Planning brain tumors resection with an atlas of cortico-subcortical structures critical for neural functions: a proof of concept.

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ABSTRACT

Background

Functional pre-operative planning for resection of lesions harboring eloquent cortico-subcortical regions is still an open challenge. Direct electrical stimulation (DES) is the recommended technique for a safer approach to these lesions. DES provides reliable functional data at the cortical and, uniquely, at the subcortical level for neurosurgical, anatomic, and neuroscience purposes. A comprehensive probabilistic atlas of critical cortical and subcortical epicenters based on DES data from hundreds of patients is now available. We propose here a pipeline for the automatic alignment of these functional maps with MRI volumetric imaging and provide a practical quantitative and qualitative demonstration of technical and operative results.

Material and methods

10 patients (7 males; mean age 47.5 years; all right-handers) underwent asleep-awake-asleep surgery (5 low-grade gliomas, 4 high-grade gliomas and 1 cavernous angioma) with DES (60Hz, 1 ms, 1.75-4 mA amplitude range) during neuropsychological monitoring were selected for testing the tool. We aligned selected cortical and subcortical functional maps of the atlas to the pre-operative T1 volumetric MRI (with and without gadolinium) of each patient. We quantitatively evaluated the alignment of the functional maps. Finally, we calculated the match between the position of the different functional responses elicited in this surgical series and the respective functional maps of the atlas at both the cortical and subcortical levels.

Results

The tool provided a reliable and accurate alignment of the functional maps with the patients' volumetric T1 with and without gadolinium (dice similarity coefficient 0.92 and 0.94 for cortical and subcortical maps, respectively). The matching analysis between functional maps and functional responses collected during surgeries was 88% at the cortical and 100% at the subcortical level.

Conclusions

The pipeline was shown to be reliable in providing a systematic alignment of DES-based functional maps to an individual patient's MRI preoperatively, and to correlate well with intraoperative stimulation data at the cortical and subcortical levels.

In summary, this tool may serve as a complementary technique for surgical planning and patient counseling for patient's undergoing surgery in or near eloquent structures by providing a reliable and useful probabilistic map of critical neural structures as they relate to the tumor, with particular regard to the subcortical functional framework.

Key words: pre-operative planning; functional atlas; direct electrical stimulation; brain mapping; neuro-oncology

INTRODUCTION

Surgical planning for intra-axial, infiltrating brain lesions is still an open challenge of modern neurosurgery. Different non-invasive approaches have been proposed for the identification of critical functional cortical and subcortical (i.e. white matter connections) structures at the individual and population levels. Tractography (for the identification of white matter connections)[5,14], functional MRI (fMRI, resting-state or task-based)[26,27] , and/or transcranial magnetic stimulation (TMS)[11] have been used to assess functional networks, and haveprovided exciting and encouraging results. Nevertheless, at this time data from non-invasive neuroimaging studies are not sufficient for establishing whether a given structure is absolutely critical for a given function. As such, these modalities cannot be fully "trusted" for neurosurgical planning[2,13,15,23,27], particularly at the subcortical level.

The widespread use of intra-operative direct electrical stimulation (DES) during awake surgery (AS) has improved the clinical and oncological outcome of patients with lesions involving eloquent areas (i.e. gliomas, cavernous angioma)[7,28,29] and has provided substantial data offering new insights into the neuroscientific challenge of mapping the highly complex structural and functional human brain connectome.[6,8] Data from DES have been used for computing cortical[9,24] and subcortical[18,20] atlases, with a high degree of reliability relative to current neuroimaging techniques. Recently, we reported a large cortical and subcortical DES data set (including 1821 functional responses in a series of 256 patients) that were used to compute probabilistic maps for 16 key human brain functions.[21,22]

Here we propose a pipeline that will be available online for alignment of these probabilistic maps of critical cortical and subcortical structures to an individual patient's MRI for use in patient counseling and pre-surgical planning.

MATERIAL AND METHODS

Pre-operative MRI data

All patients underwent a planning MRI on Clinical Optima MR450w GE 1.5 T scanner, with an imaging protocol that included a 3D T1-weighted (T1-w) inversion recovery gradient echo sequence for structural imaging (axial acquisition, TR/TI/TE=10.64/450/4.23 ms, FA=12°, square FOV=256 mm, voxel size=1x1x1 mm^3, ASSET acceleration factor=2).

Alignment tool

The tool consists of an initial preprocessing of the subject's T1-w images, followed by registration onto a template atlas (MNI 152, T1 1mm) in order to warp the labels of the functional atlas to the individual subject space (Figure 1). The preprocessing starts with AC-PC (anterior and posterior commissure) alignment, through rigid registration with the template. Then, the whole brain mask is obtained by means of a deep learning network, modeled as a 3D U-Net[3,16] trained in advance on more than one thousand examples. After the brain masking, T1-w images are corrected for bias field inhomogeneities using N4-ITK.[25] Finally, the pre-processed T1-w images are aligned to the template through affine registration and then the specific labels selected for the patients are warped to the individual native subject space, applying the inverse of the transformations. All registrations were performed using the ANTs toolkit.[1]

Surgical series and technique

We selected 10 patients (7 males; mean age 47.5 years; all right-handers at Edinburgh Handedness Inventory Test) that underwent asleep-awake-asleep surgery for resection of intrinsic brain lesions (5 low-grade gliomas, 4 high-grade gliomas and 1 cavernous angioma) at the Department of Neurosurgery of "S.Chiara" Hospital (Azienda Provinciale per i Servizi Sanitari of Trento, Italy). All patients provided their written consent approved by institutional review board for utilizing data obtained from surgery and neuro-cognitive evaluations for scientific purposes. We aligned the volumetric pre-operative T1-w images (with and without gadolinium) to the probabilistic cortical and subcortical maps considered as essential based on proximity to the previously published and validated population based cortical/subcortical functional atlas.[21,22] Patients underwent cortico-subcortical DES (60 Hz, 1 ms) mapping during neuropsychological monitoring tailored to functions of interest as previously described by our Group.[22,27] The full details of the intra-operative testing and a comprehensive description of the surgical technique and DES for each case are reported in the Supplementary Data section. Patients had nor pre-operative neurological or neuro-cognitive deficits.

For each patient we selected specific cortical and subcortical maps considering the location of the different lesions (Table 1). The threshold for cortical and subcortical mapping (range: 1.75-4 mA) was set by eliciting speech arrest during a counting task at the level of the ventral pre-motor cortex (VPMC) in all cases, excluding patients 6, 7 and 9 (see also Case Discussion and Figures 1S-10S in Supplementary Data). In these cases, the intensity threshold was set by evoking an overt motor response with stimulation of the pre-central gyrus (Pre-CG; see also Figure 6S, 7S, 9S). For neuro-cognitive monitoring we adopted the battery already described by our Group: a picture naming task for language; palm-pyramid-tree test (PPTT) for non-verbal semantic comprehension; line bisection test for spatial perception; counting test for speech planning; serial word/phrase presentation for reading; picture presentation in quadrants for positive and negative visual responses; a modified version of the reading the mind in the eyes test for mentalizing; overt muscle movement at rest for motor; patient reporting of paresthesia for somatosensory; cessation of complex movements of upper or lower limbs for movement arrest.[9,10,12,17–19,22,26,27,30] No patients experienced new permanent neurological deficits following surgery.

Collection of intra-operative functional responses

The co-first author (L.A.), who was not involved in the computation of the cortical and subcortical DES atlases cited in this work, and is a neurosurgeon trained in human brain anatomy and functional brain mapping, independently collected off-line the functional responses of the 10 surgical cases. The MNI coordinate of intra-operative stimulation points were obtained as previously reported and validated[9,18,20–22,24].

RESULTS

Alignment results

The tool succeeded in brain extraction in all cases with T1-w images. Visual inspection of the brain mask allows the assessment of an accurate segmentation of the brain volume (Figure 2). Similarly, accurate results were achieved using T1w images with gadolinium. Considering as reference the brain masks extracted from the T1-w images, the accuracy error for the brain mask extracted from T1-w images with gadolinium is lower than 7‰ with respect to the same subject.

The registration of the cortical and subcortical regions from the MNI 152 T1 (1 mm) template to patients volumetric T1-w (1 mm) was coherent with the brain structure (Figure 2 and 3). We also investigated differences in registration accuracy for contrasted T1-w images. A rigid transformation was computed between paired T1-w and T1-w with gadolinium images for each subject, and then the transformation was applied to the ROIs. For each pair of ROI, both in T1-w reference space, we measured the Dice coefficient, a quantity that provides the degree of overlap of two ROIs. The dice similarity coefficient (DSC) coefficient is 1 when two ROIs perfectly overlap. In our case the registration of ROIs is not invariant with respect to the kind of T1-w image used as reference for the computation of transformation. Nevertheless the degree of overlap is highly satisfactory, both for cortical and subcortical ROIs (DSC 0.92 and 0.94 respectively).

A third assessment on the quality of alignment was concerned with the stimulation points. The purpose was to measure whether and how the stimulation points are coherent with the ROIs registered from the functional atlas. We considered as reference ROIs those registered to T1-w with gadolinium space. We then projected the coordinates of the stimulation points with respect to this voxel space. Finally we computed whether these points fell in their respective functionally-related ROIs with an approximation of 10 mm (considering the 5mm spacing of the bipolar stimulator used and the current spreading), as previously reported by our Group.[22,26,27] We collected the results of this test and aggregated them according to case and ROI views (Figure 3). Our results indicate that the coherence between the stimulation points and the ROIs registered from functional atlas is nearly 100% (Table 2 and 3). Only 2 functional responses at intra-operative stimulation in Subject 1 and 2 in Subject 9 (specifically anomia), were not within 10 mm of the co-registered atlas.

Intra-operative brain mapping comparison

From this surgical series of 10 cases we collected comprehensively 57 intra-operative DES responses for different functional domains: motor 17 (11 cortical); somato-sensory 10 (8 cortical); speech arrest 9 (all cortical); verbal apraxia 3 (all subcortical); anomia 9 (7 cortical); semantic paraphasia 1 (subcortical); visual 8 (all subcortical). A full description of each case included in this surgical series is provided in the Supplementary Data section. We included figures summarizing the pre-operative planning provided by the cortical and subcortical functional maps alignment, the post-operative MRI and the intra-operative pictures of the cartography of functional sites at the cortical and subcortical levels (a sample is available in Figure 2 and 3). We extensively discussed the results of cortical and subcortical mapping of each case in supplementary data, providing also a visual comparison of the co-registered functional maps with respect to the intra-operative pictures of the mapping results and the post-operative MRI with the tags of the functional responses reported for each subject (a sample is reported in Figure 2).

DISCUSSION

The identification of cortical epicenters and critical subcortical connectivity during resection of intrinsic brain lesions is still an open challenge in modern neurosurgery, with the goal of reducing post-operative deficits while maximizing the extent of resection. The most reliable tool for the precise identification of cortical and subcortical eloquent structures at the individual level is DES during AS with neuro-cognitive monitoring.[7] On the other hand, AS is not always feasible. Independent of whether the surgery is done awake or asleep, incorporating accurate probabilistic functional data into pre-operative planning may be quite useful for neurosurgeons, including (a) counseling patients on the risk profile of surgery (b) establishing whether AS is necessary (c) deciding on the appropriate intraoperative testing paradigms if AS is undertaken (d) establishing regions of interest to make stimulation more efficient in the operating room and (e) continually improving an individual neurosurgeon's understanding of the complex 3-D anatomy of functional brain networks, particularly for trainees. In addition, despite its growing use for surgical planning, functional neuroimaging is intrinsically not able to distinguish the structures essential for neural functions that must be preserved during surgery (in particular the white matter tracts, which represent the main limitation of neural plasticity) from those which are part of the network and may be compensable following resection.

We propose in this study a tool for neurosurgical and other clinical uses that provides a fully automated alignment of MRI sequences with probabilistic functional maps, coming from an unprecedented DES mapping dataset including 16 networks and their probabilistic distribution at cortical and subcortical levels recently published by our Group and publicly available.[21,22]

The tool was set up to accept the most frequently used sequence for pre-operative planning and neuronavigation (i.e. volumetric T1, 1 mm), and the pipeline was set up to align probabilistic atlas data onto the T1-w images of an individual patient without modifying the original patient's imaging, which makes the tool quite practical for an individual neurosurgeon wanting to evaluate the relationship of his/her patient's tumor anatomy relative to critical cortical areas and their connections (as validated in more than 250 patients via DES).

In our test cohort of 10 patients, we demonstrated the maximum rate of success (100%) in brain extraction after uploading individual patient pre-operative volumetric T1 scans, with and without gadolinium. The linear registration was qualitatively reliable in all the cases. However, considering that brain extraction is one of the most critical steps leading to a correct final alignment of the atlas' maps), we suggest uploading the pre-operative T1 without gadolinium as the input file for the tool, as the use of this sequence does not impact on the final goal of the alignment. In addition, the tool produce separate niftii files for each functional map requested that can be opened on other sequences of the same patient (e.g., volumetric T1 with gadolinium and/or T2/FLAIR) with common neuroimaging software, or even uploaded into neuronavigation using the T1 without gadolinium as a reference for merging with other sequences.

For validation of the tool, we tested the accuracy in 10 patients undergoing awake surgery with intra-operative brain mapping in order to provide both a quantitative and qualitative assessment of reliability. In all cases but two we demonstrated accurate matching between the functional responses evoked at individual level and the relevant co-registered probabilistic group-level DES atlas components, at both the cortical and subcortical levels (88% and 100% at the cortical and subcortical levels, respectively). One possible explanation for the discrepancy in cases 2 and 9 is the larger size of the surgical cavities with respect to the others of this small series (see also Figures of the supplementary data including the intra-operative picture and the post-operative T1 MRI). In fact, in these exceptions, the discordance was seen at the cortical level where the intra-operative deformation is highest. Given the an affine transformation may not be suitable to manage high local tissue distortion, future iterations of the tool should explore high degree of freedom non-linear transformations, as this may be a more appropriate choice for the alignment in the setting of large surgical cavities. While our validation cohort is relatively small in number, it is worth noting that the high level of matching between the intra-operative DES results and the co-registered atlas maps is quite favorable in comparison to other non-invasive techniques for pre-operative functional planning (e.g. resting-state fMRI and task-based functional MRI, transcranial magnetic stimulation).[4,27]

Limitations and future developments

The results are currently limited to a relatively simple affine registration of the MNI template, with the motivation of minimizing the requirements for taking advantage of the DES functional atlas and making the tool of practical use to most neurosurgeons, including those in a community setting. In that regard, the tool only requires a standard T1 image for uploading. A more accurate registration might be obtained with a diffeomorphic transformation; nevertheless additional inputs would have to be provided, e.g. a mask of tumor and gray/white matter tissue segmentation. The trade-off between the potential benefit of diffeomorphic transformation and the margin of error in segmenting the tumor and brain tissues will require further investigations.

CONCLUSIONS

In summary, we have validated a simple and reliable pipeline for linear registration of cortico-subcortical maps (imported from our recent probabilistic functional atlas of the human brain based on DES data from >250 patients) with individual patient volumetric T1-weighted MRI with and without contrast. In the test series reported here, individual patient-derived positive stimulation points aligned well with co-registered atlas-based functional maps, and thus can be useful for presurgical planning, in particular designing an appropriate and efficient cortical and subcortical mapping strategy for the operating room. The tool will be available on line, requires only a patient's standard T1-weighted MRI for input, and will output separate nifti files, each containing critical cortical and subcortical data for16 functional domains as they relate to that individual patient's tumor anatomy, allowing for straight-forward visualization for preoperative planning as well as seamless integration into the operating room neuronavigation suite. .

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Conflicts of interest

No Authors have conflicts of interest regarding the contents of this work.

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FIGURES LEGENDS

Figure 1

Schematic of the pipeline used for the alignment of MRI T1-weighted volumetric sequences with the nifti probabilistic maps of the cortico-subcortical functional atlas.

ANT, advanced normalization tool (software); MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; ROI, region of interest.

Figure 2

Box A. Results of automatic alignment of the pre-operative volumetric T1-weighted sequence with the functional cortical and subcortical maps selected for this case (patient 1; see also a full description in Supplementary Data section).

Box B. Results of the intra-operative DES mapping with neuro-psychological monitoring and correlation with the post-operative T1-weighted sequence.

Box C. Comparison between pre-operative cortico-subcortical functional planning and the results of intra-operative functional DES mapping.

Figure 3

In these panels we show the brain-extracted 3D models of all the patients included in this series, including the anatomical location of all functional responses collected during each surgery at cortical and subcortical levels (represented as spheres of 10 mm-diameter) and the overlap with the respective cortical and subcortical functional maps.

Figure_1. Schematic of the pipeline used for the alignment of MRI T1-weighted volumetric sequences with the nifti probabilistic maps of the cortico-subcortical functional atlas. ANT, advanced normalization tool (software); MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; ROI, region of interest.

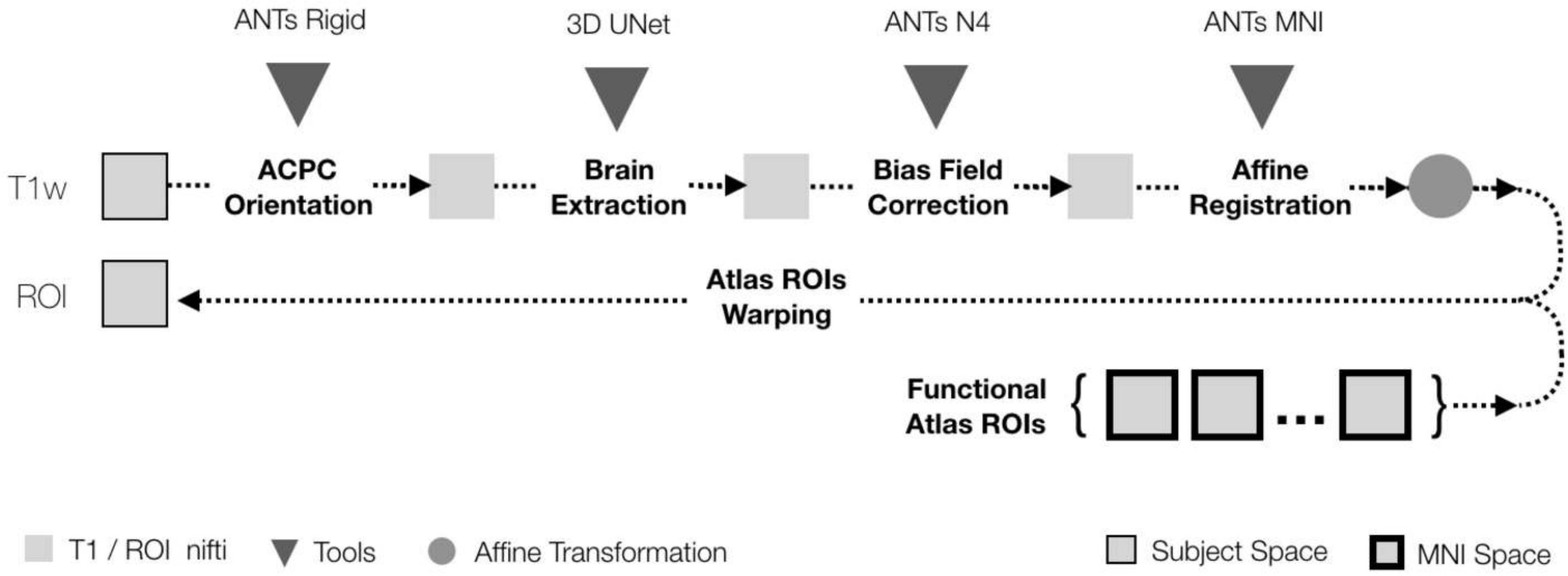
ANTs Rigid
3D UNet
ANTs N4
ANTs MNI
T1w
ACPC Orientation
Brain Extraction
Bias Field Correction
Affine Registration
ROI
Atlas ROIs Warping
Functional Atlas ROIs
T1 / ROI nifti
Tools
Affine Transformation
Subject Space
MNI Space

Figure_2. Box A. Results of automatic alignment of the pre-operative volumetric T1-weighted sequence with the functional cortical and subcortical maps selected for this case (patient 1; see also a full description in Supplementary Data section). Box B. Results of the intra-operative DES mapping with neuro-psychological monitoring and correlation with the post-operative T1-weighted sequence. Box C. Comparison between pre-operative cortico-subcortical functional planning and the results of intra-operative functional DES mapping.


A
Pre-op planning with DES cortico-subcortical functional atlas
Semantic paraphasia
Visual
Phonological paraphasia
Speech arrest
Anomia
Verbal apraxia
0.2
0.4
0.6
0.8
1.0
B
Intra-operative brain mapping and post-operative volumetric MRI
41
42
2
3
1
0
C
Comparison between pre-operative planning and intra-operative brain mapping and post-operative volumetric MRI
Semantic paraphasia
Verbal apraxia
Speech arrest
Anomia

Figure_3. In these panels we show the brain-extracted 3D models of all the patients included in this series, including the anatomical location of all functional responses collected during each surgery at cortical and subcortical levels (represented as spheres of 10 mm-diameter) and the overlap with the respective cortical and subcortical functional maps.

Patient 1
Cortical
Anomia
Speech arrest
Subcortical
Semantic paraphasia
Verbal apraxia
Patient 2
Cortical
Speech arrest
Subcortical
Motor
Verbal apraxia
Patient 3
Cortical
Anomia
Motor
Speech arrest
Subcortical
Visual
Patient 4
Cortical
Motor
Speech arrest
Subcortical
Visual
Patient 5
Cortical
Anomia
Speech arrest
Subcortical
Anomia
Patient 6
Cortical
Motor
Somato-sensory
Subcortical
Motor
Somato-sensory
Patient 7
Cortical
Motor
Somato-sensory
Subcortical
Motor
Somato-sensory
Patient 8
Cortical
Speech arrest
Patient 9
Cortical
Anomia
Motor
Subcortical
Verbal apraxia
Visual
Patient 10
Cortical
Speech arrest

Figure_1S. Box A. Patient 1 was affected by a diffuse astrocytoma (grade II WHO), harboring the left parietal lobe. Considering the cortico-subcortical diffusion of the tumor we selected for the pre-operative planning sample the maps of language functional elaboration (in particular, anomia, semantic and phonological paraphasia), the speech planning (i.e. speech arrest and verbal apraxia), and the visual network. Box B. Intensity threshold was set at 2.5 mA. The cortical margins of resection were established after identification of systematic speech arrest (tag 1), paresthesia (tag 0) and anomia (tag 2 and 3, at denomination object and PPTT respectively). The resection was stopped at subcortical level after eliciting verbal apraxia (tag 41), semantic paraphasia (tag 42). Box C. The comparison between the intra-operative brain mapping and the probabilistic cortico-subcortical distribution of functional responses in the maps selected for this case showed a good correlation with speech arrest and anomia at cortical level, and both semantic paraphasia and verbal apraxia at subcortical level. DES, direct electrical stimulation; PPTT, palm-pyramid-tree test.


A
Pre-op planning with DES cortico-subcortical functional atlas
Anomia
Phonological paraphasia
Speech arrest
Semantic paraphasia
Verbal apraxia
Visual
0.2
0.4
0.6
0.8
1.0
B
Intra-operative brain mapping and post-operative volumetric MRI
41
42
42
41
41
42
2
3
1
0
C
Comparison between pre-op planning and intra-op brain mapping
Semantic paraphasia
Anomia
42
42
2
3
41
Speech arrest
1
0
41
Verbal apraxia
0.2
0.4
0.6
0.8
1.0

Figure_2S. Box A. Patient 2 was affected by an anaplastic astrocytoma (grade III WHO), harboring the right mid-ventral pre-CG. Considering the cortico-subcortical diffusion of the tumor, we selected for the pre-operative planning sample the maps of motor, somato-sensory and negative motor networks, eyes movements, and speech planning (i.e. speech arrest and verbal apraxia). Box B. The results of intra-operative mapping. Intensity threshold was set at 1.75 mA after eliciting systematic speech arrest (tag 0). The pre-CG DES evoked systematic motor responses of mouth and superior limb. The resection was stopped at subcortical level after eliciting verbal apraxia (tag 43), and contraction of mouth and superior limb (tag 41 medial and lateral, respectively). Box C. The comparison between the intra-operative brain mapping and the probabilistic cortico-subcortical distribution of functional responses in the maps selected for this case showed a good correlation with speech arrest and with both motor and verbal apraxia at subcortical level. DES, direct electrical stimulation; pre-CG, pre-central Gyrus.

A
Pre-op planning with DES cortico-subcortical functional atlas
Eyes movement
Motor
Somato-sensory
Motor arrest
Speech arrest
Verbal apraxia
0.2
0.4
0.6
0.8
1.0
B
Intra-operative brain mapping and post-operative volumetric MRI
41
41
41
43
0
43
41
43
C
Comparison between pre-op planning and intra-op brain mapping
41
Motor
41
43
Speech arrest
0
43
Verbal apraxia
0.2
0.4
0.6
0.8
1.0

Figure_3S. Box A. Patient 3 was affected by a diffuse astrocytoma (grade II WHO), deeply sited in the left mid temporo-basal region. Considering the cortico-subcortical diffusion of the tumor, we selected for the pre-operative planning sample the maps of language functional elaboration (in particular, anomia, semantic and phonological paraphasia), speech planning (i.e. speech arrest and verbal apraxia), and reading (i.e. alexia). Box B. The results of intra-operative mapping. Intensity threshold was set at 1.75 mA after eliciting systematic speech arrest (tag 0) and motor response of the mouth (tag 1). The following cortical mapping was aimed to find a safe area to approach the deep lesion and we evoked a second speech arrest at the level of the SMG (tag 1) and anomia at the posterior third of the STG (tag 2). No other functional responses were elicited at reading, PPTT and denomination test. At subcortical level we stopped after complete resection of the lesion and after identification of the functional margins eliciting systematic semantic paraphasia and phosphenes in the upper right quadrant at denomination for quadrants (tag 44). Box C. The comparison between the intra-operative brain mapping and the probabilistic cortico-subcortical distribution of functional responses in the maps selected for this case showed a good correlation with both speech arrest and anomia at cortical level, and with semantic paraphasia at subcortical level. DES, direct electrical stimulation; PPTT, palm-pyramid-tree test; SMG, Supra-Marginal Gyrus; STG, Superior Temporal Gyrus.

A
Pre-op planning with DES cortico-subcortical functional atlas
Anomia
Phonological paraphasia
Speech arrest
Semantic paraphasia
Verbal apraxia
Alexia
0.2
0.4
0.6
0.8
1.0
B
Intra-operative brain mapping and post-operative volumetric MRI
C
Comparison between pre-op planning and intra-op brain mapping
Semantic paraphasia
Speech arrest
Anomia
0.2
0.4
0.6
0.8
1.0

Figure_4S. Box A. Patient 4 was affected by an anaplastic oligodendroglioma (grade III WHO), of the right temporal lobe. Considering the cortico-subcortical diffusion of the tumor, we selected for the pre-operative planning sample the maps of visual network, spatial perception, non-verbal semantic comprehension and speech planning (i.e. speech arrest and verbal apraxia). Box B. The results of intra-operative mapping. Intensity threshold was set at 2.5 mA after eliciting systematic speech arrest (tag 0) and motor response of the mouth (tag 1). After completing the cortical mapping with no functional responses at PPTT, denomination for quadrants and line bisection test we approached the tumor with a large cortico-subcortical resection pushed until the functional limit planned, at the border between the inferior and superior optic radiation (i.e. eliciting phosphenes at the inferior margin of the left inferior quadrant at denomination object for quadrants)(tag 42 and 43). Box C. The comparison between the intra-operative brain mapping and the probabilistic cortico-subcortical distribution of functional responses in the maps selected for this case showed a good correlation with speech arrest and positive visual responses at cortical and subcortical level, respectively. DES, direct electrical stimulation; PPTT, palm-pyramid-tree test.


A
Pre-op planning with DES cortico-subcortical functional atlas
Asemantism
Spatial perception
Speech arrest
Visual
Verbal apraxia
0.2
0.4
0.6
0.8
1.0
B
Intra-operative brain mapping and post-operative volumetric MRI
42
43
C
Comparison between pre-op planning and intra-op brain mapping
Visual
Speech arrest
0.2
0.4
0.6
0.8
1.0

Figure_5S. Box A. Patient 5 was affected by a gangliocytoma (grade I WHO), of the left posterior two thirds of the STG (i.e. Wernicke's area). Considering the cortico-subcortical diffusion of the tumor, we selected for the pre-operative planning sample the maps of language functional elaboration (in particular, anomia, semantic and phonological paraphasia), the speech planning (i.e. speech arrest and verbal apraxia) and reading (i.e. alexia). Box B. The results of intra-operative mapping. Intensity threshold was set at 2.75 mA after eliciting systematic speech arrest (tag 0). The cortical mapping elicited anomia (tag 1) at the level of the middle and posterior third of the MTG and STG, respectively. After complete resection of the lesion the subcortical mapping elicited systematic anomia in the inferior and medial portion of the surgical cavity (tag 41). Box C. The comparison between the intra-operative brain mapping and the probabilistic cortico-subcortical distribution of functional responses in the maps selected for this case showed a good correlation with speech arrest cortical level and anomia at both cortical and subcortical level. DES, direct electrical stimulation; MTG, middle temporal gyrus; STG, superior temporal gyrus.


A
Pre-op planning with DES cortico-subcortical functional atlas
Alexia
Anomia
Phonological paraphasia
Semantic paraphasia
Verbal apraxia
Speech arrest
0.2
0.4
0.6
0.8
1.0
B
Intra-operative brain mapping and post-operative volumetric MRI
C
Comparison between pre-op planning and intra-op brain mapping
Anomia
Speech arrest
0.2
0.4
0.6
0.8
1.0

Figure_6S. Box A. Patient 6 was affected by an anaplastic astrocytoma (grade III WHO), of the dorsal portion of the left pre-CG. Considering the cortico-subcortical diffusion of the tumor, we selected for the pre-operative planning sample the maps of motor, somato-sensory and negative motor networks, eyes movements and apraxia, and speech arrest. Box B. The results of intra-operative mapping. Intensity threshold was set at 1.75 mA mapping the motor strip (tag 0 mouth, tag 1 shoulder, tag 2 arm, tag 3 proximal inferior limb, tag 4 distal inferior limb). The cortical mapping was completed at the level of post-CG at the borders of the tumor, evoking paresthesia at shoulder and arm (tag 5), proximal and distal inferior limb (tag 6 and 7 respectively) and foot (tag 8). The subcortical resection was pushed up to the functional borders eliciting motor responses of foot and proximal and distal inferior limb (tag 44 and 43, respectively) and paresthesia at the level of the whole inferior limb (tag 45). Box C. The comparison between the intra-operative brain mapping and the probabilistic cortico-subcortical distribution of functional responses in the maps selected for this case showed a good correlation with somato-sensory and motor responses at both cortical and subcortical level. DES, direct electrical stimulation; pre-CG, pre-central gyrus; post-CG, post-central gyrus.


A
Pre-op planning with DES cortico-subcortical functional atlas
Motor
Eyes movement
Somato-sensory
Motor arrest
Eyes apraxia
Speech arrest
0.2
0.4
0.6
0.8
1.0
B
Intra-operative brain mapping and post-operative volumetric MRI
C
Comparison between pre-op planning and intra-op brain mapping
Somato-sensory
Somato-sensory
Motor
Motor
0.2
0.4
0.6
0.8
1.0

Figure_7S. Box A. Patient 7 was affected by a diffuse astrocytoma (grade II WHO), of the dorsal portion of the right pre-CG. Considering the cortico-subcortical diffusion of the tumor, we selected for the pre-operative planning sample the maps of motor, somato-sensory and negative motor networks, eyes movements and apraxia, and speech arrest. Box B. The results of intra-operative mapping. Intensity threshold was set at 3 mA mapping the motor strip (tag 3 inferior limb, tag 4 arm and tag 5 hand). The cortical mapping was completed at the level of post-CG at the borders of the tumor, evoking paresthesia at foot and leg (tag 1 and 2, respectively). The subcortical resection was pushed up to the functional borders eliciting motor responses of foot and proximal and distal inferior limb (tag 43) and paresthesia at the level of the whole inferior limb (tag 42). Box C. The comparison between the intra-operative brain mapping and the probabilistic cortico-subcortical distribution of functional responses in the maps selected for this case showed a good correlation with somato-sensory and motor responses at both cortical and subcortical level. DES, direct electrical stimulation; pre-CG, pre-central gyrus; post-CG, post-central gyrus.


A
Pre-op planning with DES cortico-subcortical functional atlas
Motor
Eyes movement
Somato-sensory
Motor arrest
Eyes apraxia
Speech arrest
0.2
0.4
0.6
0.8
1.0
B
Intra-operative brain mapping and post-operative volumetric MRI
C
Comparison between pre-op planning and intra-op brain mapping
Somato-sensory
Somato-sensory
Motor
Motor
0.2
0.4
0.6
0.8
1.0

Figure_8S. Box A. Patient 8 was affected by a cavernous angioma of the left temporal lobe. Considering the cortico-subcortical diffusion of the tumor, we selected for the pre-operative planning sample the maps of language functional elaboration (in particular, anomia, semantic and phonological paraphasia), speech planning (i.e. speech arrest), and reading (i.e. alexia). Box B. The results of intra-operative mapping. Intensity threshold was set at 2.75 mA after eliciting systematic speech arrest (tag 0) with motor movement arrest of the hand also (tag 1). The cortical mapping at the level of the temporal lobe with the test selected (denomination object, PPTT, reading test) did not elicited functional responses and the resection of the cavernous angioma and the hemosiderin rim around was pushed until eliciting semantic paraphasia at subcortical stimulation. Box C. The comparison between the intra-operative brain mapping and the probabilistic cortico-subcortical distribution of functional responses in the maps selected for this case showed a good correlation with speech arrest at cortical level. DES, direct electrical stimulation; PPTT, palm-pyramid-tree test.


A
Pre-op planning with DES cortico-subcortical functional atlas
Alexia
Anomia
Speech arrest
Semantic paraphasia
Phonological paraphasia
0.2
0.4
0.6
0.8
1.0
B
Intra-operative brain mapping and post-operative volumetric MRI
C
Comparison between pre-op planning and intra-op brain mapping
0
1
Speech arrest
0.2
0.4
0.6
0.8
1.0

Figure_9S. Box A. Patient 9 was affected by a diffuse astrocytoma (grade II WHO), of the left pre-cuneus. Considering the cortico-subcortical diffusion of the tumor, we selected for the pre-operative planning sample the maps of language functional elaboration (in particular, anomia, semantic and phonological paraphasia), speech planning (i.e. speech arrest and verbal apraxia) and visual network. Box B. The results of intra-operative mapping. Intensity threshold was set at 4 mA after eliciting motor response at rest of the mouth at stimulation of the ventral portion of the pre-CG (tag 1). The cortical mapping of the entire tumor and tumor-border area elicited anomia at the border with inferior and superior parietal lobule (tag 2 and 3). The subcortical resection of the lesion was pushed until the functional border were reached, eliciting verbal apraxia in the deep and anterior portion of the surgical cavity (tag 44), the border between the superior and inferior optic radiation (i.e. phosphenes between the right inferior and superior quadrants) and visual recognition troubles (tags 45). Box C. The comparison between the intra-operative brain mapping and the probabilistic cortico-subcortical distribution of functional responses in the maps selected for this case showed a good correlation with anomia at cortical level and both visual responses an verbal apraxia ati subcortical level. DES, direct electrical stimulation; pre-CG, pre-central gyrus.


A
Pre-op planning with DES cortico-subcortical functional atlas
Visual
Anomia
Speech arrest
Phonological paraphasia
Semantic paraphasia
Verbal apraxia
0.2
0.4
0.6
0.8
1.0
B
Intra-operative brain mapping and post-operative volumetric MRI
C
Comparison between pre-op planning and intra-op brain mapping
Verbal apraxia
Anomia
Visual
0.2
0.4
0.6
0.8
1.0

Figure_10S. Box A. Patient 10 was affected by a glioblastoma (grade IV WHO), of the right temporal lobe. Considering the cortico-subcortical diffusion of the tumor, we selected for the pre-operative planning sample the maps of visual network, spatial perception, non-verbal semantic comprehension and speech planning (i.e. speech arrest and verbal apraxia). Box B. The results of intra-operative mapping. Intensity threshold was set at 2.75 mA after eliciting systematic speech arrest (tag 0) and motor response of the mouth (tag 1). After completing the cortical mapping with no functional responses at PPTT, denomination for quadrants and line bisection test we approached the tumor with a large cortico-subcortical resection pushed until the functional limit planned, at the border between the inferior and superior optic radiation (i.e. eliciting phosphenes at the inferior margin of the left inferior quadrant at denomination object for quadrants)(tag 43). Box C. The comparison between the intra-operative brain mapping and the probabilistic cortico-subcortical distribution of functional responses in the maps selected for this case showed a good correlation with speech arrest and visual responses at cortical and subcortical level respectively. DES, direct electrical stimulation; PPTT, palm-pyramid-tree test.


A
Pre-op planning with DES cortico-subcortical functional atlas
Verbal apraxia
Visual
Speech arrest
Spatial perception
Asemantism
0.2
0.4
0.6
0.8
1.0
B
Intra-operative brain mapping and post-operative volumetric MRI
43
A
B
C
1
0
C
Comparison between pre-op planning and intra-op brain mapping
Visual
Speech arrest
43
1
0
0.2
0.4
0.6
0.8
1.0

	Age (years)	Lesion site	Diagnosis	Cortical functional maps	Subcortical functional maps
patient_1	41	left parietal	diffuse astrocytoma, grade II WHO	semantic paraphasia, phonological paraphasia, visual, speech arrest, anomia, verbal apraxia	semantic paraphasia, phonological paraphasia, visual, speech arrest, anomia, verbal apraxia
patient_2	63	right mid pre-central	anaplastic astrocytoma, grade III WHO	motor, motor arrest, somato-sensory, eyes movements, speech arrest, verbal apraxia	motor, motor arrest, somato-sensory, eyes movements, speech arrest, verbal apraxia
patient_3	25	left deep temporo-basal	diffuse astrocytoma, grade II WHO	semantic paraphasia, phonological paraphasia, alexia, speech arrest, verbal apraxia, anomia	semantic paraphasia, phonological paraphasia, alexia, verbal apraxia, anomia
patient_4	52	right posterior temporal	anaplastic oligodendroglioma, grade III WHO	visual, spatial perception, speech arrest, verbal apraxia, asemantism	visual, spatial perception, speech arrest, verbal apraxia, asemantism
patient_5	33	left Wernicke's area	gangliocytoma, grade I WHO	semantic paraphasia, phonological paraphasia, alexia, speech arrest, verbal apraxia, anomia	semantic paraphasia, phonological paraphasia, alexia, verbal apraxia, anomia
Patient_6	44	left dorsal pre-central	diffuse astrocytoma, grade III WHO	motor, motor arrest, somato-sensory, eyes movements, speech arrest	motor, motor arrest, somato-sensory, eyes apraxia, speech arrest
patient_7	74	right dorsal pre-central	diffuse astrocytoma, grade II WHO	motor, motor arrest, somato-sensory, eyes movements, speech arrest	motor, motor arrest, somato-sensory, eyes apraxia, speech arrest
patient_8	53	left temporo-basal	cavernous angioma	semantic paraphasia, phonological paraphasia, alexia, speech arrest, anomia	semantic paraphasia, phonological paraphasia, alexia, anomia
patient_9	53	left pre-cuneus	diffuse astrocytoma, grade II WHO	semantic paraphasia, phonological paraphasia, visual, speech arrest, verbal apraxia, anomia	semantic paraphasia, phonological paraphasia, visual, speech arrest, verbal apraxia, anomia
patient_10	37	right temporal	glioblastoma, grade IV WHO	visual, spatial perception, speech arrest, verbal apraxia, asemantism	visual, spatial perception, speech arrest, verbal apraxia, asemantism

Table 1. Summary of age, lesion site, histological diagnosis and cortical and subcortical functional maps selected for each patients included in the series.

Functional Response	**Cortical**	**Subcortical**	**Total**
Anomia	43%	100%	56%
Motor	100%	100%	100%
Semantic Paraphasia	-	100%	100%
Sensorial	100%	100%	100%
Speech Arrest	100%	-	100%
Verbal Apraxia	-	100%	100%
Visual	-	100%	100%
Total	88%	100%	98%

Table 2. Percentage of inclusion of the stimulation points in the functional ROIs with 10mm tolerance.

Patient	Cortical	Subcortical	Total
1	33%	100%	60%
2	100%	100%	100%
3	100%	100%	100%
4	100%	100%	100%
5	100%	100%	100%
6	100%	100%	100%
7	100%	100%	100%
8	100%	-	100%
9	33%	100%	71%
10	100%	100%	100%

Table 3. Percentage of inclusion of the stimulation points within the functional ROIs in the different subjects (10 mm tolerance)