Adaptive Deep Brain Stimulation in Parkinson's Disease: A Delphi Consensus Study

M. Guidetti, PhD,[1] T. Bocci, MD,[1,2] M. De Pedro Del Álamo, MD,[3] G. Deuschl, MD,[4] A. Fasano, MD, PhD,[5,6,7,8] R. Martinez Fernandez, MD,[3,9] C. Gasca-Salas, MD, PhD,[3,9] C. Hamani, MD,[10,11,12] J.K. Krauss, MD,[13] A. A. Kühn, MD,[14,15,16,17,18] P. Limousin, MD, PhD,[19] S. Little, MD, PhD,[20] A.M. Lozano, MD, PhD,[5,6,21] N.V. Maiorana, PhD,[1] S. Marceglia, PhD,[22] M.S. Okun, MD,[23,24] S. Oliveri, PhD,[1,2] J. L. Ostrem, MD,[20] E. Scelzo, MD,[2] A. Schnitzler, MD,[25,26] P.A. Starr, MD, PhD,[27,28,29] Y. Temel, MD, PhD,[30] L. Timmermann, MD,[31] G. Tinkhauser, MD, PhD,[32] V. Visser-Vandewalle, MD,[33] J. Volkmann, MD, PhD,[34] A. Priori, MD, PhD,[1,2]*.

[1]"Aldo Ravelli" Center for Neurotechnology and Experimental Brain Therapeutics, Department of Health Sciences, University of Milan, Via Antonio di Rudinì 8, 20142 Milan, Italy

[2]Clinical Neurology Unit, "Azienda Socio-Sanitaria Territoriale Santi Paolo e Carlo", Department of Health Sciences, University of Milan, Via Antonio di Rudinì 8, 20142 Milan, Italy

[3]HM CINAC, Hospital Universitario HM Puerta del Sur, HM Hospitales, Madrid, Spain

[4]Department of Neurology University Hospital Schleswig-Holstein, Campus Kiel and Christian Albrechts-University of Kiel Kiel Germany

[5]Krembil Research Institute, University Health Network, Toronto, ON, Canada

[6]CRANIA Center for Advancing Neurotechnological Innovation to Application, University of Toronto, ON, Canada

[7]KITE, University Health Network, Toronto, ON, Canada

[8]Edmond J. Safra Program in Parkinson's Disease Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Division of Neurology, University of Toronto, Toronto, ON, Canada

[9]Instituto Carlos III, CIBERNED, Madrid, Spain

[10]Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, M4N 3M5, ON, Canada

[11]Harquail Centre for Neuromodulation, 2075 Bayview Avenue, Toronto, M4N 3M5, ON, Canada

[12]Department of Surgery, University of Toronto, 149 College Street, Toronto, M5T 1P5, ON, Canada

[13]Department of Neurosurgery, Hannover Medical School, Hannover, Germany

[14]Department of Neurology, Charité-Universitätsmedizin Berlin, Berlin, Germany

[15]Bernstein Center for Computational Neuroscience, Humboldt-Universität, Berlin, Germany

[16]NeuroCure, Exzellenzcluster, Charité-Universitätsmedizin Berlin, Berlin, Germany

[17]DZNE, German Center for Neurodegenerative Diseases, Berlin, Germany

[18]Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, Berlin, Germany

[19]Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology and the National Hospital for Neurology and Neurosurgery, London, United Kingdom

[20]Movement Disorders and Neuromodulation Centre, University of California San Francisco, San Francisco, California, USA

[21]Division of Neurosurgery, Department of Surgery, University of Toronto, Toronto, ON, Canada

[22] Department of Engineering and Architecture, University of Trieste, Trieste, Italy

[23]Department of Neurology, Norman Fixel Institute for Neurological Diseases, University of Florida, United States

[24]Department of Neurosurgery, Norman Fixel Institute for Neurological Diseases, University of Florida, United States

[25]Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany

[26]Department of Neurology, Center for Movement Disorders and Neuromodulation, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany

[27]UCSF Department of Neurological Surgery, University of California San Francisco, San Francisco, CA, USA.

[28]UCSF Weill Institute for Neurosciences, University of California San Francisco, San Francisco, CA, USA.

[29]UCSF Department of Physiology, University of California San Francisco, San Francisco, CA, USA.

[30]Department of Neurosurgery, Maastricht University Medical Center, Maastricht, Netherlands

[31]Department of Neurology, University Hospital of Marburg, Marburg, Germany

[32]Department of Neurology, Bern University Hospital and University of Bern, Bern, Switzerland

[33]Department of Stereotactic and Functional Neurosurgery, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

[34]Department of Neurology, University Hospital Würzburg, Würzburg, Germany

* *Corresponding author:*

Alberto Priori, MD, PhD - alberto.priori@unimi.it

'Aldo Ravelli' Research Center for Neurotechnology and Experimental Neurotherapeutics, Department of Health Sciences, University of Milan, 20142 Milan, Italy; III Neurology Clinic, ASST-Santi Paolo e Carlo University Hospital, 20142 Milan, Italy – Via Antonio di Rudinì, 8, 20142 Milano MI

Tel. +39 0250323019

ABSTRACT

Importance: If history teaches, as cardiac pacing moved from fixed-rate to on-demand delivery in in 80s of the last century, there are high probabilities that closed-loop and adaptive approaches will become, in the next decade, the natural evolution of conventional Deep Brain Stimulation (cDBS). However, while devices for aDBS are already available for clinical use, few data on their clinical application and technological limitations are available so far. In such scenario, gathering the opinion and expertise of leading investigators worldwide would boost and guide practice and research, thus grounding the clinical development of aDBS.

Observations: We identified clinical and academically experienced DBS clinicians (n=21) to discuss the challenges related to aDBS. A 5-point Likert scale questionnaire along with a Delphi method was employed. 42 questions were submitted to the panel, half of them being related to technical aspects while the other half to clinical aspects of aDBS. Experts agreed that aDBS will become clinical practice in 10 years. In the present scenario, although the panel agreed that aDBS applications require skilled clinicians and that algorithms need to be further optimized to manage complex PD symptoms, consensus was reached on aDBS safety and its ability to provide a faster and more stable treatment response than cDBS, also for tremor-dominant Parkinson's disease patients and for those with motor fluctuations and dyskinesias.

Conclusions and Relevance: Despite the need of further research, the panel concluded that aDBS is safe, promises to be maximally effective in PD patients with motor fluctuation and dyskinesias and therefore will enter into the clinical practice in the next years, with further research focused on algorithms and markers for complex symptoms.

KEYWORDS

Deep Brain Stimulation; DBS; closed-loop DBS; adaptive DBS; Delphi consensus; Parkinson's disease; movement disorders; neuromodulation.

1. INTRODUCTION

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. In PD, DBS of the subthalamic nucleus (STN-DBS[2]), has been prominently associated with stimulation-induced speech impairments,[3] risk of falling,[4] dyskinesia,[5] stimulation-induced impulsivity,[6] and, more importantly, only partial control of clinical fluctuations.[7] 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.[8] 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 more effective characteristics of the stimulation (or changes to other parameters) to be delivered in real-time in order to address emerging symptoms or side effects.[9] Currently, in the field of movement disorders,[8] both electrocorticographic signals registered from cortical electrode strips and local field potentials (LFPs) recorded directly from the DBS electrodes have been explored in feasibility testing.[8,10]

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. For instance, in PD, where beta band STN LFPs can be applied as control signal for DBS amplitude adjustments,[11] experiments revealed an inconsistent correlation to clinical outcome scores on validated scales of PD disability and motor dysfunction,[12,13] especially with patients presenting with different phenotypes (e.g., tremor dominant or akinetic rigid PD).[14] Therefore, some experts suggested that LFP power alone might not provide a reliable biomarker for aDBS[15] because of the failure to represent the complex pathological cortical-subcortical circuital activity in PD and, in turn, to serve as a robust marker, particularly for complex symptoms.[16–18]

Such a challenging scenario demands for the integration of the knowledge derived from clinical data and from the experience of leading experts that will serve to (1) provide a clear scenario for aDBS advantages and limitations at the current state-of-the-art, (2) guide the future design of trials and (3) highlight the most promising directions for aDBS. To boost this dialogue, we identified

internationally recognized clinical and academic DBS experts to discuss the methodological and clinical challenges and we asked them to participate in a Delphi method-based study.[19]

2. METHODS

The Delphi study methodology is a multistage process designed to combine opinions into group consensus,[20] where a series of structured questionnaires (rounds) are anonymously completed by experts (panellists) and the responses from each questionnaire fed back in summarised form to the participants.[21–23] This allows the panellists 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).[24] For the purpose of our study, a modified Delphi process[25,26] was designed in three rounds, which are considered as sufficient to collect the needed information and to reach a consensus.[21,24,27,28] A Steering Committee (SC) of experts (n=8) based on the collaborative network of the leading authors discussed the topic and developed a 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).[19] In rounds one, two and three, quantitative assessments to reach the consensus were performed by SC members and a larger Expert Panel (EP, n=13). Therefore, a total of 21 panellists took part in the assessment, which is a number of experts within the recommended range.[24,29] Since no exact criterion is currently available on the definition of "expert",[30] we decided to consider positional leaders in the field, as suggested by previous works.[31] The panellists were asked to rate 42 statements on several technical (21 statements) and clinical (21 statements) aspects of aDBS (Table 1). In order to maintain the rigor of this method, we considered a response rate of >70% for each round[32] to be a minimum. 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. Although no guidelines are available,[30] consensus was achieved when ≥80% of the responses fell in the same response label.[19,33] Data were analysed and reported by descriptive statistics. We opted for median and interquartile range (IQR), as suggested by the literature.[24,34–36] 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.[30]

3. RESULTS

3.1. Specialists panel

For the SC, all the eight invited authors agreed to participate (SC=8, response rate: 100%). For the 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 panellists was 21 (overall response rate: 75%, see eTable 1 in Supplementary Materials). Demographic characteristics of the panellists are displayed in Table 2. 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.

3.2. Delphi Panel results

As for the 21 statements on the technical aspects of aDBS, the first round led to no consensus for any of the statements (see eFigure 1 in Supplementary Materials); in the second, the consensus was reached in only one statement (see eFigure 2 in Supplementary Materials); 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 panellists 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, panellists agreed that aDBS has 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, panellists 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).

As for the 21 statements on the clinical aspects of aDBS, no consensus was reached after the first round (see eFigure 3 in Supplementary Materials). After the second, the panellists agreed on one statement (see eFigure 4 in Supplementary Materials), 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 panellists 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, panellists 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).

4. DISCUSSION

In this Delphi consensus study, 21 internationally recognized clinical and scientific experts in the DBS were asked to discuss current technical and clinical challenges related to aDBS development. 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 as well as the general need of further research: 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. To inform and support present adoption, the experience and knowledge gained so far suffice to reach a consensus regarding the safety of the adaptive approach and the potential benefits of aDBS. Experts in fact agreed that aDBS may lead to faster and more stable than cDBS treatment responses in selected patient populations, including tremor-dominant PD patients and those with motor fluctuations and dyskinesia on cDBS. Another important point related to the present scenario is the general agreement on the need of high level of expertise to manage aDBS, thus underlining a potential barrier to general adoption, but they also agreed that automatic programming can be safe if properly developed. The expert community remains uncertain regarding specific algorithms and their mechanisms of action, thus suggesting that 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. Similarly, 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. Despite the high level of expertise, the lack of clinical and research evidence might have impaired the experts coming to a consensus on all the other aspects covered by the questions, both from the technical and the clinical point of view.

4.1. *Technical aspects of aDBS*

The panellists believe that despite the technological limitations of aDBS methodology, current pacemaker technology might be suitable to implement aDBS algorithms. Indeed, the recent

development of pulse generators which are also able to record LFPs offers more options for optimising DBS therapy and aDBS algorithms.[37] 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.[8] Most biomarkers have been identified with patients in "off stimulation",[38] 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 personalised biomarker. While the most used closed-loop design (i.e., STN-LFP beta band as control signal to adjust for DBS amplitude) has been questioned,[15] there is growing consensus that beta band is a fairly reliable biomarker.[39] Several alternative approaches have been proposed (e.g., using cortical-subcortical gamma rhythm[40]), but no conclusive findings have been obtained yet.

The panellist acknowledged that a high level of expertise would be required to use aDBS. Indeed, currently, the programming phase of aDBS devices might require familiarity and higher technical skills (when compared with cDBS devices[41]), however the future algorithms will likely need to become more automated. This may suggest to industries to develop in the future simplified workflows or to provide adequate education to clinicians using aDBS. Still, clinicians will maintain a crucial role in assessing LFP recordings and their relationship to patient's symptoms. As in any other new therapy, clinicians applying aDBS should keep the patient monitored to verify the persistence of an adequate control of symptoms over time and to modify pharmacological treatment if necessary. Adjustment of medications will likely be required independently of the type of stimulation (aDBS[42–44] or cDBS[45]); however, combined effects of adaptive stimulation with medication might in selected cases decrease the risk of treatment-induced side effects like dyskinesia.

From the point of view of the level of automation in the approach, the 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 avoid unpleasant side effects and an inadequate treatment of patients' symptoms, especially for upper limits. However, many algorithms tested in clinical studies to date allow reduction of stimulation amplitude to zero when beta amplitude falls below a threshold, however, this could be modified in future fast aDBS algorithms.[39,42,44,46]

From a control algorithm point of view, the experts were uncertain about whether fast adaptation methods (movement-related) would be superior or inferior when compared to slow adaptation methods (drug-related). Indeed, beta activity can immediately trigger a brief increase in stimulation to shorten prolonged beta bursts[39,47] or it can be smoothed over many seconds to serve as a medication state biomarker and then be used as feedback to drive stimulation.[44] The way fast and

slow adaptation algorithms have been implemented and studied, both reduced the total electrical energy delivered (TEED) over time by 50%, but while the first seems to reduce adverse effects on speech[48] and to achieve a better control of bradykinesia and rigidity[44] the latter seems to be more effective in reducing dyskinesias.[43] These effects should be interpreted with great caution because of the paucity of cases and lack of independent validation. Indeed, speech was not systematically assessed for the "slow adaptation", neither 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.[49] Currently, the lack of data does not allow to conclude differential benefits of both algorithms on side effects. Also, aDBS can possibly allow more TEED to be delivered, but with improved clinical efficacy and without inducing side effects;[40] therefore, reduced TEED seems to be less of a critical outcome for DBS implementation, particularly with the advent of rechargeable devices.[50]

Panellists reached a consensus that the feasibility of aDBS for patients with suboptimally positioned electrodes was a limitation, 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 feature of the motor part of the STN.[51] Therefore, suboptimally positioned electrodes will not likely detect the LFPs needed to "adapt" aDBS to patients' symptoms.

Similarly, the panellists 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.[52] The experts did concede that segmented electrodes share with aDBS the common aim to "personalise" and shape stimulation electrical fields to single 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.[52] Theoretically, these two approaches could be complementary.

4.2. *Clinical aspects of aDBS*

The panellists shared an optimistic opinion in terms of 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 scepticism of parts of the medical community, the knowledge and technology in the field of aDBS have been growing.[53] Also, recent technological advancements (e.g., directional leads[54] or multiple stimulation methods[17,55]) may limit side effects and may serve to optimise for an individual symptom or symptoms.[8]

Another important point related to aDBS adoption is its safety, on which the panellists agreed. In addition to the surgical risks that to date are comparable to those of cDBS,[56] concerns have been expressed in literature about the potential side effects of aDBS stimulation.[57] Although no significant side effects have been reported so far,[58] rapid changes of voltage or frequency induced by neurosignals could be unpleasant or even intolerable to patients in chronic stimulation. Thus, stimulation methods that balance ramp rates to avoid side effects and keep the stimulation therapeutic by responding in time to neurosignals changes are under study.[59]

One of the major potential advantages of aDBS is its ability to provide personalized therapy. The panellists 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 of 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.[60] Beta frequency correlates more with rigidity/bradykinesia than resting tremor,[61,62] while gamma activity, particularly finely-tuned gamma, has been associated with ON medication states and dyskinesia.[63,64] Beta-driven aDBS might be less activated during levodopa-ON medication state (following beta suppression[38]) 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 symptom while guaranteeing a similar or even better control of cardinal symptoms of PD.[42,44,46]

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-spectrum LFP.[65,66] Additionally, several computational models have been recently developed to test the feasibility and efficacy of aDBS methods that modulate stimulation to control different biomarkers.[67,68] 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.[69,70] Additionally, peripheral sensors may also be used for adaptive DBS for tremor.[71,72]

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,[73] whether aDBS might induce neuroplastic changes remains an open question due to the lack of evidence to support any opinion. 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[74]) that may in select cases threaten the effectiveness of cDBS in chronic conditions.[74]

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.

4.3. *Limitations*

The consensus reached among experts as for the Delphi methods provides only the lowest level of evidence for making causal inferences.[75] Therefore, the outcome of the present panel review cannot replace clinical judgments or original research, nor is it intended to define a standard of practice. Similarly, 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 current state of knowledge and future directions for research, even more for a field which is still at its infancy.

4.4. *Conclusions*

Despite experts agreed only partially on some technical aspects of aDBS, the panel concluded that aDBS will be routine in the mid-term. As for now, safety is a key aspect that reached agreement as well as the potential of aDBS to provide faster and more stable treatment response than cDBS, and in tremor-dominant PD patients and in those with motor fluctuations and dyskinesias. The expert panel also agreed that the neurophysiological mechanisms of aDBS, the best control strategy, and the relationship between this technology and other DBS-related innovations, such as segmented leads, are still to be investigated, thus orienting future research. Also, the current need of high level of expertise for the programming and management of aDBS patients represent a challenge that requires the coordination between research and industry, with automatic programming being an important development. In conclusion, the results of this Delphi consensus represent a step forward for aDBS to reach clinical adoption.

Declaration of interest

M.G., N.V.M., S.O., T.B., E.S., Y.T., C.H., 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. Deuschl G.D. has served as a consultant for Boston Scientific and Cavion and as 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 consultant and/or speaker from Abbott, Boston Scientific, Ceregate, Inbrain Neuroelectronics, Medtronic, 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 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, Fundacion ACE, Societa Italiana Parkinson e Disordini del Movimento and Asociacion Madrilena de Neurologia, 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. research is support 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 Foundation, and has received research grants from NIH, Parkinson Foundation, the Michael J. Fox Foundation, the Parkinson Alliance, Smallwood Foundation, the Bachmann-Strauss Foundation, the Tourette Syndrome Association, and the UF Foundation. M.S.O. 's research is supported by: R01 NS131342 NIH R01 NR014852, R01NS096008, UH3NS119844, U01NS119562. M.S.O. is PI of the NIH R25NS108939 Training

Grant. M.S.O. has received royalties for publications with Hachette Book Group, Demos, Manson, Amazon, Smashwords, Books4Patients, Perseus, Robert Rose, Oxford and Cambridge (movement disorders books). M.S.O. is an associate editor for New England Journal of Medicine Journal Watch Neurology and JAMA Neurology. M.S.O. has participated in CME and educational activities (past 12-24 months) on movement disorders sponsored by WebMD/Medscape, RMEI Medical Education, American Academy of Neurology, Movement Disorders Society, Mediflix and by Vanderbilt University. The institution and not M.S.O. receives grants from industry. M.S.O. has participated as a site PI and/or co-I for several NIH, foundation, and industry sponsored trials over the years but has not received honoraria. Research projects at the University of Florida receive device and drug donations.

J.L.O. received consulting payments from Abbott, Acorda, Jazz, Adamas, AcureX and Aspen as well as research or training grants from Biogen, Boston scientific, Medtronic, Neuroderm, Runelabs, Abbvie, Merz, Amneal and Acadia.

A.S. received consulting fees from Abbott, Zambon, and Abbvie, and speaker honoraria from bsh medical communication, Abbott, Kyowa Kirin, Novartis, Abbvie, and Alexion, GE Healtcare. The institution of AS, not AS personally, received funding by the Deutsche Forschungsgemeinschaft, the Brunhilde Moll Foundation, and Abbott.

P.A.S. is compensated for time spent on the data safety and monitoring board for Neuralink, Inc.

L.T. received occasional payments as a consultant for Boston Scientific, L.T. received honoraria as a speaker on symposia sponsored by Boston Scientific, AbbVIE, Novartis, Neuraxpharm, Teva, the Movement Disorders Society und DIAPLAN. The institution of L.T., not L.T. personally received funding by Boston Scientific, the German Research Foundation, the German Ministry of Education and Research, the Otto-Loewi-Foundation and the Deutsche Parkinson Vereinigung. Neither L.T. nor any member of his family holds stocks, stock options, patents or financial interests in any of the above-mentioned companies or their competitors. Lars Timmermann serves as the president of the German Neurological Society without any payment or any income.

G.T. received financial support from Boston Scientific and Medtronic; Research agreement with RuneLabs and Medtronic not related to the present work

V.V.V. received occasional payments as a consultant or speaker on symposia from Boston Scientific and Medtronic.

J. Volkmann JV reports grants and personal fees from Medtronic, grants and personal fees from Boston Scientific, personal fees from Abbott outside the submitted work. JV was supported by the German Research Foundation (DFG, Project-ID424778381, TRR 295) - JV received consulting and lecture fees from Boston Scientific, Medtronic and Newronika. Research grants from the German

Research Foundation, the German Ministry of Research and Education, Boston Scientific and Medtronic. Lecture Honoraria from UCB, Zambon, Abbott.

A.P. and S.M. are founders and shareholders of Newronika Spa, Italy.

Role of funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. G.T. received funding from the Swiss National Science Foundation (project number: PZ00P3_202166).

Contributors

M.G., A.F., J.K.K., A.A.K., A.L., M.O., A.P., L.T., and J.V. contributed to Conceptualisation and Methodology. J.O., G.D., P.S., S.L., R.M.F., G.T., C.G S., M.A.P., Y.T., A.S., P.L., C.H., and V.V.V. contributed to Methodology. M.G., S.M., N.V.M., S.O., T.B., and E.S. contributed to Data curation, Formal Analysis, Visualization and Writing – original draft. A.P. contributed to general study design, study ideation, discussion and supervision. All the authors contributed to Writing – review & editing, and accept responsibility for the decision to submit for publication.

5. REFERENCE

1. Roy HA, Green AL, Aziz TZ. State of the Art: Novel Applications for Deep Brain Stimulation. *Neuromodulation*. 2018;21(2):126-134. doi:10.1111/ner.12604

2. Peng L, Fu J, Ming Y, Zeng S, He H, Chen L. The long-term efficacy of STN vs GPi deep brain stimulation for Parkinson disease: A meta-analysis. *Medicine (Baltimore)*. 2018;97(35):e12153. doi:10.1097/MD.0000000000012153

3. Aldridge D, Theodoros D, Angwin A, Vogel AP. Speech outcomes in Parkinson's disease after subthalamic nucleus deep brain stimulation: A systematic review. *Parkinsonism Relat Disord*. 2016;33:3-11. doi:10.1016/j.parkreldis.2016.09.022

4. Xie T, Padmanaban M, Bloom L, et al. Effect of low versus high frequency stimulation on freezing of gait and other axial symptoms in Parkinson patients with bilateral STN DBS: A mini-review. *Translational Neurodegeneration*. 2017;6(1):13. doi:10.1186/s40035-017-0083-7

5. Baizabal-Carvallo JF, Jankovic J. Movement disorders induced by deep brain stimulation. *Parkinsonism & Related Disorders*. 2016;25:1-9. doi:10.1016/j.parkreldis.2016.01.014

6. Ray NJ, Jenkinson N, Brittain J, et al. The role of the subthalamic nucleus in response inhibition: evidence from deep brain stimulation for Parkinson's disease. *Neuropsychologia*. 2009;47(13):2828-2834. doi:10.1016/j.neuropsychologia.2009.06.011

7. Mahlknecht P, Foltynie T, Limousin P, Poewe W. How Does Deep Brain Stimulation Change the Course of Parkinson's Disease? *Movement Disorders*. 2022;37(8):1581-1592. doi:10.1002/mds.29052

8. Marceglia S, Guidetti M, Harmsen IE, et al. Deep brain stimulation: is it time to change gears by closing the loop? *Journal of neural engineering*. 2021;18(6). doi:10.1088/1741-2552/ac3267

9. Krauss JK, Lipsman N, Aziz T, et al. Technology of deep brain stimulation: current status and future directions. *Nature reviews Neurology*. 2021;17(2):75. doi:10.1038/S41582-020-00426-Z

10. Cagle JN, Okun MS, Cernera S, et al. Embedded Human Closed-Loop Deep Brain Stimulation for Tourette Syndrome: A Nonrandomized Controlled Trial. *JAMA Neurol*. 2022;79(10):1064-1068. doi:10.1001/jamaneurol.2022.2741

11. Kühn AA, Volkmann J. Innovations in deep brain stimulation methodology. *Movement Disorders*. 2017;32(1):11-19. doi:10.1002/mds.26703

12. Leblois A, Meissner W, Bioulac B, Gross CE, Hansel D, Boraud T. Late emergence of synchronized oscillatory activity in the pallidum during progressive parkinsonism. *European Journal of Neuroscience*. 2007;26(6):1701-1713. doi:10.1111/j.1460-9568.2007.05777.x

13. Özkurt TE, Butz M, Homburger M, et al. High frequency oscillations in the subthalamic nucleus: A neurophysiological marker of the motor state in Parkinson's disease. *Experimental Neurology*. 2011;229(2):324-331. doi:10.1016/j.expneurol.2011.02.015

14. Quinn EJ, Blumenfeld Z, Velisar A, et al. Beta oscillations in freely moving Parkinson's subjects are attenuated during deep brain stimulation. *Movement Disorders*. 2015;30(13):1750-1758. doi:10.1002/mds.26376

15. Johnson LA, Nebeck SD, Muralidharan A, Johnson MD, Baker KB, Vitek JL. Closed-Loop Deep Brain Stimulation Effects on Parkinsonian Motor Symptoms in a Non-Human Primate – Is Beta Enough? *Brain Stimulation*. 2016;9(6):892-896. doi:10.1016/J.BRS.2016.06.051

16. Marceglia S, Bianchi AM, Baselli G, et al. Interaction between rhythms in the human basal ganglia: Application of bispectral analysis to local field potentials. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*. 2007;15(4):483-492. doi:10.1109/TNSRE.2007.907893

17. Marceglia S, Foffani G, Bianchi AM, et al. Dopamine-dependent non-linear correlation between subthalamic rhythms in Parkinson's disease. *J Physiol*. 2006;571(Pt 3):579-591. doi:10.1113/jphysiol.2005.100271

18. Foffani G, Bianchi AM, Baselli G, Priori A. Movement-related frequency modulation of beta oscillatory activity in the human subthalamic nucleus. *J Physiol*. 2005;568(Pt 2):699-711. doi:10.1113/jphysiol.2005.089722

19. Hsu CC, Sandford BA. The Delphi technique: making sense of consensus. *Practical assessment, research, and evaluation*. 2007;12(1):10.

20. Lynn MR, Layman EL, Englebardt SP. Nursing administration research priorities. A national Delphi study. *J Nurs Adm*. 1998;28(5):7-11. doi:10.1097/00005110-199805000-00002

21. Ludwig B. Predicting the future: Have you considered using the Delphi methodology? *Journal of extension*. Published online 1997.

22. Turoff M, Hiltz SR. Computer based Delphi processes. *Gazing into the oracle: The Delphi method and its application to social policy and public health*. Published online 1996:56-85.

537 23. Ulschak FL. *Human Resource Development: The Theory and Practice of Need Assessment*. Reston
538 Publishing Company; 1983.

539 24. Rowe G, Wright G. Expert Opinions in Forecasting: The Role of the Delphi Technique. In: Armstrong JS,
540 ed. *Principles of Forecasting: A Handbook for Researchers and Practitioners*. International Series in
541 Operations Research & Management Science. Springer US; 2001:125-144. doi:10.1007/978-0-306-
542 47630-3_7

543 25. Ekhtiari H, Ghobadi-Azbari P, Thielscher A, et al. A checklist for assessing the methodological quality of
544 concurrent tES-fMRI studies (ContES checklist): a consensus study and statement. *Nat Protoc*.
545 2022;17(3):596-617. doi:10.1038/s41596-021-00664-5

546 26. Ekhtiari H, Zare-Bidoky M, Sangchooli A, et al. A methodological checklist for fMRI drug cue reactivity
547 studies: development and expert consensus. *Nat Protoc*. 2022;17(3):567-595. doi:10.1038/s41596-021-
548 00649-4

549 27. Custer RL, Scarcella JA, Stewart BR. The modified Delphi technique-A rotational modification. Published
550 online 1999.

551 28. Ludwig BG. *Internationalizing Extension: An Exploration of the Characteristics Evident in a State*
552 *University Extension System That Achieves Internationalization*. The Ohio State University; 1994.

553 29. Armstrong JS, Forecasting LR. From crystal ball to computer. *New York ua*. 1985;348.

554 30. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. *Journal of*
555 *Advanced Nursing*. 2000;32(4):1008-1015. doi:10.1046/j.1365-2648.2000.t01-1-01567.x

556 31. Kaplan LM. *The Use of the Delphi Method in Organizational Communication: A Case Study*. Ohio State
557 University; 1971.

558 32. Sumsion T. The Delphi Technique: An Adaptive Research Tool. *British Journal of Occupational Therapy*.
559 1998;61(4):153-156. doi:10.1177/030802269806100403

560 33. Green B, Jones M, Hughes D, Williams A. Applying the Delphi technique in a study of GPs' information
561 requirements. *Health Soc Care Community*. 1999;7(3):198-205. doi:10.1046/j.1365-2524.1999.00176.x

562 34. Eckman CA. DEVELOPMENT OF AN INSTRUMENT TO EVALUATE INTERCOLLEGIATE ATHLETIC COACHES:
563 A MODIFIED DELPHI STUDY. Published online 1984.

564 35. Hill KQ, Fowles J. The methodological worth of the Delphi forecasting technique. *Technological*
565 *forecasting and social change*. 1975;7(2):179-192.

566 36. Jacobs JM. *Essential Assessment Criteria for Physical Education Teacher Education Programs: A Delphi*
567 *Study*. West Virginia University; 1996.

568 37. Priori A, Foffani G, Rossi L, Marceglia S. Adaptive deep brain stimulation (aDBS) controlled by local field
569 potential oscillations. *Exp Neurol*. 2013;245:77-86. doi:10.1016/j.expneurol.2012.09.013

570 38. Little S, Brown P. What brain signals are suitable for feedback control of deep brain stimulation in
571 Parkinson's disease? *Ann N Y Acad Sci*. 2012;1265(1):9-24. doi:10.1111/j.1749-6632.2012.06650.x

572 39. Little S, Pogosyan A, Neal S, et al. Adaptive deep brain stimulation in advanced Parkinson disease. *Ann*
573 *Neurol*. 2013;74(3):449-457. doi:10.1002/ana.23951

574 40. Oehrn CR, Cernera S, Hammer LH, et al. Personalized chronic adaptive deep brain stimulation
575 outperforms conventional stimulation in Parkinson's disease. Published online August 8,
576 2023:2023.08.03.23293450. doi:10.1101/2023.08.03.23293450

577 41. Neumann WJ, Gilron R, Little S, Tinkhauser G. Adaptive Deep Brain Stimulation: From Experimental
578 Evidence Toward Practical Implementation. *Movement Disorders*. 2023;38(6):937-948.
579 doi:10.1002/mds.29415

580 42. Rosa M, Arlotti M, Ardolino G, et al. Adaptive deep brain stimulation in a freely moving Parkinsonian
581 patient. *Mov Disord*. 2015;30(7):1003-1005. doi:10.1002/mds.26241

582 43. Rosa M, Arlotti M, Marceglia S, et al. Adaptive deep brain stimulation controls levodopa-induced side
583 effects in Parkinsonian patients. *Movement Disorders*. 2017;32(4):628-629. doi:10.1002/mds.26953

584 44. Arlotti M, Marceglia S, Foffani G, et al. Eight-hours adaptive deep brain stimulation in patients with
585 Parkinson disease. *Neurology*. 2018;90(11):e971-e976. doi:10.1212/WNL.0000000000005121

586 45. Muthuraman M, Koirala N, Ciolac D, et al. Deep Brain Stimulation and L-DOPA Therapy: Concepts of
587 Action and Clinical Applications in Parkinson's Disease. *Front Neurol*. 2018;9:711.
588 doi:10.3389/fneur.2018.00711

589 46. Bocci T, Prenassi M, Arlotti M, et al. Eight-hours conventional versus adaptive deep brain stimulation of
590 the subthalamic nucleus in Parkinson's disease. *npj Parkinsons Dis*. 2021;7(1):1-6. doi:10.1038/s41531-
591 021-00229-z

592 47. Tinkhauser G, Pogosyan A, Little S, et al. The modulatory effect of adaptive deep brain stimulation on
593 beta bursts in Parkinson's disease. *Brain*. 2017;140(4):1053-1067. doi:10.1093/brain/awx010

594 48. Little S, Tripoliti E, Beudel M, et al. Adaptive deep brain stimulation for Parkinson's disease
595 demonstrates reduced speech side effects compared to conventional stimulation in the acute setting. *J*
596 *Neurol Neurosurg Psychiatry*. 2016;87(12):1388-1389. doi:10.1136/jnnp-2016-313518

597 49. Little S, Beudel M, Zrinzo L, et al. Bilateral adaptive deep brain stimulation is effective in Parkinson's
598 disease. *Journal of Neurology, Neurosurgery and Psychiatry*. 2016;87(7):717-721. doi:10.1136/jnnp-
599 2015-310972

600 50. Beudel M, Heijmans M, Habets JGV, Kubben PL. Future Perspectives: Adaptive Deep Brain Stimulation.
601 In: Temel Y, Leentjens AFG, de Bie RMA, Chabardes S, Fasano A, eds. *Fundamentals and Clinics of Deep*
602 *Brain Stimulation: An Interdisciplinary Approach*. Springer International Publishing; 2020:49-65.
603 doi:10.1007/978-3-030-36346-8_5

604 51. Chen CC, Pogosyan A, Zrinzo LU, et al. Intra-operative recordings of local field potentials can help
605 localize the subthalamic nucleus in Parkinson's disease surgery. *Exp Neurol*. 2006;198(1):214-221.
606 doi:10.1016/j.expneurol.2005.11.019

607 52. Cagnan H, Denison T, McIntyre C, Brown P. Emerging technologies for improved deep brain
608 stimulation. *Nat Biotechnol*. 2019;37(9):1024-1033. doi:10.1038/s41587-019-0244-6

609 53. Cuschieri A, Borg N, Zammit C. Closed loop deep brain stimulation: A systematic scoping review. *Clinical*
610 *Neurology and Neurosurgery*. 2022;223:107516. doi:10.1016/j.clineuro.2022.107516

611 54. Fricke P, Nickl R, Breun M, et al. Directional Leads for Deep Brain Stimulation: Technical Notes and
612 Experiences. *Stereotact Funct Neurosurg*. 2021;99(4):305-312. doi:10.1159/000512231

613 55. Marceglia S, Rossi L, Foffani G, Bianchi AM, Cerutti S, Priori A. Basal ganglia local field potentials:
614 Applications in the development of new deep brain stimulation devices for movement disorders. In:
615 *Expert Review of Medical Devices*. Vol 4. Taylor & Francis; 2007:605-614.
616 doi:10.1586/17434440.4.5.605

617 56. Arlotti M, Rosa M, Marceglia S, Barbieri S, Priori A. The adaptive deep brain stimulation challenge.
618 *Parkinsonism and Related Disorders*. 2016;28:12-17. doi:10.1016/j.parkreldis.2016.03.020

619 57. Baker S, Fenstermacher E, Davis RA, et al. Ethical considerations in closed loop deep brain stimulation.
620 *Deep Brain Stimulation*. 2023;3:8-15. doi:10.1016/j.jdbs.2023.11.001

58. Guidetti M, Marceglia S, Loh A, et al. Clinical perspectives of adaptive deep brain stimulation. *Brain stimulation*. 2021;14(5):1238-1247. doi:10.1016/j.brs.2021.07.063

59. Petrucci MN, Wilkins KB, Orthlieb GC, et al. Ramp Rate Evaluation and Configuration for Safe and Tolerable Closed-Loop Deep Brain Stimulation. In: *2021 10th International IEEE/EMBS Conference on Neural Engineering (NER)*. ; 2021:959-962. doi:10.1109/NER49283.2021.9441336

60. Wendt K, Denison T, Foster G, et al. Physiologically informed neuromodulation. *Journal of the Neurological Sciences*. 2022;434:120121. doi:10.1016/j.jns.2021.120121

61. Beudel M, Brown P. Adaptive deep brain stimulation in Parkinson's disease. *Parkinsonism & Related Disorders*. 2016;22:S123-S126. doi:10.1016/j.parkreldis.2015.09.028

62. Yin Z, Zhu G, Zhao B, et al. Local field potentials in Parkinson's disease: A frequency-based review. *Neurobiol Dis*. 2021;155:105372. doi:10.1016/j.nbd.2021.105372

63. Swann NC, Hemptinne C de, Miocinovic S, et al. Gamma Oscillations in the Hyperkinetic State Detected with Chronic Human Brain Recordings in Parkinson's Disease. *J Neurosci*. 2016;36(24):6445-6458. doi:10.1523/JNEUROSCI.1128-16.2016

64. Wiest C, Torrecillos F, Tinkhauser G, et al. Finely-tuned gamma oscillations: Spectral characteristics and links to dyskinesia. *Exp Neurol*. 2022;351:113999. doi:10.1016/j.expneurol.2022.113999

65. Shah SA, Tinkhauser G, Chen CC, Little S, Brown P. Parkinsonian Tremor Detection from Subthalamic Nucleus Local Field Potentials for Closed-Loop Deep Brain Stimulation. *Annu Int Conf IEEE Eng Med Biol Soc*. 2018;2018:2320-2324. doi:10.1109/EMBC.2018.8512741

66. Hirschmann J, Schoffelen JM, Schnitzler A, van Gerven M a. J. Parkinsonian rest tremor can be detected accurately based on neuronal oscillations recorded from the subthalamic nucleus. *Clin Neurophysiol*. 2017;128(10):2029-2036. doi:10.1016/j.clinph.2017.07.419

67. Tinkhauser G, Moraud EM. Controlling Clinical States Governed by Different Temporal Dynamics With Closed-Loop Deep Brain Stimulation: A Principled Framework. *Front Neurosci*. 2021;15:734186. doi:10.3389/fnins.2021.734186

68. Fleming JE, Senneff S, Lowery MM. Multivariable closed-loop control of deep brain stimulation for Parkinson's disease. *J Neural Eng*. 2023;20(5). doi:10.1088/1741-2552/acfbfa

69. Velisar A, Syrkin-Nikolau J, Blumenfeld Z, et al. Dual threshold neural closed loop deep brain stimulation in Parkinson disease patients. *Brain Stimul*. 2019;12(4):868-876. doi:10.1016/j.brs.2019.02.020

70. Sarikhani P, Ferleger B, Mitchell K, et al. Automated deep brain stimulation programming with safety constraints for tremor suppression in patients with Parkinson's disease and essential tremor. *J Neural Eng*. 2022;19(4). doi:10.1088/1741-2552/ac86a2

71. Yamamoto T, Katayama Y, Ushiba J, et al. On-demand control system for deep brain stimulation for treatment of intention tremor. *Neuromodulation*. 2013;16(3):230-235. doi:10.1111/j.1525-1403.2012.00521.x

72. Malekmohammadi M, Herron J, Velisar A, et al. Kinematic Adaptive Deep Brain Stimulation for Resting Tremor in Parkinson's Disease. *Movement Disorders*. 2016;31(3):426-428. doi:10.1002/mds.26482

73. Kricheldorff J, Göke K, Kiebs M, et al. Evidence of Neuroplastic Changes after Transcranial Magnetic, Electric, and Deep Brain Stimulation. *Brain Sci*. 2022;12(7):929. doi:10.3390/brainsci12070929

74. Peters J, Tisch S. Habituation After Deep Brain Stimulation in Tremor Syndromes: Prevalence, Risk Factors and Long-Term Outcomes. *Front Neurol*. 2021;12. doi:10.3389/fneur.2021.696950

75. Atkins D, Eccles M, Flottorp S, et al. Systems for grading the quality of evidence and the strength of recommendations I: Critical appraisal of existing approaches The GRADE Working Group. *BMC Health Serv Res*. 2004;4(1):38. doi:10.1186/1472-6963-4-38

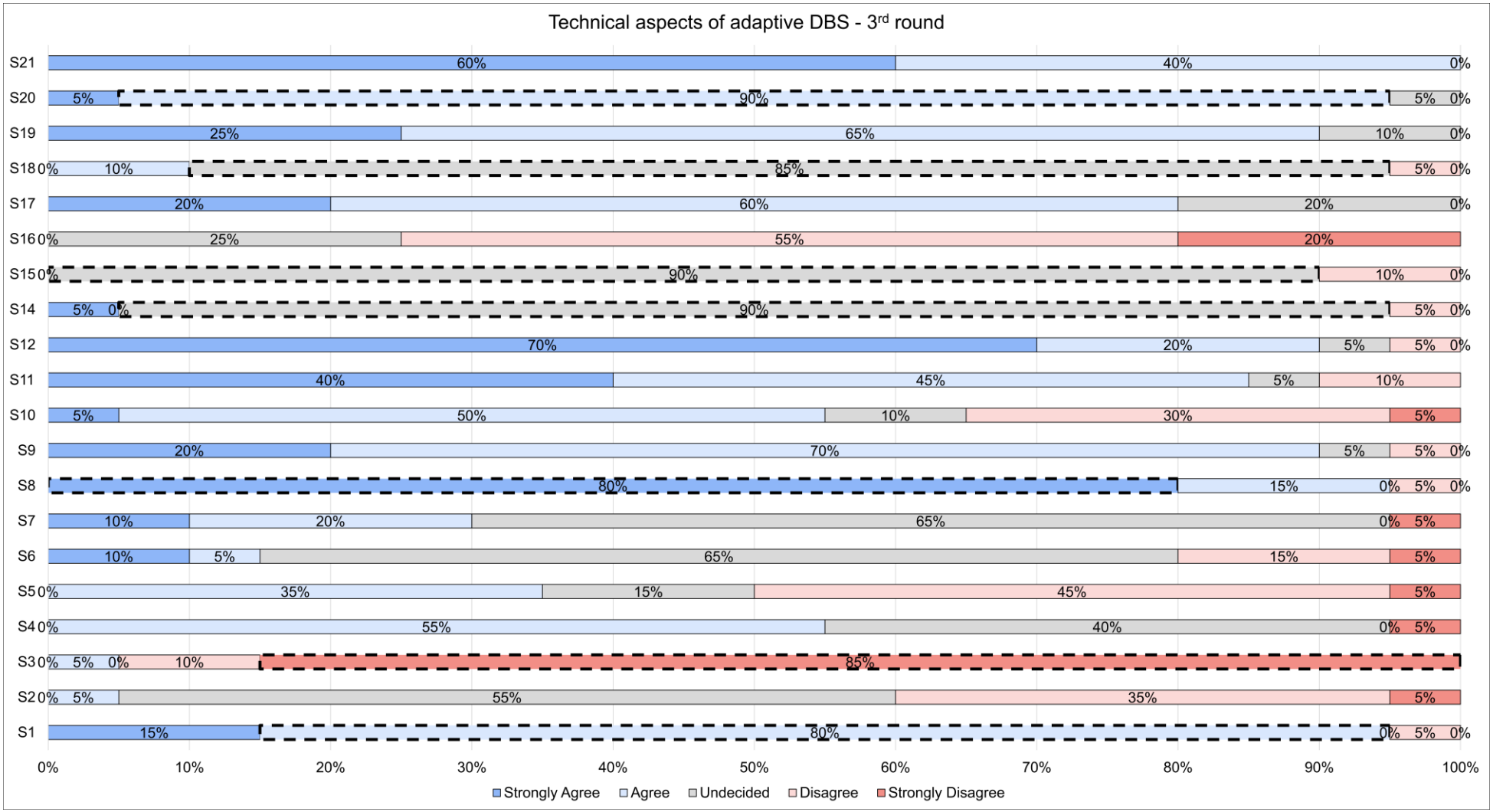

Fig.1. Percentage of agreement for the 21 statements on the technical aspects of adaptive DBS (Statement 1-21) among the Delphi Panel members, as result of the third round. A consensus was reached for Statement 1 (80% of the responses fell in the response label "Agree"), Statement 3 (85% of the responses fell in the response label "Strongly Disagree"), Statement 8 (80% of the responses fell in the response label

671 “Strongly Agree”), Statement 14 (90% of the responses fell in the response label “Undecided”), Statement 15 (90% of the responses fell in the
672 response label “Undecided”), Statement 18 (85% of the responses fell in the response label “Undecided”), and Statement 20 (90% of the responses
673 fell in the response label “Agree”). DBS = Deep Brain Stimulation; S = statement.

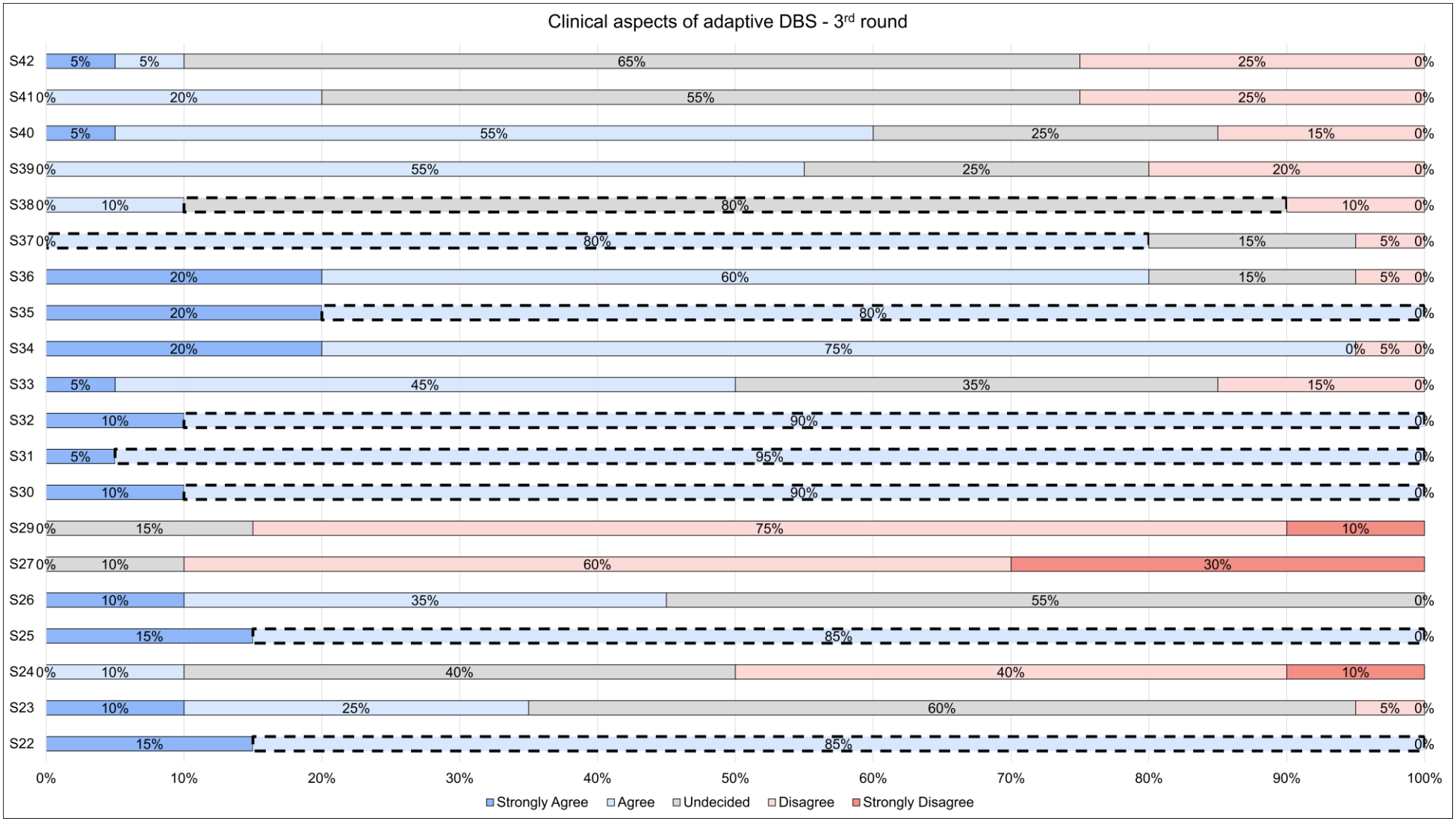

Fig.2. Percentage of agreement for the 21 statements on the clinical aspects of adaptive DBS (Statement 22-42) among the Delphi Panel members, as result of the third round. A consensus was reached for Statement 22 (85% of the responses fell in the response label "Agree"), Statement 25 (85% of the responses 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.

681 **Table 1. 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	2 ± 1	2 ± 0.25	2 ± 1

disease			
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.**
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	4 ± 1	4 ± 1	4 ± 1

medication			
S41. I think adaptive DBS decreases 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

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

684 **Table 2. 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 (yr) – 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
Canada	2	1
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 (yr)		
≤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 (yr) – n		
≤5	0	2
6-10	0	1
>10	8	10
Experience in treating patients (yr) – n		
≤5	1	0
6-10	0	0
>10	7	13

[a] one or more options were accepted