Tracing in vivo the dorsal loop of the optic radiation: convergent perspectives from tractography and electrophysiology compared to a neuroanatomical ground truth

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Abstract
The temporo-parietal junction (TPJ) is a cortical area contributing to a multiplicity of visual, language-related, and cognitive functions. In line with this functional richness, also the organization of the underlying white matter is highly complex and includes several bundles. The few studies tackling the outcome and neurological burdens of surgical operations addressing TPJ document the presence of language disturbances and visual field damages, with the latter hardly recovered in time. This observation advocates for identifying and functionally monitoring the optic radiation (OR) bundles that cross the white matter below the TPJ. In the present study, we adopted a multimodal approach to address the anatomo-functional correlates of the OR’s dorsal loop. In particular, we combined cadavers’ dissection with tractographic and electrophysiological data collected in drug-resistant epileptic patients explored by stereoelectroencephalography (SEEG). Cadaver dissection allowed us to appreciate the course and topography of the dorsal loop. More surprisingly, both tractographic and electrophysiological observations converged on a unitary picture highly coherent with the data obtained by neuroanatomical observation. The combination of diverse and multimodal observations allows overcoming the limitations intrinsic to single methodologies, defining a unitary picture which makes it possible to investigate the dorsal loop both presurgically and at the individual patient level, ultimately contributing to limit the postsurgical damages. Notwithstanding, such a combined approach could serve as a model of investigation for future neuroanatomical inquiries tackling white matter fibers anatomy and function through SEEG-derived neurophysiological data.

Keywords White matter · Temporo-parietal junction · Klinger dissection · Visual evoked potential · Inter-trial coherence · SEEG · Visual system

Abbreviations
DL  Dorsal loop
DTI  Diffusion tensor imaging
ID  Identification
IFOF  Inferior fronto-occipital fasciculus

ITC  Inter-trial coherence
LGN  Lateral geniculate nucleus
MR  Magnetic resonance
OR  Optic radiation
ROI  Region of interest
SS  Sagittal stratum
SEEG  Stereoelectroencephalography
TPJ  Temporo-parietal junction
VEP  Visual evoked potential
VOI  Volume of interest
WM  White matter

Introduction

The temporo-parietal junction (TPJ) is a complex cortical region involved in many essential functions, including language (within the dominant hemisphere), visual processing and other cognitive abilities (such as arithmetic, writing, symbol processing, working, musical memory and theory of mind) (Martino et al. 2013; Schurz et al. 2017). Despite the huge variability in defining TPJ borders, it is commonly described as the crossroad between the posterior portion of the superior temporal gyrus, the inferior parietal lobule and the angular gyrus (Schurz et al. 2017). In parallel with this functional complexity, TPJ is subserved by an intricate network of several white matter (WM) bundles, including, from the surface to the depth, the superior longitudinal fasciculus, the arcuate fasciculus, and the bundles belonging to the sagittal stratum: the middle longitudinal fasciculus, the inferior longitudinal fasciculus, the inferior fronto-occipital fasciculus (IFOF) and the optic radiation (OR) (Di Carlo et al. 2019). The tapetum separates OR from the ventricular ependymal layer (De Benedictis et al. 2014; Maldonado 2021; Martino et al. 2013). Subcortical intraoperative mapping of these bundles allowed to delineate the role of TPJ-WM, clearly related to language in the dominant hemisphere (at least for SL/AF and IFOF) (De Benedictis et al. 2014), and to visual cognition (in particular ILF, but also SLF/AF and IFOF in the non-dominant hemisphere) and vision (namely OR) (Chan-Seng et al. 2014; Berro et al. 2021).

Over the last decade, studies on the anatomo-functional organization of the TPJ and the underlying connectivity emerged, also thanks to the application of traditional methods, such as cadaver dissection (Parraga et al. 2012; Maldonado et al. 2021), or more innovative techniques, such as diffusion tensor imaging (DTI)-based tractography (Catani et al. 2017), or both (Wu et al. 2016). Growing data coming from direct cerebral electro-stimulation have also been provided (Maldonado et al. 2011; Mandonnet et al. 2017; Rolland et al. 2018), comparing intraoperative results with the anatomical counterparts in a multimodal perspective (Sarubbo et al. 2015).

To date, only a few studies have tackled the postoperative outcome and potential neurological burden associated with surgeries involving the TPJ and the underlying bundles (Maldonado et al. 2011; Sanai et al. 2012; Rolland et al. 2018). Language disturbances and visual field damages are reported in the early postsurgical period, with the possibility of long-term persistence, especially for vision (Sanai et al. 2012; Rolland et al. 2018). Such a visual field deficit depends on the disruption of the OR fibers running deeply along the SS.

The OR conveys visual information from the lateral geniculate body to the ipsilateral calcarine cortex (Schijns and Koehler 2020) and to other extra-striatal occipital structures (Yu et al. 2018). Two major components are generally described: (a) the inferior bundle (forming the Meyer’s loop), and (b) the superior bundle, which forms the dorsal loop (DL), forming the WM adjacent to the parietal cortex (Ebeling and Reulen 1988; Kamali et al. 2014). The inferior bundle has been extensively studied for both research (Lilja and Nilsson 2015; Mandelstam et al. 2012; Nowell et al. 2016) and clinical purposes, given the high rate of damage—and consequent visual deficits—encountered during temporal lobectomy (Taoka et al. 2008; Piper et al. 2014). On the contrary, the superior bundle has been more sparsely investigated, even though its damage results in a contralateral inferior homonymous quadrantanopia with consequent impairment of more vision-related activities than damages of the inferior bundle (Cheng et al. 2015).

Within OR ramifications, the superior bundle is the one candidate to cross the WM underlying TPJ. In a previous study, Burgel and coworkers (Burgel et al. 1999) digitalized myelin-stained histological series relative to ten patients and co-registered them to corresponding structural magnetic resonance (MR), warping the final results to a reference brain. The authors inferred that a highly variable course among subjects characterizes the DL course below SS, in some cases skimming the parietal cortex (Burgel et al. 1999). However, to date, no functional evidence is available to associate the DL position under the TPJ with the visual deficits experienced upon resective surgery within this region.

To overcome this gap, in the present study we adopted a multimodal approach to address the anatomo-functional correlates of DL. First, we report the structural information on DL’s topography using a standard post-mortem dissection approach. Subsequently, anatomo-functional correlates were investigated by means of stereoelectroencephalography (SEEG) performed as preoperative monitoring in patients suffering from drug-resistant epilepsy. Tractography was used to estimate the anatomical arrangement of DL, while intracerebral visual evoked potentials (VEPs), recorded from electrodes crossing the WM below the TPJ, were analyzed to provide a functional correlate complementing the ex vivo and in vivo anatomical measures. The combination of diverse and multimodal observations allows overcoming the limitations intrinsic to single methodologies and defining a unitary picture that makes it possible to investigate DL both presurgically and at the individual patient level, ultimately contributing to limit the postsurgical
damages. Notwithstanding, such a combined approach could serve as a model of investigation for successive neuroanatomical inquiries tackling WM fibers anatomy and function through SEEG-derived neurophysiological data.

**Materials and methods**

**Volume of interest identification and imaging visualization**

The definition of the anatomical region, which was selected as the putative location of DL, was based on landmark cytological, histological, imaging works and atlases, defining OR positioning at the level of the TPJ (Burgel et al. 1999, 2006; Mori and Crain 2005), following these steps:

1. Visualization of the OR volumes, downloaded from the online Juelich Institute of Neuroscience and Medicine fiber tracts repository (neurovault.org/images/1401). These volumes have been produced by means of myelin-stained histological studies (Burgel et al. 1999, 2006), and hereby visualized in a dedicated MNI-152 space (ICBM 2009c nonlinear symmetric);
2. Given the need to define the volume of interest (VOI) related to DL in the context of the OR, the posterior thalamic radiation (PTR) label obtained from the JHU-ICBM-DTI-81 WM atlas (Mori and Crain 2005) was applied to the OR volumes so that anterior, posterior, lateral and mesial limits of the DL volume were defined;
3. The inferior limit of the volume was chosen as the plane passing through the most anterior point of the calcarine fissure, parallel to that identified by the PTR label (Mori and Crain 2005), based on the segregation of OR fibers directed to the supra and infracalcarine cortices;
4. The superior limit identified by the histological studies was preserved (Burgel et al. 1999, 2006), to avoid the risk of undersampling the eventual most superior fibers of the DL (Fig. 1).

Once the VOI was defined (Fig. 1), brain MR volumetric sequences of each patient were registered to the dedicated MNI space. Each tractography and the anatomical reconstruction of the electrode contacts were visualized.

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**Fig. 1** Definition of VOI topography. Bilateral representation of the VOI rendering (in red) topography in the dedicated T1 MNI-space with multiplanar view (A–D) and 3D reconstructions (E–F). Anterior, posterior, lateral and mesial borders were identified by PTR of the JHU-ICBM-DTI-81 WM atlas (Mori and Crain 2005), the inferior limit of the volume was chosen as the plane passing through the most anterior point of the calcarine fissure, parallel to that identified by the PTR label, and the superior limit was detected by histological studies on the OR (Burgel et al. 1999, 2006).
throughout the multimodal imaging integration workflow available in our center (Cardinale et al. 2012).

**Ex vivo anatomical study**

Cadaver dissections were authorized by the Ethical Committee of the APSS of Trento. Two human cerebral hemispheres (one left and one right) were prepared according to the modified Klingler’s technique previously detailed (Sarubbo et al. 2015). Microdissection was performed in April 2019 by a neurosurgeon (MR), with the supervision of two WM dissection experienced neurosurgeons (SS, ADB). Dissection started with removing both sulcal gray matter of the lateral aspect of the brain and U-fibers. Once the three components of the superior longitudinal fascicle had been detected, the posterior portion of the inferior fronto-occipital fascicle (IFOF), the inferior longitudinal fascicle, the OR and the tapetum were identified in a stepwise manner, from outside to inside (De Benedictis et al. 2014). The gray matter at the tip of the cuneus and lingual cortex was preserved according to a cortex-sparing technique (Martino et al. 2011), to obtain the correct definition of the bundle and its terminations territories. Moreover, precuneus cortical structures were removed, helping the identification of fascicles connected only to the occipital cortex and the exclusion of those also terminating in the parietal cortex (i.e., IFOF). The WM bundles covering the OR were removed, layer by layer, until the OR was unambiguously identified, following a stepwise technique (Sarubbo et al. 2015).

**In vivo studies**

Clinical data were obtained on our prospectively maintained database. All patients or their guardians gave their informed consent. The local Ethical Committee approved this study in 2020 (ID 348-24062020).

We selected those cases on which DL was supposed to be investigated by anatomical in vivo studies (DTI-based tractography) or neurophysiological explorations (VEPs extracted from SEEG electrodes [Microdeep Intracerebral Electrodes-D08, Dixi Medical] following flash administration), excluding those patients with lesions (observed at the presurgical brain MR) undermining the OR and those with clinical abnormalities involving the visual systems.

In particular, we considered all the patients who underwent SEEG at the “C. Munari” Epilepsy Surgery Centre, in Milan, between February 2017 and March 2021. SEEG is a methodology providing relevant information about seizure-onset zone (SOZ) (Cardinale et al. 2017) when the non-invasive analysis of anatomo-electro-clinical correlations do not allow a clear definition of it. SEEG is generally followed by SOZ intraprocedural radiofrequency thermocoagulation and/or resective surgery (Cardinale et al. 2019).

The multimodal imaging, including tractography and the anatomical reconstruction of the electrodes contacts, was visualized throughout the imaging workflow established in our center (Arnulfo et al. 2015; Narizzano et al. 2017), once brain MR volumetric sequences and post-processed datasets of each patient were registered to the dedicated MNI space.

**Tractography**

All SEEG-implanted patients underwent a preoperative work-out including dedicated brain MR sequences (including DTI). MR datasets were acquired with a 1.5T Philips Achieva scanner, using a receive coil head SENSE 8 with eight channels (Supplementary File). After DICOM to NIfTI image conversion, brain volumes were extracted from DTI and T1 images. All the diffusion-weighted images of each DTI acquisition were co-registered to the baseline volume (which is the image of the brain acquired without directional gradient). All DTI volumes were then corrected for noise reduction and eddy current algorithms. Volumetric T1 images and DTI images were co-registered calculating the transformation matrix between the structural images and the first volume of DTI images using 6 degree of freedom rigid transformation and mutual information algorithm. For eddy current correction and all image co-registrations specific tools of the FMRIB Software Library were used (FSL; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Fractional anisotropy images and color maps indicating the principal diffusion directions (i.e., fiber orientations) were calculated from the DTI. DTI calculations and fiber tracking were performed with the FSL-based FDT Diffusion toolkit, using probabilistic methods based on multiple regions-of-interest approaches (ProtrackX). The OR tractography started with the definition of the seed region of interest (ROI), drawn at the level of the lateral geniculate nucleus. Waypoint ROIs were localized at the level of the green fibers (antero-posteriorly oriented) in the occipital cortex (Kamali et al. 2014). Additional ROIs were considered, in case of local anatomical distortion, or fibers tracked outside the occipital lobe. The 3D structure of the OR was defined as the volume encompassed by the 10% of maximum value of output path distribution after being co-registered with the 3D reference sequence (i.e., volumetric T1). Each patient output path distribution was co-registered through an affine transformation (12 degrees of freedom) to the dedicated MNI space, considered the reference common space. A neurosurgeon with expertise in the field of advanced neuroimaging (MR) analyzed the position of the OR as compared to the VOI volume. Tractography analysis was considered “positive” when at least a portion of the OR tractography lay in the VOI; on the other hand, if tractography did not meet the VOI, it was considered “negative”.

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A probability map was finally calculated for each hemisphere, summing up the binarized 3D OR structures of all the patients and dividing by the number of reconstructed tracts in the dedicated MNI space.

**SEEG data recording and processing**

We selected patients whose implantations explored the VOI (Fig. 1). For these patients, VEPs were collected during SEEG monitoring.

For each electrode targeting the VOI, we first identified all the contacts in the WM, thus excluding those recording from the cortex. This identification first relied on neuroimaging, that is, the co-registration of post-implantation cone-beam computed tomography scan with the pre-implantation MR. Since co-registered imaging datasets suffer from accuracy limitations, the identification of the contacts localized in the WM was assisted by analyzing the signal recorded in each contact (Greene et al. 2021).

SEEG monitoring is continuously recorded at a 1-kHz sampling rate using a 192 channel-EEG device (Neurofax EEG-1200, Nihon Kohden). The recording filters are set to include the range from 0.08 to 300 Hz, and a notch filter (50 Hz) is applied. The VEPs are sampled at 25 kHz through a 16 channel-EEG device (Neuropack M1, Nihon Kohden) and the recording bandpass filter includes from 1 Hz to 3 kHz and notch filter (50 Hz) is activated.

Visual stimulation was performed routinely to identify the explored regions involved in the visual processing. Patients wear goggles and receive 100 bilateral visual stimulations (i.e., flashes) at 1 Hz, with an intensity of 3 cd/m². Goggles have the advantage of producing a very large field of stimulation that minimizes the effect of changes in the direction of gaze so that the stimulus is delivered to the entire visual fields. Visual evoked potentials are extracted for each channel as the average of the first 50 trials and of the last 50 trials in the time window (0, 200 ms), following the stimulus delivery. Two electrophysiologists (IS, FMZ) blindly evaluated the traces for each electrode and identified the contact (defined as “election contacts”) presenting the earliest and most pronounced deflection.

To quantitatively assess the prevalence of phase-locking components in the identified channels relative to the neighbor territories, we further computed the inter-trial coherence (ITC) (Delorme and Makeig 2004) for each of the identified channels, and compared statistically this variable against the channels located before and after the selected one. In other words, we evaluated the specificity of the identified features against the same signals recorded at 3.5 mm of distance along the electrode direction. ITC was computed in the interval 0, 200 ms and for frequencies between from 0 and 500 Hz. Statistical comparison contrasting distribution of election contacts against the adjacent one was performed via t test ($p < 0.01$, 1000 permutation).

Once neurophysiological and tractography datasets had been separately and blindly analyzed, data were matched. In particular, each recording SEEG contact was labeled as intersecting, tangential or negative, according to its position relative to the reconstructed OR fibers. Intersecting contacts were defined as those lying at least partially, within the reconstructed OR. Contacts were defined as tangential if their minimum distance from OR was lower than 1.5 mm. In the case of a greater distance, they were labeled as negative. To evaluate comparatively the performance of tractographic and electrophysiological assessments, we evaluated the convergence between the two sets of results, and particularly how many times the election contacts as identified by VEPs coincided with intersecting contacts as revealed by fiber tracking.

**Results**

**Ex vivo anatomical study**

**Anterior portion of the OR**

Insulo-opercular fibers, followed by the underlying external capsule and claustrum, were removed to highlight the most anterior course of the OR. Meyer’s loop was clearly delineated in the rostral portion of the temporal WM, following the removal of the uncinate fasciculus (Fig. 2, red pin, blue line). The uncinate fasciculus was identified thanks to its twisting shape connecting the anterior temporal and the frontal regions.
Mid-posterior portion of the OR

Once the depth of the Meyer’s loop layer was established, all fibers directed to the parietal region were removed, since they were supposed to belong to the IFOF, having a typical fanned distribution. After IFOF layer level identification, its occipital component of the IFOF was removed, with the delineation of the OR fibers. OR fibers coming from the anterior part of the bundle rise toward the bottom of the pre-cuneus, followed by a mild slope to the occipital lobe and the calcarine fissure (Fig. 2, green pin). The dissection allowed one to visualize a "hump" at the most superior level of the OR, which can be considered the DL, having a thickness of 2 mm (Fig. 2, red pin, green line).

Tapetum

Once moved to the mesial intraventricular side, at atrium level, the tapetum, whose fibers presented with a superior to inferior direction, was detected. Once distinguished from the OR (whose fibers are crossed to those of the tapetum), the tapetum thickness was measured, resulting in 2 mm.

In vivo studies

Between February 2017 and March 2021, we carried out 148 SEEG procedures on 147 patients (72 males and 75 females, with a median age of 29 years [IQR 21], at the time of brain MR and SEEG study). Forty-one patients with a positive brain MR along the OR course were excluded. Three of these 41 patients also suffered from a visual field defect documented using a computerized examination.

Tractography

Unilateral or bilateral OR tractography was performed in 64 out of the remaining 106 patients (41 patients were excluded because OR was not drafted due to the SEEG planning pattern [i.e., not involving the OR course] and one because DTI sequences were not acquired).

Fiber tracking resulted “positive” in 86.7% of the patients (58 patients). This sample included 24 males and 34 females, with a median age of 30.5 years (IQR 19.25) at brain MR and SEEG study. Tractography capability to intersect the DL, at sample level, was depicted through a probability map for each hemisphere (Fig. 3).

![OR tractography probability maps. Probability maps of ORs tractography (green to white) have been represented bilaterally, using multiple planes (A-D) with bilateral VOI rendering superimposed (red). Color bars (related to the figure C and D) represent the statistical dispersion (inter-quartile range).](image)
**SEEG data recording and processing**

Following previous criteria, 16 patients out of 106 (5 M, 11 F; median age 36.5 [IQR 23.75]) were selected as having an electrode exploring the VOI and SEEG recorded during a visual stimulation. Table 1 summarizes the demographic and clinical features for the examined population.

In all patients, VEP traces exhibited one contact recording from the WM (Fig. 4; Supplementary Video 1 and 2), with a reliable burst of oscillations occurring by the first 100 ms and distinctive for a single channel (see Fig. 5). The onset of this morphology was identified (see dotted lines in Fig. 5), and values are reported in Table 2.

The comparison between the election contacts as identified via VEPs and the adjacent ones is reported in Fig. 6. An increase of phase locking was observed in both groups in the interval between 50 and 150 ms, even if the values of ITC were stronger for the first group. More importantly, the statistical comparison underlined a significant interval in the time window between 20 and 40 ms, indicating that election contacts have a phase locking significantly higher than the adjacent contacts in this period. Even from a spectral point of view, the significant interval was between 50 and 100 Hz, thus in a low-gamma frequency band.

The comparison between tractography and SEEG data identified the same contacts blindly by the two procedures for 12 out of 15 patients (80%) having complete datasets. In other words, the SEEG contacts presenting early high-frequency responses around 30 ms were labeled as intersecting the OR according to the tractographic analysis. The procedures identified adjacent contacts in 2/15, indicating an imprecision of about 3 mm. Only one patient was problematic, as DTI-based reconstruction fell apart from the SEEG electrode, despite the positive identification of the VEP component. In summary, in 14/15 patients the identification was successful and convergent across the two modalities. The full details are reported in Table 2.

**Discussion**

**From ex vivo anatomical dissection to in vivo structural and functional aspects**

In the present study, we combined information from ex vivo anatomy to the in vivo structural and functional correlates of DL to provide new insights into its traceability in patients. Dissection by Klingler’s technique is a consolidated and reliable approach to explore WM structure (Zemmoura et al. 2016; De Benedictis et al. 2012). Using this method, recent studies provided innovative insights about the courses of OR’s inferior and superior components and their spatial relationships with the other surrounding associative bundles (Parraga et al. 2012; De Benedictis et al. 2014; Sarubbo

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**Table 1** Demographics of SEEG patients selected for neurophysiological analysis

| Pt ID number | Sex | Epilepsy duration (years) | Age at MR and SEEG | Brain MR (at OR level) | Etiology | Neurological examination | Histopathology |
|--------------|-----|--------------------------|-------------------|-----------------------|----------|-------------------------|--------------|
| 1            | M   | 18                       | 46                | Negative              | Unknown  | Negative                | Gliosis      |
| 2            | M   | 6                        | 20                | Negative              | Unknown  | Negative                | Gliosis      |
| 3            | F   | 11                       | 14                | Negative              | Malformative | Negative            | Gliosis      |
| 4            | F   | 13                       | 21                | Bilateral hippocampal abnormal Gyration | Unexpected preterm delivery | Negative | Anterior temporal FCD Ia |
| 5            | F   | 29                       | 38                | Negative              | Unknown  | Negative                | Gliosis      |
| 6            | F   | 30                       | 37                | Negative              | Unknown  | Negative                | Parietal FCD Ila |
| 7            | F   | 5                        | 16                | Negative              | Unknown  | Negative                | Gliosis      |
| 8            | F   | 39                       | 43                | Negative              | Unknown  | Negative                | Gliosis      |
| 9            | F   | 8                        | 14                | Negative              | Malformative | Negative            | Insular FCD Ila |
| 10           | F   | 18                       | 39                | Negative              | Unknown  | Negative                | No surgery, RF-THC only |
| 11           | F   | 3                        | 12                | Negative              | Unknown  | Negative                | Posterior temporal FCD Ib |
| 12           | M   | 43                       | 44                | Negative              | Post-vaccine | Negative            | No surgery, RF-THC only |
| 13           | M   | 18                       | 39                | Negative              | Post-infective | Negative            | No surgery, RF-THC only |
| 14           | F   | 20                       | 39                | Negative              | Unknown  | Negative                | No surgery, RF-THC only |
| 15           | M   | 6                        | 15                | Negative              | Unknown  | Negative                | Gliosis      |
| 16           | F   | 21                       | 36                | Left basal temporo-occipital malformation | Malformative | Negative            | No surgery, RF-THC only |

FCD focal cortical dysplasia, RF-THC radiofrequency thermocoagulation
et al. 2015; Koutsarnakis et al. 2018). To date, a specific description of DL has never been reported, probably due to the challenging anatomical disambiguation from the IFOF. The posterior course of IFOF and OR shows a similar fanned and thin shape, intermingled in a densely packed anatomical region.

In the present study, we provided evidences that the “hump” in the deepest portion of the SS corresponds to the DL (Fig. 2). Our DTI-based tractography results confirm this finding, with DL successfully identified in more than 90% of the reconstructed ORs. As already shown by previous histological studies (Burgel et al. 1999, 2006), although the superior OR bundle was more heterogenous than the inferior component (Fig. 3), the method returned a reliable identification of DL. Moreover, tractography data detailed the DL topography: fibers were grouped in the posterior portion of the VOI before entering occipital territories (Fig. 3).

Neurophysiological VEPs investigation showed a surprisingly clear pattern for most of the analyzed electrodes. Indeed, within each (multi-contact) electrode, a single electrode contact had a burst of high-frequency oscillations, phase-locked with the stimulus delivery, and distinct from the neighbor contacts (Fig. 5). On average, we identified the onset of this EEG component at 30 ms (Table 2). To add a statistical comparison to this observation, we computed the ITC for all contacts exploring WM, contrasting the electrode contacts with the adjacent, non-relevant ones. Despite the variability of responses across patients, ITC was significant in a single time–frequency interval, i.e., between 20 and 40 ms in the gamma frequency band. This result corroborates the inspective report based on VEPs analysis and points to an early time window revealing whether an SEEG contact exploring WM is recording or not from the OR.

The specificity of visual-evoked early activity for a single contact within SEEG electrodes was indicative on the OR thickness at the level of DL. Indeed, in SEEG electrodes, single contact width is 2 mm, with contacts interspaced at 1.5 mm of each other. Thus, if early VEPs component are observed on a single contact, we can hypothesize that the DL thickness is below 3.5 mm. This conclusion is paralleled by both tractography results, displaying a mean thickness of 2.7 mm (±0.9 mm) in correspondence with the relevant SEEG contacts (see Table 2) and most importantly results from ex vivo dissections, indicating a DL thickness of 2 mm.

The most important finding of our study is the convergence between SEEG and DTI-based data. Identification via fiber tracking of the SEEG contact crossing the OR coincided in 12 out of 15 patients with the election SEEG contacts identified solely via electrophysiology (see Fig. 7 for the entire dataset relative to a single patient), and in 2 of the remaining patients the shift was minimal (see Table 2). This finding suggests that DL can be monitored (and double-checked) in patients undergoing presurgical investigations, returning a coherent picture from both anatomical and electrophysiological points of view. We noticed a mismatch between neurophysiological data and fiber tracking in only few cases. This aspect involves both DL detection and its thickness and could be due to the tractography accuracy limitations (Schilling et al. 2019; Zhu et al. 2012), which become particularly evident for thin and highly curved tracts located in a densely packed WM region. The relatively thin thickness of 2 mm, the high curvature at the level of DL and the high density of the investigated WM volume could explain the small shift between fiber tracking and SEEG results in the 20% of our patient sample. In addition, the above-mentioned obstacles may lead to a relaxation of the parameters employed for tractography reconstruction and ultimately to an excess of fiber tracking false positives and
inflated fiber thickness. Despite some high value, the average thickness returned by tractography is similar to that derived from ex vivo procedures, suggesting a small impact of false positives in our analysis.

In summary, we proved that the location and thickness of DL can be traced in vivo using fiber tracking (Fig. 3), and that these observations parallel the electrophysiological responses to visual stimulations as recorded by SEEG (Fig. 4). This latter aspect proposes the DL as the WM substrate explaining the visual deficits often experienced by patients undergoing resective surgery involving TPJ and opens up the development of new presurgical or intraoperative procedures.

**Clinical and surgical considerations**

Previous reports of the surgical approach to the TPJ region focused on cortical and subcortical language structures sparing, with a secondary focus on optic radiation damage risk (Maldonado et al. 2011; Rolland et al. 2018). More recently, the risks of surgical approaches to the non-dominant SS were highlighted (Berro et al. 2021). As a consequence of our study, we underline that surgical planning for TPJ resections has to consider the risk of damaging those fibers conveying information from the contralateral inferior quadrant. This aspect is of particular value in the case of resection with oncological purposes and epilepsy surgery, in which resection involves only cortical structures, but WM risks being damaged due to vessels coagulation, rupture, or manipulation. A similar scenario is observed in the posterior insular surgery, with indirect damage to the adjacent cortico-spinal tract (Delion and Mercier 2014).

Given these observations, different strategies may be indicated to minimize the risk of DL damage as follows:

- to perform a thorough surgical planning, taking into account the complex SS architecture and the actual position of DL. This awareness has to be clear since the surgical planning and preoperative discussion with the patient;
- to prepare an imaging-based WM representation of the whole OR (tractography) to be considered either for the presurgical planning and the intraoperative navigation.

Fig. 5 Visual-evoked potential in white matter contacts in the VOI. It shows four representative patients the VEP traces for contacts exploring the white matters in the VOI (see Methods for data filtering). For all patients, only one contact (further referred as election contact) exhibits a peculiar and reliable burst of oscillations occurring within 100 ms after the stimulus delivery. Latency values following inspection of VEPs morphology are reported in Table 2 for all patients. The dotted vertical bar displays the earliest latency at which an ERP deflection appears reliably on the election contact. These latencies were identified by neurologists blind to the fiber tracking results.
This study allows to display and quantify the accuracy of tractography in DL identification, with a specific methodology: to consider the use of electrophysiological monitoring to evaluate the presence of early components in response to visual stimulations. Intriguingly, such a procedure can be applied both in presurgical monitoring (e.g. SEEG), and potentially also in intraoperative procedures; – to train surgeons by cadaver dissection, to mentalize the spatial relationship between anatomical structures, including both gray and white matters (Gnanakumar et al. 2018).

**SEEG for the study of WM**

In the present study, we took advantage of SEEG recordings to provide a neurophysiological counterpart to the tractography and anatomical observation concerning the DL-OR. As discussed in a previous paper (Avanzini et al. 2016), intraparenchymal recordings also present many advantages relative to ECOG, spanning from an extensive and more distributed sampling of the cortical sheet, to the minimal or absent volume conduction issues. Beyond these aspects, it is worth noting that about 30–40% of SEEG recording contacts explore the WM (Avanzini et al. 2018). While these signals are typically used to create a virtually null reference (Cardinale et al. 2019), their EEG activity is often discarded as an activity of non-interest, especially if compared with the richer and more complex activity recorded from the cortex. We believe that this large amount of data provides a valuable information to describe the anatomical and functional correlates of several WM bundles. The coherence between tractography and anatomical data makes these studies contribute to characterize the human connectome with an innovative source of information, complementing the neuroimaging techniques with a four-dimensional, time-dependent characterization of the human WM structures.
Fig. 6 Inter-trial coherence of white matter’s contacts in the VOI. Panel A shows the results of the statistical comparison ($p < 0.01$, 1000 permutations) between ITC panels of electrode contacts against couples of adjacent ones (see Methods). Statistical significance is limited in the interval 25–40 ms in the gamma band frequency (50–100 Hz). Panel B and C depict, respectively, the average of ITC panels for the election contacts (12 contacts) and for adjacent ones (21 contacts) as detailed in Table 2. Contours in black report regions of statistical significance as shown in Panel A.
Fig. 7 Single patient (patient 9) data representing the convergence between neurophysiological and tractographical data. Panel A shows the reciprocal position of the OR (in yellow) with the relevant (in green, Y8) and the adjacent (in red; Y7 and Y9) contacts. Panel B displays neurophysiological recordings at the level of the three contacts (only Y8 reports peculiar VEP features). Panel C represents the correspondent ITC results for each of the above contacts. Contours in black report regions of statistical significance as shown in Panel A of Fig. 5. Panel D shows for the three leads the spectrogram.

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Author contributions MR conceived and designed the analysis, collected the data, performed the analysis and wrote the paper; KA-O collected the data and critically revised the paper; PA conceived and designed the analysis, performed the analysis and wrote the paper; LB collected the data and performed the analysis; ADB collected the data and critically revised the paper; MDV performed the analysis and wrote the paper; DL collected the data and performed the analysis; VM collected the data, performed the analysis and critically revised the paper; IS conceived and designed the analysis, collected the data, performed
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**Availability of data and material** Data will be made available upon reasonable request.

**Code availability** Not applicable.

**Declarations**

**Conflict of interest** Michele Rizzi is a consultant for WISE srl, a manufacturer of implantable leads for neuromodulation and neuromonitoring.

**Ethical approval** Approval number of the local ethical committee: ID 348–24062020.

**Consent to participate** Not applicable.

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