Title: Recording cortico-cortical evoked potentials of the human arcuate fasciculus under general anaesthesia

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Highlights

- We show for the first time in adults that cortico-cortical evoked potentials (CCEPs) of the major language pathway, the arcuate fasciculus, are feasible also during surgery under full general anaesthesia.
- A novel P1 component at 12 ms together with an N1 component at 21 ms were identified. The N1 component may resemble the one described during awake procedures.
- CCEPs of the arcuate fasciculus are best identified stimulating from the middle temporal gyrus and recording from the ventral premotor cortex and inferior frontal gyrus.

Abstract

Objective: We examined the feasibility of using cortico-cortical evoked potentials (CCEPs) to monitor the major cortical white matter tract involved in language, the arcuate fasciculus (AF), during surgery under general anaesthesia.

Methods: We prospectively recruited nine patients undergoing surgery for lesions in the left peri-sylvian cortex, for whom awake surgery was not indicated. High angular resolution diffusion imaging (HARDI) tractography was used to localise frontal and temporal AF terminations, which guided intraoperative cortical strip placement.

Results: CCEPs were successfully evoked in 5/9 patients, showing a positive potential (P1) at 12 ms and a negative component (N1) at 21 ms when stimulating from the frontal lobe and recording in the temporal lobe. CCEP responses peaked in the posterior middle temporal gyrus. No CCEPs were evoked when stimulating temporal sites and recording from frontal contacts.

Conclusion: For the first time, we show that CCEPs can be evoked from the peri-sylvian cortices also in adult patients who are not candidates for awake procedures. Our results are akin to those described in the awake setting and suggest the recorded activity is conveyed by the arcuate fasciculus.

Significance: This intraoperative approach may have promising implications in reducing deficits in patients that require surgery in language areas under general anesthesia.

1. Introduction

Preserving language is critical in brain tumour surgery, since aphasia impacts not only speech production and comprehension but also the elaboration of numerous cognitive functions, with a profound impact on the postoperative quality of life of patients (Osoba et al., 1996). While our understanding of language networks has been rapidly expanding, the arcuate fasciculus (AF) remains at the core of this distributed system and hence is the major target for preservation during surgery. It is routinely identified under awake intraoperative conditions using direct electrical stimulation (DES) since anatomical landmarks can be unreliable as the intervention proceeds. Surgery without DES can lead to resection of essential subcortical structures and white matter tracts causing postoperative speech and language deficits (De Witt Hamer et al., 2012). Unfortunately, not all patients are suitable for awake procedures, for example due to impaired function or scarce compliance. Different surgical strategies are required in these cases using general anaesthesia throughout. Preoperative non-invasive tools, such as functional MRI (fMRI) or navigated transcranial magnetic stimulation (nTMS) (Picht et al., 2013), help identify eloquent language cortex, and diffusion imaging tractography can indirectly trace important subcortical connections between these regions(Rojkova et al., 2016). However these approaches are not without limitations, and cannot fully prevent postoperative aphasia (De Witt Hamer et al., 2012).

The arcuate fasciculus was first delineated by Reil (1809) using blunt dissection, and connects the inferior frontal gyri, the posterior middle frontal gyrus and the ventral premotor regions with posterior superior, middle and inferior temporal regions (Yagmurlu et al., 2016). It constitutes an anatomical substrate for phonological encoding (Friederici and Gierhan, 2013) into appropriate speech (Catani et al., 2005). Although other white matter tracts play important roles in language function (Dick and Tremblay, 2012), preservation of the arcuate fasciculus is critical in neurosurgery as disconnection causes permanent

language deficits (Caverzasi et al., 2016). Matsumoto and colleagues first demonstrated that it was possible to evoke cortico-cortical evoked potentials (CCEPs) stimulating from the frontal region and recording from posterior parieto-temporal regions in patients undergoing awake surgery for intractable epilepsy (Matsumoto et al., 2004). They confirmed, electrophysiologically, the existence of a cortico-cortical connection between these two regions, likely corresponding with the arcuate fasciculus. Despite its clinical relevance, this technique it is not used routinely and, at present, is applied as an ancillary procedure within awake procedures (Saito et al., 2014, Yamao et al., 2014). If monitoring CCEPs under general anesthesia were also feasible, this would provide a useful new technique to preserve language pathways in patients who cannot be operated awake, ultimately lowering the incidence of postoperative aphasia (De Witt Hamer et al., 2012).

During asleep surgery, methods other than DES are used to identify the best cortical hotspots to stimulate the arcuate fasciculus through strip placement (Basser et al., 2000). Diffusion tensor imaging (DTI)-tractography of the arcuate fasciculus may guide strip placement, since it corresponds well with CCEPs in the awake patient, although not all stimulation and recording sites overlap (Yamao et al., 2014). Notably, tensor-based tractography does not show multiple fibre crossings within a voxel, therefore artefacts can reduce its reliability (Dell'Acqua and Tournier, 2018). High angular resolution diffusion imaging (HARDI) approaches such as spherical deconvolution overcome this limitation, and can now model multiple fibre orientations within a single voxel, which is the case in over 80% of human white matter (Jeurissen et al., 2013). HARDI tractography has not yet been combined with CCEP recordings.

In this study, we used preoperative HARDI spherical deconvolution tractography in nine patients to prospectively trace fibres of the arcuate fasciculus in the dominant hemisphere. We identified frontal and temporal cortical terminations of this tract as targets for cortical mapping. Using this preoperative information to guide intraoperative placement of strip electrodes, we set out to assess the feasibility to monitor cortico-cortical evoked potentials of the arcuate fasciculus under a fully asleep anaesthesia protocol.

2. Methods

2.1. Patient cohort

The study was a prospective case collection, and nine recruited patients (age 24–69; 6M 3F; 1 left-handed) underwent surgery at Verona University Hospital between 2019 and 2020. All patients had a left hemisphere brain tumour compressing or infiltrating the peri-sylvian area and awake surgery was not indicated. Exclusion criteria for awake procedures included the patient's decision against awake surgery, anxiety/scarce cooperation and/or over 30% baseline naming errors as assessed by the neuropsychologist using the Italian Batteria per l'analisi dei deficit afasici (BADA, (Miceli et al., 1994)). Handedness was assessed using the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971). Eight patients suffered from a glioblastoma (WHO IV) and one from a cavernoma. Six patients presented with a history of seizures, two patients with language deficits and one patient had right-sided hyposthenia. Two patients had lesions in the frontal lobe, three in the parietal lobe and four in the temporal lobe. A resection showing no residual tumour or more than 96% of tumour resected on postoperative MRI was considered gross-total (GTR). Surgeries where tumour resection was not complete but above 78% were considered subtotal (STR) (Sanai et al., 2011). The stimulation paradigms for the recording of CCEPs were included in our intraoperative neurophysiological monitoring protocol for which patients provided a written, informed, consent. The parameters of cortical stimulation never exceeded the safety limits that we routinely adopt when performing DES. The use of cortical strips also did not differ from their routine use in brain surgery.

Accordingly, no specific, additional, ethical approval was required. Patient demographics are described in Table 1. The surgical protocol for evoking cortico-cortical evoked potentials is shown in Fig. 1.

Table 1. Patient demographics.

Patient	Age	Sex	Symptoms	Tumour location	Histological diagnosis	Extent of Resection	Handedness
#1	69	M	Right hyposthenia	Parietal	GBM	GTR	RH
#2	49	F	Repetition deficits, dyslexia	Temporal	GBM	STR	RH
#3	59	M	Articulation deficits	Parietal	GBM	GTR	RH
#4	24	F	Focal seizures, articulation deficits	Parietal	GBM	GTR	LH
#5	57	F	Focal seizures, phoemic paraphasias	Temporal	GBM	GTR	RH
#6	52	M	Articulation deficits	Frontal	GBM	GTR	RH
#7	66	M	Focal seizures, naming deficits	Temporal	GBM	GTR	RH
#8	64	M	Focal seizures	Frontal	GBM	GTR	RH
#9	38	M	Focal seizures	Temporal	Cavernoma	GTR	RH

GBM: Glioblastoma; GTR: gross-total resection; STR: subtotal resection; RH: right-hander; LH: left-hander.

2.2. MR acquisition

MRI scans were acquired for each patient before surgery on a Signa 3T scanner fitted with an eight-channel head coil (General Electric Healthcare, Milwaukee, USA). T1-weighted 3D MPRAGE images with Gadolinium were acquired for contrast-enhancing lesions, while T2-weighted, FLAIR 3D images were used to identify the non-contrast enhancing lesions. A diffusion weighted imaging (DWI) sequence was acquired in 48 directions with a b-value of 2000 s/mm , with three interleaved non-diffusion-weighted volumes.

2.2.1. DWI processing for HARDI tractography

DWI data was pre-processed using ExploreDTI (Leemans et al., 2009), and spherical deconvolution deterministic tractography was generated using StarTrack software (www.mr-startrack.com) using a damped Richardson-Lucy algorithm (Dell'Acqua et al., 2010). Virtual dissection of the fronto-temporal segment of the arcuate fasciculus (AF) was performed in the lesioned hemisphere using a manual ROI-based approach by the first author using TrackVis, using anatomical landmarks as described by Rojkova and colleagues (Rojkova et al., 2016). The arcuate fasciculus was registered to the structural MRI using FSL

(FLIRT; FMRIB Software Library, www.fmrib.ox.ac.uk/fsl) (Smith et al., 2004) and uploaded into the neuronavigation system (StealthStation S7®; Medtronic, Minneapolis, MN, USA). Arcuate fasciculus terminations were selected for neuronavigated-intraoperative strip placement prior to surgery. Sites were recorded on the patient T1 using neuronavigation. Following surgery, sites were registered to an averaged brain, the Montreal Neurological Institute (MNI) template, using enantiomorphic normalisation (SPM Clinical Toolbox, www.fil.ion.ucl.ac.uk/spm).
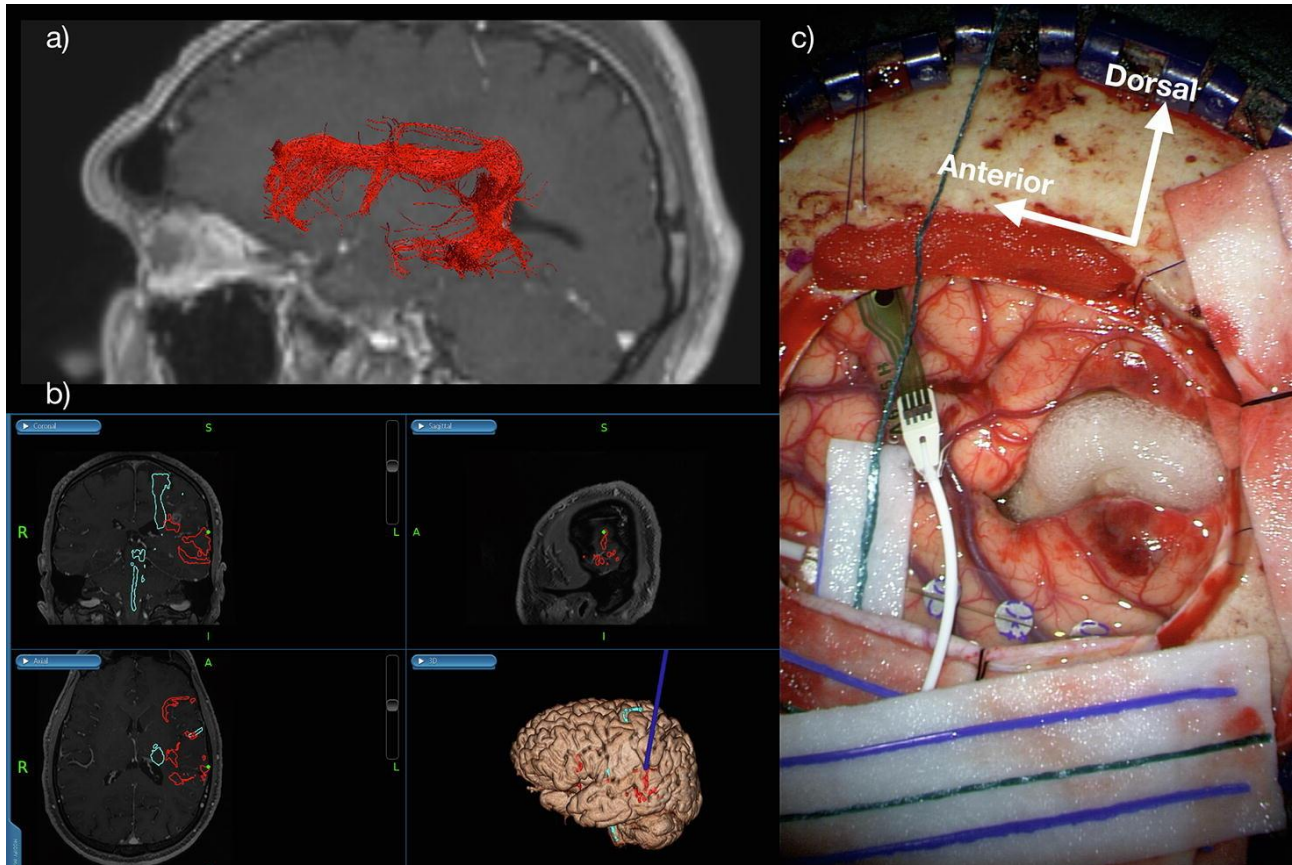

Fig. 1. Surgical protocol for asleep cortico-cortical evoked potentials (CCEPs). (a) Preoperative diffusion-weighted sequences for High Angular Resolution Diffusion Imaging (HARDI) tractography was acquired in order to dissect the arcuate fasciculus (AF, in red). The tract is dissected using a region-of-interest approach as reported in Rojkova and colleagues (Rojkova et al. 2016). (b) Tract uploaded into the intraoperative neuronavigation for tractography-targeted strip electrode placement. (Cortical terminations in the posterior temporal gyrus shown with green dot in axial, coronal and sagittal view, indicated by the probe in the 3D reconstruction). Blue: Corticospinal tract. (c) Intraoperative photograph showing the cortex exposed with two strip electrodes placed to intraoperative record CCEPs. Data were analyzed online and offline (not shown). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.3. Intraoperative neurophysiological monitoring (IONM) and data analysis

A Total IntraVenous Anaesthesia protocol was used (T.I.V.A) with continuous infusion of Propofol (100–150 μg/kg/min) and Fentanyl (1 μg/kg/min), avoiding bolus. Halogenated anaesthetic agents were not used. Neurophysiological monitoring and mapping required simultaneous acquisition and recording of continuous electroencephalography (EEG), switching to electrocorticography (ECoG) as soon as the cortex

was exposed. Free-running electromyographic (EMG) activity (ISIS-IOM, Inomed Medizintechnik GmbH, Emmendingen, Germany) was also recorded. ECoG was acquired with the following parameters: low frequency filter (LFF) 0.5 Hz; high frequency filter (HFF) 70 Hz; range 10 mVpp, 30 mm/s. Patients underwent motor transcranial and/or cortical/subcortical mapping and motor evoked potential monitoring according to the lesion site.

During surgery, neuronavigation was used to place two 6- or 8-channel strip electrodes over the identified cortical terminations of the arcuate fasciculus in the frontal and temporal lobe respectively (Fig. 1). The frontal lobe strip was used for stimulation and the temporal lobe strip to record, as described by Matsumoto and colleagues (Matsumoto et al., 2004). CCEPs were evoked with a single stimulus (stimulation: pulse width 0.5 ms, with the exception of patient 6 in whom a 0.3 ms pulse width was used, current 20–30 mA, stimulation frequency 0.5–1 Hz, alternate monophasic pulse form; recording: filters LFF 1 Hz–HFF 5000 Hz, sampling rate 10 kHz). Continuous EEG and ECoG were monitored to identify and exclude afterdischarges. Moreover, CCEPs stimulation was performed once burst suppression phenomena were excluded after careful ECoG evaluation, since CCEPs amplitude may sharply decrease with depth of anaesthesia (Suzuki et al., 2019). Bipolar stimulation was used with two contacts of strip electrode covering the frontal cortical termination of arcuate fasciculus. Recording was monopolar, with all contacts referenced to a contact of the recording strip to reduce stimulation artefacts. Sixty to 120 responses were averaged following opening of the dura. We recorded a post-stimulus period of 100 ms only, as later waveforms should not be related to monosynaptic connections and may reflect other integrative cortical potentials (Valentin et al., 2002, Keller et al., 2011, Silverstein et al., 2020). It is important to emphasize that in the present setting CCEP recording was not used to guide the surgical procedure, and therefore was performed for research purposes at the end of the resection. The cortical recordings were exported in text format and processed offline using custom-made MATLAB scripts. The criteria used to identify a deflection of interest were driven by the previous literature on peri-sylvian CCEPs. We first sought to identify a similar N1 waveform to that described by Matsumoto and colleagues. To do so a trained neurophysiologist (L.C.) identified the negative peaks occurring between 15 and 40 ms after the stimulus: the peak amplitude of the putative N1 peak was calculated as in Matsumoto et colleagues (Matsumoto et al., 2004).

2.3.1. Control conditions

We evaluated the efficacy of strip electrode placement by comparing CCEP amplitude along the recording strip electrode, with particular focus on areas corresponding with cortical terminations of the arcuate fasciculus. We also performed temporal stimulation with frontal recording to test whether there was bidirectionality of CCEPs. Depending on the clinical timeframe, we further evaluated CCEP variation when slightly modifying strip position.

2.4. Data availability statement

The CCEP data that support the findings of this study are available on the OSF framework (https://osf.io/t2agp/). The clinical data is available on reasonable request to the first or last author (D.G. or F.S.).

3. Results

3.1. Preoperative results

3.1.1. Tractography

The arcuate fasciculus was dissected in all but one patient due to extensive oedema. Frontal terminations were identified to include the pars opercularis (8 patients), the ventral precentral gyrus (7 patients), the

pars triangularis (5 patients) and the posterior middle frontal gyrus (1 patient). Temporal terminations were identified to include the middle temporal gyrus (8 patients), the superior temporal gyrus (7 patients) and the inferior temporal gyrus (5 patients). The arcuate fasciculus was infiltrated by the tumour in 5 cases, displaced in 3 cases, and ran adjacent to the tumour in 1 case (Table 2).

Table 2. Anatomical characteristics of the arcuate fasciculus.

Patient	Arcuate fasciculus Relationship to tumour	Frontal projections	Temporal projections	Total length (mm)	Total volume (ml)	HMOA	MD
#1	Infiltrated	PrC, pOP	STG, MTG	105	19	0.01	0.91
#2	Displaced	PrC, pOP, pTRI	STG, MTG, ITG	145.67	9.17	0.01	0.76
#3	Infiltrated	PrC, pOP	MTG	126.42	15.52	0.01	0.69
#4	Infiltrated	PrC, pOP, pTRI	STG, MTG	96.01	19.2	0.02	0.66
#5	Infiltrated	pOP, pTRI	STG, MTG, ITG	131.8	20.3	0.01	0.73
#6	Displaced	-	-	-	-	-	-
#7	Displaced	PrC, pOP, pTRI	STG, MTG, ITG	103.73	8.8	0.01	0.78
#8	Infiltrated	PrC, pOP, pTRI	STG, MTG, ITG	112.46	12.87	0.02	0.73
#9	Bordered	PrC, pOP, pTRI, pMFG	STG, MTG, ITG	125.31	34.2	0.02	0.61
Mean	-	-	-	118.22	17.38	0.01	0.73
s.d.	-	-	-	16.69	8.12	0.005	0.08

HMOA: Hindrance modulated orientational anisotropy; MD: Mean diffusivity; pOP: pars opercularis; pTRI: pars triangularis; pMFG: posterior middle frontal gyrus; PrC: precentral gyrus; STG: superior temporal gyrus; MTG: middle temporal gyrus; ITG: inferior temporal gyrus.

3.2. Intraoperative results

3.2.1. Recording of cortico-cortical evoked potentials

Cortico-cortical evoked potentials between posterior inferior frontal regions and posterior superior temporal regions were recorded in 5/9 patients. At the population level, a reproducible waveform was evoked consisting of a positive component (P1), but also the negative component (N1) resembling what has previously been described in the awake patient (Matsumoto et al., 2004). The mean peak latency for the P1 component was 12.8 ms (SD 1.3) with an amplitude of 25.2 µV (SD 12.2). The N1 component had a peak latency of 21.3 ms (SD 3.1) with a mean amplitude of 43.4 µV (SD 38).

The identified contacts with maximal responses and relative reported CCEP measurements are reported in each subject in Table 3. Individual results are shown in Fig. 2.

Table 3. Summary of cortico-cortical evoked potential measurements.

Patient		Cortico-cortical evoked potentials Frontal strip	Temporal strip	Intensity (mA)	Contact with highest response	N1	P1 Peak latency (ms)	Amplitude (µV)
#1	PrC	STG; MTG	20	EL3	26.4	108	12.5	47
#2	PrC, pOP	MTG	30	EL4	21.9	28	12.8	20
#3	PrC	MTG	20	EL3	20.3	14	14.9	18
#4	PrC	MTG	25	EL2	19.7	21	11.3	20
#5	pOP, pTRI	MTG	23	EL5	18.4	46	12.6	21
#6	pOP	STG	20	-	-	-	-	-
#7	PrC	STG, MTG	20	-	-	-	-	-
#8	PrC	STG, MTG	20	-	-	-	-	-
#9	pOP, pMFG	MTG	20	-	-	-	-	-
Mean	-	-	23.6	-	21.3	43.40	12.8	25.2
s.d.	-	-	4.1	-	3.1	38	1.3	12.2
Patient		Cortico-cortical evoked potentials Frontal strip	Temporal strip	Intensity (mA)	Contact with highest response	N1	P1 Peak latency (ms)	Amplitude (µV)

pOP: pars opercularis; pTRI: pars triangularis; pMFG: posterior middle frontal gyrus; PrC: precentral gyrus; STG: superior temporal gyrus; MTG: middle temporal gyrus; ITG: inferior temporal gyrus; EL: electrode.

3.2.2. Anatomical specificity of evoked potentials for the arcuate fasciculus

Overall, all frontal stimulations eliciting CCEPs occurred in the ventral part of the precentral gyrus or the pars opercularis. Evoked potentials in the temporal lobe were specific for the middle temporal gyrus. Two restricted areas with the highest responses were identified in the central portion of the middle temporal gyrus and a second in the posterior third of the middle temporal gyrus. In all patients these areas overlapped with the cortical terminations of the dissected arcuate fasciculus. Eighty one percent (13/16) of contacts evoking CCEPs occurred at terminations of the arcuate fasciculus. The individual anatomical location of CCEPs is shown in Fig. 3. The normalised location of all recording contacts for all strip positions is shown in Supplementary Table S1.
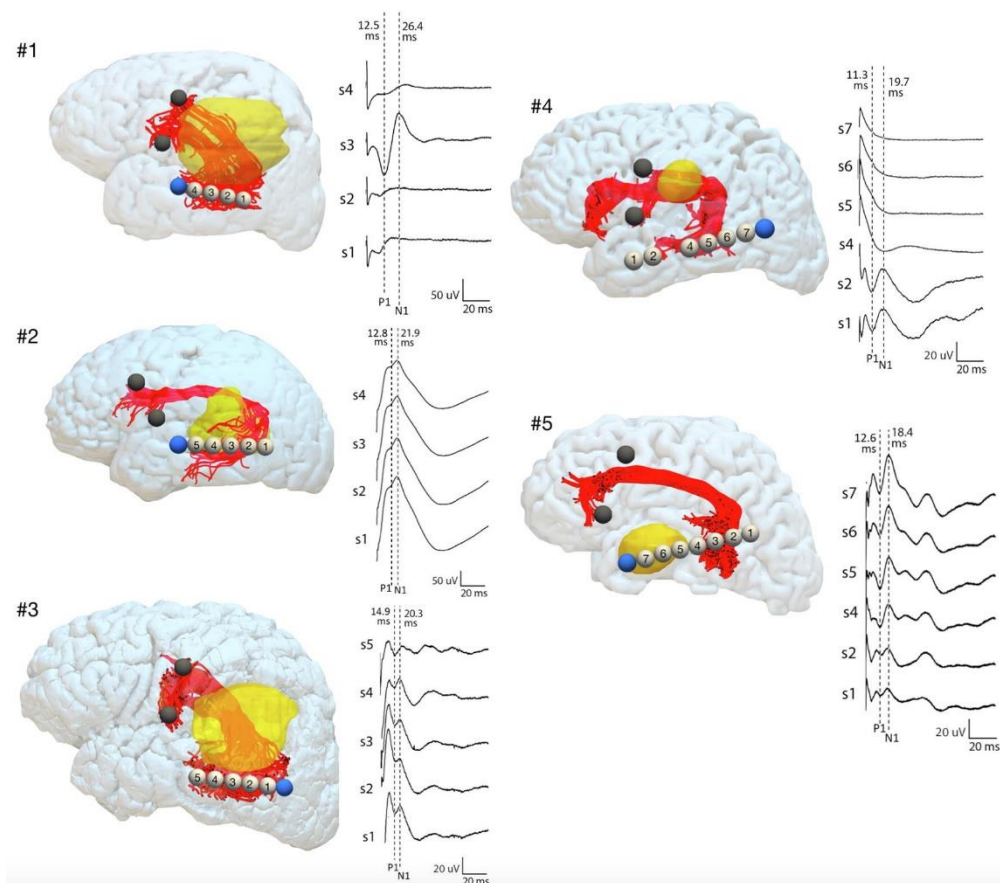
Fig. 2. Individual cortico-cortical evoked potentials (CCEPs) recorded from the strip electrode positioning with highest CCEPs amplitude in five representative patients. Rendering of the individual cortical surface is shown in grey, superimposed the individual arcuate fasciculus (in red) and tumor (yellow). Black spheres indicate the site of stimulating electrodes, while white numbered spheres indicate the cortical position of the recording electrodes. Monopolar references for recording is shown in blue. Waveforms evoked in each contact electrode of the recording strip are shown: first dotted line represents P1 while the second represents N1. Other strip placements are not shown in the figure. Negative components are shown as superior deflections. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
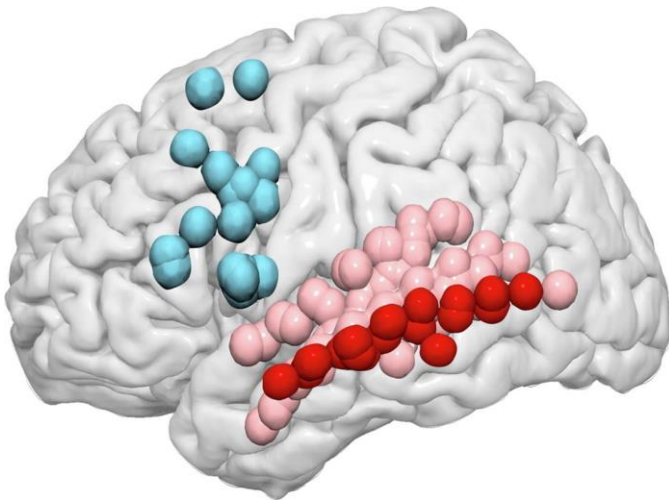
Fig. 3. Map of all strips contact registered to a standard template (Montreal Neurological Institute, MNI). Recording contact electrodes in the temporal lobe for each patient are displayed with identified cortico-cortical evoked potentials (CCEPs) in red and no responses shown in pink. Stimulating contacts are displayed in light blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2.3. Reversed stimulation-recording trials

In 8 out of 9 patients, the cortical location for stimulation and recording were inverted keeping the same stimulation parameters. Evoked potentials were not identified in any patients when stimulating from the temporal cortex and recording from the frontal lobe.

3.2.4. Altered strip electrode placement

In 3 out of 5 patients for whom CCEPs were evoked, strip electrodes were shifted to test the reliability of other stimulation sites recorded using intraoperative navigation. CCEPs were evoked in one patient (P1) when another contact electrode covered the previous position for CCEPs in the middle temporal gyrus. All other contacts in the three patients that covered regions in the superior temporal gyrus did not evoke CCEPs, even when the contacts overlapped cortical terminations of the arcuate fasciculus in this region.

4. Discussion

In the present study we used preoperative tractography for anatomically-guided strip placement to evoke cortico-cortical evoked potentials (CCEPs) of the arcuate fasciculus in adult patients for whom awake surgery was not indicated. This is, to our knowledge, the first report of CCEPs evoked intraoperatively specifically for patients operated under complete general anaesthesia. We showed a waveform with two components: a positive one (P1) at 13 ms and a negative one (N1) at 23 ms, with little inter-group difference in peak latency (±1.3 ms for P1 and ±3 ms for N1). The N1 component showed striking similarity with the negative waveform previously described in the awake setting. These components occurred at cortical terminations of the arcuate fasciculus in all subjects and in 13/16 contacts evoking CCEPs, suggesting they may have been conveyed by this pathway. On a group level, these potentials were primarily evoked in the middle temporal gyrus. Strict fronto-temporal directionality was identified: no potentials were evoked when stimulating in the temporal lobe and recording from the frontal lobe (Matsumoto et al., 2004, Keller et al., 2011, Entz et al., 2014). We show that CCEPs are feasible also under complete general anaesthesia. We speculate that CCEP monitoring during surgery could be used to predict,

and potentially prevent, arcuate disconnection in patients operated under general anaesthesia as in the awake setting (Saito et al., 2014, Yamao et al., 2014). This may help reduce postoperative aphasia and improve patients' quality of life.

4.1. Putative N1 component

The first documentation of conducted potentials from one cortical area to another can be traced back to Adrian (Adrian, 1936). However "cortico-cortical evoked potentials" (CCEPs) as direct electrophysiological connections recorded between frontal and parieto-temporal language areas in awake subjects before epilepsy surgery were first reported by Matsumoto and colleagues (Matsumoto et al., 2004). They were obtained by averaging electrocorticograms (ECoGs) recorded from peri-sylvian and extra-sylvian basal temporal language areas time-locked to the stimulus (Saito et al., 2014, Yamao et al., 2014). We show that these can be reproduced also under general anaesthesia in adult patients and report that a putative N1 component can be identified with a peak latency of 23 ms, akin to what has previously been reported in the awake subject (22–36 ms ; 25–33.2 ms) (Matsumoto et al., 2004, Yamao et al., 2014). Interestingly, the N1 peak latency was less variable than has been reported in the awake setting, with a range of variability within 3 ms compared to 50 ms (Silverstein et al., 2020). It is possible that Propofol, by activating inhibitory GABA networks, decreases waveform amplitude (Suzuki et al., 2019, Sarasso et al., 2015), hence cortical stimulation is less susceptible to ongoing brain activity compared to during wakefulness. Accordingly, TMS-EEG studies comparing brain responses to cortical perturbation during Propofol sedation show lower complexity compared to wakefulness, and this observation is directly related to the depth of anaesthesia (Sarasso et al., 2015). However, a recent study by Suzuki and colleagues has shown that even if CCEPs amplitude is sharply modified by the depth of anaesthesia, latency is not (Suzuki et al., 2019), suggesting other reasons for the decrease in peak latency variability in our group of patients.

The paradigm for strip placement may have played a role. Generally, strip electrode placement for CCEPs has been performed blind to the subcortical anatomy. Hence, functional language cortices are tested using grids across widespread frontal and temporal areas (Matsumoto et al., 2004, Keller et al., 2011) which may affect specificity for a given white matter tract. In our setting, strip placement was targeted to stimulate and record cortical terminations of the arcuate fasciculus, using anatomical priors determined by preoperative diffusion tractography. Using this approach, evoked CCEPs corresponded with the arcuate fasciculus in all subjects, with 81% of CCEPs occurring from contacts at its cortical terminations, suggesting specificity for this tract. However, it should be noted that N1 responses with similar latencies occur aspecifically in the cerebral hemispheres (Keller et al., 2011), and it is well established that surface electrical stimulation can produce direct cortical responses adjacent to stimulated cortex with stereotypical post-synaptic responses with latencies around 20 ms (Goldring et al., 1994, Vincent et al., 2017). Although N1 preservation does correspond with preserved postoperative language ability (Yamao et al., 2014) and the N1 latency correlates with the fractional anisotropy of the arcuate fasciculus (Silverstein et al., 2020), it is possible that other earlier waveforms may be more specific to this tract.

4.2. Putative P1 component

Our data indicate that a putative P1 component with a peak latency at 13 ms also exists which differs from both the stimulation artefact and N1 onset latency. The P1 peak latency was much earlier than the N1 component, suggesting N1 may not represent a direct connection. CCEPs are network-specific (Fox et al., 2020, Keller et al., 2011), with latencies that should reflect tract length (Silverstein et al., 2020) as well as fibre diameter (Waxman and Swadlow, 1977). The conduction time for the earliest orthodromic response via the arcuate fasciculus in humans should range between 4 and 12 ms for an estimated tract of 10–13 cm length (Matsumoto et al., 2004). This corresponds well with our results both in terms of the length of arcuate fibres and expected latency. N1 and P1 components were identified in all patients. We speculate they may represent two components of the same phenomenon, whereby P1 represents synaptic input

from a distant cortical area and N1 a locally generated response. However, as N1 decrease is correlated with postoperative language deficits, this may reflect the arcuate fasciculus (Yamao et al., 2014). As the direct fronto-temporal connection and indirect fronto-temporo-parietal connections are linked to language function (Catani et al., 2005), an alternative interpretation is that the P1 component reflects the direct segment and N1 the indirect segments, although this requires dedicated study.

4.3. CCEP responses in the middle temporal gyrus

CCEP responses were clearly clustered in the middle temporal gyrus, and CCEPs were not evoked even when sliding the strip electrode into the superior temporal gyrus. This was surprising, considering that tractography and dissection studies indicate that the arcuate fasciculus extends into the posterior superior, middle and the inferior temporal gyrus (Fernández-Miranda et al., 2015, Yagmurlu et al., 2016). CCEPs are commonly evoked from the middle temporal gyrus (Matsumoto et al., 2004, Saito et al., 2014, Yamao et al., 2014). Although the superior temporal gyrus can evoke CCEPs (Matsumoto et al., 2004, Yamao et al., 2014), a recent exploration of CCEPs evoked from the inferior frontal gyrus evidenced that the most posterior part of the inferior frontal gyrus was connected almost exclusively with the middle temporal gyrus (Nakae et al., 2020). Notably, Fernandez-Miranda and colleagues (Fernández-Miranda et al., 2015) showed in a combined tractography-dissection study that the pars opercularis connects with the superior temporal gyrus, while a larger component connects the precentral gyrus with the middle temporal gyrus. The volume of CCEPs conducting fibres could potentially be important for identifying responses. In this scenario, selectivity for the middle temporal gyrus may have been caused by positioning of frontal stimulation electrodes which predominantly covered the ventral premotor cortex rather than more anterior inferior frontal regions.

Further, we show that CCEP stimulation and recording sites are not reciprocal, supporting previous findings (Matsumoto et al., 2004, Entz et al., 2014). When reversing stimulation and recording from salient frontal and temporal sites we did not elicit CCEPs. CCEP directionality was reported in their first clinical description: the arcuate may have a large number of fibres extending from the frontal to temporal lobe but fewer running in the opposite direction (Matsumoto et al., 2004). However, this should not be assumed as a general rule for CCEPs: in a recent study confronting CCEPs from parieto-temporal and infero-frontal areas, Nakae and colleagues found a strong reciprocality when switching stimulating and recording dipoles for areas connected to the pars orbitalis, potentially representing connections of the inferior-fronto-occipital fascicle (Nakae et al., 2020). Therefore, even if differences in latencies and amplitudes between cortical areas when reversing stimulation and recording have been described for the motor system, limbic system and the insular cortex, directionality may not always be expected for fibres making up a tract (Matsumoto et al., 2004, Entz et al., 2014, Enatsu et al., 2016).

4.4. CCEPs for asleep surgery of peri-sylvian areas

Preservation of language function is a primary goal in brain surgery, since its impact on quality of life is profound (Osoba et al., 1996). Postoperative aphasia often precludes further oncological treatment, which impacts life expectancy (Weller et al., 2014). The arcuate fasciculus is one of many white matter tracts involved in language function (Dick et al., 2014), however its disconnection commonly linked to long-term aphasia (Caverzasi et al., 2016). Awake surgery is currently used to test language function intraoperatively, nevertheless these results can be unreliable in situations of low compliance, such as when longer operating times cause patient tiredness. Further, not all patients are candidates for awake surgery, particularly children, as awake surgery is not indicated for children under 10 years old and is tolerable only in a selected group of older children (Lohkamp et al., 2019). Furthermore, in spite of its popularity, awake surgery is still not used across all centres (Spena et al., 2017).

Developing a tool to preserve fibre tracts under general anaesthesia would reduce postoperative functional deficits. In the awake setting, monitoring CCEPs for the arcuate fasciculus helps preserve language function. We show here that CCEPs are feasible also under general anaesthesia, with comparable waveforms to

those evoked under awake settings. It will be important to assess whether this technique helps preserve language ability in a large cohort of patients in future studies (Saito et al., 2014, Yamao et al., 2014).

Practically, we advise positioning the stimulation strip electrode over the ventral premotor cortex and the recording strip over the middle temporal cortex to reproduce our results.

In this study we did not evaluate systematically the effect of depth of anaesthesia on our potentials, which may have been conspicuous. To compensate for this, we rigorously performed CCEPs after careful ECoG evaluation in order to exclude burst suppression. As a recent study by Suzuki and colleagues (Suzuki et al., 2019) showed that anaesthesia may substantially depress CCEP amplitude, despite having minimal effects on latency, we caution to control for depth of anaesthesia since it may bias CCEP interpretation. If confirmed in a larger cohort, CCEPs for the arcuate fasciculus may be adopted to clinically monitor the arcuate fasciculus in a fully sedated patient, offering a tool to improve functional outcome and therefore quality of life.

5. Limitations

First, as a feasibility study for CCEPs performed under general anaesthesia, we are not evaluating the effect of the lesion on CCEPs, and therefore we could not draw any evidence of CCEP monitoring with regards to neurological outcome, extent of resection or neuroplasticity exerted by the lesion. Second, we report these findings in a relatively small patient cohort, due to a strict selection criteria. Third, this method does not strictly target language function, rather the circuits associated with this function. Fourth, as the clinical workflow implied MEP monitoring to be prioritised to CCEPs, they were performed when MEP monitoring was terminated. Accordingly, as they were performed at the end of the surgery, this may have added bias to our CCEPs evaluation. Finally, as it lied outside the aim of this study, we could not correlate the clinical relevance of this technique, but this remains of paramount importance to be proven.

6. Conclusion

To conclude, our results indicate that CCEPs can be monitored under general anaesthesia in patients who cannot undergo awake procedures. By using a targeted neuronavigation method for strip placement, we identified consistent CCEP latencies across subjects: an N1 latency (23 ms) and a P1 at 13 ms that matched the cortical terminations of the arcuate fasciculus. These results may offer a new intraoperative technique for patients that cannot undergo awake surgery for language function, with the aim to further contribute to prevent neurological deficits and hence to preserve quality of life.

7. References

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