al., 2019; Rothoerl et al., 2003; Zweckberger et al., 2017), further studies investigating NFB as a rehabilitation training of cognitive functions are warranted.

Limitations and Future Perspectives

Our study presents several limitations. Firstly, the concurrent antiepileptics medication might have played a role in the EEG wave symmetry; nevertheless, it is unlikely that pharmacological effects would be effective in such a short time, and they do not exert a role in hemispheric symmetry. In addition, the patient underwent motor rehabilitation

to regain mobility, balance, and motor autonomy. As strongly documented in existing literature, physical activity exerts a central role in regaining bodily and cognitive functions, so we hypothesize that physiotherapy could have facilitated neural plasticity and played a role together with the NFB training (Ali et al., 2018). The reduced treatment time before discharge is an important limitation since it precluded the investigation of whether the patient would have continued to improve more or would remain stable.

Uncertainty regarding the long-term effects of NFB training is an open issue. Regarding long-term effects, there is some evidence regarding the presence of a "homeostatic rebound" (or "homeostatic plasticity"; Marder & Goaillard, 2006), or the ability of neurons to regulate their own excitability relative to the activity of the circuit, after NFB training. It is unclear to what extent homeostatic plasticity impairs long-term changes in brain activity and behavior, as there is evidence that these changes can occur days, months, or even many years after training (Gevensleben et al., 2010; Harmelech et al., 2013; Megumi et al., 2015). In the case described, it would have been interesting to evaluate whether homeostatic plasticity appeared or not after one year from the treatment. It has yet to be discovered whether the cognitive improvements remain stable over time.

To conclude, NFB training requiring the active participation of the subject can offer the possibility of endogenously manipulating brain activity. There are still several open questions regarding NFB. Future studies should focus on the development of standardized protocols, as well as the understanding of interindividual differences in the achievement of self-regulation, learning abilities, and the possibility of generalizing the gain obtained during NFB training to everyday life. Given the paucity of studies in the literature on this topic, the present case illustrates the potential usefulness of NFB to improve cognitive impairment in TSM patients in the subsequent postoperative period. It is mandatory in the future to rule out any confounding of results by nonspecific training effects.

Compliance with Ethical Standards

Conflict of Interest. The authors declare that they have no conflicts of interest.

Ethical Approval. Consent to participate: written informed consent was obtained from the patient for publication of this case report and accompanying images. The institutional ethics committee approved this case study.

Author Disclosure

Author Contributions

GL, RS, and PB contributed substantially to the conception and design of the work, drafting and revising the manuscript for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work. GL, RS, FM, and PB performed the analyses. SDT, EL, and PF drafted corresponding sections of the manuscript. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

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