The parietal architecture binding cognition to sensorimotor integration: a multimodal causal study

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Abstract

Despite human's praxis abilities are unique among primates, comparative observations suggest that these cognitive motor skills could have emerged from exploitation and adaptation of phylogenetically older building blocks, namely the parieto-frontal networks sub-serving prehension and manipulation. Within this framework, investigating to which extent praxis and prehension-manipulation overlap and diverge within parieto-frontal circuits could help in understanding how human cognition shapes hand actions. This issue has never been investigated by combining lesion mapping and direct electrophysiological approaches in neurosurgical patients.

To this purpose, seventy-nine right-handed left-brain tumor patients candidate for awake neurosurgery were selected based on inclusion criteria. First, a lesion mapping was performed in the early post-operative phase to localize the regions associated to an impairment in praxis (imitation of meaningless and meaningful intransitive gestures) and visuo-guided prehension (reaching-to-grasping) abilities. Then, lesion results were anatomically matched with intraoperatively identified cortical and white matter regions, whose direct electrical stimulation impaired hand-manipulation task.

The lesion mapping analysis showed that prehension and praxis impairments occurring in early post-operative phase were associated to specific parietal sectors. Dorso-mesial parietal resections, including the superior parietal lobe and precuneus, affected prehension performance, while resections involving rostral intraparietal and inferior parietal areas affected praxis abilities (covariate clusters, 5000 permutations, CFWER $p < 0.05$). The dorsal bank of the rostral intraparietal sulcus was associated to both prehension and praxis (overlap of non-covariate

clusters). Within praxis results, while resection involving inferior parietal areas affected mainly the imitation of meaningful gestures, resection involving intraparietal areas affected both meaningless and meaningful gesture imitation. In parallel, the intraoperative electrical stimulation of the rostral intraparietal and the adjacent inferior parietal lobe with their surrounding white matter during hand-manipulation task evoked different motor impairments, i.e. the arrest and clumsy patterns respectively.

When integrating lesion mapping and intraoperative stimulation results, it emerges that imitation of praxis gestures first depends on the integrity of parietal areas within the dorso-ventral stream. Among these areas, the rostral intraparietal and the inferior parietal area play distinct roles in praxis and sensorimotor process controlling manipulation. Due to its visuo-motor "attitude", the rostral intraparietal sulcus, putative human homologue of monkey AIP, might enable the visuo-motor conversion of the observed gesture (direct pathway). Moreover, its functional interaction with the adjacent, phylogenetic more recent, inferior parietal areas might contribute to integrate the semantic-conceptual knowledge (indirect pathway) within the sensorimotor workflow, contributing to the cognitive up-grade of hand-actions.

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Introduction

Praxis is the neurological process by which cognition directs motor action[1,2]. This process allows an abstract, conceptual and extremely flexible use of our hand sensorimotor repertoire, which is considered a hallmark of the human evolution. Praxis embraces several skills, from the ability to functionally interact with tools or pantomime their use (transitive actions), to imitation of meaningless and meaningful gestures (intransitive actions). These skills can be dramatically impaired following brain lesions resulting in the so-called *apraxia*, a deficit in the execution of purposive hand movements, not attributable to elementary motor and sensory disorders.

Converging comparative evidence suggests that phylogenetic old brain mechanisms subserving transitive actions, such as object prehension and manipulation, may represent the *building blocks* from which the human praxis abilities have emerged[3–5]. Specifically in this regard, humans and non-human primates share similar dorso-dorsal and dorso-ventral parieto-frontal streams for controlling distinct, although complementary, aspects of the hand-object oriented actions[6,7]. In humans, the presence of the *building blocks* and the parallel expansion of the frontal, parietal, and temporal areas[8] led to a significant sophistication of the sensorimotor repertoire, which represents the substrate fostering in humans a rapid cultural evolutionary process. Coherent with this view, fMRI studies showed that the hand-related parieto-frontal connectivity extends in humans to compose the so-called *praxis representation network* (PRN[9,10]). The human PRN is a large-scale, left-lateralized, temporo-parietal-frontal circuit claimed to be involved in translating conceptual and sensorimotor information into purposeful hand skilled acts (praxis), including transitive and intransitive hand gestures[9,11]. Pivotal lesion studies in stroke patients support the evidence that impairment of specific parietal and temporal sectors of this large-scale-pathway results in the onset of distinct apraxia symptoms[12–15].

Overall, these results suggest that the exploitation and modification of the pre-existing parieto-frontal *building blocks* under the guidance of evolutionary processes[16–18] has been critical for the achievement of sophisticated and cognitive directed hand actions. Among them, intransitive "communicative" hand-arm gestures represent a distinguishing feature of humans with respect to the monkeys that hardly use their hand for such purposes[19]. Within this framework, investigating

to which extent the pathways subserving object-oriented actions (including visuo-guided prehension and object-manipulation) and the pathways subserving intransitive praxis gestures overlap and differentiate within the parieto-frontal circuits, seems crucial to disclose the neural mechanisms shaping the motor action based on high-level cognitive information.

To this aim, the present study was grounded in the clinical setup for patients undergoing awake neurosurgery for brain tumor resection allowing to use complementary causal approaches and specifically 1) the lesion symptom mapping (LSM) and 2) the intraoperative direct electrical stimulation (DES). Specifically in this study, the LSM was performed in the early post-operative (7 days post-surgery) phase to localize the brain regions associated to lower scores in praxis (imitation of meaningless and meaningful intransitive hand gestures) and prehension (reaching-to-grasping) performance. The regions highlighted by the LSM were then anatomically matched with cortical and white matter regions related to haptic hand-object manipulation identified intraoperatively with direct electrical stimulation (DES) within the same cohort of patients. The intraoperative hand-manipulation task (HMt) was performed without visual guidance in order to isolate and preserve mainly motor (and/or somatomotor) components of the parieto-premotor areas subserving hand manipulation functions[20–26]. Primary input to the rationale of this study has been the observation that the application of the intraoperative HMt actually turned out to reduce also long-term upper-limb ideomotor apraxia deficits. This observation suggests a close proximity between manipulation and praxis substrates, fostering the hypothesis that the exploitation of specific hand-related *building blocks* might be an important aspect for the emergence of cognitive praxis gestures as well as a relevant clinical tool guiding the intraoperative monitoring. However, even though the permanent apraxia was avoided, about 20% of patients suffered of transient ideomotor apraxia symptoms in the early post-operative phase[20]. These transient symptoms may be explained by the marginal impairment of the praxis-related neural substrates, possibly interleaved with motor and/or somatomotor object-manipulation substrates and/or lying in the tissue along the resection cavity's borders draw with the HMt. In particular, in the early post-operative phase, the resection borders undergo to a transient inflammation possibly altering their correct functioning.

Overall, these clinical considerations fostered the need to investigate the degree of co-localization between the intraoperative DES sites associated to HMt, and the regions associated to lower scores

in praxis functions in early post-operative phase. However, the intraoperative HMt involved only the distal control of the hand-object interaction, therefore the full deployment of the visuo-guided prehension (from the direction of arm movements to the shaping of the hand according to the object shape and location), i.e. reaching-to-grasping, was intraoperatively unexplored. To fill this gap and provide the most comprehensive view of all the areas involved in the hand-object oriented action (from proximal-reaching to distal-grasping/manipulation), the spatial matching between the regions associated to lower scores in visuo-guided prehension assessment and the intraoperative hand-manipulation-related sectors was performed. Notably, the complementary use of three tasks (HMt, visuo-guided prehension and praxis) all constrained to the dexterous use of the hand as a final common path, grounds on four pillars: 1) the tasks rely on different sensory and sensorimotor modalities: visuomotor (both prehension and praxis) and somatosensory-motor (or somatomotor, all the tasks); 2) the tasks investigated distinct hand-action domains: *transitive* hand-object oriented actions (HMt and prehension) and imitation of *intransitive* gesture (praxis); 3) within transitive action, the haptic execution of the HMt investigated the somatomotor component involved in the hand-object oriented action, while the visuo-guided prehension extended the investigation to the visuomotor component; 4) within praxis, gestures to be imitated differed in the cognitive content: communicative (meaningful) or not (meaningless).

The combined use of the tasks along the four pillars allowed to investigate the degree of co-localization between the areas involved in *transitive* object-related actions (HMt and prehension) and the areas more specifically involved in the imitation of the observed *intransitive* action. The combination of these tasks within the same framework aims to investigate to which extent the intransitive praxis gestures, requiring the purposeful use of the hand for imitating meaningless or meaningful (communicative) gesture, exploit phylogenetically ancient parieto-frontal pathways subserving transitive object-oriented actions.

Materials and methods

Patients' selection

Enrolled in the study were 79 right-handed patients undergoing awake neurosurgery for a left-brain tumour resection (WHO Tumor grade: high-grade glioma (HGG) n=48, 61%; low-grade glioma (LGG) n= 27, 34%; others n= 4, 5%; Age: average = 49.5 ± 14.8, range 19 – 76; gender: 69% male n=55, 64%; female n=24, 31%). All patients were assessed for handedness using the Edinburgh Handedness Inventory and underwent a pre-operative, 7-days and 1-month postoperative neuropsychological evaluation and objective neurological examinations. The seventy-nine patients were included meeting the following inclusion criteria:

1) first procedure of tumour resection, to minimize the impact of the disease and treatments on brain functional reorganization;

2) tumour not infiltrating the Supplementary motor area, the precentral/postcentral hand-knob in order avoid the inclusion of patients with invalidating basic motor and somatosensory impairments.

3) post-operative MRC (Medical Research Council) upper-limb score ≥ 4 in order to ensure the absence of elementary motor deficits affecting the praxis and prehension assessments.

4) post-operative absence of severe sensory (tactile and visual) deficit assessed by means of neurological assessment.

5) post-operative absence of language comprehension deficits impacting the reliability of the assessments.

6) pre-operative absence of pathological score for ideomotor apraxia (De Renzi global score > 53)

7) pre-operative absence of any clinically observable deficit during object prehension-manipulation (ARAT global score = 48)

According to tumor localization patients were categorized mainly as frontal/fronto-temporal (n=27, mean cavity volume: 113.378±75.868 voxels, range 3.607-259.376), parietal/parieto-temporal (n=34, mean cavity volume: 48.528±32.429 voxels, range 12.949-152.927), and temporal (n=18, mean cavity volume: 61.679±38.321 voxels, range: 13.952-135.001).

All participants gave written informed consent to the surgical mapping procedure (IRB1299) and data analysis for research purposes, following the principles outlined in the Declaration of Helsinki.

Intraoperative mapping with hand-manipulation task and workflow of the study

All patients underwent the standard brain mapping for language[27], motor[28–31], executive functions[32,33], visual field[34] and manipulation abilities[20–24]. Specifically, the areas crucial for manipulation abilities were assessed intraoperatively with a dedicated task, the Hand Manipulation Task (HMt, see Fig 1). During HMt, patient was asked to grasp and rotate continuously, with thumb and index opposition (precision grip), a specific manipulandum-shaped object. The HMt was performed in absence of visual guidance. During HMt execution, the surgeon stimulated with DES the cortical and subcortical areas required by the clinical needs. During task execution, the hand behavior and the intrinsic and extrinsic hand muscles' electrical activity (EMG) were recorded and synchronized with DES. Intraoperative distinction between brain sites where stimulation interfered (effective sites) or did not interfere (ineffective sites) with task execution was based on both visual inspection of hand behavior and the online monitoring of the EMG activity. An offline analysis of the EMG activity synchronized with video recordings of hand-movement was then performed, allowing a more refined quantitative analysis (for further details see[21–24]).

Aside to the intraoperative assessment, a peri-operative evaluation of patients was performed before, at 7 days (early phase) and at 1-month from the surgery by using an extensive neuropsychological evaluation[35] and specific tests to assess: A) elementary sensory and motor disorders (objective neurological evaluation), B) visuo-guided prehension (reaching-to-grasping) and C) praxis abilities (imitation of intransitive gestures).

The pre-operative assessment was needed to set the baseline condition of each patient (see inclusion criteria). The post-operative scores for prehension and praxis abilities of the selected patients were used in the Support Vector Regression Lesion Symptom Mapping (SVR-LSM) analysis to localize, among the brain areas surgically resected, those associated to lower scores in

prehension and praxis performances. These results were spatially matched with the probability maps reporting the main cortical and subcortical intraoperative sites where DES interfered with manipulation abilities. See Fig 1 for a resume of the methodological approach.

Clinical Assessments

Prehension assessment

The visually guided reaching-to-grasping abilities were assessed by using the ARAT (Action Research Arm Test) scale, which is composed of 18 items divided in four sub-scales: grasp, grip, pinch and gross movements[36]. For the specific purpose of the study, the items were performed with the right upper-limb (contralateral to the affected hemisphere). The ARAT was performed following a standardized protocol and scoring[37]. Instructions were read aloud and a visual demonstration for each item was provided. A time limit of 60 seconds was set to complete each task. The performance of each task was scored from 0 to 3: score = 3 was given when the task was performed correctly in < 5 seconds (behavioral criteria outlined by [37]); score = 2 when the task was completed with overt abnormal hand and/or arm movements or with delay (from 6 to 60 seconds); score = 1 when the task was partially performed within the 60 seconds; score = 0 when none of the hand or arm movement required by the task was performed in 60 seconds. Relevant parameters adopted for the evaluation of the hand-arm performance of all sub items were: 1) smoothness and precision of the reaching movement toward the object-space and, 2) stability and congruency of the grip for each specific target. Since the focus of the ARAT, in the present study, was the clinical assessment of the visually guided reaching-to-grasping movements, the score obtained with gross movements was not included in the analysis, thus the maximum ARAT score (ARAT global score) was 48.

Ideomotor Apraxia assessment

Praxis abilities were assessed with De Renzi test[38,39]: patients were asked to imitate 24 intransitive gestures with the fingers, hand and arm. The task was performed with the contralesional right hand. During test, the patients were asked to maintain the same body posture adopted during the ARAT while the examiners, sitting in front, showed each item to be imitated. To ensure the full

understanding of the instructions by the patients, the assessment started with a simple, test-unrelated, gesture to be imitated (rise the hand). Each gesture was presented up to three times and the performance scored from 3 to 0 depending on whether the execution was correct the first, second, third attempt or never. Among the 24 items, 12 were symbolic (meaningful) and 12 non-symbolic (meaningless) gestures. The total score was 72 (De Renzi global score). Notably, the imitation of the intransitive gesture relies on visual, proprioceptive and tactile feedback provided by contact between different fingers, between the hand/fingers and another body part or another external surface (see some examples in Fig 1). In this regard, the tactile feedback is crucial for the correct execution of the gesture and its monitoring as well as for the correct object-grip during the visuo-guided prehension (ARAT).

Image acquisition and lesion analysis

As part of the clinical routine, pre- and postoperative MRI was performed on a Philips Intera 3 T scanner (Koninklijke Philips N.V.) and acquired for lesion morphological characterization and volumetric assessment[28]. A post-contrast gadolinium T1-MPRAGE sequence was performed using the following parameters TE: 2.75 ms, TR: 1600 ms, flip angle 9°, IT 900 ms; 176 slices; isotropic voxel size of 1 mm.

Resection cavity tracing and Spatial Normalization

For each patient, the resection cavity was manually drawn on the post-operative volumetric T1-weighted images acquired at 5/7 days after surgery by L.F. with MRIcron software[40]. This approach, with respect to the follow-up MRI (>1 month), had the benefit to avoid interference with adjuvant treatments and it is closest in time to the early post-operative praxis/prehension evaluation. Post-operative T1 and cavities of the patients were normalized to 1x1x1mm resolution to Montreal Neurological Institute (MNI) space using the Clinical Toolbox implemented in SPM 12. In all patients, the normalization procedure was applied by using the enantiomorphic algorithm and lesion masking procedure. Since the study was based on performance assessments in early postoperative phase the cavity estimation was smoothed (FWHM 3 mm, Threshold 0.05) for including a small amount of surrounding tissue. The rationale was that the tissue surrounding the resection cavity, spared from the resection, during the early post-operative phase undergoes

inflammation that transiently impairs its functions possibly affecting the behavioral performance. In addition, for each patient we also estimated in the post-operative DWI MRI sequence the occurrence of ischemic lesions, in order to exclude patients with post-operative vascular diseases. Following the normalization procedure, for each patient the results were checked with CheckReg function in SPM 12.

Lesion–Symptom Mapping

Multivariate Lesion symptom mapping has been performed by using support vector regression-LSM (SVR-LSM[41]) implemented by DeMarco and Turkeltaub in a MATLAB-based toolbox[42]. The analysis was performed by applying functionalities of the Statistic and Machine Learning Toolbox within MATLAB 2019b. Optimization of hyperparameters was performed via resubstitution loss and Bayesian optimization with 200 iterations and 5-fold cross-validation, as implemented in Matlab (bayesopt) and recently applied by the authors of the MatLab-base software and others group[44–46]. In addition, the range for the optimized parameters was set following the range of C and Gamma suggested by Zhang et al.[41] and more recently adopted by Wiesen et al.[43]. C range = 1-80, Gamma equivalent Sigma range = 0.1-30 (conversion was performed by using *function=gamma2sigma* available in SVR-LSM gui). A default Epsilon range was set. For each analysis and combination of parameters selected after optimization procedure, both prediction accuracy and reproducibility were evaluated. Based on other studies using similar procedure[44,45], we considered reliable the LSM results when showing accuracy ≥ 0.25 and reproducibility ≥ 0.85.

SVR-LSM was used to identify in the early post-operative phase significant voxels included in the resection cavities and/or around the borders associated with lower scores in the visuo-guided prehension (ARAT) and imitation of intransitive gestures (De Renzi) performance. Large lesions often result in more severe behavioral impairments, regardless of location, decreasing the specificity of the results. Thus, in the present study this aspect was controlled by applying the direct Total Lesion Volume Control (dTLVC) as implemented by Zhang et al.[41]. The resulting SVR-β values were thresholded at $p < .005$ and corrected with cluster size at $p < .05$ both based on 5000 permutations. In addition, continuous permutation-based family wise error (CFWE) correction was configured to permit 1.0 mm^3 of false positives (desired $v = 1$ whole voxels) and accept a family-wise error rate (FWER) of 0.05.

Matching the SVR-LSM results (praxis and prehension) and intraoperative DES (HMt)

Anatomical reconstruction of intraoperative DES results.

In order to match the post-operative SVR-LSM clusters associated to prehension and praxis lower scores with intraoperative cortical and white matter manipulation sites, the anatomical localization of each intraoperative effective site in each patient was needed.

Cortical sites: the exact position of the sites was reported on the 3D MRI (pre-operative) cortical surface of each patient reconstructed with FreeSurfer by means of Brainstorm[46] under the guidance of the flap-video and intraoperative coordinates from neuronavigation (BrainLab). Subsequently the MRI and site were co-registered to MNI space using Brainstorm and clinical toolbox in SPM 12.

Subcortical white matter sites: included in this analysis were the effective stimulated sites located in the white matter below the sulci and/or gray matter as reported by intraoperative coordinates in native space and surgical flap. During postoperative reconstruction, the site was drawn on the preoperative axial volumetric T1 as spherical ROI (6mm diameter, similar to the resolution of the bipolar probe) based on image and related native coordinates acquired with neuronavigation system. The localization of the site was also verified using as reference the postoperative T1. Being the effective sites used as functional borders to stop the resection, the edge of the resection cavity represents an optimal landmark to confirm the site positioning. To this aim, in each patient, the stimulation sites, the preoperative T1 and the postoperative T1 were co-registered to the MNI space by means of the Clinical Toolbox implemented in SPM12.

The accuracy of each co-registration was visually confirmed using the SPM12 CheckReg function. Finally, the anatomical localization of each site in each patient was confirmed by the first operating surgeon (L.B.).

To investigate whether the effective sites clustered in specific subsectors, a modified in-house version of probability kernel density estimation (PDE analysis) implemented in MatLab was applied (see[21,22]for details regarding PDE for cortical sites and[24] for PDE for subcortical sites).

Results

In all the enrolled patients the impact of basic (primary) motor disorders in performance of the ARAT and De Renzi tests, was excluded by enrolling patients with MRC score > 4 and with score = 3 in grasping the "heaviest" wooden cube (10 cm) of the ARAT. The level of whole handgrip strength and somatosensory feedback needed to execute the task excludes the occurrence of primary somatosensory and motor deficits possibly affecting ARAT and De Renzi tasks. Based on these criteria, 7 patients initially recruited were not included in the final analysis.
Results will report: A) ARAT and De Renzi clinical scores distribution; B) SVR-LSM results; C) intraoperative DES results; D) Spatial matching between SVR-LSM and DES.

ARAT and De Renzi clinical scores

ARAT. Since ARAT scores are a continuous measure, without categorical cutoff scores, patients were ranked based on the number of items showing a performance decrease with respect to the pre-operative assessment. **Pre-operative phase**: none of the patients showed observable deficits. **Early post-operative**: 19 out of 79 patients reported a lower score in the early post-operative phase subdivided as follows: A) 10 out of 79 patients with a score decrease only in the pinch subscale (12.6% of patients, average global score 45.2, range 38-46); B) 5 out of 79 patients with a score decrease in pinch-grip items (6.3% of patients, average global score 38.2, range 33-42); C) 4 patients with a score decrease in grasp-grip-pinch (5% of patients, average global score 27.25, range 20-35). **Post-operative 1 month**: at population level, the ARAT global score significantly improved compared to the early post-operative phase with no significant difference with the pre-operative phase (Fig 2B: ARAT scores distribution and statistics).

De Renzi. Pre-operative phase: none of the included patients had a pathological score and only 3 patients showed a borderline global score. **Early post-operative:** 11 out of 79 patients global score fell below the cut-off (13.9% of the patients, cut off < 53, average 41.5, range 30-51) while 6 patients were borderline (7.6%, cut off 53-62, average 59.2, range 53-62). The remaining 62 patients scored above the cut-off (78.5%, average 70.9, range 63-72). **Post-operative 1 month**: at population level, De Renzi global score significantly improved compared to the early post-

operative phase with no significant difference with the pre-operative phase. These results, coherent with previous study of our group[20], confirm the transitory nature of the early post-operative outcome (Fig 2C: De Renzi scores distribution and statistics).

See Supplementary Table 1 for clinical details.

De Renzi and ARAT scores correlation. To assess whether the De Renzi and ARAT early post-operative scores are correlated, a Spearman correlation was performed on the global scores. At population level ARAT and De Renzi global scores significantly correlated (Spearman correlation r=0.557, p<.05). However, among ARAT items, the regression analysis showed that only score of the pinch item significantly predicted a decline in the De Renzi performance (predictors: grasp, grip, pinch; dependent variable: De Renzi global score; F(3,75)=9.74, p<.000, $R^{2\ adjusted}$ =0.25; grasp F=1.72, p=0.19, beta=-0.22; grip F=2.3, p=0.13, beta=0.306; pinch F=6.17, p=0.015, beta=0.408).

SVR-LSM results

Localization of surgical cavities

The SVR-LSM analysis was restricted to the minimum overlap of 7 patients (about 9% of the whole sample). The minimum overlap involved the frontal areas (excluding BA4-BA6), parietal lobe (excluding area 3a, 3b, 1 and marginally including area 2), the temporal lobe, the insular cortex and adjacent opercular regions (Fig 2A). Due to the significant correlation between prehension and praxis global scores, we performed SVR-LSM analysis with and without covariate in order to investigate specific (covariates results) and common (overlap of non-covariate results) voxels for prehension and praxis. SVR-LSM analysis was performed for both early post-operative and 1-month De Renzi and ARAT scores. We report only the early post-operative results, since the prediction accuracy and reproducibility values for the SVR-LSM at 1-month fell below the threshold considered (accuracy < 0.25, reproducibility < 0.85).

Prehension abilities (De Renzi covariate). Results showed that a decrease in the visuo-guided object-prehension abilities was associated to CFWER cluster involving: 1) the superior

parietal lobe (7AL, 7PC, 5L and LIP) and 2) the precuneus (31pd) (Fig 3A-C). Hyperparameters: Cost/Box Constraint = 77, Sigma/Kernel scale = 1.54, Epsilon = 1.9; Prediction accuracy = 0.41, reproducibility index r = 0.86.

Praxis abilities (ARAT global score covariate). Results showed that a decrease in the imitation of intransitive gesture was associated to a CFWER cluster involving: 1) the intraparietal (AIP, IP2) and 2) the inferior parietal lobe (PF/PFm) (Fig 3B-C). Hyperparameters: Cost/Box Constraint = 75, Sigma/Kernel scale = 1.25, Epsilon = 0.1; Prediction accuracy = 0.54, reproducibility index r = 0.86.

Meaningful vs Meaningless praxis gestures (ARAT global score covariate). Results showed that although the two CFWER clusters overlapped within the intraparietal sulcus (IPS), meaningful gesture clustered in a wider area in the inferior parietal lobe (IPL) with respect to meaningless gesture, including mainly PF (Fig 3B). Hyperparameters Meaningful: Cost/Box Constraint = 79, Sigma/Kernel scale = 1.29, Epsilon = 1.8; Prediction accuracy = 0.53, reproducibility index r = 0.87. Hyperparameters Meaningless: Cost/Box Constraint = 79, Sigma/Kernel scale = 1.13, Epsilon = 2.49; Prediction accuracy = 0.48, reproducibility index r = 0.85.

Common region (overlap between ARAT and De Renzi not covariate results). Results showed that common voxels were found mainly within the dorsal bank of the intraparietal sulcus and adjacent dorsal postcentral sulcus (Fig. 3D). Hyperparameters ARAT: Cost/Box Constraint = 30.6, Sigma/Kernel scale = 1, Epsilon = 0.1; Prediction accuracy = 0.45, reproducibility index r = 0.85. Hyperparameters De Renzi: Cost/Box Constraint = 45.3, Sigma/Kernel scale = 1.23, Epsilon = 0.38; Prediction accuracy = 0.59, reproducibility index r = 0.86.

Intraoperative DES results.

Previous studies of our group reported evidence that intraoperative DES delivered on specific premotor[21] and parietal areas[22] as well as on frontal white matter[24] affects the performance of tasks requiring hand-object manipulation (HMt). Since the SVR-LSM analysis performed in the present

study highlighted significant clusters only in the parietal lobe, the spatial matching analysis between lesion results and intraoperative DES results was constrained to the intraoperative data recorded within the parietal lobe[22] at cortical and, as novel finding here, at subcortical level within the parietal white matter. Cortical and subcortical data together allow a more comprehensive spatial matching with SVR-LSM results.

Cortical results. These results were previously published[21]. In brief, intraoperative DES of specific parietal sectors interfered with performance of HMt by disrupting the hand-muscles' recruitment. Probability density estimation, obtained by contrasting effective sites (n=111) with ineffective sites, highlighted significant responsive clusters in the post-central gyrus (somatosensory fingers representation), the putative human homologue of monkey AIP (phAIP[47]) and, more marginally, the anterior PF/PFt within the IPL. (Fig 4A and B(i-ii)). Within the posterior parietal cortex, DES effect on HMt ranged from an abrupt arrest (task-arrest) mainly reported within phAIP, to a lack of finger coordination (task-clumsy) mainly reported within anterior IPL (PF), both associated to different degree of muscle suppression (Fig 4B(iii)).

White matter results. Considering the 8 patients showing effective sites in the deep white matter of the posterior parietal cortex, 16 effective sites were localized (according to the patient native space) in the white matter below the fundus of rostral IPS and postcentral sulcus, broadly corresponding to the white matter below phAIP and PF/PFt. Task-arrest (n=7) responses were mainly found below AIP while task-clumsy (n=9) were adjacent to the white matter below PF (Fig 4C(i)), coherently with cortical distribution.

Matching praxis and manipulation cortical and subcortical sites. The spatial matching analysis showed that intraoperative manipulation-sites and praxis-related clusters co-localized within rostral IPS and IPL regions. More specifically:

1) Within rostral IPS, the intraoperative manipulation-sites clustered within the anterior part of phAIP, while praxis-related voxels at the transition between phAIP and dorso-anterior intraparietal sulcus (DIPSA) (Fig 4B(i-ii)).

2) Within the rostral IPL, despite the lower level of probability, intraoperative manipulation-sites clustered in anterior PF, while praxis-related voxels at the transition between PF and PFm (Fig 4B(i-ii)).

3) The matching obtained at cortical level was specular at subcortical level (Fig. 4C(i-ii)).

4) The anterior IPS was associated to both meaningless and meaningful gestures, while anterior IPL was associated to meaningful gestures. Parallel to this distinction, the manipulation-sites within rostral IPS (phAIP) and IPL (PF) showed different features of motor impairment induced by DES during HMt, task-arrest and clumsy respectively (Fig. 4B(iii-iiii) and 4C(i)).

Discussion

In the present study, we used complementary causal techniques in brain tumor patients: the post-operative lesion mapping to investigate prehension and praxis-related regions, and the intraoperative direct electrical stimulation to investigate object manipulation-related regions. A spatial matching between the results of the two techniques was employed in order to investigate the anatomo-functional relationship between the neural substrates subserving praxis abilities (imitation of intransitive gestures) and the phylogenetically old *building blocks* subserving object-oriented actions (prehension and object-manipulation).

Studies in stroke patients significantly contributed to outline the current theoretical, anatomical and clinical framework in the field of praxis-related disorders. However, several aspects related to the different etiology and clinical outcome prevent a strict comparison between LSM results collected in stroke and brain tumor patients[48]. In this regard, brain tumor is a focal lesion and the resulting resection cavity following the brain mapping technique is *well-identifiable* and *functionally* delimited.

In a different frame, also fMRI studies provided important insight in the field of praxis movements. However, fMRI data are correlational by nature and do not allow to investigate the causal functional role of the different nodes belonging to the PRN. In this regard, the LSM and DES are historically considered the gold standard for causal mapping of human brain functions allowing to draw causal inferences about the role of a specific region with respect to the investigated function, a crucial aspect for translating knowledge into therapeutic targets[49].

However, despite the aforementioned advantages, both LSM and DES have limitations in the present clinical context, in particular the pre-operative brain functional reorganization and the morphological displacement due to tumor mass. Our group adopts specific patients' inclusion criteria for reducing the impact of tumor displacement[22] and for estimating the quality of the coregistration[24]. Despite these criteria cannot fully prevent the impact of such variables on results, the spatial matching between the intraoperative DES and post-operative LSM results is in line with the clinical aim of the intraoperative brain mapping, supporting a good reliability of the results obtained by integrating different methods, at least within the sample of patients enrolled in this study. Finally, based on recent guidelines[50], another potential limitation of the present study is the low sample of patients required to optimally model voxel-wise lesion location in SVR-LSM. However, considering that brain tumor is a rare pathology and the patients' inclusion criteria adopted for the aim of the present study, the resection cavities equally covered frontal, parietal and temporal areas, allowing to causally test the main nodes of the dorso-dorsal and dorso-ventral pathways.

The dorso-ventral stream is specifically implicated in praxis abilities

The first result emerging from this study was the higher relevance of the left posterior parietal lobe, with respect to prefrontal or temporal, in the onset of ideomotor apraxia, in agreement with very first observations[51]. Within the parietal lobe, neuroimaging and lesion studies provided evidence of the involvement of several dorso-dorsal and dorso-ventral parietal sectors in imitation of intransitive gestures[52]. The present study, investigating ideomotor apraxia by using prehension performance as covariate, clearly showed that specific ideomotor praxis deficits were associated to parietal sectors included in the dorso-ventral stream rather than in the dorso-dorsal one. Specifically, the borders of resections adjacent to rostral IPS and IPL are associated to a transient impairment in imitation of intransitive gestures, while more dorsal resections involving the anterior SPL and the precuneus cause a specific impairment in visually guided object-prehension. Notably, the absence of a quantitative kinematic-based approach to prehension movements prevent, in the present study, the investigation of micro-features of movement. However, coherently with our finding, these areas are classically associated to optic ataxia, a high order deficit in reaching visual goals, hand pre-shaping and on-line correction during reaching[53–55].

The dissociation found in the present study is in agreement with evidence suggesting that, although highly coordinated, dorso-dorsal and dorso-ventral pathways play distinct roles in hand actions. In this regard, converging evidence has shown that the dorso-dorsal system, also called *Grasp system*, processes visual-related object physical features for the purpose of prehensile action, while the dorso-ventral stream, also called *Use system*, is involved in the long-term storage of the particular skilled actions associated with familiar objects[56]. Coherently, the two systems are differently connected with temporal (ventral stream) areas and are involved in the extraction of different type of object affordances. Accordingly, the invariant object features, i.e *stable affordances*, emerge from the slow "offline" processing of the visual information based on memorized object knowledge taken over by the dorso-ventral pathway. Differently, changing or temporary object physical features, i.e. *variable affordances*, emerge from the fast online processing of visual information during actual object interaction mainly in charge to the dorso-dorsal pathway[57]. The present results may extend these distinctions showing that specific parietal nodes within the dorso-ventral pathway are crucial also for imitation of intransitive gestures. In this regard, the gesture execution occurs through its observation and recently it has been proposed that visual encoding of other's actions, i.e. *social affordances* -conceived as the variety of action possibilities offered to an individual by other agent's behavior-, exist alongside object affordances. This hypothesis extends the concept of affordances from inanimate object to the other's action[58]. In line with this view, the present results may suggest that dorso-ventral pathway not only encodes stable (complex) affordances related to purposeful interaction with objects, but may extract also social affordances via the observation of the gesture to be imitated. The latter mechanism may be crucial in ideomotor apraxia, possibly favoring the visuomotor conversion of the observed gesture.

Furthermore, although the two streams process distinct action features, the IPS emerge as convergence zone[57]. This finding is coherent with the results of the present study, which points to the dorsal bank of the IPS, mainly corresponding to the transition between dorso-anterior and posterior intraparietal sulcus (DIPSA and DIPSM), as a potential common region. This fits with the positive correlation found between prehension and praxis scores, which suggested that to some extent the two pathways work along a functional continuum rather than in dichotomous way. In this regard, the existence of this intraparietal hub, may subserve common functional aspects and/or the exchange of information between dorso-dorsal and dorso-ventral streams[57], possibly contributing at the extremely flexible use of our hand sensorimotor repertoire, from concrete action

specification to abstract action goals[59]. Interestingly, the regression analysis showed that the sole ARAT item significantly predicting the De Renzi performance was the pinch. The pinch item requires a higher level of dexterity with respect to the other ARAT items and often requires an "unusual" or "less functional" grip posture (i.e. to execute a precision grasping with thumb-ring/thumb-middle finger opposition). Although the interpretation of this result is challenging, it might suggest that, when the required hand-action is less consolidated in our daily sensorimotor repertoire, an efficient communication between streams via intraparietal hubs could be crucial for its implementation.

Parietal lobe hosts distinct praxis route and sensorimotor processes: a comparative perspective

As previously reported[22], DES delivered during HMt onto phAIP evoked an abrupt arrest (task-arrest) while on PF evoked a loss of finger's coordination (i.e. task-clumsy). We suggested that the task arrest might reflect the "transient impairment" of a parietal sector shaping, with a relatively direct access, the motor output. Differently, the clumsy pattern might reflect the "transient impairment" of a parietal sector hierarchically far with respect to the cortical motor output. Overall, we suggest that the different impairments may ultimately arise from a different role of rostral IPS and IPL regions in shaping hand-motor output.

Paralleling the anatomical distribution of the different effects of DES on HMt, the LSM results showed that the parietal sectors adjacent to phAIP and PF were associated to different deficits in imitation/execution of gestures. Resections involving the rostral IPS affected the imitation of both meaningless and meaningful gestures (no gesture type selectivity), while resections involving the rostral PF complex affected mainly the imitation of meaningful gestures (gesture type selectivity), in line with the evidence of a dissociation between the two types of intransitive gestures[60,61]. Taking together, the co-localization between intraoperative DES and LSM results suggests that the different motor impairments evoked by DES within phAIP and PF may reflect different sensorimotor process, possibly subserving different pathways for gesture imitation. In this regard, gesture imitation is indeed subserved by two pathways: the *direct* pathway involved in the execution of the observed gesture regardless to its content; the *indirect* pathway controlling

gestures reproduction through the access to their meaning in the semantic memory[62]. In this light, our results suggest that the former may take place within rostral IPS (cortical area hosting task-arrest and no gesture type selectivity), while the latter within the PF complex (cortical area hosting task-clumsy and gesture type selectivity).

The rostral intraparietal sulcus and the direct pathway

The co-localization within rostral IPS of DES-related effects on manipulation (the arrest effect) and voxel associated to imitation of the observed gestures (no gesture type specificity) might suggest that the integrity of this region could be crucial for both the motor implementation and the visuomotor conversion of the observed gesture.

In this regard, recently has been shown that monkeys and human rostral IPS hosts neurons selective for observed manipulative actions claimed to support a stable read out of the observed actions across visual formats[58,63–65]. Despite the impressive similarities between human and monkey results, neurons in humans showed a greater invariance and generalization across viewpoint compared to monkey, including responses to reading action verbs. The human's greater invariance and generalization may reasonably point to the human IPS as the encoder of a wide variety of actions formats, including non-manipulative actions such as the processing of the observed intransitive gesture. This hypothesis is coherent with fMRI studies in healthy subjects, showing that both transitive and intransitive gestures are processed within the left-lateralized praxis representation network, including the rostral IPS[10,66,67]. The selectivity for the observed manipulative actions within the rostral IPS, essential for action planning during social interaction and interindividual coordination, is suggested to work in parallel with the neural population involved in the sensorimotor transformation for object-oriented action[58]. Based on this premise we may hypothesize that praxis-significant voxels within phAIP/DIPSA transition, could reflect the role of this sector in the visual processing of the observed gesture. Moreover, since the DES of rostral phAIP affected the hand-manipulation motor output evoking task-arrest responses, we might speculate that visual information of the observed gesture might be exploited by phAIP and its connectivity with premotor areas for the motor implementation of the gesture itself. This

functional organization fits with the supposed role of phAIP and DIPSA as motor and visual sector of monkey AIP respectively[47].

Despite obtained by the complementary use of different tasks (HMt and De Renzi) testing distinct action features (transitive vs intransitive), these results could be coherent with the idea of a direct pathway within the rostral IPS subserving visuo-motor conversion during gestures observation/imitation. Notably, this pathway seems to rely prevalently on phylogenetically old rostral IPS nodes, with its main hub within phAIP, a core area belonging to the *lateral grasping network* originally described in monkey (LGN[3]). The LGN belongs to the dorso-ventral pathway and is considered a cognitive interface for hand actions[4]. Our finding about the co-localization of manipulation and praxis voxels within the human rostral IPS strengthens the hypothesis that the anatomo-functional features of the monkey's LGN fostered the cognitive upgrade of the dorso-ventral pathway further subserving the unique human praxis repertoire. Moreover, the dual role in hand-object and hand-gesture oriented actions could reasonably explain why the preservation of the rostral IPS during intraoperative mapping with the HMt, a task actually not assessing directly praxis functions, resulted in prevention of permanent ideomotor apraxia symptoms.

The inferior parietal lobe and the indirect pathway

Conversely, according to LSM results, lesions within PF complex impairs critically imitation of meaningful gestures, pointing at this region, with access to semantic knowledge, as a key structure in the indirect pathway for gesture imitation. Interestingly, DES of PF and its surrounding white matter alters motor execution by evoking task-clumsy responses, hypothesized to reflect a remote access to the motor output with respect to task-arrest. In light of this evidence, we may speculate that the properties of the parietal clumsy region, PF complex, might subserve the integration and gating of conceptual and semantic knowledge into the pragmatic sensorimotor workflow. This hypothesis is in agreement with theories suggesting that meaning or conceptual knowledge would emerge from interactions between multimodal areas and the pathways processing motor information[68]. Rostral PF complex might favor this connection. In this frame, the overall IPL is considered a semantic hub active during semantic processing of cross-modal spatial and temporal configurations[69], thus we hypothesize that PF-related pathways may act as passageway integrating

this information from parietal and temporal high-order multimodal areas, into the sensorimotor workflow taken over by rostral IPS.

Conclusion

Overall, the anatomo-functional interaction between rostral IPS and IPL areas likely represents the neural mechanism by which cognition shapes sensorimotor processing ultimately promoting the unique human hand actions repertoire.

From a clinical perspective, our results suggest that the preservation of this mechanism is crucial for avoiding long standing ideomotor apraxia in brain tumor patients. Preservation of these dorso-ventral parietal regions was possible thanks to the DES applied during HMt, which allowed to identify the functional borders of these areas at cortical and subcortical level, as clearly showed by the spatial matching between DES and LSM results. Therefore, the transient nature of the symptom may be due to the inflammatory state of the tissues preserved at the edge of the resection and/or to a partial impairment of its functioning. Regarding the latter point we could not exclude that, since their role as hub regions within the PRN, these areas might host an extended connectivity, which may promote functional compensatory mechanisms[70].

To summarize, the present results showed a functional dissociation between dorso-dorsal and dorso-ventral streams and within the dorso-ventral one. First, it emerged the existence of a parietal dorso-lateral functional continuum subserving the transition from transitive object-oriented actions (dorso-dorsal pathway) to intransitive praxis gestures (dorso-ventral pathway), with specific rostral IPS sectors possibly working as convergent zone and regulating the flow of information between streams. Moreover, within the dorso-ventral stream our results showed a further dissociation between the role played by rostral IPS (mainly phAIP/DIPSA) and rostral IPL (mainly PF) in the type of gesture to be imitated (meaningless vs meaningful), to same extent mirroring the anatomo-functional distinction between object-manipulation and object(tool)-use[5,71]. Notably, the DES applied to these parietal regions evoked different type of motor impairments during the HMt execution, furthermore suggesting that these sectors may subserve distinct pathways for gesture imitation (direct vs indirect) via different hand-related somatomotor process.

Finally, these areas in addition to be part of the PRN and the LGN respectively in human and non-human primates, in particular IP2 and PFm areas are also core regions within the multiple demand network (MDN[72]). Since its definition, the MDN is implicated in a range of cognitively demanding tasks and appear central to intelligent action[73]. Taking together, this evidence highlights the multidimensional nature of the human praxis abilities and the importance of sensorimotor substrates adjacent and/or interleaved with multimodal areas in translating both gesture-related visual information and conceptual knowledge into a coherent motor representation.

Regarding limitations, a potential bias for the present results could be the lack of systematic control conditions allowing to quantify the integrity of the various modalities of sensory feedbacks exploited by the tasks, in order to exclude them as confounding factor. This is a relevant issue, since intraoperative HMt and postoperative tasks rely on sensory-guided modalities not completely overlapping. In this regard, this bias was qualitatively overcome by excluding patients that showed clinically overt basic visual and tactile deficits during neurological assessment. However, this procedure might be not exhaustive since the posterior parietal lobe hosts high-order sensory modalities crucial for the sensorimotor guidance of the three tasks. To reduce as possible also this confounding aspect, we used the ARAT score as covariate in LSM analysis for praxis functions. Since the ARAT execution rely on both somatosensory (shared with the HMt and praxis tasks) and visual-guidance (shared only with the praxis tasks), its use as covariate for investigating praxis abilities allow to isolate task-specific voxels for the imitation of the observed gesture. Finally, these methodological aspects allowed a spatial matching between ARAT vs De Renzi and HMt vs De Renzi mainly reflecting intrinsic tasks features.

Data availability

The data that support the findings of this study is available from the corresponding author, upon reasonable request.

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Competing interests

The authors have no conflicting interests to report.

Supplementary material

Supplementary material is available at *Brain* online.

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Figure legends

Figure 1 Schematic representation of the workflow of the study.

Figure 2 Resection Cavities overlap and scores. A) Overlapping map of patients' resection cavities; B) distribution of De Renzi and C) ARAT scores and pre/post-surgery statistical results.

Figure 3 SVR-LSM results. A) SVR-LSM results for the ARAT global score covariate with the De Renzi global score. B) SVR-LSM results for the De Renzi global score covariate with the ARAT global score and SVR-LSM results for Meaningless and Meaningful gestures both covariate for the ARAT global score. C) Overlap between ARAT and De Renzi covariate CFWER clusters with HCP-MMP1 parietal regions. D) Overlap between ARAT and De Renzi CFWER covariate results and common region resulting from overlap of non-covariate CFWER results.

Figure 4 Spatial matching between DES and SVR-LSM results. A) HMt and sampling of parietal stimulation from Fornia et al. 2021. B(i-ii) Co-localization between HMt probability density estimation (effective areas in white and ineffective areas in black), praxis cluster (red) and prehension-praxis common region (orange). On the upper part of B(i), examples of EMG interference patterns evoked by parietal DES of phAIP and PF. B(iii) HMt probability maps showing the parietal region associated to different EMG-interference pattern (task-clumsy vs task-arrest) regardless ineffective sites. B(iiii) Co-localization between HMt task-arrest and clumsy pattern probability with meaningful (blue), meaningless (red) gestures CFWER (covariate ARAT) and posterior parietal regions (phAIP, DIPSA, DIPSM, PF). C(i) Anatomical localization of effective sites recorded within the parietal white matter. C(ii) Probability density estimation of HMt effective sites within the white matter and their co-localization with Praxis CFWER (covariate ARAT). D) Example of two patients showing transient post-operative apraxia: A) effective site was located in the white matter below AIP and evoked a task-arrest pattern; B) effective sites were located in the white matter below PF and evoked task-clumsy patterns.

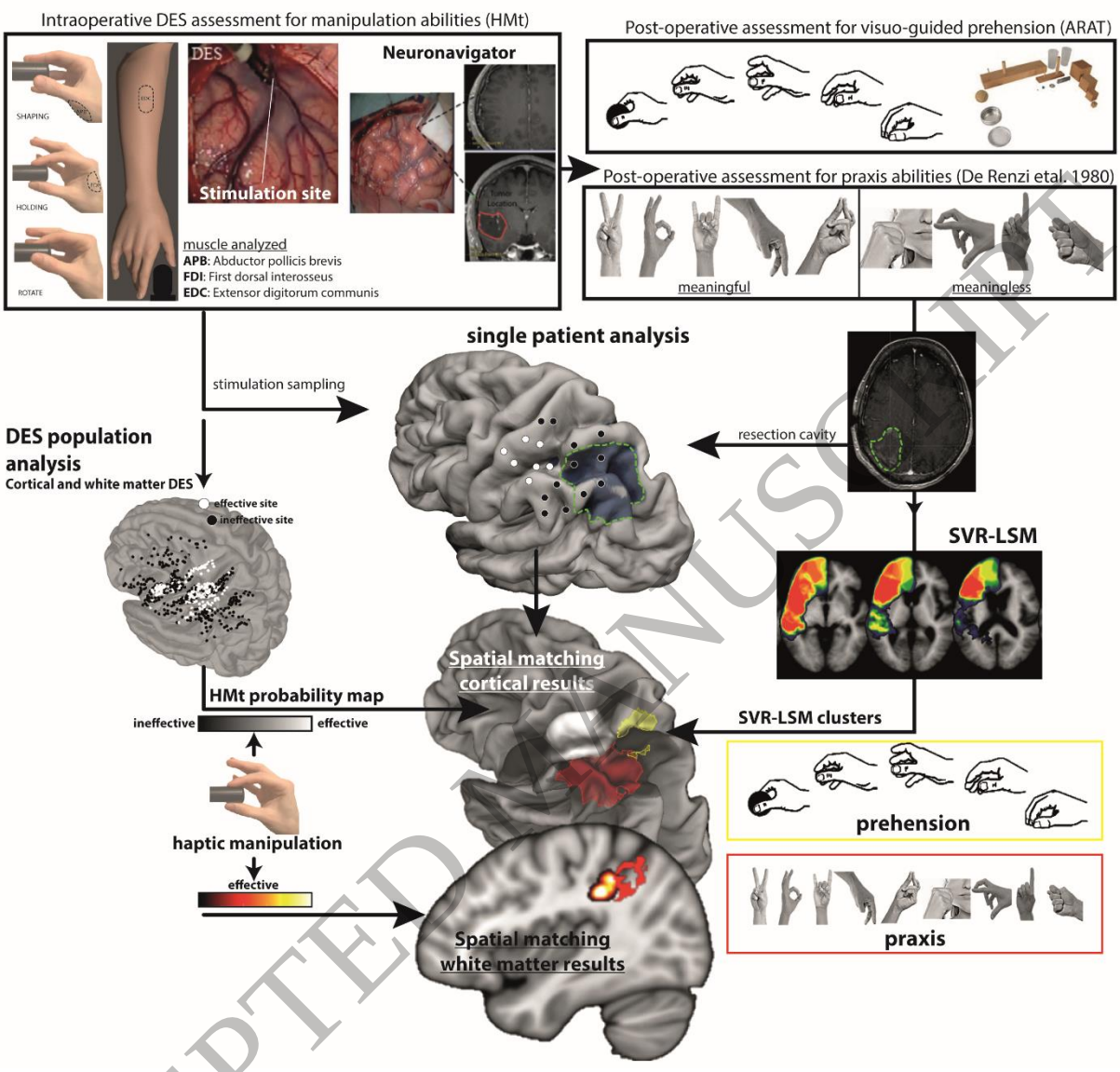

Figure 1
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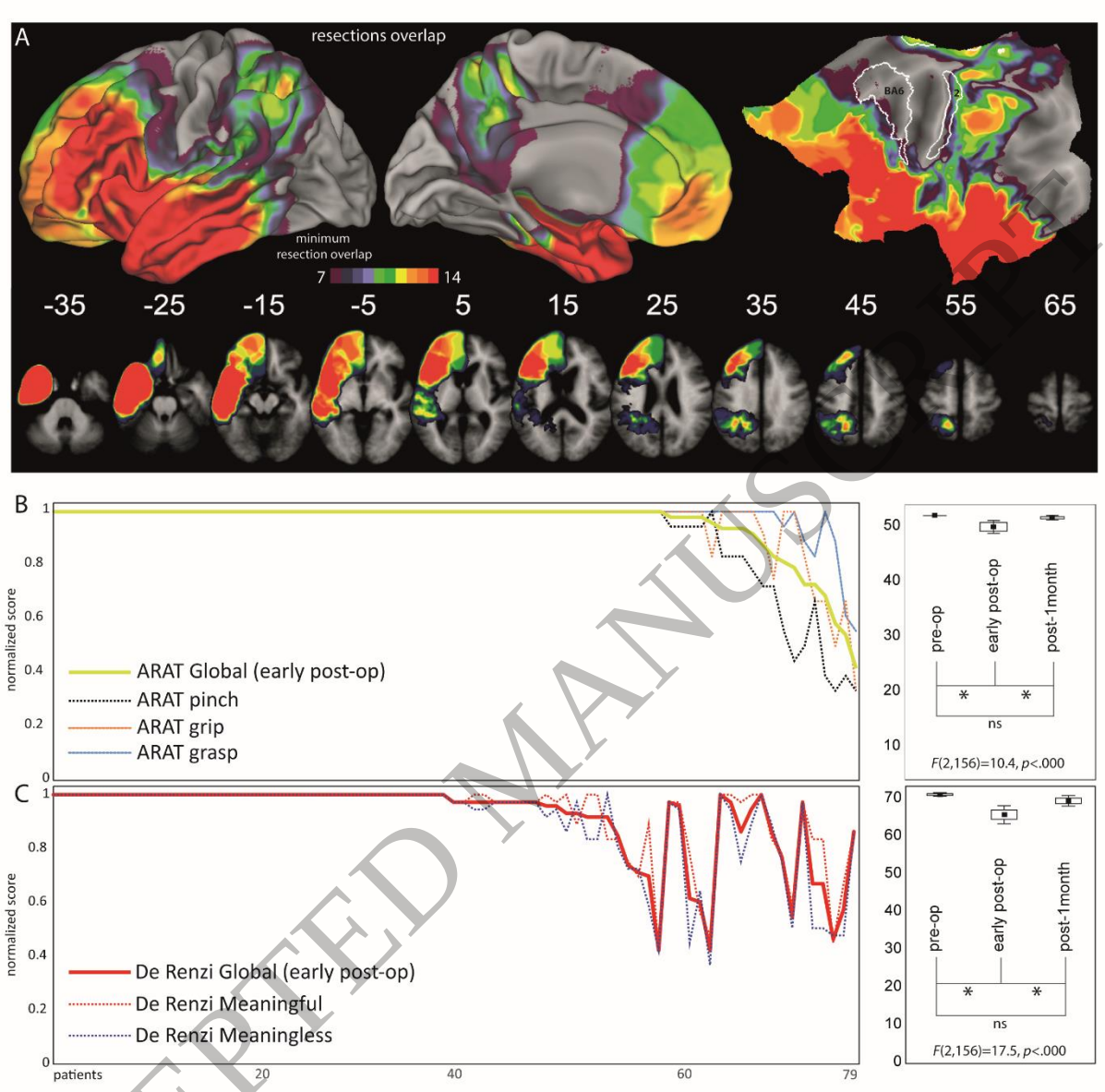

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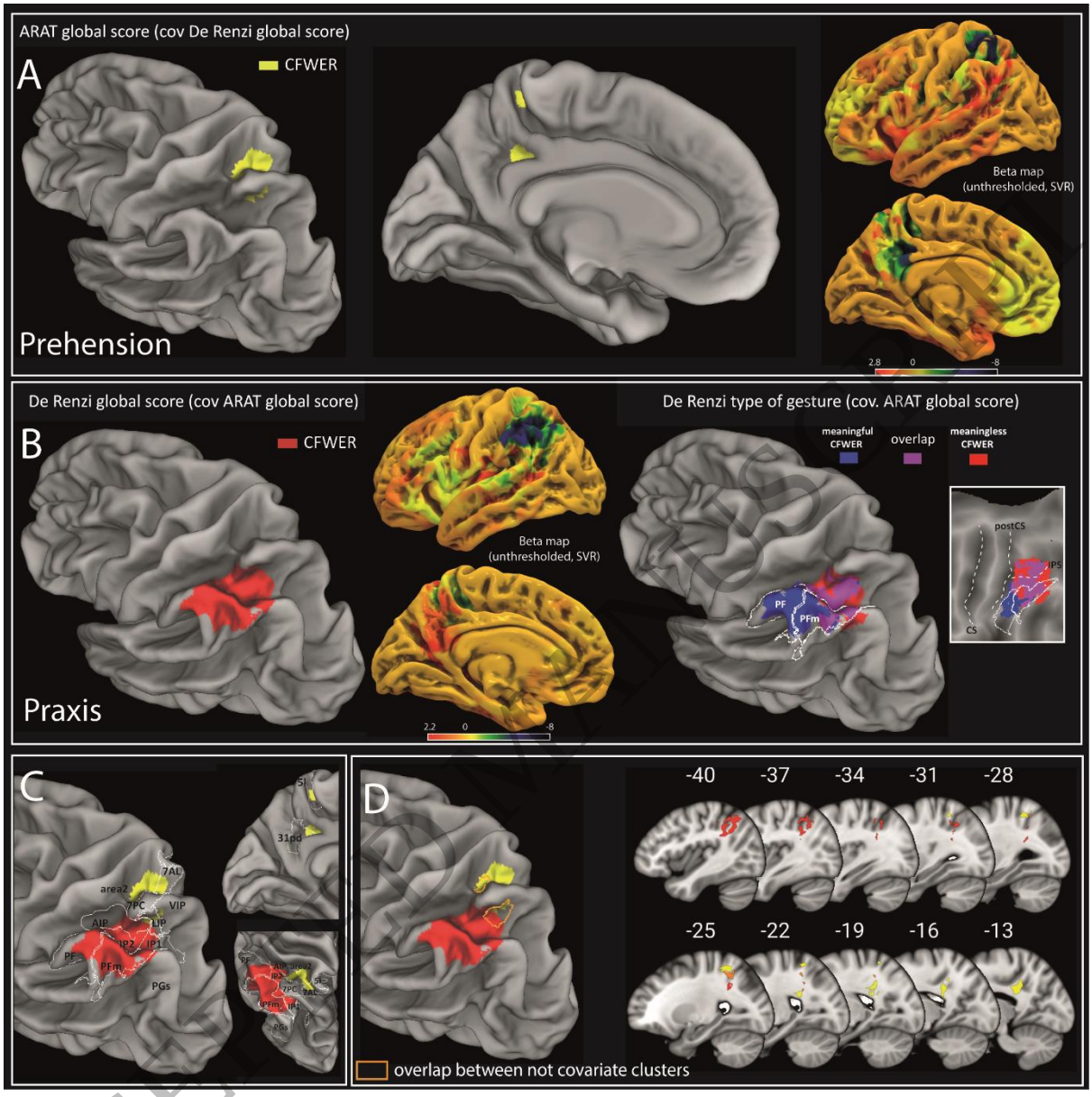

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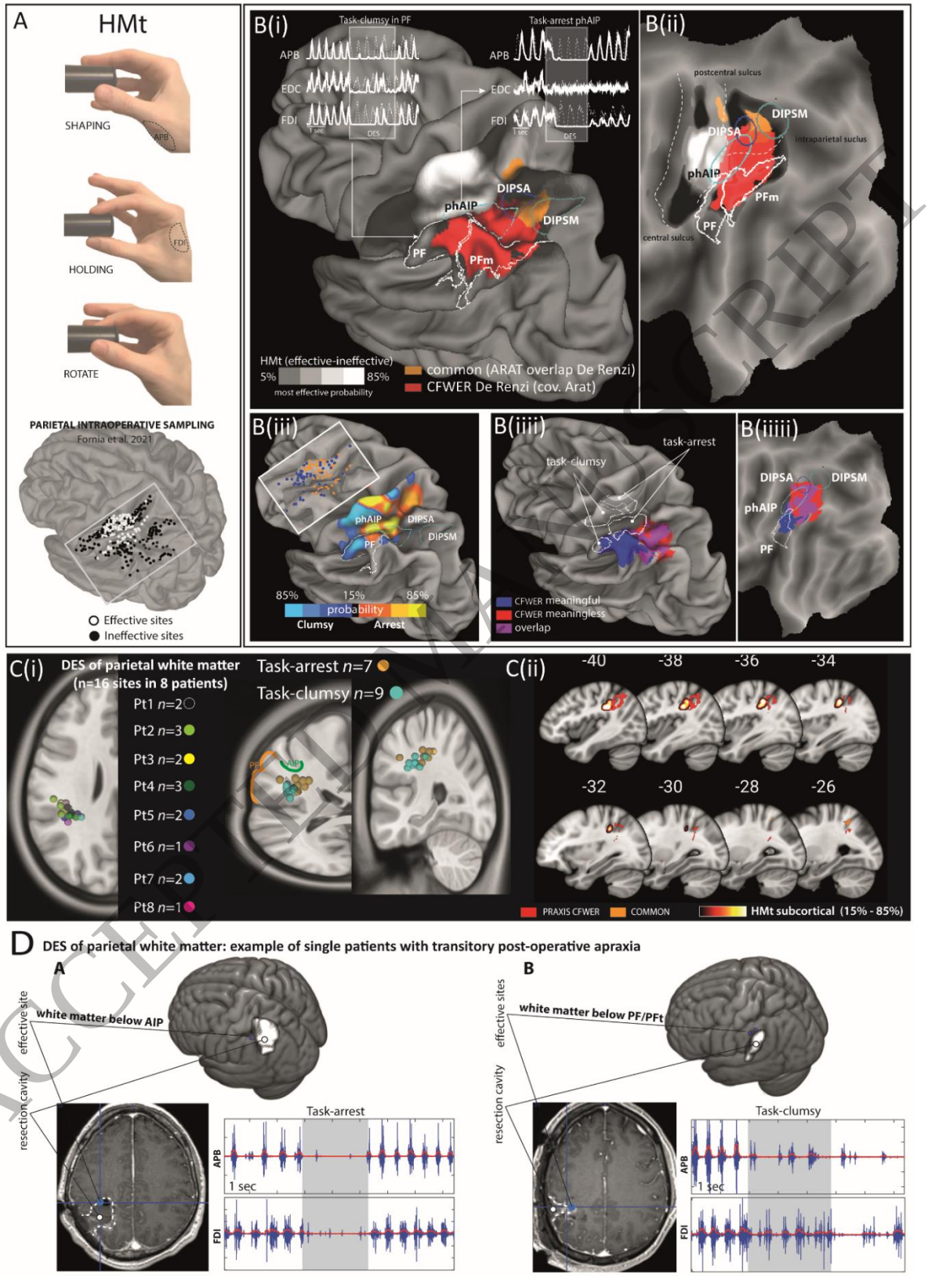

Figure 4

159x225 mm (x DPI)