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# **The orientation of the stimulating bipolar probe modulates axono-cortical evoked potentials**

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Direct electrical stimulation (DES) can be applied on cortical areas and white matter pathways (WMP) for brain mapping (Duffau, 2015). The orientation of the bipolar DES probe has a limited impact in the gray matter due to isotropism in the horizontal plane. By contrast, in the WMP, the alignment of the axons along a preferential direction induces an anisotropy in the plane passing between the two poles. This makes their orientation critical. This problem is well known in the stimulation of the peripheral nerve to exploit the spatial selectivity of the stimulated axons (Dali et al. 2018). On the other hand, due to a relatively recent use of stimulation for awake brain surgery (Duffau 2015), the classic approach has, until now, consisted exclusively of placing the poles perpendicular to the targeted WMP to increase the sensitivity of the technique. We focused on low frequency DES applied in the resection cavity on the WMP to induce Axono-Cortical Evoked Potentials (ACEPs: Yamao et al. 2015, Mandonnet et al. 2016, Vincent et al. 2017, 2020, Boyer et al. 2021), that can be used to track on-line the connectivity. For a bipolar probe, when injected currents are opposite in the two poles (e.g. +I for the anode and -I for the cathode respectively), the local potential at a given point M in an infinite homogenous and isotropic medium is given by:

$$V(M) = \frac{I}{4\pi\sigma} \left( \frac{1}{r_2} - \frac{1}{r_1} \right) \quad (1)$$

With  $I$  the absolute current at one pole:  $\sigma$  the conductivity of the tissue,  $r_1$  and  $r_2$  the distance from each pole to  $M$ . For all locations equidistant from the two poles, the potential is null, thus defining a plane of vanishing potential. It has been demonstrated that activations of axons increase with an increase of the second spatial derivative of the potential (Rattay 1989), which remains relatively weak in the vicinity of this plane (see figure 1 A-B). Accordingly, all axonal fibres aligned close to this plane should be hardly activated by stimulation. This situation may potentially affect the intraoperative effect of 60Hz DES or the tracking of ACEPs. By contrast, in a parallel orientation of the two poles, no axon would be aligned with this quasi-null isopotential (but would rather be orthogonal to it): each axon below the two poles would be activated for moderated current amplitude, being exposed to voltage gradients.

Based on these considerations, we made the following predictions (Figure 1A: practical interest) regarding ACEPs obtained by stimulating the gyral WMP (in the resection cavity) and recording over the cortical gyrus:

- when the bipolar probe is applied orthogonally to the WMP, ACEPs should be reduced in the middle of the terminations of the WMP
- when the bipolar probe is parallel to the WMP, ACEPs should be more focal and of higher amplitude.

Two patients underwent awake brain surgery for a low-grade glioma. Patient 1 was a 31 year-old woman, right handed, with a 21 cm<sup>3</sup> low grade glioma in the left junction between the pre-central gyrus and the pre-motor region. Patient 2 was a 36 year-old man, right handed, with a 5.8 cm<sup>3</sup> low grade glioma in the left, inferior frontal gyrus. The study (UF 965, n° 2014-A00056-43) was approved by the local ethics committee. Usual cortical and white matter 60 Hz mappings were completed on awake patients. Then, for electrocortical recordings (ECoG), a low-frequency DES (3 or 9Hz) was performed at 2-3 mA for different subcortical sites, identified as functional areas during the brain mapping (for more details about the method please see captions of Figure 1-D). For each patient, two DES were applied in the gyral WMP, between 1 to 2 cm below the grey matter, one with the probe oriented parallel or orthogonally. In Figure 1-D, ACEPs are reported for the two orientations. As expected, when the bipolar probe is oriented parallel to the gyral WMP (green color), the amplitude of the ACEPs is more important for ECoGs in the alignment of the poles than for lateral ECoGs. Conversely, when the probe is oriented perpendicularly to the gyral WMP (red color), the amplitude of the ACEPs is lower for central ECoG and even remarkably cancels out for patient 1, while a certain level of evoked activity remains for lateral ECoGs. Importantly, for patient 2, the activity generated close to the ECoG 16 is greater in the parallel condition, but it should be kept in mind that ECoGs contacts also capture an image of nearby electrically active sources (due to volume conduction), limiting the impression of focal distribution. Indeed, for this orientation, ECoGs 12, 16, 1 and 2 clearly overlap by a given scaling factor and are time-locked. Conversely, the activity generated for the orthogonal orientation is more diffused homogeneously over all the electrodes.

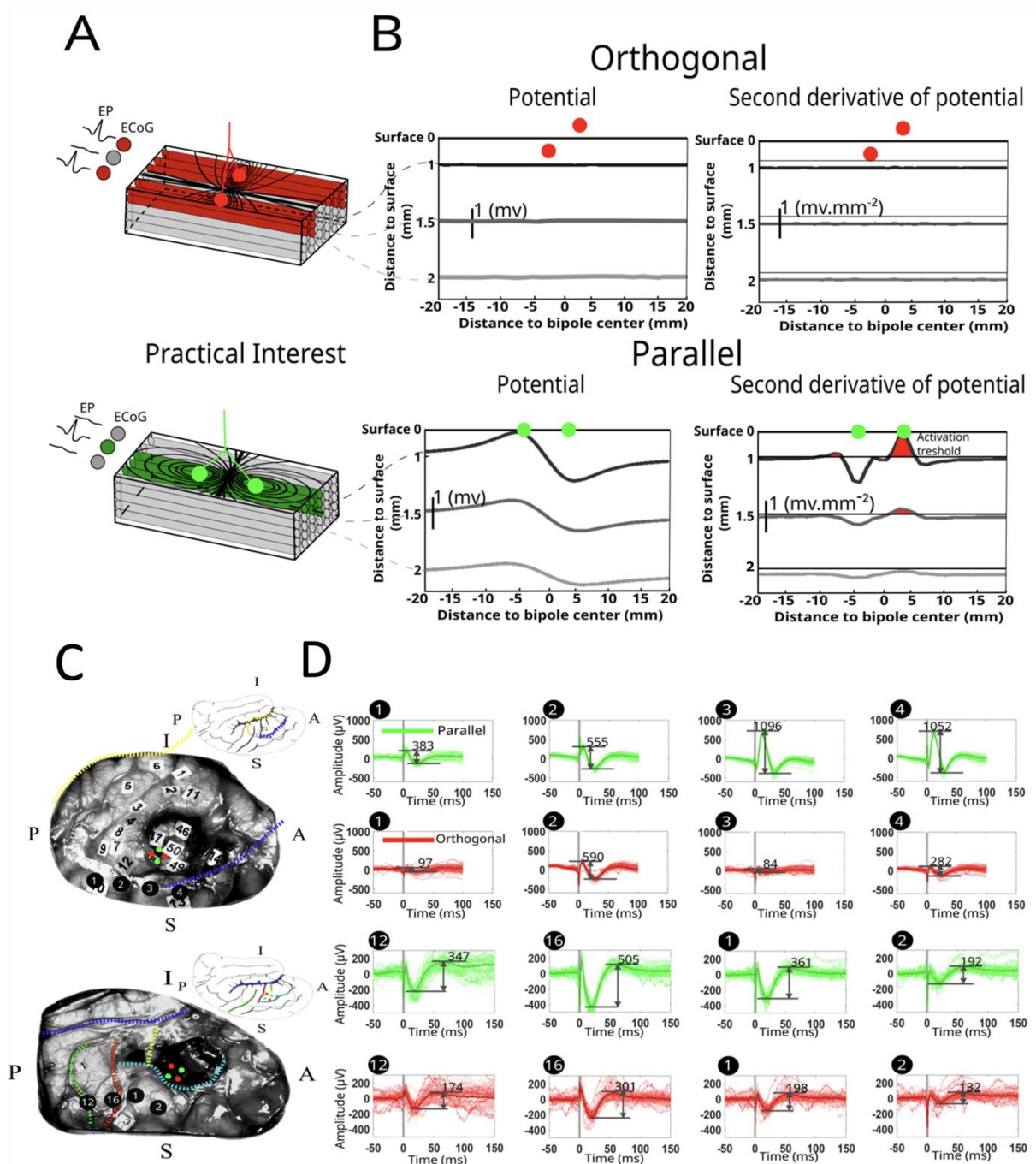


Figure 1. A) Theoretical diagram showing a portion of WMP composed of axons stimulated with an orthogonal (red) or parallel (green) orientations of the poles. For the orthogonal orientation, axons in between the poles are not activated (in grey). The activation overflows onto lateral axons projecting elsewhere. The straight thick black line represents the slice of the plane for which the potential is zero, perpendicular to the line joining the poles. Parallel orientation activates only axons in the axis of the two poles. Level lines under the poles represent the variations of potential only for the surface. They are not shown in the depth. Expected ACEPs are represented for the two cases. B) Variations of potential and its second spatial derivative for the orthogonal and parallel orientations (only the cathode and the anode are represented in the parallel condition without phase alternation in this case for sake of clarity). Variations of potential and its second spatial derivative remain very low in between the two poles for the orthogonal condition. They are more important in the same plane

passing through the two contacts for the parallel one. Values are normalized and an activation threshold was arbitrary chosen. C) Positionings of ECoG strips on the cortex and of stimulation poles in the cavity for the two orientations. D) ACEPs obtained for bipolar DES applied in parallel (green) or orthogonally (red). For **Patient 1**, greater ACEPs are observed on ECoGs 3-4 in the alignment of DES poles positioned in parallel and are attenuated laterally for ECoGs 1-2. During orthogonal DES, complete attenuation is clearly observed for the center with lower but significant lateral ACEPs. For **Patient 2**, greater ACEPs are observed on ECoG 16 and 1 located in the alignment of the DES poles parallel to the WMP. ACEPs attenuate as they move away from this epicenter. For orthogonal DES, ACEPs are reduced but still remain homogeneous for all ECoGs. For Patient 2, 3 different ECoG strips are used, only contacts showing ACEPs are shown.

The orientation of a bipolar probe when measuring ACEPs and during intraoperative mapping (even if behavioural effect during 60 Hz DES remain to be investigated) is critical. To identify a specific WMP, the parallel orientation is more selective. Greater sources can be recorded on remote ECoGs, with volume conduction reducing the focality of the ACEPs. By contrast, to be more sensitive by recruiting further WMP to stop the resection accordingly, an orthogonal orientation of the DES seems more appropriate.

The homogenous and parallel alignment of axons in the gyral WMP (about 1 to 2 cm below the grey matter) might be an optimal setting to illustrate these effects. More deeply in the cavity, the crossing of multiple WMPs, three-dimensionally more complex (i.e. more torsion and curvature), might reduce this effect. In addition, when DES is applied remotely from its cortical output, the evoked responses may be smaller due to the divergence of WMP (i.e. reduced summation of electrophysiological events, Boyer et al. 2021).

Manipulating the orientation of the probe jointly with the observation of the ACEPs spatial distribution could allow identifying on-line the terminal distribution of the stimulated WMP. A strict parallel orientation of the stimulating contacts would induce focused and increased ACEPs. Whereas a rotation of the probe and the contacts towards an orthogonal position would decrease their amplitude. Performing these rotations while visualizing ACEPs is promising to track intra-operatively the WMP. The distance between the two contacts is an important parameter: if they are not enough spaced the effects of the orientation onto the ACEPs may be limited. This approach opens perspectives for intra-operative on-line electrophysiological dissection of WMP.

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