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Should asleep deep brain stimulation in Parkinson's disease be preferred over the awake approach? – Cons

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Accuracy is key. This statement obviously applies to neurosurgery in general, but probably even more so for deep brain stimulation (DBS) surgery in particular. The goal is to modulate the function of a very specific pre-defined group of dysfunctional brain cells – in an area which is typically very small and deeply located – to provide clinical benefit. The more dysfunctional cells are modulated, the greater the benefit. On the other hand, normally functioning neighbouring cells should be spared to avoid side-effects. Here, the smaller the target and the closer the surrounding healthy structures, the thinner the line between optimal and non-optimal results – and the more important the role of maximal accuracy.

DBS in the subthalamic nucleus (STN) for the treatment of Parkinson's disease is a paramount example of the importance of accuracy. While the subthalamic nucleus has many advantages over alternative nuclei with regard to efficacy [1], it is also a particularly delicate target with regard to side-effects, given its small size and close proximity to critical structures such as the corticospinal tract [2]. In addition, the subthalamic nucleus is not homogeneous but consists of functionally distinct subdivisions that cannot be visualised by MRI. Here, the precise stimulation spot within the dorsal motor subthalamic nucleus is considered the single most important predictor of treatment success, even more important than levodopa response or disease duration [3].

To maximise accuracy and optimise clinical outcome, STN-DBS lead implantation has traditionally been performed in the awake patient under local anaesthesia [4–6]. Here, wakefulness has been considered critical for high-quality microelectrode recording to electrophysiologically map the subthalamic nucleus and for test stimulation to assess efficacy and side-effects [4, 6]. In case of suboptimal test results, the lead can be relocated intraoperatively.

Today, more and more DBS centres are dispensing with wakefulness and perform asleep implantations under general anaesthesia instead [7]. This development is remarkable because it contrasts with the growing understanding of the paramount value of lead localisation in STN-DBS surgery. Also, it is not without a certain irony that the exact opposite trend can be observed in other neurosurgical subspecialties, e.g. neuro-oncology, where the use of awake surgery is steadily expanding [8].

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The supporters of asleep DBS claim that it is equally effective yet less troublesome as compared to the awake approach. We disagree with this statement and want to present our arguments that awake interventions (1) offer an important extra benefit in providing maximal efficacy with minimal side effects, defining a more favorable therapeutic window, (2) are less burdensome than many assume, provided support is optimal, and (3) therefore offer a superior benefit-cost ratio for many patients.

What is the extra benefit of wakefulness in subthalamic nucleus-deep brain stimulation implantation?

As a first step, we must acknowledge that the scientific literature on awake versus asleep STN-DBS surgeries is currently inconclusive. While some studies report no significant differences in efficacy and safety outcomes [9–14], others demonstrate a lower rate of side-effects following awake intervention [7]. Also, the largest prospective randomised trial to date, the GALAXY trial, was not designed and powered to solve this issue but primarily tested the hypothesis that awake interventions increase the risk for neuropsychiatric adverse effects – which, however, had to be rejected [13]. Moreover, the unexpected finding of an increased rate of brain haemorrhages in the asleep group raises questions regarding the study's validity [13]. Thus, the controversy is not (yet) settled, as the supporters of the asleep approach claim, but remains a matter of debate. So, what arguments are there to support awake STN-DBS implantations?

First, operating on fully awake patients reduces the risk of lead misplacement, in a strict sense, outside the subthalamic nucleus, e.g. due to intraoperative brain shift [15], MRI-CT fusion errors [16] or other technical problems. Given that it is the last of many steps before final implantation, intraoperative test stimulation is the ultimate safety measure to confirm correct lead positioning.

Second, wakefulness also increases the chance for maximal benefit through optimal lead placement at the best possible spot within the subthalamic nucleus. Most importantly, it allows assessment of both efficacy and side-effect thresholds (including subtle ones [2]) and, thus, identification of the full therapeutic window of a given stimulation

site. If the efficacy or side-effect profile is not optimal, other sites can be tested. This is particularly helpful when two microelectrode recording trajectories show good subthalamic nucleus signals, as therapeutic windows of different stimulation sites can be directly compared (see video available on Vimeo for an illustrative case: https://vimeo.com/989415003). We systematically examined the Zurich outcomes and found that at least one of nine patients benefits from this approach by receiving a corrected and optimised final lead placement [17].

Moreover, wakefulness provides higher-quality microelectrode recordings to sharply delineate the borders of the subthalamic nucleus [18]. This facilitates targeting of the neighbouring zona incerta and substantia nigra to treat dyskinesia [19, 20] or gait freezing [18] through interleaved co-stimulation. Importantly, as the disease progresses over time, therapy demands change. Thus, a given lead localisation may be satisfactory at the beginning but unsatisfactory at a later disease stage when a certain clinical demand is impossible to meet.

Supporters of asleep STN-DBS implantations claim that recent advances in stimulation technologies compensate for imperfect lead localisation. However, neither directional stimulation [21] nor brain sensing seem to significantly enlarge a given therapeutic window – and both tools are, for sure, no adequate substitute for a significantly misplaced lead [8]. Moreover, while probably every tool, including these new ones, adds a certain degree of benefit, it is the sum that is decisive – and why should we deliberately waive arguably the most powerful tool?

What is the true cost of wakefulness?

While we must admit that awake STN-DBS implantations are possibly more burdensome for most patients and slightly more expensive than asleep interventions, the question is whether this outweighs the benefits.

First, the psychological load of an awake operation is probably not as heavy as many assume. When patients were questioned *after* surgery, overall satisfaction did not significantly differ between awake and asleep groups despite higher rates of discomfort and anxiety in the awake group [22]. Of note, only 28% of awake patients would have preferred to be operated upon under general anaesthesia, indicating that 72% were positive about awake surgery. On the other hand, at least 12% in the asleep group would have favoured an awake approach [22]. This demonstrates that patient preferences are heterogeneous and underlines the importance of good education, preparation and psychological support [23]. Here, the role of a trustful relationship between patients and their medical team cannot be overestimated. Indeed, the challenge of an awake operation may also be a chance to grow together as a team including patients, caregivers, nurses, neurologists and neurosurgeons. Additionally, other measures can be applied to improve patient comfort, including short-acting sedatives such as remifentanil [13, 24] to bypass parts of the operation where wakefulness is dispensable and to reduce the duration of full wakefulness to a minimum if this is necessary. Accordingly, in >500 patients operated under local anaesthesia in Zurich – often with significant disease burden and advanced age – we only once had a panic reaction, obliging us to "change gear" and administer general anaesthesia.

Second, the risk of surgical complications such as intracranial haemorrhage is not increased by remaining awake. A positive correlation was found between bleeding risk and the number of microelectrode recording trajectories [25]. However, microelectrode recording was applied in roughly every second trial on asleep DBS [7] and is, thus, used independently of the anaesthesia method. One could even argue that waiving test stimulation increases the need for multiple microelectrode recording trajectories, which further fuels the bleeding risk. Moreover, the GALAXY trial has shown that awake operations do not carry a higher risk of postoperative confusion and subsequent neuropsychiatric sequelae [13], possibly because the burden of wakefulness is compensated by the burden of longer-lasting general anaesthesia in the asleep group [26].

Third, while microelectrode recording (independently of the anaesthesia method) and test stimulation increase operation time [13] – albeit by not more than 26 minutes (!) on average [13] – other tools such as surgical robots [27] or intraoperative imaging can be applied to shorten it again [27] and reduce costs.

So, it's worth it in the end!

Based on these arguments, we are convinced that the benefits of awake surgery clearly outweigh the costs that are on average lower than many assume. This positive benefit-cost calculation particularly holds true in the long run. To put it another way, the few, possibly burdensome, extra hours of staying awake pale into insignificance when compared to the days, weeks, months and years of suffering due to insufficient therapy or the burden of searching for the right stimulation settings given a suboptimal lead position.

Nevertheless, we must admit that awake STN-DBS is not suitable for everyone. Hence, we should beware of being dogmatic and solely sticking to one method – instead we should practice personalised medicine. The question is: What is your primary choice and how do you communicate with patients? In this context, we warn against oversimplified advertisements praising the comfort of asleep interventions while claiming that there is no "proven" extra benefit of staying awake. Clearly, it is much more time-consuming and cumbersome to rationally inform a patient about this complex matter. However, in the interests of our patients, we are convinced that it is worth it!

Informed consent

The patient shown in the video provided her informed consent for this video to be publishedto be published to accompany this article.

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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