Our data proved that interhemispheric processing is impaired in early HD and significantly correlates with clinical and genetic data. In the past, many papers have been published about TMS for understanding HD pathophysiology and a number of different, sometimes contradictory, findings has been described, from an abnormal cortical silent period (cSP) to changes in short intracortical facilitation (Priori et al., 1994). More consistent data have recently proved higher thresholds for short intracortical inhibition (SICI) compared with healthy subjects (Schippling et al., 2009), in line with those reported for focal hand dystonia (Stinear and Byblow, 2004).

Our results could have implications for the disruption of both sensorimotor integration and voluntary motor control in HD. Immediately before voluntary movements, interhemispheric interactions are likely responsible both for the temporary inhibition of ipsilateral primary motor cortex (M1) and the increased excitability of contralateral one (Leocani et al., 2000). Concurrently, especially during non-dominant hand movements, enhanced interhemispheric inhibition from the ipsilateral hemisphere suppresses superfluous activation arising from the contralateral cortex (Kobayashi et al., 2003). These mutual interactions may be lost in symptomatic HD, thus contributing to early motor symptoms such as hyperkinesias.

This is the first study using TMS to assess the functional disconnection between hemispheres in HD. iSP and TCT offer a unique opportunity to explore the whole callosal machinery, as these parameters refer to different callosal functions: the first one likely reflects the callosal inhibition, while the second relates to the synchronization of cortical activity. That agrees with data in healthy adults, showing a shortened iSPD, paralleled by a lengthening in iSPOL and TCT, with increasing age (Petitjean and Ko, 2014). A recent paper, studying the so-called movement-related potentials (MRPs) as neural correlates of voluntary movement execution, has proved an impaired interhemispheric inhibition in early HD (Beste et al., 2009).

A possible pitfall is about the intriguing hypothesis of a non-callosal origin of iSP (Compta et al., 2006); in fact, although iSP relies on transcallosal phenomena, it originates also from subcortical motor tracts with bilateral projections at the level of the brainstem or the spinal cord. Among other measures of ipsilateral inhibition, the so-called interhemispheric inhibition (IHI) is thought to be generated at the motor cortical level; while IHI reflects inhibition of synchronized activation of the corticospinal system, iSP represents interruption of voluntary muscle activity, possibly supporting its callosal origin (Chen et al., 2003).

Overall, no study exists to date about the use of TMS to explore interhemispheric function in the whole field of hyperkinetic movement disorders; this approach may lead to a better knowledge of disease mechanisms, also in pre-symptomatic patients and other hyperkinetic movement disorders.

Conflict of interest

The authors have no conflict of interest to report.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2015.10.036.

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Case report: Remote neuromodulation with direct electrical stimulation of the brain, as evidenced by intra-operative EEG recordings during wide-awake neurosurgery

Real-time functional mapping of the brain with direct electrical stimulation (DES) is used to guide the resection of slow-growing infiltrative tumours during wide-awake surgery. The DES technique reduces the probability of resecting essential areas near or within the tumour (Duffau, 2005). During the neurosurgery, patients perform a number of neuropsychological tests while DES

is applied both cortically and subcortically, in order to detect and thus preserve connectivity online. This technique is especially useful for critical white matter pathways. This functional mapping of the area near the tumour enables the removal of as much as non-eloquent infiltrated tissue as possible, while minimizing sequelae.

The local electrophysiological effects of DES have only been partially characterized. By using electrocorticography and an implanted grid on the surface of the grey matter for pre-surgical planning in drug-resistant epileptic patients, Matsumoto et al. (2004, 2007) observed "corticocortical" evoked potentials around 10–50 ms after the start of low-frequency DES (1 Hz, 10–12 mA) at a cortical site. The evoked potentials were measured in contiguous cortical areas whose centres were up to three centimetres apart and were linked by axons in the grey matter or in local U-shaped subcortical fibres. In contrast, the propagation of DES and its remote effects have not yet been investigated (Mandonnet et al., 2010; Szelényi et al., 2010).

Here, we report on a case of wide-awake surgery for a slow-growing, right frontal brain tumour in a 33-year-old man. Intraoperative electroencephalographic (iEEG) recording was used to determine whether cortical or subcortical DES can have remote neuromodulatory effects on electrophysiological signals. The volume of the resection was 116.8 cm^3. DES (60 Hz, with biphasic current: $I = 2$ mA, pulse duration = 1 ms) was applied at different locations during the recordings (Fig. 1a). iEEG signals were recorded at four scalp sites: three on the contralesional hemisphere (F3, C3 and O1) and one on the ipsilesional hemisphere (O2). An additional reference electrode was placed on the right mastoid. During the recording itself, the Biosemi system's common-mode sense electrode served as the reference electrode. Electrophysiological signals were sampled at 2048 Hz and acquired with ActiView software. iEEG signals were detrended, and different stimulation periods were determined based on DES induced artefacts. For cortical DES, we obtained 23 periods with durations ranging from 1.3 to 10.2 s, separated by intervals of at least 2.3 s. For subcortical DES, we obtained nine periods with durations ranging from 3.3 to 11.6 s, separated by intervals of at least 5.1 s. Mean spectrograms were first determined (moving window: 500 ms; overlap: 90%, Hamming window: 1024 samples, nfft = 2048 samples) in order to detect noise (at 50 Hz, plus 60 Hz for DES artefacts). Mean power spectral densities (PSDs) were computed for the [0, 40] Hz frequency band, which clearly contained most of the iEEG signals.

When DES was applied to the right frontal lobe, the median frequency of the mean PSD computed for the [0, 40] Hz frequency band increased at C3 for both cortical and subcortical stimulation ($p = .045$ and $p = .006$, respectively), at F3 for cortical stimulation only ($p = .002$) and at O1 and O2 for subcortical stimulation only ($p = .004$ and $p = .026$, respectively). Furthermore, the power of the [20, 30] Hz frequency band also increased at C3, F3, O1, and O2 for subcortical DES (Fig. 1b and c, $p < .029$ in all cases). Interestingly, the increase in the median frequency, averaged over the different periods, at O1 was found to be progressive when DES was applied subcortically (see Fig. 1d, $p = .04$). In contrast, the power of the [10, 15] Hz frequency band decreased during DES ($p = .038$). After cortical DES, the power of a [0, 10] Hz frequency band increased at F3 ($p = .026$). A non-significant trend was

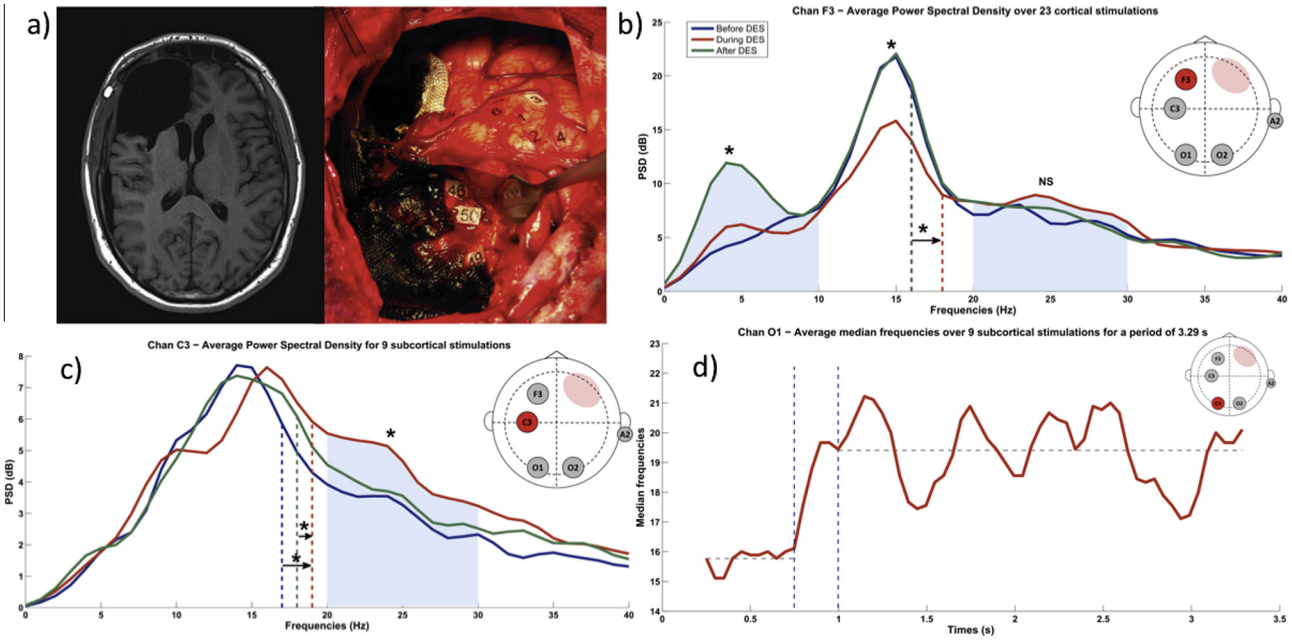

Fig. 1. (a) Post-operative MRI of the patient's brain, showing the right frontal cavity and an intraoperative view of the brain with the main anatomical landmarks. Cortical mapping: the premotor cortex with speech impediments in 6, 5 and 3; more medially, the motor cortex of the face with facial movements in 1, 2 and 4; no functional sites detected in the frontal area. Subcortical mapping with movement interruption induced by the DES: the anterior arm of the internal capsule in 46; periventricular structures in 49, just in front of the pyramidal tract from the motor cortex; and the junction between the corona radiata and the posterior arm of the capsule in 50, with complete anarthria when DES was applied (suggesting that fibres from the motor cortex of the face are stimulated). (b) The mean PSD of the iEEG signal before (blue), during (red) and after (green) each period of cortical DES (computed for durations of 2.3 s, [1.3, 10.2] s and 2.3 s, respectively), as measured at F3. The red ellipse on the top view of the head corresponds roughly to the tumour site and the resection. The median frequency increased with time when DES was applied. Interestingly, the power of the [0, 10] Hz frequency band increased (although after DES was applied), inducing after-effects in the theta band. (c) The mean PSD of the iEEG signal before (blue), during (red) and after (green) each period of subcortical DES (computed for durations of 5.2 s, [3.3, 11.6] s and 5.2 s, respectively), as measured at C3. The median frequency and power of the [20, 30] Hz band increased with DES. (d) The moving window median frequency (500 ms, with an overlap of 90%) averaged over nine subcortical DESs periods for PSD measured at O1. The median frequency was quite stable during the first 750 ms (at around ~16 Hz) and then increased after 1 s (to around ~19 Hz). These measurements were made for the first 3 s of DES (~the shortest period of subcortical DES). NS: non-significant. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

observed for the [0, 10] Hz frequency band at F3 with subcortical DES (p = .063).

We observed significant changes in the frequency content at different iEEG sites during DES. Subcortical DES (i.e. stimulation of white matter pathways) led to neuromodulation at more sites than cortical DES. This may have been due to (i) better conduction and propagation following the direct stimulation of large, myelinated axons and (ii) the greater current intensity in subcortical DES. Further research will have to characterize these aspects more carefully and apply cortical and subcortical DES with identical current intensities. Most of the observed changes occurred immediately after the start of DES. However, for subcortical DES, the median frequency at O1 increased progressively during the first second of the stimulation train. This observation suggests that immediate changes and progressive changes have differing mechanisms. The O1 electrode was furthest from the stimulation site; when more neural elements within a network are involved, neuromodulation with DES may be delayed by intermediary electrophysiological interactions. For some electrodes, we observed that the power increased within the [20, 30] Hz frequency band (i.e. the beta band) with cortical or subcortical DES. At F3, we also observed an effect of increasing power on the [0, 10] Hz frequency band. At this stage, it is premature to link DES-associated electrophysiological modulations to particular cognitive aspects: a variety of tasks were performed during surgery, and clinical assessments are performed by a neuropsychologist in real-time to detect perturbations. It remains to be seen whether DES induces these effects indirectly (i.e. through behavioural changes) or directly.

Although we investigated evoked potentials in the time domain, the method needs to be modified because the frequency used for DES (60 Hz) and the propagation time of the evoked potential (10–20 ms) are close enough to either mask the interesting signal or induce error in the determination of sequences of events. Accordingly, time-domain analyses are not yet possible; one would have to change the frequency of DES, which would require a specific scientific rationale and approval by an investigational review board since this change in DES is not part of routine clinical practice. On the basis of the present case report, we are developing a protocol for application to a series of patients undergoing wide-awake surgery. We expect a time-domain assessment of the future series to provide very useful, complementary information.

In conclusion, DES may induce some remote neuromodulatory effects and electrophysiological changes in both the contralesional and ipsilesional hemispheres.

Conflict of interest

None.

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Adult onset ictal aphasia with epileptic discharges in Broca's and Wernicke's areas

Aphasia can sometimes present with epileptic seizures, especially in temporal lobe epilepsy affecting the dominant hemisphere. Child-onset epilepsy with aphasia is known as Landau–Kleffner Syndrome (Caraballo et al., 2014), whereas adult-onset epilepsy presenting with aphasia is quite rare, as aphasia more often presents with stroke in adult patients. Here we describe a patient with adult-onset epilepsy exhibiting ictal aphasia, and whose epileptic discharges were detected by magnetoencephalography (MEG) in the motor and sensory speech areas.

A 22-year-old man was admitted to our hospital due to sudden loss of consciousness. He had already recovered consciousness on admission, but his speech was restricted to a single utterance, "yes," which he used as a response to any questions he was asked. He had a past history of head trauma in his childhood, although no detailed information on this injury was available. He had no past history or family history of epilepsy. He also appeared to have difficulty in understanding what was being spoken to him. Thus the patient was considered to have mixed aphasia, with both motor and sensory components. No weakness or sensory disturbance was identified during neurological examinations.