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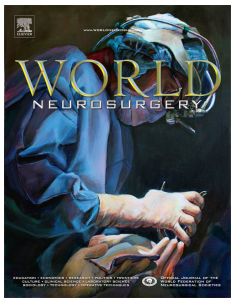

Proposal of Brain Plasticity index based on nTMS: metric of functional displacement for Language function

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TITLE:

Proposal of Brain Plasticity index based on nTMS: metric of functional displacement for Language function

Short Title: Brain Plasticity Index based on L-nTMS

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MANUSCRIPT

Introduction:

Brain Plasticity (BP) represents a pivotal concept in modern Neuroscience, whose measurability is still challenging, although the technological advances. Neuroplasticity represents the ability of neural networks to activate compensation mechanisms for the functional consequences of an injury to the brain architecture[1]. In case of Gliomas, different biochemical, paracrine, and synaptic transmission are involved in parallel to macroscale network remodeling[2], including local and extended modulations of functional brain activities [3,4] and tumor volume within associated cortical areas[3,5,6]. Three principle BP biomarkers have been identified[1]: 3D tumor location and white matter (WM) infiltration, velocity of expansion over time, and cognitive compensation (i.e.Metaplasticity). Brain-to-glioma cross-talk determines the type of brain networks rearrangement, and strictly depends on the histological diagnosis [according to the World Health Organization Classification (WHO)2021[7]], speed of progression and WM-fiber-tracts infiltration, with an evolving framework of plasticity potential. Modulation of the Metaplasticity, according to individual characteristics, represents a challenge to propose dynamic therapeutic strategy for individual BP profiling, inspired by previous relevant works[8], and to understand the prospective cognitive compensation and functional reshaping[9]. Based on this background, Brain Plasticity Index (BPI) has not been specified so far, although several models have been proposed. Considering noninvasive system of brain stimulation and cognitive study, Navigated TMS (nTMS) is a noninvasive, well-tolerated, safe, and reliable method to investigate cortical activity, commonly used for preoperative mapping and integration in the neurosurgical setting. Cognitive functions, have been explored with nTMS to optimize its potential: Motor function[10-15], Language[12,16-18], and also rehabilitation programs for postoperative motor functions' recovery[19]; Calculation[20-22] and Visuo-Spatial networks[23,24] have been investigated with the use of nTMS to map and preserve cognitive functions, with comparison of nTMS data and intraoperative Direct Cortical Stimulation (DCS), i.e. the gold standard.

Objectives: This study aims at identifying a possible cortical Brain Plasticity Index (BPI) that accounts for the cortical variation in Language function, based on the pre-op/post-operative nTMS mapping, determining the quantitative-qualitative displacement of cortical areas, and investigating the potential correlation between BPI and cognitive performance status. An innovative method to calculate BPI is illustrated.

Methods:

To achieve these objectives, we designed a monocentric prospective clinical observational study, approved by the ethics committee CEAVC (Comitato Etico Area Vasta Centro), section of the Regional Ethics Committee of the Region of Tuscany, in compliance with the Declaration of Helsinki. We enrolled 40 neuro-oncological patients who were followed from January to December 2024 at the Neurosurgical Department of the University Hospital of Florence, harboring primitive (intra-axial/extra-axial tumors) or secondary brain lesions (i.e. Brain metastases) or vascular lesions (i.e. cavernomas, lymphomas) or Focal Cortical Dysplasia (FCD), inducing epilepsy. All surgeries were performed by the same senior neurosurgeon (ADP). The surgical goal was Gross Total Resection (GTR; >90% tumor removal), with subtotal resection reserved for cases involving functional boundaries to prevent neurological deficits[25]. We collected pre- and post-operative imaging data (MRI DTI scans and tractography based on DTI sequences), nTMS data for Language (Ln), Calculation (C) and Neglect (N) (acquired bilaterally whenever possible, according to patients' compliance and tolerability), evaluation of logopedic and cognitive performance.

Imaging and MRI sequences: preoperative magnetic resonance imaging (MRI) was performed at our Neuroradiological Department, using a 3T Tesla M.R.I. machine (Ingenia 3T, Philips Medical Systems, Best, The Netherlands) with Diffusion Tensor Imaging (DTI) sequences. Multiple Regions-of-Interest (ROIs) were used to create subcortical pathways, based on nTMS preoperative mapping.

Motor evaluation: we used the Muscle Power Assessment (MRC Scale)[26] for testing strength on the upper and lower limbs during clinical evaluation.

Cognitive Assessments:

The cognitive tests included*:* MiniMental State Examination (MMSE)[27], Aachener Aphasie Test (AAT)[28], Neuropsychological test for aphasia (ENPA)[29], items for written calculations, additions, subtractions and multiplications, the Oxford Cognitive Screen (OCS), item Barrage [30], the Bells test [31], Wechsler adult Intelligence Scale IV (WAIS)[32], Frontal Assessment Battery(FAB)[33], Babcock Test, Italian version[34]. All tests were performed by our logopaedist (FF).

I) ***nTMS Data acquisition***

We used the rnTMS system (Galileo NetBrain Neuronavigator 9000, EB Neuro Corp., Florence, Italy). The mapping method and the protocol were the same illustrated in our previous works[11,22]. Volumetric T1-weighted MRI sequences were used to reconstruct the patient's 3D brain model. The search for the hand-hotspot (regularly on the first dorsal interosseous_FDI) began from the anatomically identified hand-motor-area within the precentral gyrus. The Resting Motor Threshold (RMT) was then determined (i.e. the lowest nTMS intensity capable of eliciting a MEP amplitude ≥100μV in the relaxed FDI muscle, in at least 5/10 stimulations). Preoperative Cognitive Mapping (PCM) was then performed with a stimulation intensity of 105% of the RMT for the upper limbs, and 110% of the RMT for the lower limbs.

The mapping of eloquent cortical areas for Language was performed through the object naming task (D080), using a repetitive nTMS pulse trains (5 pulses/5Hz; inter-picture presentation interval (IPI) of 1000 ms; pictures presentation time (PPT) of 4000 ms).

II) ***Data processing pipeline for the calculation of the Brain Plasticity Index***

Pre- and post-operative nTMS mapping data were acquired and processed with application of an image processing pipeline, see **Figure 1.** The pipeline has been developed with Python with open-source frameworks itk v5.4[35,36] [1,2], itk-elastix v0.19.1[37,38] [3,4], opencv v4.9 [39][5], scipy v1.12 [40][6] and scikit-image v0.22 [41][7]. First, negative and positive TMS points (x, y, z locations) were used to generate two binary volumes indicating the location of the TMS data in the MRI volume. This volume was then registered (affine transform) on the T1 volume. For each cerebral function, we considered if nTMS tests have been performed for both hemispheres. Using the registered binary nTMS volume, two 2D maps were created with an orthogonal projection of the volume on the sagittal plane of Rh and Lh.

To provide an example of how we used the presented pipeline, for patient 17, we represented in **Figure 2** the orthogonal projection on the Rh obtained for the language task. Using this projection, we removed the false-positive nTMS points from the analyses (i.e. those for which both negative and positive nTMS identifications were found). The comparison was made separately for points obtained pre-and post-operatively. In **Figure 2**, the dotted black rectangle indicates the region of interest in which both pre- and post-operative tests have been performed. All points not included in this rectangle were excluded from our analysis. This is because it is not possible to calculate a brain plasticity metric for points that have not been identified in a common region (since mapping areas were not adequately comparable/overlaying between pre and post operative phases).

Then, negative/ positive nTMS points were used for calculating a map of the specific function for each hemisphere. For this purpose, a 2D nearest-neighbor interpolation was separately performed for pre- and post-operative TMS points. The objective of this interpolation is to create an image that delineates the extent of the tested function. For the interpolation, the input data was negative TMS points (identified with an intensity of 0) and the positive points (identified with an intensity of 1). Using this input data, pixels in the entire sagittal plane were interpolated based on the intensity of their "nearest" neighboring pixel, see **Figure 3.**

Using these maps delineating the preoperative and postoperative brain functions, BPI can be calculated as a displacement metric (DM) to evaluate the displacements between preoperative and postoperative functions. As we can see in **Figure 3**, the preoperative and postoperative functions are identified with Npreop and Npostop blobs. For this patient, Npreop=4, = Npostop =2, however the numbers could be different depending on the patient or the tested function. The BPI consists of indicating the displacement (in millimeters, mm) of the Npreop blobs measured before the operation into Npostop blobs identified after the operation.

For each Npreop blob, we calculated Npostop translation maps (affine transform) to independently match each postoperative blob. The deformation map represents the magnitude of displacement (in mm) of the preoperative blob to match a postoperative blob. A mean deformation map was calculated by averaging all deformation maps. This operation was repeated on each preoperative blob. The BP deformation maps were then projected on the cerebral surface of the T1 volume, computed with the open-source tool HD-Bet[42].

III) ***The Brain Plasticity Maps:***

- ***Quantitative displacement:*** BP maps were then registered on a neuro-anatomy atlas (NMI) space by combining affine and non-rigid (b-spline) registration procedures. When applying the b-spline transform, a binary volume masking the location of the tumor in the T1 volume was necessary to ensure a correct registration on the neuro-anatomy atlas. The tumor segmentation was performed with BRATS toolkit [43]. Then, a normalized BP map for all patients was defined by the weighted sum of all brain plasticity maps. The weight attributed for each voxel was defined by 1/M, with M, the number of overlaps (number of patients having an identification at the same pixel area).

- ***Qualitative displacement:*** the use of HarvardOxford atlas overlay on the brain cortical surface allowed identifying specific cortical regions[44]. We graphically did overlay the atlas regions on the brain parenchyma (Lh/Rh) and identified the regions where nTMS blobs were located (either preoperatively or postoperatively). The results were obtained with an average of couple of cortical regions' numbers, according to the displacement from one area to another.

All statistical and bioengineering results were performed and controlled by Dr E.P and Dr C.C, according to the details of the pipeline.

Results:

During the period between January 2024 and December 20204, we conducted a prospective monocentric observational study on 40 patients operated on at the Neurosurgical Department of Careggi in Florence. They were selected based on pathology, and the preoperative logopedic/neuropsychological evaluation was done to let them access the nTMS motor and cognitive pre-operative mapping. The aim was to acquire a preoperative functional mapping to integrate in the neuronavigational system, used during surgery, relying especially on the Negative Predictive Value of nTMS, to spare active areas[11,12,21,22,24,45,46]. All clinical, radiological, pre-, intra- and post-operative data were collected and analyzed. Mapping with nTMS was also used for tractography, based on nTMS functional maps[16,46-50] .

According to the adopted protocol, our patients underwent a preoperative evaluation around 48-72 hours before surgery, then nTMS mapping. Considering the location and nature of the lesion, awake or asleep procedure was privileged, the postoperative re-evaluation was performed immediately after surgery and before discharging the patient, after 30±10 days, 90±10 days with repetition of rnTMS. Among about 100 patients studied with preoperative nTMS, we finally selected those who had either pre- and post-operative mapping to study the functional reorganization induced by tumors first, and surgery secondly.

The final number of patients enrolled was n=40, with final number of nTMS mapping procedures=41, since one patient who was operated on twice for a relapse of an Astrocytoma Grade II.

General characteristics: M: F=22:19, level of scholarship 8-15 years.

We enrolled mainly oncological patients:

Lesions Characteristics:

LGG (n=15): 12 astrocytomas, 7 oligodendrogliomas (1 G2-G3).

HGG (n=22): 10 IDH-wildtype glioblastomas, 2 gliosarcomas, 7 G3, 3 other.

Non-glial (n=6): 3 FCD, 2 meningiomas (1 atypical), 1 lymphoma, 1 cavernoma.

Surgical Procedures:

Awake: 20/41 (48.78%); asleep: 21/41 (51.22%).

First-time surgeries: 33 (80.48%); repeated surgeries: 8 (19.52%).

Concerning nTMS mapping, 63.4% (26/41) was bilateral cognitive mapping. More in detail, the motor mapping was only monolateral (on the affected side of the tumour), whereas the language mapping was bilateral (i.e. either affected or contralateral healthy side) in ~63% of cases.

Considering the lesions' volumes, we obtained average: Mean ± SD: 60.9 ± 66.0 cm^3; median: 35.0 cm^3. To evaluate the BPI specific to Language function, a subcategory of 14 patients was investigated more accurately because of the highest overlay between pre- and post-operative mapping. We distinguished and compared LGG and HGG. According to **Table1**, we finally considered 14 patients, slipped up into two groups: 7 HGG (5 left, 1 right, 1 bilateral splenium CC), 7 LGG (6 left, 1 right). Among 7 LGG, 6 were left lesions (P1-P19-P29-P31-P32-P36), and 57.14% (4/7) was operated on in awake surgery, whereas among 7 HGG, 5 were on the Lh (P5-P10- P11- P16- P25), 1 was bilateral because of the involvement of the Corpus Callosum (P17), 1 was in Rh (P30). The median age is 47.28 years (24-70). Age of scholarship between 8 and 16 years. All the selected 14 analysed patients completed the follow up period up to 90±10 days. All patients enrolled in the study received a post-operative rnTMS during the follow-up period.

1) Quantitative displacement

We identified a metric for Rh/Lh and then for the whole functional displacement. **Figure 4.** As we can be observed (**Figure 5, Table 2**), for Language function, for LGG from the Lh an average BPI of 21.81 mm (median 22.39 mm and std 8.61 mm) was obtained, while for HGG a mean value of 54.65 mm (median 46.07 mm and std 35.63 mm). Instead, in the Rh, for patients with LGG a mean BPI of 57.58 mm was obtained (median 57.58 mm and std 2.11 mm), while for HGG a mean value of 33.30 mm (median 33.30 mm and std 25.65 mm). In most cases, both the average and median BPI values resulted higher in the Rh than in the Lh in patients with HGG. In patients with LGG, the trend seemed reversed. Analyzing these images, for linguistic functions the high displacement of functional reorganizations mirrors the complexity of a multilevel function, whose coordination implies several cortico-subcortical circuits (i.e.AF, ILF, SLF, IFOF, FAT), with predominancy on the Lh, for HGG cases, and on the Rh for LGG, according to our results. These were reported graphically for each patient, considering the final map (deriving from the comparative analyses of the pre-op and post-op maps) with a false color map: yellow

blobs indicated preoperative functional areas, and red blobs indicated preoperative functional areas. The white arrows indicated the mean displacement direction. **Figure4.**

We reported images for the projection of BPI metrics on the NMI atlas and the HarvardOxford parcellation system (areas contoured in black and indicated with numbers) (**Figure 5**). The corresponding names are given in HarvardOxford.csv file **(Supplementary Materials).**

1.1) Distinction between BPI for patients with LGG and HGG in correlation with tumor volume: the correlation between BPI and lesion volume was evaluated, dividing LGG from HGG. For Language, given the limited number of patients for whom BPI for the Rh was estimated, only data relating to the Lh were considered. The correlation value between BPI and lesion volume resulted low ($R = 0.28$ for LGG, and $R = 0.31$ for HGG, linear regression), presumably due to the limited sample. However, the correlation value is higher for HGG than for LGG.

2) Qualitative displacement

Since we knew the metrics (in mm) and the average of displacement (quantitative representation), our purpose was achieving the qualitative representation of the anatomic areas involved by displacement of Language (i.e. where the function goes, based on the cps). We identified the reiterative couples of numbers in the brain parenchyma surface and the results were translated into histograms (**Supplementary Materials**).

For Language functions the most reported couples of regions involved in cortical reshaping were on the Lh: 42-6,42-20, 46-41, on the Rh 20-41, 42-41, 43-41, 46-6, 46-20, 46-21. According to the cps anatomical categorisation (HarvardOxford Atlas), it means on the Lh displacement from central opercular cortex to the pars opercularis of the IFG, the SMG of the parietal cortex, and to the temporal area of the planum. On the Rh: from the SMG and central opercular cortex to the frontal operculum cortex, from the parietal operculum cortex to the frontal operculum cortex, from temporal planum to the pars opercularis of IFG, from the temporal planum to the SMG and AG of the parietal cortex. The cortical front-parieto-temporal circuits are inter-connected and subcortically related with WM fiber tracts.

3) Clinical results and correlation with BPI

Finally, we evaluated the clinical results and the average of functional recovery immediately after surgery and during the follow-up period, to evaluate any correlation between BPI and age of scholarship/ intellectual status of each patient, distinguishing patients harbouring LGG or HGG. We searched for any correlation between the final

performance in the AAT test and histology. We collected clinical evaluation and neuropsychological assessment with Language, summing the results and correlating with

BPI for each patient. Then we correlated the previous results with the MMSE.

First, we evaluated the correlation between the estimated BPI and the variation of the MMSE test values (expressed in percentage, considering the maximum value of the test). Only for Lh, results were counted (because of l not enough data on Rh). For HGG patients: there was a good correlation between BPI value and MMSE variation ($R = -0.80$): the higher the BPI, the more difficult cognitive recovery was ($R = -0.80$). Coherently, for LGG the trend was the same, although the correlation was much lower (R=-0.17).

Clinical performance on the AAT test for LGG and HGG: once more, the distinction between LGG and HGG was considered. We analyzed the clinical results at the different linguistic items (Language comprehension, production, semantic, phonological, denomination, repetition, written language). Clinical evaluations were performed by our Speech Therapist (Dr F.F.) following our protocol. The last evaluation was performed using rnTMS. We designed a score between 0 and 6 (i.e. 0=complete aphasia, 6=normal performance). The clinical data results were normalized, with the min-max scaling method, respecting the minimum and maximum values, test threshold values, to ensure that higher test values correspond to better cognitive functioning. All clinical results were reported as percentages, to make test results comparable. **Figure 6** Spider plots summarize data sets of patients with glioma. Considering the *variation in different linguistic components at the AAT test*: for LGG there was an average variation of Language function from 91.1% (pre-op), to 78.66% (post op at 30±10 days FU), with final recovery to 90.67% (post op at 90±10 days FU). For HGG the average variation counted form 91% (pre-op), to 87.34%% (post op at 30±10 days FU), with final recovery to 90% (post op at 90±10 days FU). Although the linguistic performance had an average higher value for HGG patients, the final recovery was comparable (90.67% vs 90%).

Discussion:

- Neuroplasticity and Metaplasticity

Neuroplasticity represents a pivotal concept in modern neuroscience, and it has been described as the brain's capacity to reorganize itself by forming new neural connections[51]. The innovative idea of 'Metaplasticity', recently introduced by Professor Duffau[52], refers to the flexible and re-shaping functional architecture of the brain parenchyma, able to

activate parallel and interactive large-scale neural networks. This idea goes beyond the localizationist theory, based on the inflexible cerebral architecture relying on discrete specialized areas, each of them being supposed to correspond to a specific function. Indeed, the dynamic "meta-networking" (network-of-networks) framework, with perpetual modulation of within- and between-circuit spatiotemporal integration, opens the door to neuroplasticity.

This work aims at proposing a method to calculate a cortical BPI, based on nTMS data, to customise the surgical approach and the postoperative rehabilitation program. Analysing the cortical plasticity through the non-invasive method of nTMS represent a beneficial strategy to modulate plasticity and predict the functional reorganisation of cortical circuits.

- BPI Patterns in LGG vs. HGG

BPI values specific for Language resulted higher in the Lh (46.07 mm) than in the Rh (33.30 mm). Conversely, for LGG a higher BPI was in Rh (57.58 mm) than in the Lh (22.39 mm). However, the overall higher BPI value was obtained for HGG (46.70 mm) than for LGG (28.19 mm). The correlation between BPI and tumor volume was estimated from a linear regression (only for Lh: LGG R=0.28, HGG R=0.31) and documented an irrelevant role of tumor volume on conditioning the final BPI, meaning that correlations (R=0.28/0.31) were non-significant. Qualitative displacement showed linguistic pathway reshaping from temporo-parietal areas to the inferior frontal gyrus and specific cortical areas highlighted with the HarvardOxford cps.

- Clinical Correlations (MMSE, AAT)

Moreover, we analyzed the relation between BPI and MMSE: either for HGG and LGG, the higher the BPI, the more difficult cognitive recovery was, although the correlation resulted lower for LGG (R=-0.17 vs R=-0,80).

We finally considered the variation in different linguistic components at the AAT test: Although the linguistic performance had an average higher value for HGG patients, the final recovery was comparable in the two groups (90.67% vs 90%).

- Language function: a complex network

Language is the most complex function whose impairment may have a serious impact on the routine life of a patient and several studies have demonstrated the WM fibre tracts underneath this function[9,53,54]. In this study we have proposed a model, completely based on nTMS data, to compute functional re-shaping of Language in Lh/ Rh, according to the

adequate tests provided, and making a distinction between LGG and HGG, reducing bias of selection.

❖ Tumor Biology & Plasticity Mechanisms

LGG and HGG exhibit distinct growth patterns and connectivity disruptions, necessitating tumor-specific approaches to preserve plasticity.

- LGG have been studied considering the mechanism of growth and relationship with WM. The presence of a dynamic functional dialogue between brain parenchyma and tumoral lesion implies induction of plasticity and network re-organization, since there is a bidirectional relationship[1]: (i) the glioma proliferation is triggered by microstructural electrical-functional activities and further affected by whole-brain network dynamics; (ii) the functional connectivity between gliomas and other brain areas, and in-between remotely situated brain areas, is intensely reshaped to maintain network efficiency and cognitive performances (i.e. the compensatory mechanisms of lesion-induced neuroplasticity). The surgical treatment of oncological patients' needs to consider these aspects, distinguishing between HGG vs LGG, to preserve quality of life (QoL) or accessing the postoperative treatment with a satisfactory outcome. Moreover, every therapeutic step may play a role in the modulation of BPI, fragilizing microcircuits that convey functional remodeling, and surgery is one of the first-line-treatment whose aims are removing the lesion (extent of resection strictly connected with Overall Survival_OS_ and Progression Free Survival_PFS[55,56]), obtaining seizure control[57]. Our cortical BPI aligns with the 'minimal connectome' theory, where low-plasticity regions (e.g., unimodal cortex, associative tracts) limit functional reshuffling: unimodal cortical areas and WM structures (especially associative WM tracts) were found to represent a major limitation of plastic potential, with low plastic indices. Delineating the pattern of tumor diffusion within critical WM tracts is necessary to predict the expected extent of resection in a surgical perspective and the expected neurocognitive declines following surgery or radiotherapy. The next step of our research is aimed at WM infiltration pattern analysis,

- For HGG and GBM, connectome has been demonstrated to play a role for structural and functional connections within hierarchical networks,[58]. Considering HGG as intrinsic entities, inducing structural-functional alterations in the brain parenchyma, implies a radical change for therapeutic options, which could

optimize surgical strategies and adjuvant treatments. Not only for LGG but also for HGG, connectivity must be considered, as we did in our work, obtaining comparable results in terms of quantitative-qualitative BPI. Then, non-invasive brain stimulation could disrupt pathological neuron–glioma interactions within specific networks, and nTMS may play a role not only for functional mapping but also to induce a functional reshaping of circuitry. Other authors have already proposed to use of priming nrTMS compared to unprimed nrTMS, to modulate plasticity and optimize recovery time[59]. Finally, like Krieg et al.[18,60], we observed nTMS-driven language plasticity, but our BPI metric further quantifies reshuffling by tumor type; plastic reshaping of cortical language areas was evaluated by navigated transcranial magnetic stimulation in a surgical case of GBM[61]. Our study has the innovative role of creating a nTMS-based BPI, conversely to prior DCS/tractography studies.

- Studies on brain plasticity have important practical implications. To the best of our knowledge, our work is the first one that offers a qualitative and quantitative analysis of Brain Plasticity based on nTMS data, relying on the functional cortical map, comparing pre- and post-operative results. Different studies have discussed about the concept of brain connectivity and functional reshaping after surgery on oncological neurosurgical patients[1,51,62,63]. In Price et al[63], nTMS language mapping was performed for a 56-year-old lady presented with a recurrent speech deficit seventeen months after her initial craniotomy for a language eloquent glioblastoma (GBM). During the second awake surgery, speech arrest was found (during Direct Cortical Stimulation) in a new position posterior to the previous surgical cavity and away from tumour recurrence (where speech arrest was previously located). This case report shows language function neuroplasticity in glioblastoma. Recently, some authors[64] focused the attention on the possible hallmarks of brain plasticity, such as molecular characteristics of changes in brain plasticity which may reveal disease course and the rehabilitative potential of patients. The authors published a review about the association of brain plasticity and its homeostasis with cerebral non-coding RNAs (ncRNAs) microRNAs, which make them putative targets for RNA-based diagnostics and therapeutics.

  However, all these studies used techniques that are different from ours to ‘calculate’ the plasticity.

❖ <u>Therapeutic Implications & Future Directions</u>

We can easily understand that we are facing a very crucial topic in the neuroscientific domain, which involves physicians, surgeons, oncologists and radiotherapist who are committed to optimise the type of treatment and the quality of life of oncological patients. However, the value of the present work is the proposal of a non-invasive technique to study cortical plasticity, analysing pre- and post-operative data that could easily be obtained at different times during the follow-up period, allowing analysing an immediate post-operative functional reshaping and a secondary (longer) response over time.

Limitations:

1) Number of patients analyzed for estimation of BPI: the number of patients available was limited (n=40) and not all harbored a glioma (7 had different histological diagnoses). The subgroup of 14 patients whose pre-and postoperative mapping were overlapping properly were analyzed in detail with the pipeline created.

2) Clinical evaluation results: the results of the clinical assessments for AAT were divided into classes, rather than reporting the absolute value of the scores. Conversely, in the case of the MMSE test we had absolute values of the scores reported.

Conclusions:

This preliminary work proposed an innovative and original model to 'measure' BP at a cortical level, creating a quantitative-qualitative metric of functional displacement, to evaluate the correlation between BPI and linguistic outcome of oncological patients. Based on our promising results, we have created an original pipeline to process data, we have learnt how to use the 3D volume of cortical functionally active nTMS points, and finally designed a metric, distinguishing between HGG and LGG. The adaptative mechanisms for LGG and HGG are timely different and might justify the differences between BPI and clinical results for those pathological categories. Identifying a subject-specific BPI may non-invasively define functional reshaping of cortico(-subcortical) circuits after surgery, providing personalised surgical-therapeutic approach. Further data is needed to study other functions and corroborate our results.

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Figure Legend:

Figure 1: Image processing pipeline for the calculation of the nTMS-based-Brain Plasticity Index (BPI). As explained in the chapter Materials&Methods: first, negative and positive TMS points (coordinates x, y, z, acquired in CSV files from the EB Neuro system) were used to generate two binary volumes indicating the location of the TMS data in the MRI volume. This volume was then registered (affine transform) on the T1 volume. For each cerebral function, we considered if nTMS tests have been performed for both hemispheres. Using the registered binary nTMS volume, two 2D maps were created with an orthogonal

projection of the volume on the sagittal plane of Rh and Lh. We obtained Orthogonal projection on the right hemisphere of the TMS points for the language task; subsequentially a nearest neighbor interpolation for the language tasks was performed to acquire volumes (blobs): red blobs are nTMS pre-op volumes, whereas green blobs are nTMS post-op volumes. The average distance of pre- and post-operative blobs defines the metric of displacement, defined as BPI.

Figure 2: Orthogonal projection on the right hemisphere of the TMS points for the language task (patient 17).

Figure 3: Nearest neighbor interpolation for the language tasks for patient 17 in the Right Hemisphere (Rh). The interpolation was calculated with data presented in Figure 2.

Figure 4: Brain plasticity metric (in mm) represented in false color maps on functions identifying before the surgical operation. The red contours indicate the delineation of the postoperative identifications. The white arrows indicate the mean displacement direction. A: we represented the BPI of Language function for patient P17 on the Right Hemisphere. B: we represented the BPI of Language function for patient P31 on the Left Hemisphere.

Figure 5: BPI for Language Function (complete cumulative results) for patients with low-grade and high-grade gliomas. Right and Left hemisphere are represented with overlay of the anatomical atlas HavardOxford. The darker the violet is, the closer the cortical functional displacement is, whereas the more yellow area corresponds to those that had a higher displacement. It is possible to notice the higher functional complexity and re-organization present on the left rather than on the right side, either for HGG and LGG, since language networks are more developed in the dominant hemisphere. A: BPI fro LGG, B: BPI for HGG. Our approach consisted of calculating a weighted sum of the plasticity metrics weighted by the number of patients having a non-null metric at the voxel position. For example, if only one patient (among n patients) has a plasticity displacement of 2 mm in the motor cortex, the value of (2 mm/1) appears in the final image.If 10 patients have a plasticity displacement of 4 mm in the visual cortex, the value of (4 mm/10) appears in the final image.

Figure 6: Dataset of individual cognitive test results administered to assess language function. The test results were divided into patients with LGG and HGG. In green, the values of the tests administered in the pre-operative trial; in orange, the results obtained in the immediate post-operative period; in red, the results obtained after 3 months from the operation. All test results were normalized by transforming them into percentages, considering the maximum value and range of the individual tests.

Table 1: Patients' characteristics

Table 2: Summary table of BPI metrics for Language function. The average, median and standard deviation values are reported, divided into patients with Low Grade (LGG) and High Grade Gliomas (HGG) and with respect to the left and right-brain hemispheres.

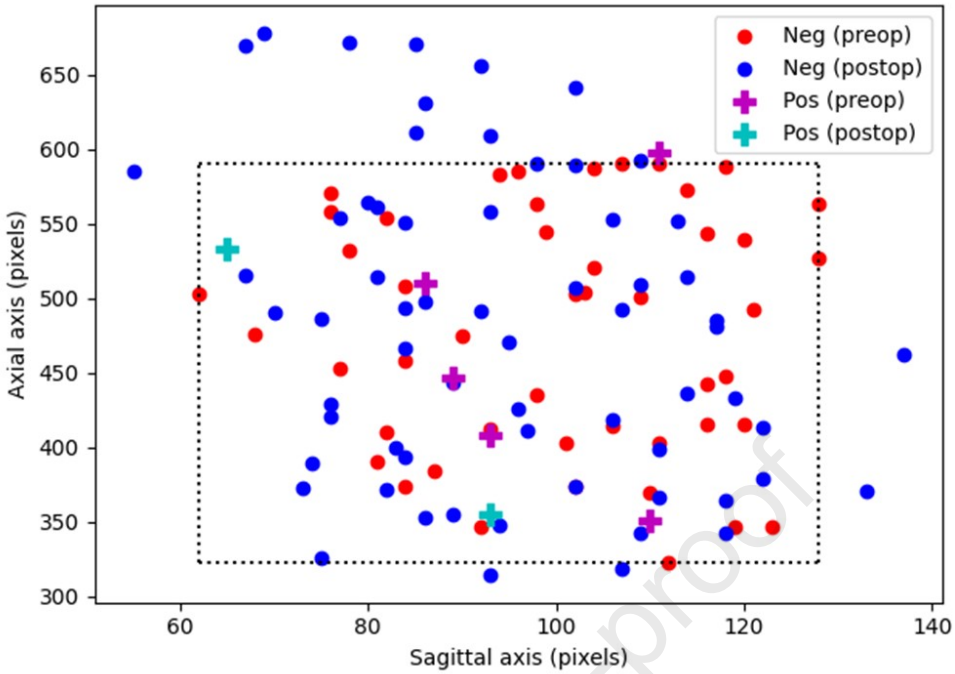
Table 1: Patients' characteristics

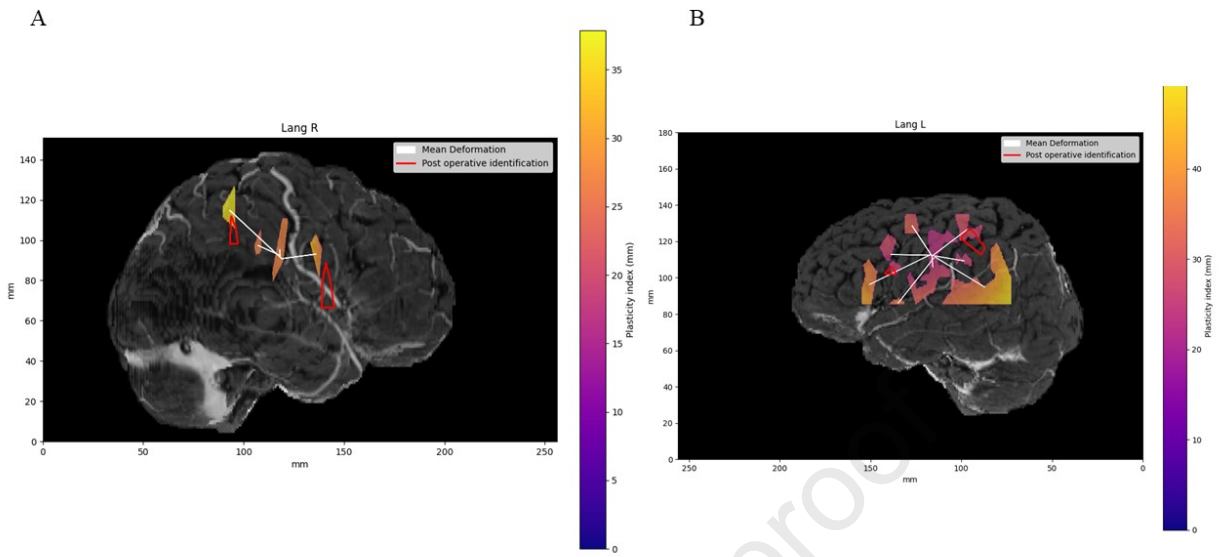
P Code	Operation	Type	Lobe	Site (L/R)	Grade WHO 2021	IDH (0=wt, 1=muted)	Hystology WHO2021	nTMS functional mapping	nTMS side
1	1°	Awake	T	L	2	1	Astrocytoma	M/L/C	Bilat
4	1°	Asleep	F	R	2		Oligodendroglioma	M*no post/L	Bilat
5	1°	Awake	F	L	4	0	GBM	M/L	Left
10	1°	Awake	P	L	3	1	Astrocytoma (focal anaplasia)	M/L/C*no post op/N	Left
11	1°	Asleep	T	L	4	0	GBM	M (*R)/L	Left
16	1°	Asleep	P	L	4		GBM	M/L/C/N *No post op	Left
17	1°	Asleep	Splenium CC	L and R	3	1	Diffuse Astrocytoma	M/L/C	Bilat
19	1°	Awake	F -T- In		2	1	Oligodendroglioma	M *No pre op/L	Left
25	1°	Awake	P	L	3	1	Astrocytoma	M/L/C/N	Bilat
29	2°	Awake	F	L	2	1	Oligodendroglioma	M/L/C/N	Bilat
30	1°	Asleep	F-I	R	4	0	GBM	M/L/N/C*Not possible	Bilat
31	2°	Asleep	T-I	L	2	1	Astrocytoma	M/L/C	Bilat
32	1°	Asleep	T-I	L	2	1	Oligodendroglioma	M*no post op/L/N/C*Not possible	Bilat
36	1°	Awake	T	L	2-->3	1	Low grade glioma (focal anaplasia)	M/L/C	Left

Table 2: Summary table of BPI metrics for Language function. The average, median and standard deviation values are reported, divided into patients with Low Grade (LGG) and High Grade Gliomas(HGG) and with respect to the left and right-brain hemispheres.

LOW GRADE GLIOMAS (6L, 1 R)		
Average [mm]	**Median [mm]**	**Std [mm]**
LEFT HEMISPHERE		
21.81	22.39	8.61
RIGHT HEMISPHERE		
57.58	57.58	2.11

HIGH GRADE GLIOMAS (5L, 1 R, 1 BILATERAL)		
Average [mm]	**Median [mm]**	**Std [mm]**
LEFT HEMISPHERE		
54.65	46.07	35.63
RIGHT HEMISPHERE		
33.30	33.30	25.65





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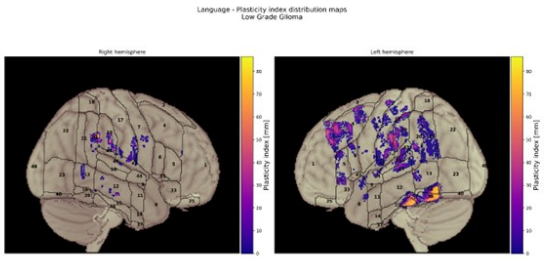

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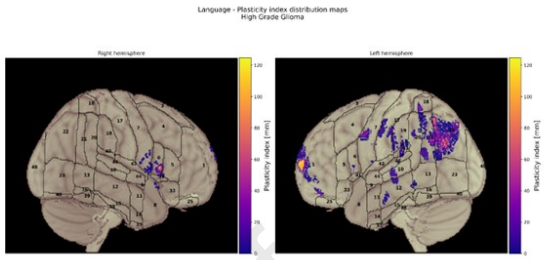

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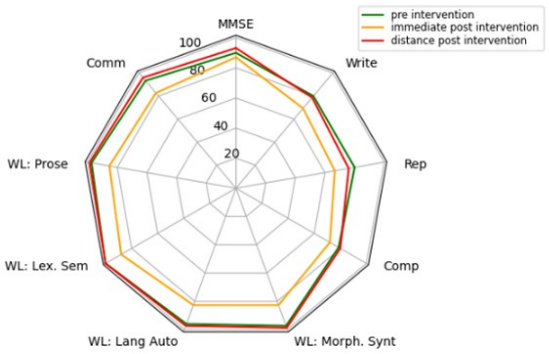

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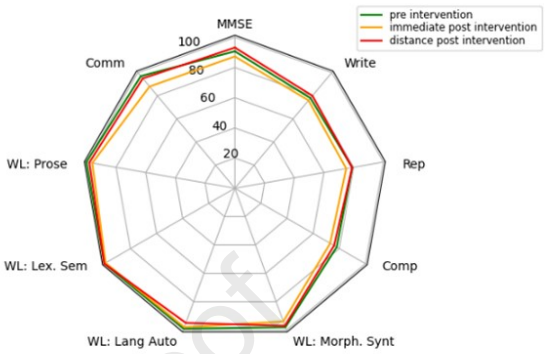

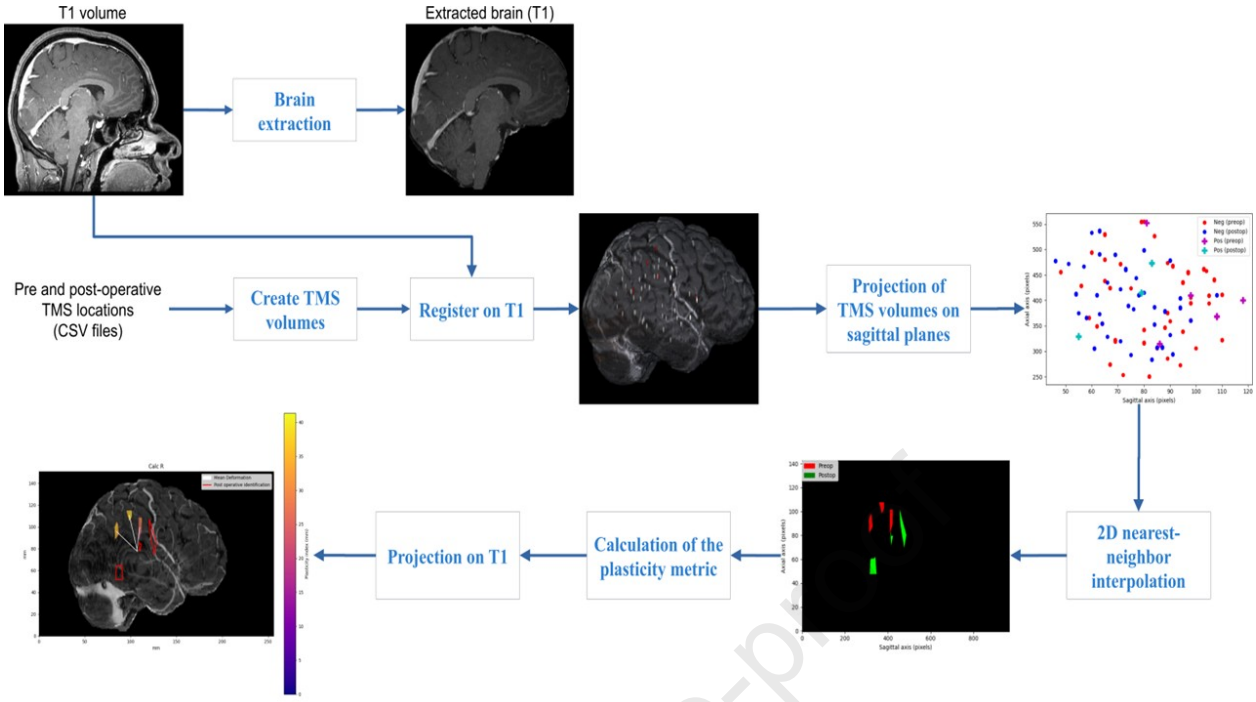

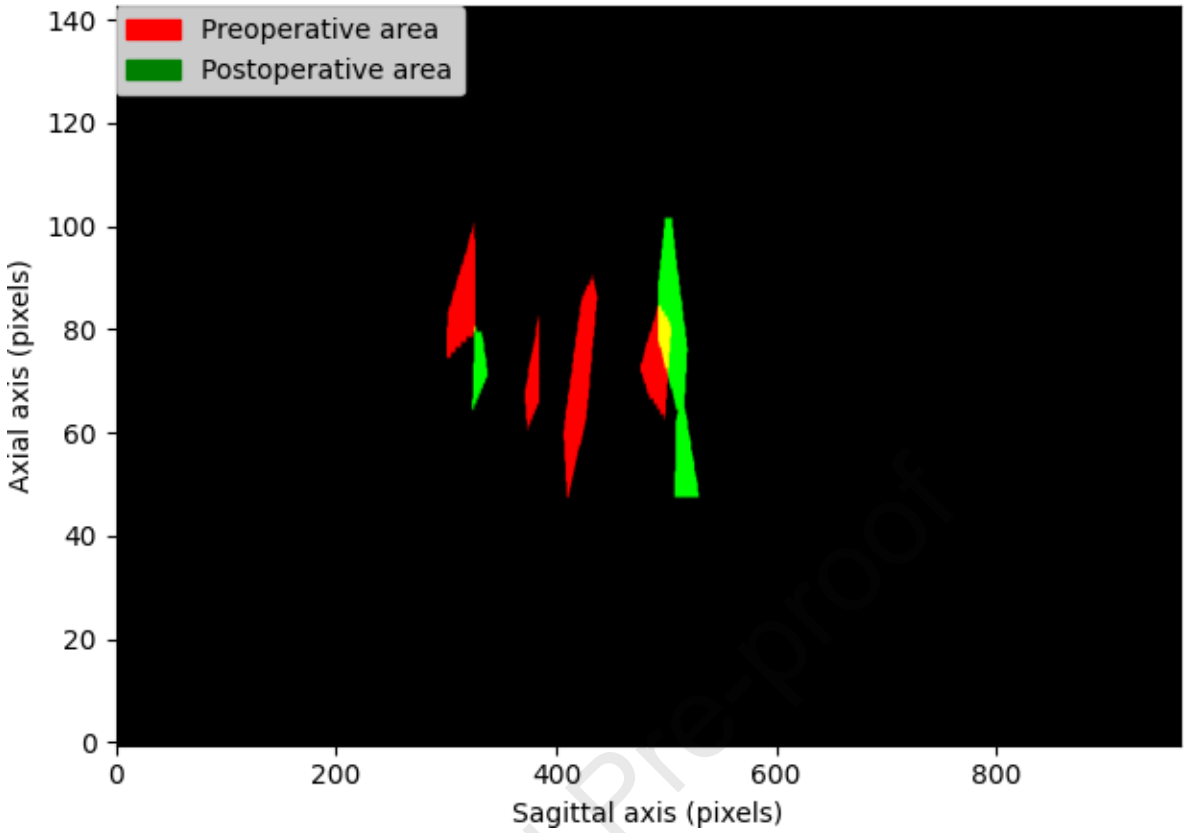

Abbreviations' List

BPI: Brain Plasticity Index

Lh: Left Hemisphere

Rh: Right Hemisphere

AAT: Aachener Aphasia Test

nTMS: navigated Transcranial Magnetic Stimulation

rnTMS: repetitive navigated Transcranial Magnetic Stimulation

FCD: Focal Cortical Dysplasia

Ln: Language

C: Calculation

N: Neglect

RMT: Resting Motor Threshold

HGG: High Grade Glioma

LGG: Low Grade Glioma

DISCLOSURE: The authors have no conflict of interest to declare