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Will adaptive deep brain stimulation for Parkinson's disease become a real option soon? A Delphi consensus study

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While conventional deep brain stimulation (cDBS) treatment delivers continuous electrical stimuli, new adaptive DBS (aDBS) technology provides dynamic symptom-related stimulation. Research data are promising, and devices are already available, but are we ready for it? We asked leading DBS experts worldwide ($n = 21$) to discuss a research agenda for aDBS research in the near future to allow full adoption. A 5-point Likert scale questionnaire, along with a Delphi method, was employed. In the next 10 years, aDBS will be clinical routine, but research is needed to define which patients would benefit more from the treatment; second, implantation and programming procedures should be simplified to allow actual generalized adoption; third, new adaptive algorithms, and the integration of aDBS paradigm with new technologies, will improve control of more complex symptoms. Since the next years will be crucial for aDBS implementation, the research should focus on improving precision and making programming procedures more accessible.

Deep Brain Stimulation (DBS) is a standard neurosurgical therapy to treat selected patients with neurological disorders, including essential tremor (ET), Parkinson's disease (PD), and dystonia[1]. Traditionally, DBS has been employed using open-loop stimulation techniques, i.e., delivering continuous, uninterrupted stimulation at the same parameter setting (conventional DBS, cDBS) that is independent of the real-time patient's functional status or of the side effects induced by intermittent stimulation[2]. Despite the evident positive results, DBS of the subthalamic nucleus (STN-DBS[3]) in PD has been prominently associated with stimulation-induced speech impairments[4,5], risk of falling[6,7], dyskinesia[8], stimulation-induced impulsivity[9], and, more importantly, only partial control of clinical fluctuations[10]. Adaptive DBS (aDBS) was conceived to overcome some of the disadvantages of cDBS by facilitating optimized current delivery to improve symptoms and drive improved outcomes[11]. This technology relies on the principle of on-demand or contingency-based stimulation, where clinically relevant biofeedback signals (e.g., brain signals) can be used to determine and deliver a real-time, more effective stimulation parameters in order to address emerging symptoms or side effects[12]. Although the aDBS concept is perceived as a natural evolution of current cDBS, in line with the historical development of cardiac pacemakers, the evidence collected on its clinical application needs to be expanded, especially to better understand the emerging limitations, and to boost its adoption and understanding in everyday clinical practice.

The challenges aDBS field is facing might be divided into technical (i.e., the technological open questions) and clinical (i.e., applications to patients). Among the technical challenges, the reliability of the biomarker(s) used to control stimulation (i.e., how precisely the biomarker that drives the stimuli correlates with the patient's clinical status) is of crucial importance to allow optimal adaptation. Local field potentials (LFPs) recorded directly from the DBS electrodes, while being the most used biomarkers in movement disorders, still have limitations[13–15], especially with patients presenting different phenotypes (e.g., tremor dominant or akinetic-rigid PD)[16]. Also, aDBS needs to be integrated with current (e.g., segmented electrodes[17]) or new (e.g., artificial intelligence, AI[18]) technologies for a large-scale application. Although preliminary results suggest the successful combinations of technologies[19], solid knowledge is still lacking. Similarly, the introduction of

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Table 1 | Demographic and academic information for the Delphi Panel members

	Steering Committee (*n* = 8)	Expert Panel (*n* = 13)
Gender—*n*		
Female	1	4
Male	7	9
Prefer not to say	0	0
Age (year)—*n*		
25–30	0	0
31–39	0	1
40–49	1	5
50–59	4	4
60–69	3	3
Prefer not to say	0	0
Highest academic degree—*n*		
Bachelor's Degree	0	0
Master's Degree	0	0
Doctor of Medicine (MD)	3	5
Doctor of Philosophy (PhD)	5	8
Other	0	0
Country of residence/work—*n*		
Italy	1	0
UK	0	1
Germany	4	3
France	0	0
Canada	2	1
The Netherlands	0	1
Spain	0	3
Switzerland	0	1
USA	1	3
Primary place of work[a]—*n*		
Private Company	0	1
Hospital	5	6
University	7	9
Research Institute (public)	1	1
Research Institute (Independent)	0	1
Experience in DBS field (year)		
≤5	0	0
6–10	0	2
>10	8	11
Field(s) of research (besides neurostimulation) [a]—*n*		
Biomedical Engineering	1	2
Cognitive Science	2	2
Computational Modelling	0	1
Epidemiology	0	0
Neurology	7	8
Neuroscience	5	8
Neurosurgery	3	7
Pharmacology	1	0
Psychiatry	0	0
Psychology	0	0
Neurorehabilitation	0	0
Other (Systems Neuroscience, EEG, MEG)	1	0
Experience in DBS clinical trials (year)—*n*		
≤5	0	2
6–10	0	1
>10	8	10
Experience in treating patients (year)—*n*		
≤5	1	0
6–10	0	0
>10	7	13

[a]One or more options were accepted.

aDBS raises questions about the specific expertise required to program the devices, the costs (in terms of economic and time burden) of implantation, and the management of the programming phase with stimulation algorithms that might change according to symptoms and clinical outcomes[20–22].

Among the clinical challenges, aDBS needs to further prove its safety and tolerability for the patients. Although growing evidence suggests that aDBS can be used safely, with comparable effects to cDBS[23,24], the aDBS community has not defined the characteristics of patients who might benefit the most from the adaptive stimulation, yet. First, it is likely that, apart from PD, also ET and epilepsy patients[25], likewise psychiatric patients[25], could benefit from an adaptive approach. Second, despite PD being the first and most studied use case of aDBS, it is not clear which clinical manifestation (e.g., akinetic-rigid or hyperkinetic PD) or symptoms (e.g., non-motor, stimulation side effects) is more sensible to aDBS, as well as the exact mechanism of interaction between adaptive stimulation and pharmacological therapy[25].

In such a challenging scenario, it is difficult to understand whether this innovation will be able to reach all patients, and when. To answer this question, we identified internationally recognized clinical and academic DBS experts to discuss the methodological and clinical challenges of aDBS, and we asked them to participate in a Delphi method-based study[26].

Results

Specialists panel

For the Steering Committee (SC), all eight invited authors agreed to participate (SC = 8, response rate: 100%). For the Expert Panel (EP), out of the 20 authors identified, two declined to participate and five did not reply (EP = 13, response rate: 65%). Therefore, the overall number of panelists was 21 (overall response rate: 75%, Supplementary Table 1). Demographic characteristics of the panelists are displayed in Table 1. Briefly, most of them were male (16, 76%), >50 years old (14, 66.6%) and high-experienced in clinical routine (20, 95.5% with >10 years of clinical experience) and research (19, 90.4% and 18, 85.7% with >10 years of experience in, respectively, the DBS field and DBS clinical trials) settings.

Delphi Panel results: technical aspects

As for the 21 statements on the technical aspects of aDBS, the first round led to no consensus for any of the statements (Supplementary Fig. 1); in the second, the consensus was reached in only one statement (Supplementary Fig. 2); finally, in the third round, consensus was reached in other seven statements, for a total of eight out of 21 statements (see Fig.1). More specifically, in the second round, the panelists agreed that automatic programming would be safe as long as stimulation intensity is constrained by upper and lower limits (90% agreed, median ± IQR: 4 ± 0). After the third round, panelists agreed that aDBS has

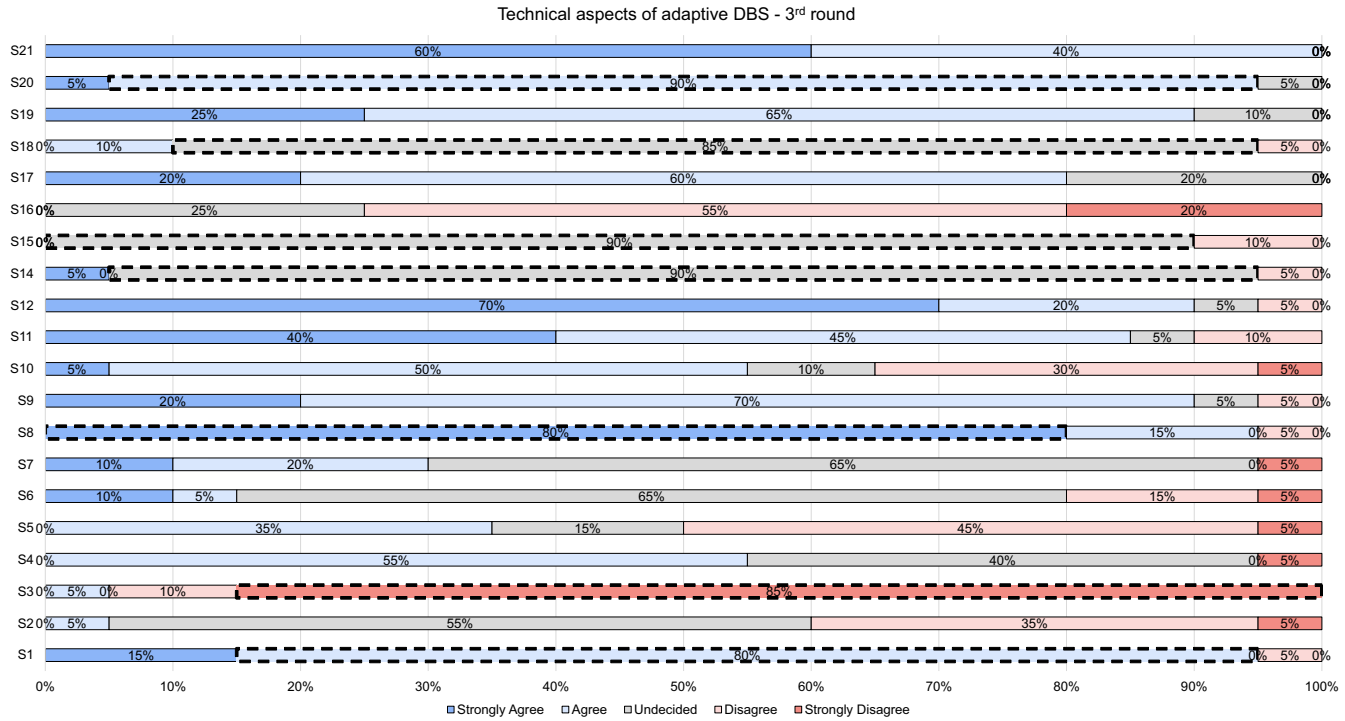

Fig. 1 | Percentage of agreement for the 21 statements on the technical aspects of adaptive DBS (Statements 1–21) among the Delphi Panel members, as a result of the third round. A consensus was reached for Statement 1 (80% of the responses fell in the response label "Agree"), Statement 3 (85% of the responses fell in the response label "Strongly Disagree"), Statement 8 (80% of the responses fell in the response label "Strongly Agree"), Statement 14 (90% of the responses fell in the response label "Undecided"), Statement 15 (90% of the responses fell in the response label "Undecided"), Statement 18 (85% of the responses fell in the response label "Undecided"), and Statement 20 (90% of the responses fell in the response label "Agree"). DBS Deep Brain Stimulation, S statement.

technological limitations (Statement 1—80% agreed, median ± IQR: 4 ± 0), but that current pacemaker technology might be suitable to implement aDBS algorithms (Statement 20—90% agreed, median ± IQR: 4 ± 0). They strongly agreed that it requires high levels of expertise (Statement 8—80% strongly agreed, median ± IQR: 5 ± 0), but strongly disagreed in its feasibility for patients with not well-positioned electrodes (Statement 3—85% strongly disagreed, median ± IQR: 1 ± 0). Lastly, panelists were undecided on the role of aDBS in spreading segmented electrodes use (Statement 18—85% undecided, median ± IQR: 3 ± 0), or whether fast adaptation methods are superior or inferior than slow adaptation methods (Statement 14 and Statement 15—90% undecided, median ± IQR: 3 ± 0 for both). The secondary analysis performed on the third round of answers revealed an agreement on further statements (Supplementary Fig. 3). Specifically, experts agreed that aDBS is feasible only in centers with neurophysiological expertise (Statement 9—90% agreed), that programming is time-consuming (Statement 11—85% agreed) but automatic programming will allow to save time (Statement 12—90% agreed). Also, they agreed that current pacemaker technology allows aDBS installation (Statement 20—95% agreed), and that AI will spread its use (Statement 19—90% agreed). Lastly, common agreement was reached on the use of signal recording from DBS electrodes as a biomarker for electrical stimuli delivery (Statement 17—80% agreed).

Delphi Panel results: clinical aspects

As for the 21 statements on the clinical aspects of aDBS, no consensus was reached after the first round (Supplementary Fig. 4). After the second, the panelists agreed on one statement (Supplementary Fig. 5), and other eight after the third round, for a total of 9 out of 21 statements (see Fig.2). In particular, in the second round the panelists agreed on the use of aDBS technology also for tremor-dominant PD patients (Statement 28—80% agreed, median ± IQR: 4 ± 0). After the third round, an agreement was reached on the safety of aDBS technology (Statement 25—85% agreed, median ± IQR: 4 ± 0) and that it will enter clinical routine in 10 years (Statement 22—85% agreed, median ± IQR: 4 ± 0), with positive long-term impact for patients (Statement 35—80% agreed, median ± IQR: 4 ± 0), also for those with significant motor fluctuations before surgery (Statement 30— 90% agreed, median ± IQR: 4 ± 0) and on cDBS treatment (Statement 31—95% agreed, median ± IQR: 4 ± 0), and for patients with significant dyskinesias on cDBS treatment (Statement 32—90% agreed, median ± IQR: 4 ± 0). Lastly, panelists agreed that aDBS might lead to a faster stable treatment response after the definition of stimulation settings (Statement 37—80% agreed, median ± IQR: 4 ± 0), but were uncertain if fast adaptation technology could lead to long-term plastic changes (Statement 38—80% undecided, median ± IQR: 3 ± 0). The secondary analysis performed on the third round of answers revealed an agreement on four further statements (Supplementary Fig. 6). Experts disagreed that aDBS is applicable only for PD non-tremor patients (Statement 27—90% disagreed) and that primary clinical indication will be ET patients, more than PD patients (Statement 29—85% disagreed). Conversely, they agreed that aDBS will reduce DBS-induced side effects (Statement 34—95% agreed) and will easily adapt to pharmacological changes (Statement 36—80% agreed).

Discussion

In this Delphi consensus study, 21 internationally recognized clinical and scientific DBS experts were asked to discuss current technical and clinical challenges related to aDBS research and technical development in the next few years. The integration of the knowledge derived from clinical data and from the experience of leading experts provided (1) a clear scenario for aDBS advantages and limitations at the current state-of-the-art, (2) guidance on the near-future design of trials, and (3) highlights regarding the most promising directions for aDBS. Interestingly, out of the 42 open questions on aDBS proposed, a consensus was reached for 17, thus underlining the complexity and heterogeneity of the scenario and experiences: experts agreed on a time frame of 10 years for aDBS to reach clinical practice, whereas the time frame of 5 years did not achieve the agreement. Such a time

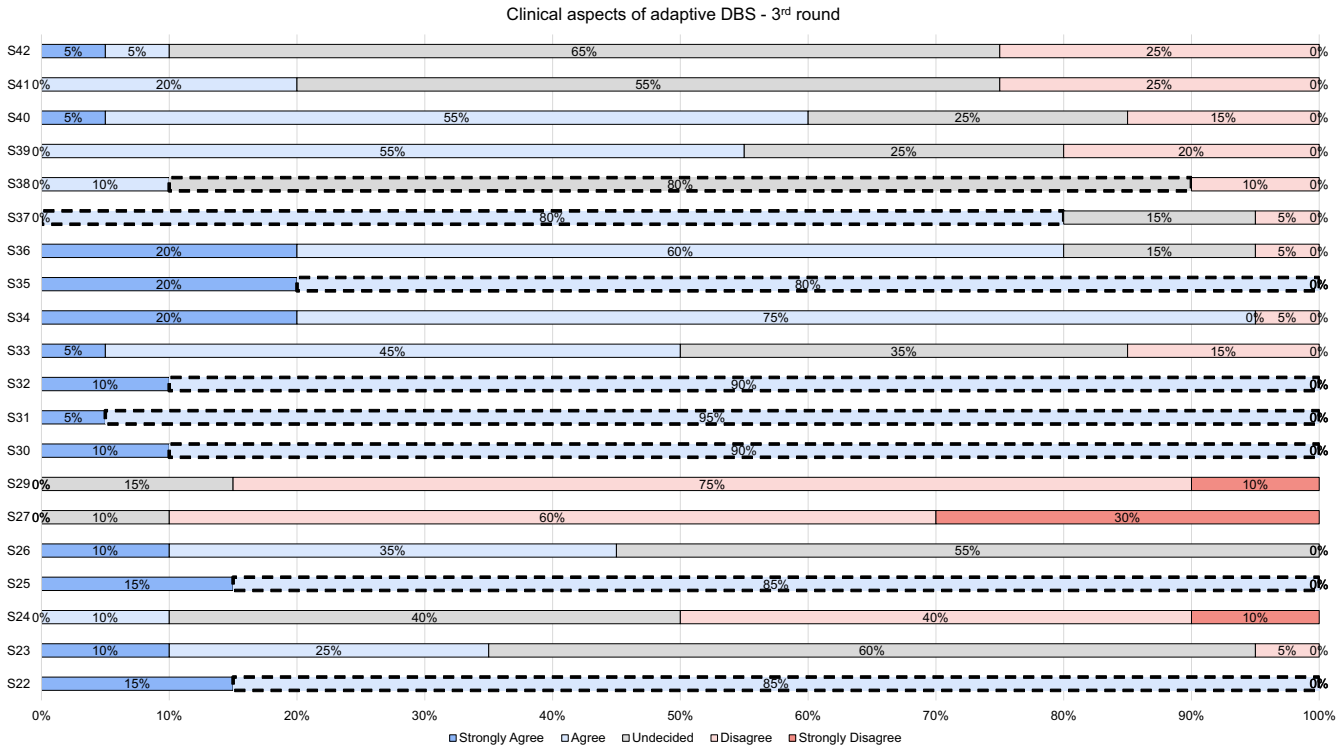

Fig. 2 | Percentage of agreement for the 21 statements on the clinical aspects of adaptive DBS (Statement 22–42) among the Delphi Panel members, as a result of the third round. A consensus was reached for Statement 22 (85% of the responses fell in the response label "Agree"), Statement 25 (85% of the responses fell in the response label "Agree"), Statement 30 (90% of the responses fell in the response label "Agree"), Statement 31 (95% of the responses fell in the response label "Agree"), Statement 32 (90% of the responses fell in the response label "Agree"), Statement 35 (80% of the responses fell in the response label "Agree"), Statement 37 (80% of the responses fell in the response label "Agree"), and Statement 38 (80% of the responses fell in the response label "Undecided"). DBS Deep Brain Stimulation, S statement.

frame should therefore be used to focus research towards the clinical and technological gaps between experimental and clinical aDBS treatment.

(I) First, while the experience and knowledge gained so far sufficed to reach a consensus regarding the safety of the adaptive approach and its potential benefits, personalization (i.e., define which population of patients and/or which clinical phenotype of pathology would benefit more from aDBS) rose as a line of research to be explored. Experts, in fact, agreed that aDBS may lead to faster and more stable treatment responses than cDBS in selected patient populations, including tremor-dominant PD patients and those with motor fluctuations and dyskinesia on cDBS.

(II) Second, an important point highlighted with general agreement, and possibly limiting the future widespread adoption, was the need for a high level of expertise to manage aDBS. Automatic programming based on data can be considered as a valuable and safe support for this complex task, if properly developed.

(III) Third, the expert community remained uncertain regarding specific algorithms and their mechanisms of action, thus suggesting that, in the near future, research and trials need to be directed towards the collection of data relevant both for understanding the neurophysiology of the adaptive approach and for identifying better biomarkers and the related stimulation patterns. A last line of research should consider the integration of aDBS paradigm with sensing technologies. For example, the possible combined benefits of aDBS and segmented electrodes remain unclear, while there is general agreement on the fact that aDBS would not help in patients with electrodes that are not well-positioned.

The panelists believe that, despite the technological limitations of aDBS methodology, current hardware technology is suitable to support aDBS optimization, thanks to the recent development of pulse generators, which are also able to record LFPs[27]. One of the main limitations of aDBS application in routine clinical care remains the uncertainty about which and how many signals could entirely represent patients' clinical state and whether many of them need to be used together in multimodal algorithms[11,28]. Most biomarkers have been identified with patients in "off stimulation"[29], but, in the aDBS concepts, signals should be recorded in "on stimulation". Therefore, the availability of devices able to record during stimulation is crucial to shed light on how to select the optimal personalized biomarker[28]. While the most used closed-loop design (i.e., STN-LFP beta band as control signal to adjust for DBS amplitude) has been questioned[30], there is growing consensus that the beta band is a fairly reliable biomarker[31]. Several alternative approaches have been proposed (e.g., using cortical-subcortical gamma rhythm[32]), but no conclusive findings have been obtained yet. The panelist acknowledged that a high level of expertise would be required to use aDBS. Also, the secondary analysis added that aDBS would be feasible only in centers with neurophysiological expertise, and that aDBS programming is currently time-consuming. Indeed, currently, the programming phase of aDBS devices might require familiarity and high technical skills (when compared with cDBS devices[28]); however, the future algorithms will likely become more automated. A suggestion to industries would be to develop simplified workflows or to provide adequate education to clinicians using aDBS. Automatic programming technologies under investigation might reduce this time burden, provided that clinicians maintain a crucial role in assessing LFP recordings and their relationship to patients' symptoms. Experts agreed that automatic programming would be safe if stimulation intensity were constrained by combined upper and lower limits. The answer is in line with the need to both avoid unpleasant side effects (upper limit) and inadequate treatment of patients' symptoms (lower limit). However, many algorithms tested in clinical studies to date allow reduction of stimulation amplitude to zero when beta amplitude falls below a threshold, and this should be modified in future aDBS algorithms[21,31,33,34].

From a control algorithm point of view, the experts were uncertain about whether fast adaptation methods would be superior or inferior when compared to slow adaptation methods. In fast adaptation algorithms, beta

activity immediately triggers a brief increase in stimulation (threshold-based) to shorten prolonged beta bursts[31,35], while in slow algorithms, beta activity is smoothed over many seconds to serve as a medication state biomarker and then be used as feedback to drive stimulation[21]. As for current research, both fast and slow adaptation algorithms reduced the total electrical energy delivered (TEED) over time, but while the first seemed to reduce adverse effects on speech[20] and to achieve a better control of bradykinesia and rigidity[21], the latter seemed to be more effective in reducing dyskinesias[22]. These effects should be interpreted with great caution because of the paucity of cases and lack of independent validation, especially in chronic applications with implanted devices[36]. Indeed, speech was not systematically assessed for the "slow adaptation", nor dyskinesias for the "fast adapting" algorithms. However, fast beta aDBS did also show the ability to adjust how often aDBS was triggered according to (slower) medication state, with stimulation becoming less frequent in the medication ON state. This suggests that "fast" aDBS algorithms can operate on both fast and slow timescales, and therefore could theoretically help medication-induced dyskinesias[37]. Currently, the lack of data does not allow us to conclude differential benefits of both algorithms on side effects. Also, aDBS can possibly allow more TEED to be delivered, but only for small time frames, with improved clinical efficacy and without inducing side effects[32,38]; therefore, reduced TEED seems to be a less critical outcome for DBS implementation, particularly with the advent of rechargeable devices[39]. Panelists reached a consensus on the unfeasibility of aDBS for patients with suboptimally positioned, meaning that it will likely not be effective. This expert opinion was in line with the evidence that the peak in beta activity is a specific feature of the motor part of the STN[40], and, therefore, suboptimally positioned electrodes will not likely detect the LFPs needed to "adapt" aDBS to patients' symptoms.

Similarly, the panelists were doubtful about the role of aDBS in facilitating the use of segmented electrodes, which may be used to widen the therapeutic window between efficacy and adverse effects by steering the field of stimulation[41]. The experts did concede that segmented electrodes share with aDBS the common aim to "personalize" and shape stimulation electrical fields for individual patients. Indeed, this technology increases spatial specificity while aDBS improves temporal specificity through the delivery of a dynamic stimulation that changes over time according to disease-related feedback[41]. Theoretically, these two approaches could be complementary. Differently, experts expressed an optimistic opinion about the use of AI to accelerate aDBS development. Indeed, in recent years, AI and machine learning (ML) have been applied to neurological treatments, in a way that can be categorized into three key areas: (I) Predicting treatment outcomes: In PD, various ML techniques were used to distinguish between the DBS-on and DBS-off states to predict motor performance[42], classify the ON / OFF levodopa states[43], predict real-time state or classify behavioral tasks[44–47], improving therapy personalization and diagnostic precision. Similarly, ML-based analyses of neurophysiological biomarkers have enabled accurate tic detection in Tourette syndrome[48]; (II) Determining treatment parameters: In PD, personalized biomarkers have been applied to classify the ON/OFF levodopa states, enabling precise adjustment of parameters[43]. Similarly, in ET, linear classifiers[49] and linear regression models[50] in implanted aDBS systems have shown to be feasible, no energy-consuming and effective in suppressing tremor[49] or reducing stimulation times with improved therapeutic efficacy[50]; (III) Dynamically optimizing treatment over time: In PD, aDBS systems have utilized non-linear dynamical features[51] and hierarchical and multiple kernel learning approaches[52] to initiate or stop stimulation based on the onset of tremors enabling real-time adjustments of DBS parameters. State estimates, in conjunction with fuzzy control mechanisms, have been employed to dynamically adjust stimulation frequencies, thereby enhancing therapeutic effects[53]. For ET, aDBS devices have adeptly modulated stimulation voltages in real time according to patient feedback, resulting in effective tremor suppression while reducing superfluous stimulation[54]. All these experiences will ground the future integration of AI/ML to aDBS.

The panelists shared an optimistic opinion in terms of the development and applications of aDBS in clinical routine, and its potential ability to allow a faster and more stable treatment response in select patients. Indeed, despite the initial skepticism of parts of the medical community, the knowledge and technology in the field of aDBS have been constantly growing[55]. Also, recent technological advancements (e.g., directional leads[56] or multiple stimulation methods[57,58]) may limit side effects and may serve to optimize the response to individual symptoms[11]. Another important point related to aDBS adoption is its safety, on which the panelists agreed. In addition to the surgical risks that to date are comparable to those of cDBS[59], concerns have been expressed in the literature about the potential side effects of aDBS stimulation[60]. Although no significant side effects have been reported so far[25], rapid changes of amplitude or frequency induced by neurosignals could be unpleasant or even intolerable to patients in chronic stimulation. Therefore, algorithms limiting these rapid changes (like the "linear adaptive" algorithm[61]) or others that balance ramp rates to avoid side effects[62] are preferable. One of the major potential advantages of aDBS is its ability to provide personalized therapy. The panelists agreed that aDBS is suitable both for PD patients experiencing motor fluctuations and dyskinesias before surgery or on cDBS, and for tremor-dominant PD patients. This consensus boosts the need for gaining more insights on the "precision medicine" potential of aDBS, i.e., investigating which patients are likely responders to stimulation, or which technology (e.g., which biomarker) is right for a specific patient[63]. More experimental studies are needed, in which the efficacy of aDBS can be actually tested through different outcomes on different, larger populations, using different biomarkers. For example, Beta frequency correlates more with rigidity/bradykinesia than with resting tremor[64,65], while gamma activity, particularly finely-tuned gamma, has been associated with ON medication states and dyskinesia[66,67]. Beta-driven aDBS follows the dynamic of the levodopa-ON/OFF medication states[29] and hence reduces the likelihood of inducing levodopa-induced dyskinesia. Indeed, studies on aDBS in patients with PD and dyskinesia report good efficacy in reducing such symptoms while guaranteeing a similar or even better control of cardinal symptoms of PD[21,33,34]. Tremor can be detected from brain signals, either by the presence of lower frequency oscillations (3–7 Hz) or more accurately by combining multiple features from the whole LFP spectrum[68,69]. Additionally, several computational models have been recently developed to test the feasibility and efficacy of aDBS methods that modulate stimulation to control different biomarkers[70,71]. In these cases, the best control may be provided by selecting between multiple controllers depending on context or patient symptoms (i.e., tremor or beta oscillations). Recent studies suggest a similar efficacy of aDBS both for tremor and bradykinesia dominant patients[72,73]. Additionally, peripheral sensors may also be used for aDBS for tremor[74,75]. Major uncertainties remain on the mechanisms of action of aDBS: the experts were uncertain that fast adaptation technology could lead to long-term plastic changes. Although one might expect an effect close to what has been supposed for cDBS[76], whether aDBS might induce neuroplastic changes remains an open question due to the lack of evidence to support any opinion[77,78]. Similarly, it is still to be determined what impact aDBS will have on the habituation phenomenon (i.e., the progressive loss of DBS benefit in time due to a decreased biological response of the neuronal networks[79]) that may, in select cases, decrease the effectiveness of cDBS in chronic conditions[79]. However, some experts believe that habituation of DBS in the setting of PD is rare and that most of the worsening of symptoms is driven by PD progression.

In summary, the panel of experts participating in this study expressed measured optimism on the advancement and implementation of aDBS in clinical practice. However, based on some concepts highlighted by items reaching consensus during the process and on others that emerged from the items that did not reach consensus, it is possible to identify some areas of research that will need to be prioritized soon for aDBS to become a reality in the next 10 years. From a technical point of view:

Table 2 | Five-point Likert questionnaire with the results (median ± IQR) for each round

Statement	1st round (n = 19; RR = 90.5%)	2nd round (n = 20; RR = 95.2%)	3rd round (n = 20; RR = 95.2%)
Technical aspects of adaptive DBS			
S1. Adaptive DBS is at the beginning of its clinical applications, but I think that there may still be technological limitations	4 ± 1	4 ± 0.25	**4 ± 0—C.R.**
S2. I think that a possible limitation of the diffusion of adaptive DBS are high costs	3 ± 1	3 ± 1.25	3 ± 1
S3. I think adaptive DBS is applicable in patients with not well-positioned electrodes	1 ± 1	1 ± 1	**1 ± 0—C.R.**
S4. I think adaptive DBS is applicable when one side only is able to record	3 ± 1	4 ± 1	4 ± 1
S5. I think that only modulating the amplitude might be a limiting factor of adaptive DBS	3 ± 2	2 ± 2	2.5 ± 2
S6. I think an actual risk for adaptive DBS is overstimulation	3 ± 1	3 ± 1	3 ± 0
S7. I think an actual risk for adaptive DBS is under stimulation	3 ± 1.5	3 ± 1	3 ± 1
S8. I think adaptive DBS requires high level of expertise	4 ± 1	5 ± 1	**5 ± 0—C.R.**
S9. I think adaptive DBS is feasible only in experienced DBS centres with neurophysiological expertise	4 ± 1.5	4 ± 0.25	4 ± 0
S10. I think adaptive DBS surgery is time-consuming	3 ± 2	4 ± 2	4 ± 2
S11. I think adaptive DBS programming is time-consuming	4 ± 3	4 ± 1	4 ± 1
S12. I think that automatic programming will reduce programming time	5 ± 1	5 ± 1	5 ± 1
S13. I think that automatic programming is safe as long as the neurologist can set upper and lower limits for stimulation intensity	4 ± 0	**4 ± 0—C.R.**	–
S14. I think fast adaptation adaptive DBS methods are superior to slow adaptation adaptive DBS methods	3 ± 1	3 ± 0	**3 ± 0—C.R.**
S15. I think slow adaptation adaptive DBS methods are superior to fast adaptation adaptive DBS methods	3 ± 1	3 ± 0	**3 ± 0—C.R.**
S16. I think adaptive DBS will be based more likely on feedback from wearables than on signal recording from the DBS electrodes	2 ± 1	2 ± 0	2 ± 0.25
S17. I think adaptive DBS will be based more likely on signal recording from the DBS electrodes than on feedback from wearables	4 ± 1	4 ± 1	4 ± 0
S18. I think adaptive DBS would help to diffuse DBS with segmented electrodes	3 ± 1	3 ± 0	**3 ± 0—C.R.**
S19. I think the rapid development of artificial intelligence (AI) will fuel the clinical use of adaptive DBS	4 ± 1	4 ± 1	4 ± 0.25
S20. I think current pacemaker technology in principle allows to install adaptive DBS algorithms	4 ± 0.5	4 ± 0.25	**4 ± 0—C.R.**
S21. I think changes in technology are still necessary to foster adaptive DBS soon	4 ± 1	4 ± 1	5 ± 1
Clinical aspects of adaptive DBS			
S22. I think adaptive DBS will be clinical routine in 10 years from now	4 ± 0	4 ± 1	**4 ± 0—C.R.**
S23. I think adaptive DBS will be clinical routine in 5 years from now	3 ± 1.5	3 ± 1	3 ± 1
S24. The side effects (ramping) will lead to many patients being unable to tolerate adaptive DBS	2 ± 1	2.5 ± 1	2.5 ± 1
S25. I think adaptive DBS is a safe technology	4 ± 0.5	4 ± 0	**4 ± 0—C.R.**
S26. I think adaptive DBS is applicable on a large scale	3 ± 1	3 ± 1	3 ± 1
S27. I think adaptive DBS is applicable only for non-tremor patients with Parkinson's disease	2 ± 1	2 ± 0.25	2 ± 1
S28. I think adaptive DBS is applicable also for tremor-dominant patients with Parkinson's disease	4 ± 0.5	**4 ± 0—C.R.**	–
S29. I think the primary clinical indication for adaptive DBS will rather be tremor then Parkinson's disease	2 ± 1	2 ± 1	2 ± 0
S30. I think the patient profile who will likely benefit from adaptive DBS is the patient with significant motor fluctuations before DBS	4 ± 1.5	4 ± 1.25	**4 ± 0—C.R.**
S31. I think the patient profile who will likely benefit from adaptive DBS is the patient with significant motor fluctuations on conventional DBS	4 ± 0	4 ± 0	**4 ± 0—C.R.**
S32. I think the patient profile who will likely benefit from adaptive DBS is the patient with significant dyskinesias on conventional DBS	4 ± 1.5	4 ± 1	**4 ± 0—C.R.**
S33. I think that adaptive DBS will improve non-motor aspects of Parkinson's disease	3 ± 1	3 ± 1	3.5 ± 1
S34. I think that adaptive DBS will reduce stimulation induced side effects	4 ± 1	4 ± 0.25	4 ± 0
S35. I think the long-term impact of adaptive DBS might be positive for the patients	4 ± 0.5	4 ± 1	**4 ± 0—C.R.**

Table 2 (continued) | Five-point Likert questionnaire with the results (median ± IQR) for each round

Statement	1st round (*n* = 19; RR = 90.5%)	2nd round (*n* = 20; RR = 95.2%)	3rd round (*n* = 20; RR = 95.2%)
S36. I think adaptive DBS might more easily adapt to pharmacological changes	4 ± 1	4 ± 1	4 ± 0
S37. I think adaptive DBS leads to faster stable treatment response after DBS surgery once a setting is defined	4 ± 1	4 ± 1	**4 ± 0—C.R.**
S38. I think fast adaptation adaptive DBS leads to long term plastic changes	3 ± 1	3 ± 0.25	**3 ± 0—C.R.**
S39. I think adaptive DBS will improve patient's well-being because adaptive DBS automatically increases stimulation if patient forgets to take medication	3 ± 1.5	4 ± 1	4 ± 1
S40. I think adaptive DBS will improve patient's well-being because adaptive DBS automatically decreases stimulation if patient accidentally takes too high a dose of medication	4 ± 1	4 ± 1	4 ± 1
S41. I think adaptive DBS decrease the number of patient visits to neurologists for programming	3 ± 1.5	3 ± 2	3 ± 0.25
S42. I think adaptive DBS makes medication titration easier – with less precision required	3 ± 1	3 ± 0.25	3 ± 0.25

Delphi Panel members were asked to rate their agreement with each statement (1 = strongly disagree; 2 = disagree; 3 = undecided; 4 = agree; 5 = strongly agree). RR response rate, C.R. consensus reached, PD Parkinson's disease, DBS deep brain stimulation.
Bold represents consensus reached.

1. Integration with technologies: future research should focus on optimizing existing technologies. A key area of investigation will be the improvement of the device in terms of reliable sensing technologies, refining current methods, and exploring new approaches to enhance the overall performance of aDBS systems. Also, given the promises of integrating AI and ML technologies in the biomarker discovery pipeline, research should focus on developing robust AI/ML models aimed to provide a solid foundation for the aDBS paradigm. This also underscores the need for ongoing collaboration between researchers and AI/ML companies.
2. Device management and costs: future research should focus on improving the aDBS device management and addressing its associated costs. Studies should develop automated programming algorithms assisting the clinicians, simplified workflows, and comprehensive training programs. Also, unlike DBS[80], health economics studies on aDBS cost-effectiveness are not available because of the lack of long-term data on large populations of patients. On the one hand, aDBS is expected to decrease health costs per capita for patients because it should improve patients' condition and autonomy; on the other hand, it could increase costs related to the production of technology, time consumed by physicians to be trained, and to review the patient's state.

   From a clinical point of view:
3. More solid clinical research: large-scale, multicentric RCTs to evaluate the widespread applicability of aDBS are necessary before moving to routine clinical practice. These studies should assess the long-term safety and efficacy of aDBS across different populations, using different feedback biomarkers to monitor various outcomes. For example, it is to be determined whether aDBS could improve non-motor symptoms in PD. Clinical studies should explore the interaction between aDBS and medication, investigating whether aDBS can adjust stimulation automatically if patients miss or take incorrect doses, or the potential risk due to incorrect stimulation (over- or under-stimulation).
4. Treatment personalization: future research and clinical trials should contemplate the collection and storage of recorded data to both deepen the understanding of aDBS on neurological tissues and to facilitate the identification of personalized biomarkers and stimulation patterns. Indeed, a fundamental characteristic of aDBS is the ability to increase treatment personalization, i.e., identifying patient subgroups or specific clinical phenotypes that are likely responders to aDBS, and determining which technologies (e.g., personalized biomarkers) and therapeutic strategies are best suited for individual patients. This research will be critical in refining the application of aDBS and enhancing its clinical efficacy.

However, although consensus achieved through Delphi methods can offer valuable insights, it neither replaces clinical judgment nor original research, and it is not intended to define standards of practice. Also, the feasibility of the consensus reached should be further debated and scientifically demonstrated—even more when considering stimulation targets commonly used for DBS (e.g., globus pallidus internus) not explored for aDBS. Rather, since our results aggregate the opinion of experts who could count on both personal expertise and scientific knowledge, they appear to be relevant in terms of the current state of knowledge and future directions for research, even more for a field which is still at its infancy. Therefore, although we might expect aDBS to reach clinical adoption in the next 10 years, several uncertainties remain that need to be addressed through solid experimental studies, particularly regarding economic barriers, accessibility, and patient-specific factors.

Methods

The Delphi study methodology is a multistage process designed to combine opinions into group consensus[81], where a series of structured questionnaires (rounds) are anonymously completed by experts (panelists) and the responses from each questionnaire are fed back in summarized form to the participants[82,83]. This allows the panelists to reassess their initial judgments, considering the positive aspects of interacting groups (e.g., inclusion of different backgrounds) without the negative ones (e.g., influence of dominant members)[84]. For the purpose of our study, a modified Delphi process[85–87] was designed in three rounds, which are considered as sufficient to collect the needed information and to reach a consensus[84,88]. The Delphi consensus process does not involve human research participants, and therefore, ethics approval is not required. However, data gathering from the experts and analysis occurred, guaranteeing the compliance with the Declaration of Helsinki and the current legislation on the collection and processing of personal data.

Steering Committee and Delphi Panel selection

An SC of experts ($n = 8$) based on the collaborative network of the leading authors was selected to define the questionnaire. Then, together with the SC, a larger EP ($n = 13$) was involved in the Delphi consensus process. Therefore, a total of 21 panelists took part in the consensus, which is a number of experts within the recommended range[84,89]. Since no exact criterion is currently available on the definition of "expert"[90], we considered positional leaders[91] in the field according to the number of peer-reviewed publications[92,93], as suggested by previous works[26].

Questionnaire definition

The SC was in charge of outlining the scope of the research, discussing the topic, defining the questions, and developing the structured questionnaire, including

key items pertinent to aDBS using five-point Likert scales (1 = strongly disagree; 2 = disagree; 3 = undecided; 4 = agree; 5 = strongly agree)[26].

Delphi process

In rounds one, two, and three, quantitative assessments to reach the consensus were performed by SC and EP members. The panelists were asked to rate 42 statements on several technical (21 statements) and clinical (21 statements) aspects of aDBS (Table 2). In order to maintain the rigor of this method, we considered a response rate of >70% for each round[94] to be a minimum, with missing or incomplete responses excluded from the analysis. Electronic questionnaires were used in all steps of the process. In case one item reached a consensus during the first or second round, it was excluded from the following round to avoid confirmation bias; otherwise (i.e., if no consensus was reached), it was included in the following round[90]. Although no guidelines are available[90], consensus was achieved when ≥80% of the responses fell in the same response label[26,95].

Data analysis

Data were analyzed and reported by descriptive statistics using JASP (Version 0.19.3) [Computer software]. We opted for median and interquartile range (IQR), as suggested by the literature[84,96]. We report the results of each round separately in both textual (i.e., with median ± IQR) and graphical representation, to better illustrate the strength of support for each round[90]. As an additional analysis, we chose to convert the 5-point Likert scale into a 3-point Likert scale, considering the middle point (undecided) and only two points (agree and disagree) as union of the two highest (4 = agree; 5 = strongly agree) and lowest (1 = strongly disagree; 2 = disagree) points, respectively. Only the outcomes of the third round were subjected to this secondary analysis.

Preprint

This work was published as a preprint in the online archive medRxiv[97].

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Abbreviations

DBS	Deep Brain Stimulation
ET	Essential Tremor
PD	Parkinson's disease
cDBS	conventional DBS
STN-DBS	Deep Brain Stimulation of the Subthalamic Nucleus
aDBS	Adaptive Deep Brain Stimulation
LFPS	Local Field Potentials
SC	Steering Committee
EP	Expert Panel
STN-LFP	Local Field Potentials of the Subthalamic Nucleus
TEED	total electrical energy delivered
AI	Artificial Intelligence
ML	Machine Learning

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Author contributions

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Competing interests

M.G., N.V.M., S.O., T.B., E.S., Y.T., C.H., and P.L. declare no conflict of interest. M.A.P is a consultant for Boston Scientific, Insightec, Medtronic, and Abbott. She has received reimbursement of travel expenses to attend scientific meetings by Palex, Boston Scientific, and Medtronic. She has received speaker honoraria from Palex. G.D. has served as a consultant for Boston Scientific and Cavion and as a DSMB member for Functional Neuromodulation. He has received royalties from Thieme Publishers and funding from the German Research Council (SFB 1261, T1). A.F. has received payments as a consultant and/or speaker from Abbott, Boston Scientific, Ceregate, Inbrain Neuroelectronics, Medtronic, and Iota, and has received research support from Boston Scientific, Medtronic. R.M.F. has received speaker honoraria from the Spanish Neurological Society research foundation, Insightec, Palex, Bial, and Zambon; has a consulting agreement with Treefrog Therapeutics; has received reimbursement of travel expenses to attend scientific meetings by Palex, Zambon, the International Parkinson and Movement Disorder Society, the IAPDRD, and the World Parkinson's Congress; and has received research funding from Instituto de Salud Carlos III, Madrid, Spain for health research projects (PI21 Proyectos de Investigacion en Salud, AES 2021). C.G.S. has received lecture honoraria from Exeltis, Zambon, Palex, Insightec, Fundación ACE, Società Italiana Parkinson e Disordini del Movimento, and Asociación Madrileña de Neurología, and reimbursement of travel expenses to attend scientific conferences from Boston Scientific and Esteve. J.K.K. is a consultant to Medtronic, Boston Scientific, aleva, and Inomed. A.A.K. is a consultant to Medtronic, Boston Scientific, and Teva. S.L. is a consultant for Iota Biosciences and has previously received honorarium from Medtronic. S.L.'s research is supported by NINDS NIH grants R01NS131405, K23NS120037, and Wellcome Discovery Award 226645/Z/22/Z. A.M.L. is a consultant to Abbott, Boston Scientific, Insightec, Medtronic, and Functional Neuromodulation (Scientific Director). M.S.O. serves as Medical Advisor in the Parkinson's Foundation, and has received research grants from NIH, Parkinson's Foundation, the Michael J. Fox Foundation, the Parkinson Alliance, Smallwood Foundation, the Bachmann-Strauss Foundation, the

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Additional information

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