



# How to avoid pneumocephalus in deep brain stimulation surgery? Analysis of potential risk factors in a series of 100 consecutive patients

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Received: 27 June 2020 / Accepted: 16 September 2020 / Published online: 22 September 2020  
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## Abstract

**Background** Accuracy of lead placement is the key to success in deep brain stimulation (DBS). Precise anatomic stereotactic planning usually is based on stable perioperative anatomy. Pneumocephalus due to intraoperative CSF loss is a common procedure-related phenomenon which could lead to brain shift and targeting inaccuracy. The aim of this study was to evaluate potential risk factors of pneumocephalus in DBS surgery.

**Methods** We performed a retrospective single-center analysis in patients undergoing bilateral DBS. We quantified the amount of pneumocephalus by postoperative CT scans and corrected the data for accompanying brain atrophy by an MRI-based score. Automated computerized segmentation algorithms from a dedicated software were used. As potential risk factors, we evaluated the impact of trephination size, the number of electrode tracks, length of surgery, intraoperative blood pressure, and brain atrophy.

**Results** We included 100 consecutive patients that underwent awake DBS with intraoperative neurophysiological testing. Systolic and mean arterial blood pressure showed a substantial impact with an inverse correlation, indicating that lower blood pressure is associated with higher volume of pneumocephalus. Furthermore, the length of surgery was clearly correlated to pneumocephalus.

**Conclusion** Our analysis identifies intraoperative systolic and mean arterial blood pressure as important risk factors for pneumocephalus in awake stereotactic surgery.

**Keywords** Brain shift · Deep brain stimulation · Surgical technique · Neurosurgery · Safe surgery · Stereotactic surgery

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This article is part of the Topical Collection on *Functional Neurosurgery - Other*

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## Introduction

Stereotactic neurosurgery offers diagnostic and therapeutic options to target highly eloquent located and deep-seated brain structures, such as the basal ganglia or the brain stem [10, 11]. Classical applications are brain biopsies or cyst and abscess drainages [28]. Further applications include placement of deep brain stimulation (DBS) leads to treat neurological and psychiatric disorders or local therapeutic strategies in neurooncology such as placement of radioactive seeds, drug delivery catheters, or laser interstitial thermal therapy probes.

Due to small skin incisions, burr hole trephinations, and thin probes, it harbors low perioperative risks and can be performed in awake patients [4, 7, 8]. Apart from classic frame-based stereotactic surgery, optical magnetic resonance imaging (MRI)-based stereotactic systems and robotic solutions became more and more common in recent times [16, 18].

Accurate probe placement is a key element of success in all stereotactic approaches and enables procedures with up to sub-millimeter precision [2].

This precision is reached by meticulous preoperative anatomic planning, which is commonly based on high-resolution tomography imaging [17].

During surgery, the most ideal preoperative planning will become void if brain shift due to intraoperative pneumocephalus occurs. Therefore, avoidance of excessive intraoperative cerebrospinal fluid (CSF) loss and associated pneumocephalus is of utmost importance for every surgeon who performs stereotactic procedures [6, 21, 24, 30].

The intention to avoid brain shift leads to individual and different surgical strategies including choice of burr hole size, patient positioning, or switchover from awake to asleep surgery protocols [1, 12, 22, 24, 26].

The aim of this study is to investigate the impact of various procedure-related and patient-specific parameters on pneumocephalus in a representative sample of patients undergoing stereotactic implantation of DBS electrodes in a single tertiary neurosurgical center.

## Methods

### Ethics approval

The study protocol was approved by the local ethics committee (Kantonale Ethikkommission Zürich: ID 2017-00440, version 1.2) in accordance to the Declaration of Helsinki. All patients gave their written consent to participate in the study.

### Study design

We performed a retrospective single-center study by analysis of prospectively acquired patient-specific datasets documented in our clinical database. All data was collected, encrypted, processed, and analyzed according to the study protocol.

### Patient selection

Data files of 100 consecutive adult patients who underwent stereotactic lead placement for DBS were analyzed. All patients had confirmed diagnosis of Parkinson's disease (PD) responding to levodopa, disabling motor fluctuations or severe functional impairment despite best medical therapy (BMT), and underwent awake bilateral implantation of a DBS system in the subthalamic nucleus (STN). Patient selection was performed by an interdisciplinary board of neurosurgeons and neurologists according to the guidelines of the German, Austrian, and Swiss neurological societies for the diagnosis and treatment of PD [5]. Absence of contraindications such as severe neuropsychological or psychiatric

impairment, intracranial mass lesions, coagulopathy, or relevant anesthesiologic perioperative risk constellation was mandatory. Due to a procedural change in burr hole trephination, both patients before and after the procedural change were similarly included. Minor patients were excluded from the analysis. Patient characteristics such as sex, age, and primary neurological disorders as well as procedure-related parameters such as length of surgery (LOS), intraoperative systolic blood pressure (SBP), or burr hole size (BHS) were recorded from anesthesia and surgery protocols, respectively.

### Surgical procedure

All procedures were performed by three experienced functional neurosurgeons (LS, MO, PK), as previously described [15]. In brief, DBS surgery was performed awake using frame-based stereotactic lead implantation (Riechert-Munding stereotactic frame; Inomed, Emmendingen, Germany) based on preoperative stereotactic MRI direct targeting. Following a preoperative stereotactic computed tomography (CT) scan, the patients were transferred to the operation theater, and both the body and head were strictly positioned supine, horizontal, and straight, without elevation/inclination. Lead implantation was performed following burr hole trephination with either an 8-mm-diameter stereotactic frame-mounted drill (Precisis AG, Heidelberg, Germany) or a conventional 14-mm trepan (Adeor medical AG, Unterhaching, Germany) with subsequent cross-shaped durotomy. Directly thereafter, a single central guide cannula was inserted and slightly pushed into the parenchyma, followed by immediate sealing of the burr hole site with fibrin glue (Baxter Inc., Deerfield, IL, USA). The procedure was performed in an identical fashion on the contralateral site. Additional test electrodes were inserted according to interoperative neurophysiology or clinical intraoperative testing when indicated. After fluoroscopic-guided permanent lead placement, an immediate postoperative stereotactic CT was performed to verify definite lead positions. Surgery was performed under continuous anesthesiologic surveillance.

### Quantification of pneumocephalus

The amount of pneumocephalus was calculated for all patients based on the postoperative CT scan data. The amount was calculated using a custom-made MATLAB R2018b (the MathWorks, Natick, MA, USA) protocol for image and voxel quantification based on Hounsfield units. All preoperative high-resolution T1-weighted imaging was segmented into gray and white matter, and CSF probability maps using SPM 12 (Statistical Parameter Mapping Software, Wellcome Department of Imaging Neuroscience, University College of London, London, UK). The probability maps were thresholded and combined to represent the intracranial volume. The probability map was then co-registered to the CT

scan and resliced (nearest neighbor) to fit the dimensions of the CT scan. Subsequently, we determined all voxels within the probability scan with Hounsfield units of  $-1023$  to  $-900$ .

All patient datasets were visually checked for potential segmentation error (PK, BvN). The volume of pneumocephalus was expressed as  $\text{cm}^3$ .

### Quantification of brain atrophy

A brain atrophy score was calculated for every patient based on preoperative individual 3.0 T 3D MRI scans. Automatic segmentation of supratentorial parenchymal volume as well as intra- and extraventricular CSF space was performed using an automated segmentation algorithm (FreeSurfer, Martinos Center for Biomedical Imaging, MA, USA) [3, 9]. The brain atrophy score was calculated as total supratentorial CSF space divided through total supratentorial parenchyma volume ( $\text{Parenchyma}/\text{Parenchyma} + \text{CSF} = \text{atrophy score}$ ) from that data.

### Statistics

Statistical analysis was performed using the software SPSS Statistics™ (version 25, IBM Corp, Armonk, New York, USA). Normal distribution was assumed according to the central limit theorem. An unpaired 2-tailed student's *t* test was used to compare the significance of means between two groups and corrected for alpha-error using the Holm-Bonferroni method. Pearson's or Spearman's correlation was used respectively. In categorical variables, an unpaired Mann-Whitney test was used to compare two samples. Data in text and graphs are shown as mean  $\pm$  standard deviation (SD). A *p* value  $\leq 0.05$  was considered significant and indicated by “\*,” *p* values  $\leq 0.01$  were indicated by “\*\*,” and values  $\leq 0.001$  by “\*\*\*.”

## Results

### Patient population

We included 100 patients (39 females, 61 males) with a mean age of  $62.3 \pm 9.7$  years. All patients underwent bilateral implantation DBS leads in the subthalamic nucleus (STN) for Parkinson's disease (PD).

### Pneumocephalus

The mean absolute amount of pneumocephalus was  $1.3 \pm 2.8 \text{ cm}^3$  (Fig. 1). This represented only  $0.13 \pm 0.29\%$  of the total supratentorial intracranial volume ( $1054 \pm 135 \text{ cm}^3$ ).

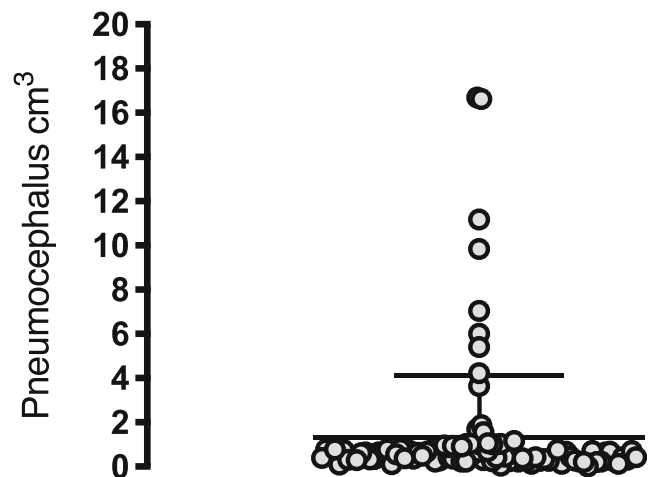


Fig. 1 Dot plot of absolute amount of pneumocephalus in  $\text{cm}^3$ ; one dot represents a single patient, shown with mean  $\pm$  standard deviation

### Burr hole size

A total of 49 patients underwent burr hole trephination using the 14-mm inner diameter trepan (large) compared with 51 patients with 8-mm inner diameter stereotactic drill (small) trephination. No significant difference in the amount of pneumocephalus was found between the large and small trephination modalities ( $1.7 \pm 2.9 \text{ cm}^3$  vs.  $1.0 \pm 2.7 \text{ cm}^3$ ; Student's *t* test:  $p = .21$ ,  $r = .13$ ). This finding remained stable regarding the relative amount of pneumocephalus according to the total intracranial volume ( $0.17 \pm 0.31\%$  vs.  $0.09 \pm 0.28\%$ ; Student's *t* test:  $p = .23$ ,  $r = .12$ ).

### Brain atrophy

The mean brain atrophy score was  $0.9993 \pm 0.0003$ . The amount of brain atrophy does neither influence the absolute volume of pneumocephalus (Pearson's  $r^2$ : 0.005;  $p = .47$ ), nor the relative amount according to the total intracranial volume (Pearson's  $r^2$ : 0.007;  $p = .39$ ) in a significant way.

### Length of surgery and parenchymal penetrations

The mean LOS was  $252 \pm 42$  min and significantly influenced the amount of pneumocephalus. Absolute pneumocephalus volume (Pearson's  $r^2$ : 0.04;  $p = .041$ ) as well as relative volume according to the total intracranial volume (Pearson's  $r^2$ : 0.05;  $p = .032$ ) are positively correlated to the LOS. The mean amount of brain passages was  $3.1 \pm 1.7$  per patient. The number of brain passages correlates positively with the amount of pneumocephalus. This reaches statistical significance only if looking at the relative volume of pneumocephalus according to the total intracranial volume (Spearman's rho: 0.20;  $p = .039$ ) but not for the absolute volume of pneumocephalus (Spearman's rho: 0.18;  $p = .069$ ).

## Intraoperative arterial blood pressure

The mean arterial intraoperative blood pressure (MAP) was  $91.9 \pm 8.6$  mmHg, and the mean SBP was  $135.3 \pm 12.4$  mmHg. No significant correlation between MAP and absolute amount of pneumocephalus (Pearson's  $r^2$ : 0.03;  $p = .13$ ) or the relative amount of pneumocephalus (Pearson's  $r^2$ : 0.02;  $p = .20$ ) was detected (Fig. 2A). The mean SBP showed a significant negative correlation with absolute (Pearson's  $r^2$ : 0.10;  $p < .01$ ) and relative amount of pneumocephalus (Pearson's  $r^2$ : 0.08;  $p < .01$ ) (Fig. 2B).

## High-volume pneumocephalus

Nine out of 100 patients showed an absolute pneumocephalus volume  $> 3$  cm<sup>3</sup> ( $8.96 \pm 4.99$  cm<sup>3</sup> vs.  $0.56 \pm 0.35$  cm<sup>3</sup>; 2-tailed Student's  $t$  test:  $p < .001$ ) An exemplary case is shown in Fig. 3. The relative pneumocephalus volume in the high-volume pneumocephalus group was  $1.00 \pm 0.52\%$  vs.  $0.06 \pm 0.06\%$  (2-tailed Student's  $t$  test:  $p < .001$ ). Patients with high-volume pneumocephalus displayed a significantly lower intraoperative SBP (Table 1). A ROC analysis revealed an optimal cutoff point of 146 mmHg SBP to avoid  $> 3$  cm<sup>3</sup> pneumocephalus with a sensitivity of 0.222 and a specificity 0.837 but an AUC of 0.74 and a negative predictive value (npv) of 0.9, reflecting an intermediate diagnostic value. The ROC analysis of MAP showed a sensitivity of .222, a specificity of .663, and an AUC of .631 for a cutoff point of 95 mmHg, resulting in a npv of 0.9 to avoid  $> 3$  cm<sup>3</sup> pneumocephalus. No significant differences were found for LOS, the brain atrophy score, or intraoperative MAP (Table 1).

Five outlier patients had a 14-mm burr hole, whereas four patients received an 8-mm-diameter trephination. Patients in the high-volume group show significantly more parenchymal passages and a higher rate of trajectory changes according to the initially planned one 28% vs. 15% with a 6% vs. 7% adjustment rate towards a more posterior trajectory (Table 1).

## Adverse events

In our cohort, one symptomatic intracranial bleeding occurred in a patient with a pneumocephalus volume of 16 cm<sup>3</sup>. This

patient had 5 parenchymal passages and a lower mean MAP of  $84 \pm 13$  mmHg (min: 60 mmHg, max: 110 mmHg) and SBP of  $117 \pm 19$  mmHg (min: 90 mmHg, max: 169 mmHg) compared with the remaining cohort (MAP:  $92 \pm 9$  mmHg; SBP:  $135 \pm 12$  mmHg). The patient developed a transient weakness of the contralateral side, which resolved completely after three months.

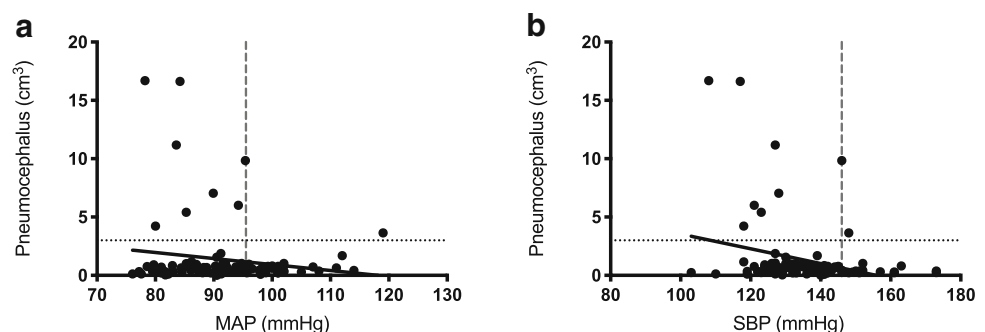
## Discussion

In this study, we investigated possible influencing factors for intraoperative pneumocephalus in 100 consecutive patients undergoing stereotactic implantation of DBS leads in the STN for PD.

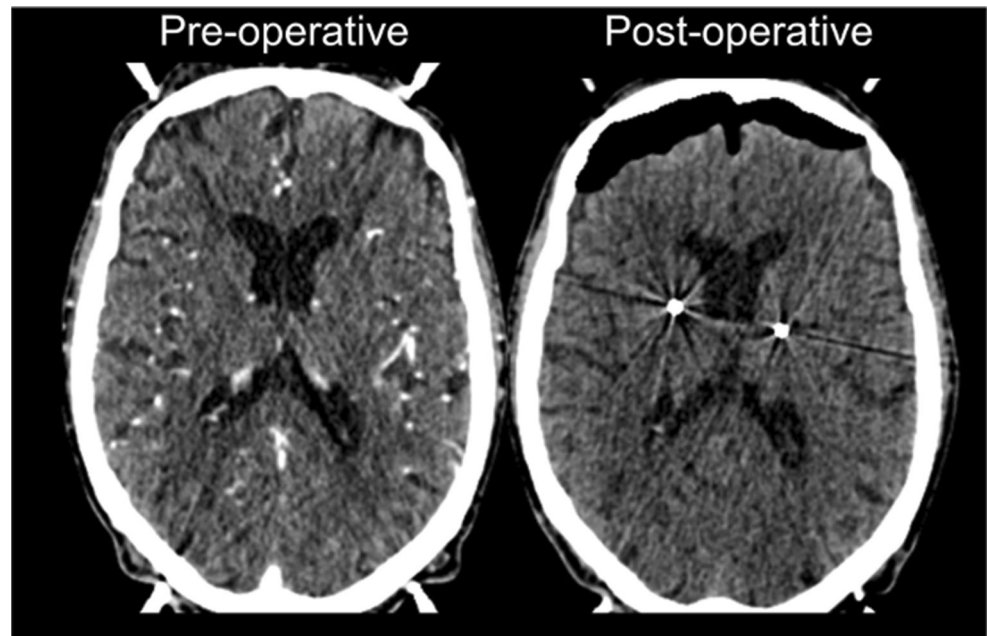
## Pneumocephalus

The volume of pneumocephalus, in general, was very low, with a mean relative volume of  $< 1\%$  of the total supratentorial intracranial volume. In the literature, no clear cutoff volume for the significant impact of pneumocephalus is reported. Brain shift in neurosurgery due to pneumocephalus is a known phenomenon after craniotomy but even simple head rotation without dural opening can provoke a significant shift of intracranial structures [23, 25, 32]. This seems more relevant for superficial cortical than for deep-seated brain regions as the basal ganglia. Still, as stereotactic neurosurgery nowadays mostly relies on pre-planned trajectories with basically no anatomical feedback during surgery except intraoperative real-time MRI, cortical shifts can raise the risk for intracranial bleedings due to sulcal vessel laceration or even tension pneumocephalus and inaccuracy of lead placement and associated suboptimal stimulation results [13]. Furthermore, pneumocephalus surrounding the intracranial lead tip might lead to inadequately high impedance and has to be taken into consideration for troubleshooting if encountering insufficient impedance levels [19]. Whether this influences intraoperative neurophysiological testing in clinical practice remains unclear.

**Fig. 2** (A) Mean arterial blood pressure (MAP) (mmHg), (B) systolic blood pressure (SBP) (mmHg), shown with linear regression line; dotted line, 3 cm<sup>3</sup> pneumocephalus; dashed line, ROC cutoff



**Fig. 3** Exemplary case of “high-volume” pneumocephalus in 75-year-old patient with PD. Implantation and postoperative course were without complications; 5 parenchymal passages were performed in this patient. Left, preoperative CT scan; right, CT scan after lead implantation



### Risk factors

Over time, functional neurosurgeons cultivated very diverse surgical nuances to minimize CSF loss and brain shift to lower the risk of inaccuracy [22, 24, 26]. For cranial lead fixation, different techniques reaching from industrially developed burr hole caps to custom-made fixation strategies like bone cement or covered titanium plates exist [31]. Most of the industrial burr hole caps only fit with larger trephinations, such as a 14-mm burr hole. In our study, the size of cranial trephination and related durotomy did not relevantly influence the rate and amount of pneumocephalus. This is in accordance with previous findings comparing BHS and pneumocephalus in DBS patients [26].

Surgeons performing DBS on dystonia patients often encounter severe cortical atrophy due to disease-related changes

in brain morphology, but also usually older PD patients can develop serious cortical atrophy. It is debated whether CSF loss can be attributed to enlarged arachnoid space, whereas less atrophy might lead to occlusion of the space between trephination and brain tissue and diminution of CSF outflow. In our study population, we used a rather ruff estimation of cortical atrophy by relating supratentorial parenchymal volume to the supratentorial intra- and extraventricular CSF space. Surprisingly, no clear relation between intraoperative pneumocephalus and the amount of brain atrophy was found. Therefore, we assume that regarding our method of awake surgery, brain atrophy might not relevantly influence pneumocephalus or brain shift.

The length of surgical procedure is often assumed to be an additional risk factor for brain shift [24]. In DBS surgery, this is often associated with intraoperative neurophysiological

**Table 1** Comparison between large- ( $\geq 3 \text{ cm}^3$ )  $n = 9$  and small- ( $< 3 \text{ cm}^3$ )  $n = 91$  volume pneumocephalus patients regarding (A) systolic blood pressure (SBP) (mmHg), (B) mean arterial blood pressure (MAP) (mmHg), (C) length of surgery (LOS) (min), (D) brain atrophy coefficient, and (E) parenchymal passages ( $n$ ), shown as mean  $\pm$  standard

	Pneumocephalus $\geq 3 \text{ cm}^3$ ( $n = 9$ )	Pneumocephalus $< 3 \text{ cm}^3$ ( $n = 91$ )	$p$	$r$
SBP (mmHg)	126.1 $\pm$ 13.1	136.2 $\pm$ 11.0	< 0.01*	0.25
MAP (mmHg)	89.9 $\pm$ 12.3	92.2 $\pm$ 8.2	0.46	0.08
LOS (min)	272.9 $\pm$ 12.3	250.8 $\pm$ 41.4	0.134	0.15
Brain atrophy	0.9992 $\pm$ 0.0003	0.9992 $\pm$ 0.0003	0.92	0.06
Parenchymal passages ( $n$ )	4.6 $\pm$ 2.2	2.9 $\pm$ 1.6	< 0.01*	0.26
Definite electrode location ( $n$ )	C13; M3; A1	C156; M12; A2; L1; P13	-	-
Burr hole size (large/small; $n$ )	5/4	44/48	-	-

deviation, definite electrode location ( $n$ ) according to central (C) planned trajectory (A = anterior, M = medial, L = lateral, P = posterior) and burr hole size (large vs. small;  $n$ ); if applicable, a 2-tailed Student's  $t$  test was performed

testing. For this reason, among others, various surgeons abandoned intraoperative neurophysiology, test stimulation, and awake surgery [14]. In our cohort, the LOS did significantly correlate with the amount of pneumocephalus. Furthermore, the number of brain passages and doing so and the number of test stimulations correlated significantly with pneumocephalus. Whether multiple brain passages more often led to pneumocephalus or brain shift due to increased CSF loss led to additional brain passages based on insufficient neurophysiological response cannot be reliably answered due to the retrospective design of our study.

### Blood pressure

Avoidance of arterial hypertension is of utmost importance in stereotactic surgery since it has been identified as a major risk factor for surgery-related intracranial bleeding [33]. Raised intracranial blood pressure might be associated with higher intracranial pressure or more prominent parenchymal pulsations leading to increased CSF loss. Contrary to expectations, SBP correlated negatively with the amount of pneumocephalus. We hypothesize that this observation might be caused by brain swelling, leading to occlusion of the subdural space at the burr hole site, preventing relevant and excessive CSF outflow. In our cohort, we identified a mean SBP of around 146 mmHg seeming to be an optimal value in order to prevent CSF loss of  $> 3 \text{ cm}^3$ . Furthermore, with a MAP  $\geq 95$  mmHg, barely no high-volume pneumocephalus was found. Based on these results, we propose a preferred SBP range of 145–160 mmHg and a MAP  $\geq 95$  mmHg on the one hand in order to avoid CSF loss but, on the other hand, to reduce hypertension-related risks of intracranial hemorrhage.

### High-volume pneumocephalus

The overall amount of pneumocephalus in our study cohort was very low, and we additionally identified a subgroup of nine patients with CSF loss  $> 3 \text{ cm}^3$ . As there are no data on the lowest clinically relevant amount of pneumocephalus, the authors chose the cutoff according to their personal experience. Not surprisingly, the absolute and relative amount of pneumocephalus differed significantly between both groups. Comparing these subgroups, we also found a significant impact of intraoperative SBP. This supports our findings towards a beneficial effect of moderately elevated SBP and MAP on CSF loss. Furthermore, patients with higher amounts of pneumocephalus required relevant more brain electrode tracks and higher adjustment rates of definite electrodes. Whether these numbers are caused by prior brain shift or are a consequence of extensive neurophysiological testing finally remains unclear. We expected that excessive brain shift might lead to a posterior shift of the target region,

resulting in an increased rate of posterior lead corrections. Surprisingly, this could not be observed as the posterior correction rate was only 6% ( $n = 1$ ) in the high-volume pneumocephalus group when compared with 7% ( $n = 13$ ) in the low-volume group, posing the question of the impact of CSF loss for actual brain shift in the target region. Patients with higher CSF loss also showed higher parenchyma penetration rates and higher rates of intraoperative trajectory adjustments of the definite lead position. Considering the fact that for insertion of each additional electrode, the fibrin glue sealing has to be removed for a short while, this might explain the increased pneumocephalus rates observed. However, if additional electrodes have to be inserted, the initially placed test electrode remains in situ and thus might stabilize the target brain area and relativize CSF loss. Nevertheless, whether these findings impact stereotactic surgery in a relevant way needs to be investigated in a prospective study.

### Study limitations

There are several important study limitations that need to be addressed. The retrospective character does not allow final conclusions on the impact of pneumocephalus on lead adjustment.

One might argue that using Ben's gun guidance always requires dural opening of 6 mm irrespectively of the size of burr hole trephination. We perform a durotomy of the complete size of trephination to ease cannula insertion, to prevent dural contact, and to better visualize the cortex to avoid blood vessel laceration and bleeding. This finally leads to a parenchymal exposure of  $\sim 50 \text{ mm}^2$  for small and of  $\sim 150 \text{ mm}^2$  for large burr hole trephinations. Furthermore, as many surgeons use industrial burr hole caps that require larger diameter burr holes, we regarded this question as relevant to assess for surgical practice.

In this study, the position of the patient did not vary and, therefore, should not influence our results. Whether a higher body position or variable angles of head inclination might play a relevant role in increased CSF loss finally cannot be ruled out and need to be addressed in further studies although significant amounts of pneumocephalus in a study performing DBS in strictly supine and straight head position was not found [22].

We assume that most of the CSF leakages are likely to occur during durotomy and fibrin glue sealing being routinely applied in many DBS centers. This sealing has been shown to play an important role [29], although its definite impact on our findings cannot be addressed by the study design and data. Further CSF loss during removal of fibrin glue for insertion of additional microelectrodes or implantation of the permanent lead might be an additional relevant issue.

The most important limitation represents the lack of direct quantification of brain shifts but only indirect quantification by evaluation of pneumocephalus. Due to the retrospective design of the study and lack of postoperative MRI scans, no detailed morphometric analysis of intraoperative brain shift could be performed as the CT examinations seem not to be appropriate and fusion of preoperative MRI and postoperative CT would not enable sufficient anatomic localization of the actual lead [27, 32]. Nevertheless, it has been shown recently that pneumocephalus influences cortical and deep-seated structure displacement in stereotactic procedures [20]. To further investigate the impact of pneumocephalus on the actual anatomic location of leads, especially the causality regarding the number of penetrations and pneumocephalus, a real-time intraoperative MRI-assisted approach with intraoperative clinical testing and macrostimulation might be most suitable.

Finally, to which extent pneumocephalus affects clinical outcome of DBS cannot finally be answered in this study but reducing pneumocephalus and brain shift is one prerequisite to optimal lead placement which can be flanked by intraoperative techniques such as neurophysiology, clinical testing, and imaging in order to find the “sweet spot” of treatment.

## Conclusions

We identified low intraoperative SBP and MAP as a clear risk factor for pneumocephalus during stereotactic DBS surgery. Therefore, we propose a SBP value between 145 and 160 mmHg and a MAP  $\geq$  95 mmHg to avoid unnecessary CSF loss without increasing the risk of intraoperative intracranial hemorrhage. LOS, burr hole trephination size, or brain atrophy seem not to play an important role concerning the risk of pneumocephalus. Whether the number of brain penetrations leads to an increased rate and amount of pneumocephalus or themselves are a relevant cause of pneumocephalus remains unclear. To further evaluate the impact of pneumocephalus on brain shift and accuracy in stereotactic DBS surgery, additional trials with an appropriate prospective design and immediate postoperative MRI scans are highly desired.

**Authors' contributions** All authors confirm that the manuscript and the order of listed authors have been read and approved by all named authors.

PK: Conceptualization, data curation, formal analysis, investigation, methodology, writing—original draft

BvN: Data curation, formal analysis, methodology, software, review and editing

GM: Data curation, formal analysis, investigation, methodology, software, review and editing

PS: Data curation, investigation, review and editing

MFO: Supervision, writing—review and editing

LHS: Supervision, writing—review and editing

**Funding** No funding was received for this research.

## Compliance with ethical standards

**Conflict of interest** All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee (Kantonale Ethikkommission Zürich KEK) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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