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Research Article

Neurosurgeons perspective on the shift towards earlier use of deep brain stimulation for Parkinson disease

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ABSTRACT

Background: The US Food and Drug Administration approved in 2015 the use of deep brain stimulation for Parkinson disease after "four years duration and with recent onset of motor complications". The aim of this study was to identify neurosurgeons' attitudes and perspectives around the use of deep brain stimulation for Parkinson disease earlier in the disease course.
Methods: An anonymous survey examining attitudes and perceptions towards deep brain stimulation practice and timing in Parkinson disease was developed by the study team and distributed by the American Society for Stereotactic and Functional Neurosurgeons to its members. Results from 32 subjects with answers to at least 50% of the survey were included. Data were analyzed with descriptive statistics and chi-square test.
Results: Motor fluctuations, dyskinesia, quality of life impairment, and medically refractory tremor were the most important reasons to proceed with deep brain stimulation, which was overall considered more useful after the onset of motor symptoms. Unresponsiveness to levodopa, cognitive impairment, and unclear diagnosis were important reasons not to consider deep brain stimulation. Earlier surgery was considered to be less risky compared to later in the disease progression. Ten out of 25 neurosurgeons reported considering deep brain stimulation as a therapeutic option after a minimum disease duration of three to four years.
Conclusions: We conclude that neurosurgeons support the use of earlier deep brain stimulation, but not preceding motor complications. Further research surrounding the benefits and adverse effects of earlier deep brain stimulation is needed to guide practice and better inform potential candidates.

1. Introduction

Subthalamic nucleus (STN) and Globus Pallidus pars interna (GPi) deep brain stimulation (DBS) for Parkinson disease (PD) are effective in decreasing dyskinesia, motor fluctuations, and tremor, as well as improving quality of life [1–3]. With disease progression, axial and gait problems arise, which are challenging to treat with DBS [4,5]. To maximize the benefits of DBS before gait and non-motor symptoms predominate, an interest towards earlier use of DBS has been observed in the past decade [2]. Among the benefits cited supporting the earlier use of DBS are the potential to reduce loss of social function and rates of early retirement [6–8]; and reduction in health care costs [8–10].

In addition, early results suggested that quality of life may be considerably improved by STN DBS in patients younger than 60 [11], as there is a potential correlation between age at disease onset and time to development of dyskinesia and motor fluctuations [12]. Considering that patients who develop PD before the age of 40 are at high risk of levodopa-induced complications, there may be an increased role for DBS in younger patients [13].

Earlier use of DBS was first shown to be beneficial in an open label study published in 2007 [14], and further investigated in the EARLYSTIM trial [4,15]. This large study (n = 251) included patients younger than 61 years (mean age at inclusion was 52.6 years) with PD symptoms for at least four years (mean disease duration was 7.5 years), motor complications for up to three years (mean duration of complications was 1.7 years), and no impaired psychosocial functioning [15]. In

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2015, following the publication of the EARLYSTIM trial results, the FDA's approval of Medtronic devices for DBS was extended to patients with at least four years of PD and recent onset of motor complications [16]. The possibility of expanding DBS use to before the onset of motor complications ("early DBS") was investigated in a pilot study including 30 subjects; it demonstrated a reduction in medications [17] and slower progression of rest tremor in patients undergoing DBS [18]. However, larger clinical studies remain needed around early DBS use in PD.

Despite the positive results of EARLYSTIM and the most recent FDA approval for STN DBS, physician surveys and interview studies have found a wide range of disease duration requirements prior to DBS referral, with an average of less than four and up to six years depending on the survey, and some physicians reporting no minimum duration [19]. In light of the lack of guidance regarding when to consider DBS, the shifting to earlier and earlier uses of DBS, and the lack of consensus among experts on the merits of earlier DBS, we sought to investigate functional neurosurgeons' perspectives, as they play an important role in determining patient candidacy.

2. Methods

A 19-question online survey comprising of Likert-type, multiple choice, and rank-order questions examining attitudes and perceptions towards use and timing of DBS in PD was developed drawing upon results from a pilot interview survey [20] and expert opinion (movement disorder neurologists) to evaluate attitudes around DBS and its timing in PD. The developing survey drafts were also reviewed by patient advocates and clinical experts from the Parkinson's Foundation, Parkinson's Alliance, and Michael J. Fox Foundation, to ensure quality control for content, readability, survey navigation and item clarity. The first part of the survey asked questions about clinical experience and practice, including years of practice and number of DBS cases per year. Remaining questions focused on patient selection, target choice, and thoughts on earlier DBS. The survey was piloted among members of the study team. Institutional Review Board approval was obtained from the institutions of the two co-PI's (Michigan State University, STUDY00002041, and Weill Cornell Medicine, # 1901019902).

2.1. Survey distribution

We received approval from the American Society for Stereotactic and Functional Neurosurgeons (ASSFN) to distribute the survey among its members (see Survey Instrument, Supplemental Digital Content 1). The ASSFN Administrator sent the initial invitation with the link to the survey to the members via email on September 17, 2019, and a reminder was sent on October 7. Data collection was completed on October 22, 2019. All responses were anonymous.

2.2. Data preparation

Forty-three survey responses were obtained. We excluded from analysis six responses as >50% of their survey was incomplete. Another five responses were removed due to duplication of IP addresses. The final dataset for analysis consisted of 32 unique participants.

2.3. Data analysis

All variables were nominal or ordinal. Descriptive statistics are reported as frequencies and round percentages. We used chi-square test to compare responses to the following questions based on years of clinical experience (defined as number of years since fellowship) and numbers of surgeries: (1) presence or absence of a cut off prior to proceeding with surgery; (2) minimum duration of disease required prior to proceeding with DBS; (3) whether the current FDA approval for DBS in PD is considered earlier use or not; and (4) how many years after diagnosis for implantation would the use of DBS be considered earlier use. All selected variables had answers by more than five subjects. Data were analyzed using IBM SPSS Statistics for Windows.

3. Results

About a third of physicians had completed fellowship (11/32, 34.38%) or residency (9/31, 29%) >20 years prior to completing the survey. Recent fellowship graduates (10/32, 31.25%) and residency graduates (9/31, 29%) within the past five years were similarly represented. More than a third of participants (12/32, 37.5%) reported performing 11 to 20 DBS surgeries for PD per year, while only 25% (8/32) perform over 50 per year. The STN was the most frequently preferred target for DBS (20/28, 71.43%), while 17.86% (5/28) of the surgeons used STN and GPi equally (Table 1).

Neurosurgeons were fairly equally distributed among those who required a strict cut-off of improvement in total Unified Parkinson Disease Rating Scale (UPDRS) Part III motor scores after levodopa challenge prior to DBS (13/27, 48.15%) and those (14/27, 51.85%) who did not. Those who answered that they did, were given options regarding the improvement they required prior to DBS and could select multiple choices. Among the main standard cut-offs for surgical candidacy were medically-refractory tremor (listed by 8/13, 61.54%), a 30-point improvement in UPDRS or Movement Disorder Society-sponsored UPDRS revision (MDS-UPDRS) off to on scores (6/13, 46.15%), and a 33% improvement in UPDRS or MDS-UPDRS off to on scores (6/13, 46.15%). There was a free-text answer citing 30% improvement albeit in an unspecified scoring system.

When asked about the three most important medications that must be tried prior to considering a patient for DBS, carbidopa/levodopa immediate release (listed by 23/28, 82.14%), controlled released carbidopa/levodopa (17/28, 60.71%), and dopamine agonists (15/28,

Table 1
Survey responders' experience and DBS practice data.

Surgeon	Years since end of fellowship	Years since end of residency	Average number of DBS surgeries for PD per year	Most common DBS target (STN versus GPi)
1	>20	>20	>50	STN
2	0–5	0–5	21–30	STN
3	>20	>20	>50	GPi
4	0–5	0–5	11–20	both
5	0–5	0–5	11–20	STN
6	11–15	11–15	0–10	n/a
7	6–10	11–15	11–20	STN
8	16–20	16–20	>50	STN
9	6–10	6–10	>50	STN
10	>20	>20	11–20	STN
11	6–10	6–10	31–40	STN
12	11–15	11–15	11–20	both
13	0–5	0–5	11–20	GPi
14	0–5	n/a	31–40	STN
15	>20	>20	31–40	STN
16	>20	>20	>50	GPi
17	>20	>20	21–30	STN
18	>20	>20	0–10	n/a
19	6–10	0–5	>50	n/a
20	6–10	6–10	11–20	STN
21	0–5	0–5	0–10	n/a
22	>20	>20	31–40	STN
23	>20	>20	11–20	STN
24	>20	>20	>50	STN
25	16–20	16–20	21–30	STN
26	11–15	11–15	>50	STN
27	6–10	>20	11–20	STN
28	0–5	0–5	21–30	both
29	0–5	0–5	11–20	both
30	>20	>20	31–40	STN
31	0–5	6–10	11–20	STN
32	0–5	0–5	11–20	Both

Abbreviations: DBS, deep brain stimulation; PD, Parkinson disease; STN, subthalamic nucleus; GPi, globus pallidus pars interna; n/a, not available.

53.57%) were among the top three. No neurosurgeon required an amantadine trial prior to surgery. Two out of 28 neurosurgeons (7.14%) did not base their determination of DBS candidacy on trials of specific medications.

When asked to rank their most important reasons to proceed with DBS, presence of motor fluctuations not managed by medications was selected by all interviewees (25/25) and received the most 1st place votes with 12/25 (48%). Other important reasons were: dyskinesia not managed by medications (24/25, 96%); significant quality of life impairment (23/25, 92%); presence of medically-refractory tremor (20/25, 80%); and 30% improvement in UPDRS with levodopa (17/25, 68%) (Fig. 1, see also Table 1 Supplemental Digital Content 2).

Among reasons not to proceed with DBS the following were the most common overall choices among respondents: unclear diagnosis (listed by 22/25, 88%); severe cognitive impairment (20/25, 80%); unrealistic expectations by the patient (19/25, 76%); lack of levodopa response (16/25, 64%); medical contraindications to surgery (15/25, 60%); psychiatric comorbidities (13/25, 52%); and lack of social and family support (7/25, 28%) (Fig. 2, see also Table 2 Supplemental Digital Content 3).

When asked to rank their top three choices regarding their personal attitudes towards DBS, the response that received the most first and second place votes was "DBS is more useful when used after the onset of motor complications" (18/25, 72%). The response "DBS in PD allows for a better management of symptoms than medications alone" was also a frequently selected response. Neurosurgeons ranked very closely that earlier DBS has either less or similar risks than when used later (Fig. 3, see also Table 3 Supplemental Digital Content 4).

When asked about the minimum duration of disease before DBS should be considered, ten of 25 surgeons (40%) indicated that three to four years is the minimum duration, while four (16%) answered that there is no minimum duration. No physician answered that seven or more years of disease duration are required prior to DBS consideration. Most participants (19/25, 76%) did not consider the FDA approval for use in PD "of at least four years duration and with recent onset of motor complications, or motor complications of longer-standing duration that are not adequately controlled with medication" as earlier use.

When asked about how they counsel patients about having DBS earlier versus later in the disease course, the most common answers included: DBS replicates the best on state that can be obtained with levodopa, which may decline with disease progression (16/23, 70%); significant motor benefits (15/23, 65.2%); and the increasing risk of hemorrhage and cognitive decline with increasing age (13/23, 56.5%). In terms of hardware, most neurosurgeons counsel regarding the risks of hardware complications (23/25, 92%) and the type and location of the implant (21/25, 84%). Twenty-four out of 25 neurosurgeons also discuss one or more technical features of available devices and stimulation parameters, including the option of rechargeable batteries (21/24 87.5%), MRI compatibility (20/24, 83.3%), and the differences between segmented and non-segmented leads (18/24, 75%).

Most surgeons (22/25, 88%) answered that they have DBS conferences. All the respondents noted the presence of the treating neurologist and neurosurgeon in the conferences, with 90% (20/22) noting the participation of a neuropsychologist. Less commonly nurse practitioner, psychiatrist, the patient, or a social worker were included in these conferences.

We did not find any significant relationship between duration of clinical experience or number of surgeries and the presence of a cut-off in UPDRS part III improvement prior to proceeding with surgery, the minimum duration of disease prior to DBS, whether the current FDA approval for DBS in PD is considered earlier use, and what would qualify as earlier use.

4. Discussion

The aim of this study was to identify functional neurosurgeons' attitudes and perspectives around the use and timing of DBS for PD. The possibility to continue shifting the use of DBS for PD earlier in the disease progression has met with opinions ranging from groups advocating for an even earlier use [17] and others warning against its risks [21].

Compared to prior observation from a survey published in 2016 identifying an average minimum duration of disease before DBS of five to six years [19], a more recent survey indicated an average of less than four years [20]. The fact that in our sample, most of the neurosurgeons indicated four years or less or no minimum duration of disease before DBS, may suggest a progressive trend toward earlier consideration. Overall, the observed attitude in our sample appears to be in favor of DBS at a stage which may be considered early compared to the most recent FDA approval.

A small pilot study of 30 subjects suggested that early DBS, that is prior to motor complication development, does not hasten PD progression compared to medical treatment alone, maintains the benefits of lower medication usage, as well as a similar rate of adverse events compared to those nationally reported [17]. However, these results have

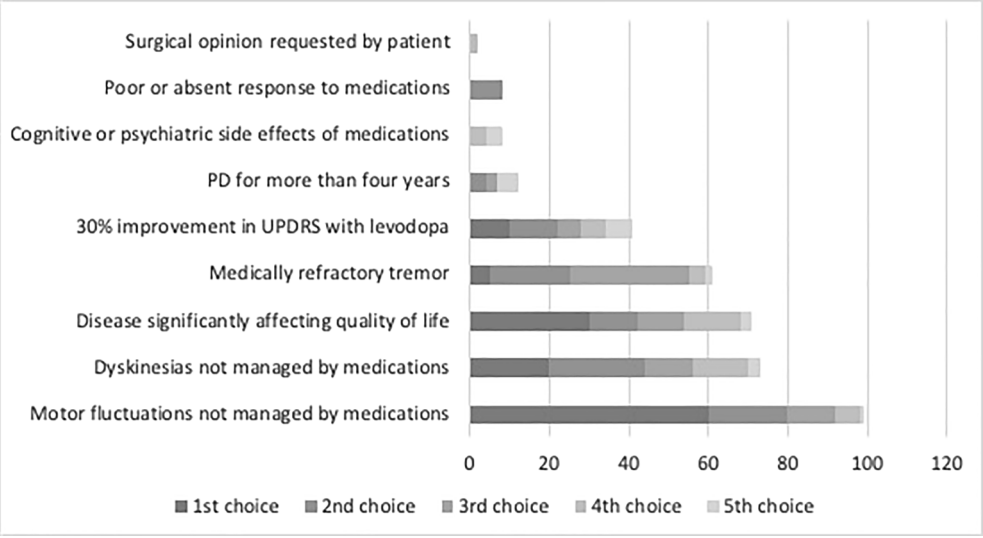

Fig. 1. Reasons to proceed with deep brain stimulation. Abbreviations: PD, Parkinson disease; UPDRS, Unified Parkinson's Disease Rating Scale. Caption: Cumulative ranking for each option, with each bar length determined by the sum of each answer count represented based on ranking.

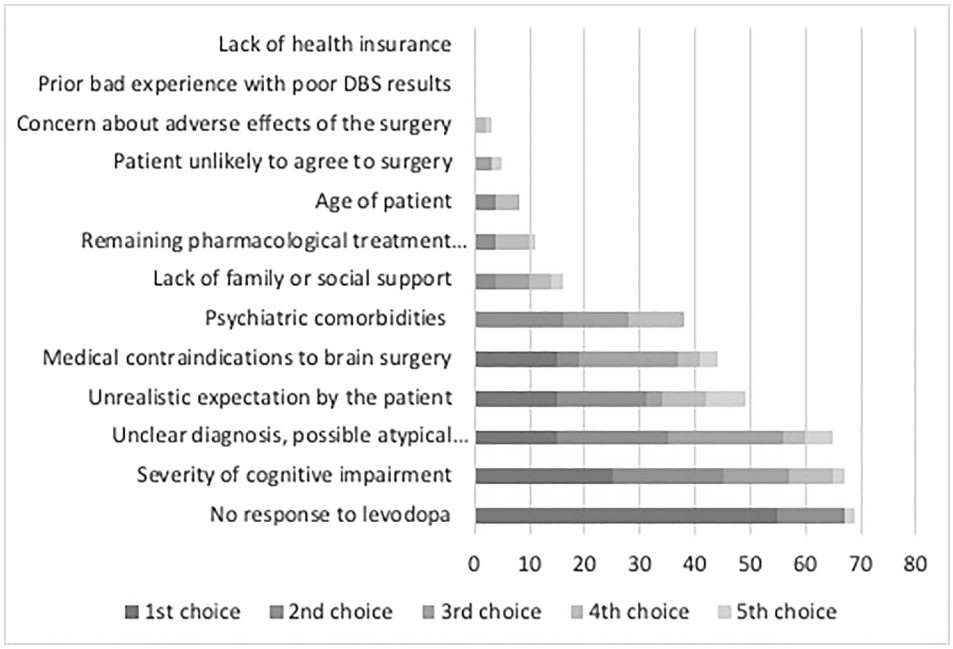

Fig. 2. Reasons not to proceed with deep brain stimulation. Abbreviations: DBS, deep brain stimulation. Caption: Cumulative ranking for each option, with each bar length determined by the sum of each answer count represented based on ranking.

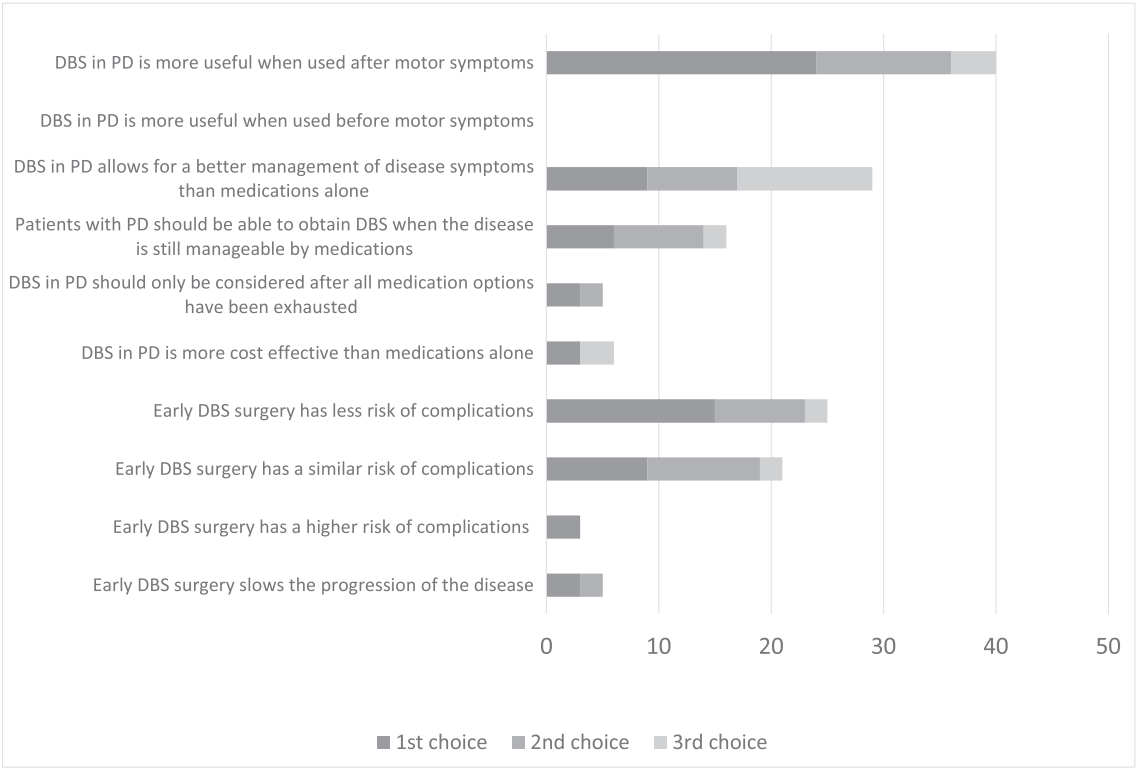

Fig. 3. Attitudes towards deep brain stimulation. Abbreviations: DBS, deep brain stimulation; PD, Parkinson disease. Caption. Cumulative ranking for each option, with each bar length determined by the sum of each answer count represented based on ranking.

been strongly criticized because potentially unnecessary surgeries caused adverse events in two out of 15 subjects, with one having permanent neurological deficits [22]. Our results suggest that, while participants support the use of earlier DBS, they would only consider it after the onset of motor complications, which typically occurs five years after levodopa usage in approximately 50% of patients [12,23,24], and cite motor complications among the main reasons to proceed with DBS.

Connected to the issue of whether or not DBS is more cost effective than medication alone, published studies, which are based on predictive models, have suggested earlier DBS as cost effective when considering both an increase in medical care costs and the improvement in quality-adjusted life years with earlier DBS [8–10]. However, we only found that a small number of participants held such a perspective. Patients in other studies have reported challenges in returning to independence following

the onset of disability and loss of function [6,7], which may contribute to earlier DBS-related improvement in quality-adjusted life years.

While our results demonstrated that age of patients is rarely a detrimental factor for surgery, earlier DBS carries a theoretically higher risk of hardware complications due to the longer duration of implantation, and some of the surgical risks may be compounded by the potential increased number of implantable pulse generator (IPG) changes [25]. With the advent of and increasing use of rechargeable IPGs, frequent surgeries will be limited, potentially making earlier DBS more desirable [26]. In fact, our study showed that most neurosurgeons think that earlier DBS has either similar or fewer risks than later DBS, and only one reported concern for higher complication risk, confirming previous findings that for clinicians the risk profile is better in earlier DBS [21].

The most commonly cited reason not to proceed with DBS in our survey was the concern for a misdiagnosis of atypical parkinsonism, and although our survey did not specify whether this was a concern in earlier DBS or in the overall patient population, this concern represents an established argument against earlier application of DBS [21]. The possible misdiagnosis of atypical parkinsonism as PD has been a clinician's concern for decades [27]. A recent clinicopathological study showed that the positive predictive value of a clinical diagnosis of probable PD increases after five years of disease and with the presence of motor complications [28]. While there is acknowledgement of this concern, our sample still considered that three to four years is the minimum duration of PD before DBS should be considered. There are ongoing efforts in the scientific community to improve diagnostic accuracy with various imaging modalities [29–32] and other measures including wearable sensor arrays [33]. However, until definitive diagnostic conclusions can be drawn from imaging modalities, PD and atypical parkinsonisms remain clinical diagnoses, potentially continuing to limit early application of DBS.

5. Limitations

Limitations of the present study include the relatively low number of responses. ASSFN membership is around 300, which would indicate a response rate of just over 10%, and lower response rate for some sections of the questionnaire. A 10–15% response rate on an online physician-directed survey is common [34]. No participant demographic data including age and gender were collected and therefore no observation could be made regarding the correlation between age or gender and attitudes toward DBS and its timing. In addition, the distributions of the survey by ASSFN among its members likely provided a selection bias of surgeons who are active in the ASSFN, limiting the generalizability of the results.

6. Conclusions

Our findings suggest that functional neurosurgeons support the FDA approval of earlier DBS and that further investigations into even earlier application of this treatment would be supported. Further studies inclusive of DBS centers with variable capabilities studying the benefits of earlier DBS are warranted to establish necessary practice guidelines which would improve the use of DBS by standardizing referrals and by defining patient inclusion and exclusion criteria. Such guidelines would address not only current disparities in referrals but also a part of patients' concerns and fears related to DBS.

CRediT authorship contribution statement

Paola Testini: Writing - original draft, Data curation, Formal analysis. **Harini Sarva:** Conceptualization, Methodology, Supervision, Writing - review & editing. **Jason Schwalb:** Writing - review & editing. **Samantha Barkan:** Data curation, Formal analysis, Writing - review & editing. **Laura Y. Cabrera:** Conceptualization, Methodology, Investigation, Supervision, Project administration, Writing - review & editing.

Declaration of Competing Interest

All authors have seen and approved the manuscript in the form submitted to the journal. The authors declare that they have conformed to the highest standards of ethical conduct in the submission of accurate data and that they acknowledge the work of others when applicable.

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I, Laura Cabrera, as corresponding author of the paper declare to have obtained agreement from all of the authors of this paper to declare their compliance as well.

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Appendix A. Supplementary data

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