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ORIGINAL ARTICLE

3D transcranial ultrasound as a novel intra-operative imaging technique for DBS surgery: a feasibility study

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Abstract
Purpose Intra-operative image guidance during deep brain stimulation (DBS) surgery is usually avoided due to cost and overhead of intra-operative MRI and CT acquisitions. Recently, there has been interest in the community towards the usage of non-invasive transcranial ultrasound (TCUS) through the preauricular bone window. In this work, we investigate, for the first time, the feasibility of using 3D-TCUS for imaging of already implanted DBS electrodes. As a first step towards this goal, we report imaging methods and electrode localisation errors outside of the operating room on eight previously operated DBS patients.
Methods We evaluate the feasibility of using 3D-TCUS by registering volumes to pre-operative T1-MRI. US-MRI registration is achieved through a two-step point-based approach. First, a rough surface scan of the subjects' skin surface in 3D-TCUS space is registered to a segmented skin-surface point cloud from MRI. Next, we perform a refinement using rigid registration of multiple pairs of manually marked anatomical landmarks. We validate against post-operative CT scans which are also registered to pre-operative MRI.
Results Qualitative results are given in form of 3D reconstruction examples at 2.5 and 3.5 MHz TCUS image frequency, overlaid on pre-operative T1-MRI and post-operative CT. Quantitative evaluation is performed by reporting the accuracy of electrode tip localisation at 2.5 and 3.5 MHz after our US-MRI approach. As a baseline, we also report RMSE errors for pairs of anatomical landmarks in pre-operative MRI and 3D-TCUS.
Conclusion Multiple image examples show the appearance and quality of 3D-TCUS scans, depending on the bone window. Overall accuracy of anatomic point pairs lies on the order of 3.2 mm, using our registration approach. Compared to this baseline, electrode tip localisation in 3D-TCUS has a mean accuracy on the order of 4.8 mm and a precision on the order of 2.3 mm. While insufficient at first glance, we argue why these results are promising nonetheless. Our work motivates further future work in improved TCUS scanning, advanced TCUS-MRI registration and computer-aided electrode detection in 3D-TCUS.

Keywords New intra-operative sensors · Ultrasound · Magnetic resonance imaging · Neurosurgery · Deep brain stimulation

Introduction

Deep brain stimulation (DBS) is an established surgical treatment for neurodegenerative diseases, in particular movement disorders such as Parkinson's disease (PD) or Dystonia [7]. DBS electrode implantation aims at neurostimulation in diseased focal brain areas, often the basal ganglia involved in motor control. Colloquially referred to as a brain pacemaker, the neurostimulation has a beneficial effect on the connectivity of brain networks which can result in drastic improvement of disease symptoms such as tremor in PD or involuntary chronic muscle contractions in Dystonia.

From a medical imaging point of view, the peri-operative workflow of DBS surgery contains three main steps [15]. Pre-operatively, a MRI scan of the brain is acquired for planning of the electrode trajectory. Intra-operatively, stimu-

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lation micro-electrodes, so-called lead electrodes, are steered into an anatomic target region through thin insertion cannulas. Usually, intra-operative image-based guidance is avoided during this step, e.g. due to cost of MRI scans and contra-indications of metallic DBS electrode contacts, or due to radiation exposure and additional complexity when acquiring CT scans. C-arm fluoroscopy is sometimes used to assess the penetration depth qualitatively at a few specific time points, but in most cases, the assessment is neither continuous nor quantitative, e.g. by means of registration to pre-operative CT or MRI. Instead, neuronal response patterns recorded with the micro-electrode tip tell the surgeon its anatomic location. Post-operative control of electrode placement is usually performed through acquisition of high-resolution spiral CT and registration with the pre-operative MRI in order to localise the electrode tip with respect to surrounding brain tissue.

An attractive, alternative intra-operative imaging modality could be ultrasound (US) imaging. In contrast to CT and MRI, ultrasound is mobile and requires no specially equipped operating room. It is low cost, offers real-time and vascular imaging through colour Doppler and has no ionising radiation. Consequently, several studies exist concerning the usage of 2D and 3D ultrasound imaging during open craniotomy neurosurgery, e.g. towards the correction of brain shift [12,16]. In DBS, however, the small size of the circular burr-hole craniotomy is a limiting factor. Specialised burr-hole transducers for intra-cranial US imaging in key-hole neurosurgery do exist, but have not been investigated for DBS surgery yet, probably because it is not easily possible to place the transducer next to required instrumentation in the burr-hole during the electrode insertion phase.

Instead, there has been interest recently in the community towards the usage of non-invasive transcranial ultrasound (TCUS) through the pre-auricular bone window. The scan site through the temple bone lies out of the way of surgical instrumentation in the burr-hole and could in principle even lie outside of the sterile field if drapes are arranged accordingly. Compared to C-arm fluoroscopy, TCUS imaging would be non-invasive and could be performed continuously, while registration to pre-operative imaging would allow for quantitative assessment of the surgical progress. In a series of works, Walter et al. [20] have investigated the general safety of intra-operative TCUS imaging, the efficacy of DBS electrode monitoring during DBS surgery for Dystonia [21] and PD [18], the usefulness of TCUS for post-operative placement assessment and monitoring due to delayed brain shift [19], as well as the post-operative diagnosis of electrode dislocation (also known as electrode migration) and the prediction of clinical outcome [18]. According to Walter, both intra-operative electrodes (0.8 mm diameter) and post-operative DBS electrodes (1.27 mm diameter) can be localised exactly, despite hyper-echogenic artefacts, such as reverberation, and despite low image quality of TCUS due to dephasing and defocussing of the US beam when scanning through the skull bone.

It should be noted that all analyses presented so far have been performed on single, carefully selected 2D TCUS slices. A quantitative comparison to pre-operative MRI or post-operative CT could not be performed so far since this would require accurate registration. Moreover, it should be noted that next to Berg et al. [2], who see potential in TCUS mainly for early diagnosis of PD, Walter et al. are internationally one of the groups with the most experience in TCUS imaging. The excellent results on DBS electrode imaging seem to be easily reproducible; however, they are based on the experience and refined technique after examination of thousands of patients. It is therefore argued that less experienced groups may have difficulties achieving similar results, due to the difficulty of selecting optimal bone window and cross-cuts through the brain [17].

In a previous work [14], we proposed the extension of the 2D TCUS examination technique to 3D, in order to make acquisition and analysis of the data easier, more objective and more accessible to the inexperienced sonographer. In this work, we investigate, for the first time, the feasibility of using volumetric 3D-TCUS for imaging of deep brain stimulation (DBS) electrodes. As a first step towards this goal, we report electrode localisation errors outside of the operating room on eight previously operated DBS patients. Compared to our previous work, and beyond the seminal works by Walter et al., we report qualitative and quantitative results on a fully volumetric dataset of 3D-TCUS co-registered to pre-operative MRI and post-operative CT, which allows us to assess the feasibility of 3D electrode tip localisation. Qualitatively, we show numerous images of 3D-TCUS quality depending on the scan frequency and on the bone window. We also show artefacts in TCUS and how they transcend to 3D. Quantitatively, we report localisation errors for the ipsi-lateral tip and for the contra-lateral tip, as well as under different imaging conditions (2.5 and 3.5 MHz US frequency). We will discuss the potential of the technique, and limitations that we have observed, which, on the other hand, could motivate a series of interesting future research challenges to the community.

Materials and methods

Our overall methods' pipeline is made up of three main steps. First, we retrieve pre-operative MRI and post-operative CT data for a patient. The CT is then registered to the MRI. After acquisition of 3D-TCUS, the US data are registered to MRI using a different registration approach, independent from the CT-MRI registration. Electrode tips are identified in both CT and 3D-TCUS data independently and compared for evaluation in "Experiments and results" section. The processing workflow is depicted in Fig. 1.

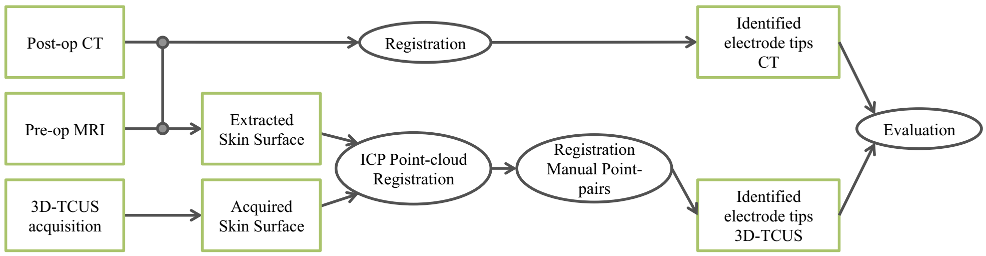

Fig. 1 Workflow of data processing. Post-operative CT and 3D-TCUS scans are registered independently to pre-operative T1 MRI. Electrode tips are identified in CT and 3D-TCUS independently and then compared for evaluation

Clinical data pre-processing

For each patient, we retrieved pre-operative and post-operative scans from our clinical database. All clinical data were anonymised before further processing, under consent of participating patients. An overview over clinical data available for our patient dataset is reported in "Dataset" section. In order to mimic a pre-operative planning scenario, we always assume the pre-operative T1 scan to be the reference coordinate system and we register all post-operative and 3D-TCUS data to this reference frame. Pre-processing of the data requires a rigid registration of the post-operative CT scan to pre-operative MRI. We achieve this using the Advanced Normalisation Toolkit (ANTs) [1], and the affine registration script `antsaffine.sh` using default parameters (multi-scale, multi-resolution, Normalised Mutual Information based), assuming strictly rigid transformation (`-rigid-affine` flag set to true). Registration results were checked qualitatively, making sure that especially the skull surface is registered. This was achieved accurately and robustly, achieving near-perfect bone overlap, despite post-operative swelling of outer skin and intra-cranial air cavities in CT causing brain shift.

3D freehand ultrasound acquisition

In terms of hardware, our 3D Freehand TCUS set-up employed a MyLab 25 XVG ultrasound machine (ESAOTE SpA, Italy) with VGA frame grabbing using the digital USB frame grabber DVI2USB 3.0 (Epiphan Systems Inc., USA/Canada). For tracking of objects, we used the NDI Polaris Spectra optical tracking system (Northern Digital Inc., Canada). In terms of software, the Public software Library for UltraSound imaging research (PLUS) provides all necessary tools for calibration, acquisition and reconstruction [11]. Using PLUS and the 3D-printed fCal 3.1 N-wire phantom, the final calibration error was reported to be 0.63 mm. TCUS acquisition was always performed at 15 cm penetration depth, using the vendor-provided imaging preset for transcranial B-Mode and Doppler imaging, but with two different imaging settings at 2.5 and 3.5 MHz. The lower frequency provides better penetration depth and less dependence on the bone window quality, while the higher offers better resolution. Apart from that, the time-gain-compensation (TGC) was left equal for all subjects, and the only setting that was changed on a patient-by-patient basis was the overall gain of the image, which varied between 75 and 95 % depending on the electrode and anatomic visibility. For each subject, 2–3 sweeps (between 700 and 1600 images per sweep) for each frequency and for each bone window were acquired to investigate repeatability and precision of scans and tip localisation, depending on frequency. Reconstruction was performed based on a backward-compounding approach, using the PLUS reconstruction algorithm with linear interpolation, full optimisation, backward-compounding with Gaussian hole filling with a kernel of size 3, standard deviation 1 and a minimum known voxels ratio of 0.5. We reconstructed all volumes at an isotropic voxel size of 0.5 mm. In our set-up, freehand 3DUS acquisition took less than 1 min for each sweep, and reconstruction around 2–3 min, which would fit into the time constraints of DBS surgery.

During acquisition, head motion is often unavoidable due to mostly involuntary head movements of patients. As described in [14], we use a head band to attach an additional optical tracking target as rigidly as possible to the forehead of the subject, allowing us to acquire and reconstruct all US data with respect to the reference target and compensate for head motion during acquisition.

Two-step US-MRI patient registration

The final step is to perform registration of the TCUS data to the pre-operative MRI. DBS surgery is usually performed using stereotactic navigation with a stereotactic frame that is rigidly fixed to the skull bone. Due to the rigid set-up, patient registration of US could be simply and accurately performed in an intra-operative scenario by attaching a reference target to the stereotactic frame, e.g. registering fiducials attached to the frame. In our scenario, since we are performing TCUS on previously operated patients, we examine without a stereotactic frame. Hence, we need to perform US-

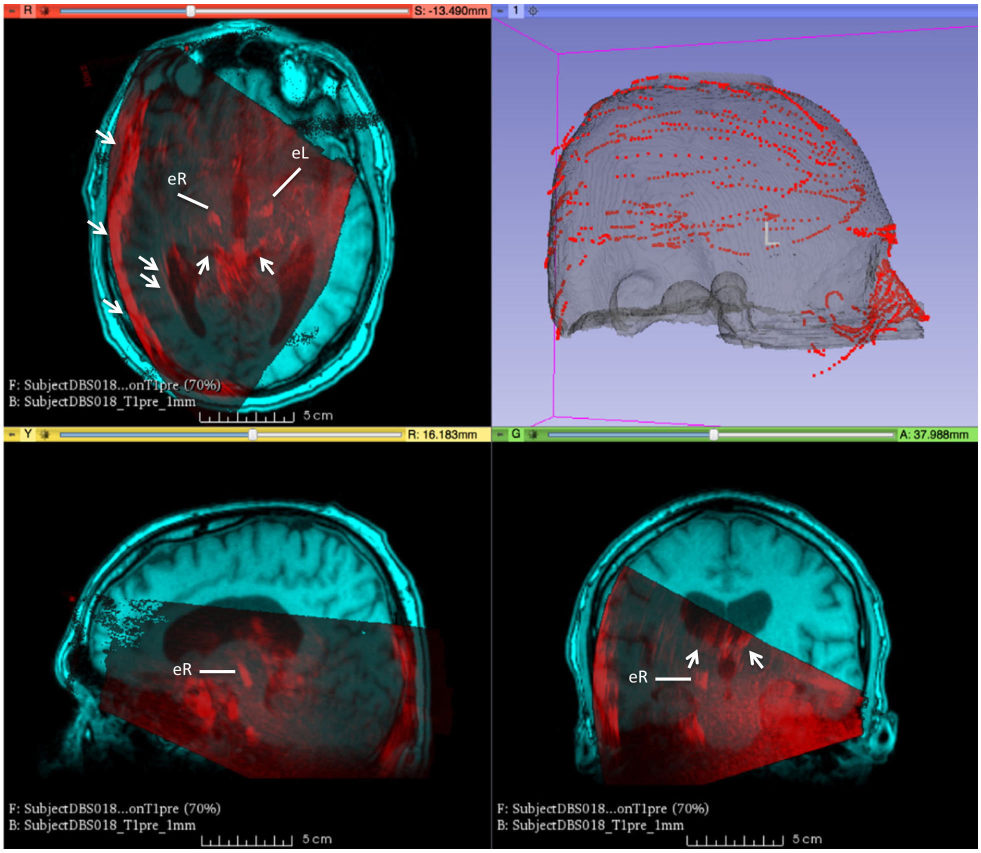

Fig. 2 Exemplary overlap result after ICP-based skin surface registration for subject #8 and least-squares rigid point-pair matching. The 3D view shows the extracted skin surface from MRI (*grey*) and sampled surface points transformed from 3D-TCUS space (*red*). The cable echoes of the right (eR) and left (eL) electrode are *highlighted*. *Arrows point* to 3D-TCUS echo boundaries (*red*) overlapping well with the pre-operative MRI (*cyan*), indicating a satisfactory overlap

MRI registration in a different manner. Our registration is of two steps, namely (1) head surface registration and (2) manual refinement using corresponding landmarks. The following steps were performed using the 3DSlicer[1] software platform [8].

Head surface registration We perform an initial registration between the coordinate system of the tracked US reference target and the MRI pre-operative T1 coordinate system through a registration of point clouds representing the skin surface. In MRI, we extract the skin surface using a foreground segmentation algorithm based on Otsu thresholding implemented in 3DSlicer. In 3D-TCUS space, we use PLUS to sample the skin surface in world coordinates using a calibrated pointing tool, which is traversed lightly across the skin surface. The transformation from 3D-TCUS space into MRI space is first initialised manually using 3DSlicer and then refined using Iterative Closest Point (ICP) registration [4]. An exemplary point cloud can be seen in the top right pane of Fig. 2. The resulting transformation is applied to all reconstructed 3D-TCUS sweeps.

Manual refinement The skin-surface registration already yields a very good overlap with the MRI volume, bringing several anatomical regions into close but not fully satisfactory overlap. Refining this surface-based registration could be achieved, e.g. using an image-based registration. Recently, two promising approaches were proposed [6,9], but could not yet be considered for this work. Also, the low image quality of 3D-TCUS could pose a significant challenge to such image-based registration algorithms. Instead, we performed a registration refinement for this work, based on rigid registration of manually selected point pairs. Identifying unique points in 3D-TCUS systematically is relatively difficult, since not every scan reveals always the same anatomical structures. Therefore, corresponding pairs of salient features of anatomical structures were used, which were identifiable mainly for midbrain and ventricle boundaries in both MRI and 3D-TCUS. The transformation is achieved by computing the optimal registration in a least-squares sense. An overall registration result is shown in Fig. 2. This point-pair

[1] Documentation and download under: http://www.slicer.org.

refinement was performed for each subject and left/right side separately, in order to compensate for slight reference target movement due to head rotation when changing the side.

Electrode tip localisation

The electrode tips in CT and 3D-TCUS were manually identified and marked using 3DSlicer by a single observer. Compared to CT, where identification of electrode tips is straightforward, 3D-TCUS is slightly more challenging. A quick scan through the 3D-TCUS volume in axial direction usually reveals the location of electrodes due to the large echo response. Once the electrode cable and tip were identified, the tip location was marked with the additional help of sagittal and especially coronary cuts through the 3D-TCUS volume. It is important to note that, as depicted in the flowchart Fig. 1, electrode tips in both modalities were identified in a "blinded" manner, i.e. separately and with several days difference between.

Experiments and results

We will first describe the dataset of eight DBS patients that we acquired for this study. Next, we provide qualitative results from our database by showing 3D-TCUS volume cross sections under different bone window conditions, in order to give an impression of the imaging modality. Finally, we report quantitative results on electrode tip localisation under different imaging conditions. Overall, we try to answer the following questions in our experiments:

– Are the electrode cables and tips sufficiently visible in 3D-TCUS?
– With which accuracy can the tips be located, compared to a CT scan registered to the pre-operative MRI?
– How is electrode localisation affected by selection of the scan side and US frequency?

Dataset

We collected data from nine subjects, eight of which could be included in our evaluation. One subject had to be excluded due to insufficient bone window quality, resulting in low visibility of electrode echoes and especially of brain structures necessary for refining US-MRI registration. This is comparable to the general finding that approximately 10 % of subjects cannot undergo transcranial ultrasound examination due to an insufficient bone window [3].

Of the eight included subjects, three had bilateral DBS electrodes implanted into the internal globus pallidus (GPi), two subjects due to treatment of dystonia, and one due to Tourette's syndrome with motoric tics. The remaining five subjects had bilateral DBS electrodes implanted into the subthalamic nucleus (STN) as a treatment for Parkinson's disease (PD). The time since surgery ranged between few days to several months or years, which is interesting regarding the question whether post-operative brain-shift relaxation has an effect on electrode localisation. All subjects except one had previous radiological data in form of a pre-operative planning T1-MRI and T2-MRI and a post-operative CT scan at 1 mm/2 mm/1.25 mm slice spacing, respectively. For subject #1, pre-operative MRI data could only be retrieved at 3 mm slice spacing, which was still sufficient for CT registration and for establishing manual point correspondences between 3D-TCUS and MRI. A summary of patient details is given in Table 1.

Table 1 Subject details for patients included in our database

#	Age	Disease	DBS target	Time since surgery
1	72	Dystonia	GPi L/R	>1 year (2006)
2	58	PD AKR	STN L/R	13 days
3	61	PD AKR	STN L/R	6 days
4	72	Dystonia	GPi L/R	>1 year (2009)
5	38	Tourette	GPi L/R	3 months
6	64	PD Tremor	STN L/R	10 months
7	71	PD AKR	STN L/R	10 months
8	65	PD Tremor	STN L/R	10 months

Qualitative results

We scanned each subject with several 3D sweeps under two different imaging settings, as mentioned at 2.5 and 3.5 MHz, in order to investigate to what degree the electrode localisation accuracy depends on the US machine settings. Here, we present data in form of 3D-TCUS cross sections, in order to give the reader an impression of the image quality we encountered with our set-up.

In Fig. 3, we show a comparison of image qualities of two exemplary scans through the left bone window, at 2.5 (middle row) and 3.5 MHz (bottom row) for subject #4 in our database. We also show corresponding MRI slices to give better anatomic context. The arrows mark electrode wire echoes in axial, sagittal and coronary cross sections. As expected, it can be seen that the base frequency of the US machine has an effect on the resolution of anatomic structures and the electrode wire. Images at 2.5 MHz appear considerably blurrier than at 3.5 MHz, where especially the ipsi-lateral electrode echo appears as a sharp dot with higher contrast compared to 2.5 MHz. On the other hand, and again as expected, it may happen that the contra-lateral electrode appears less distinct or vanishes completely, as in this example. This is due to

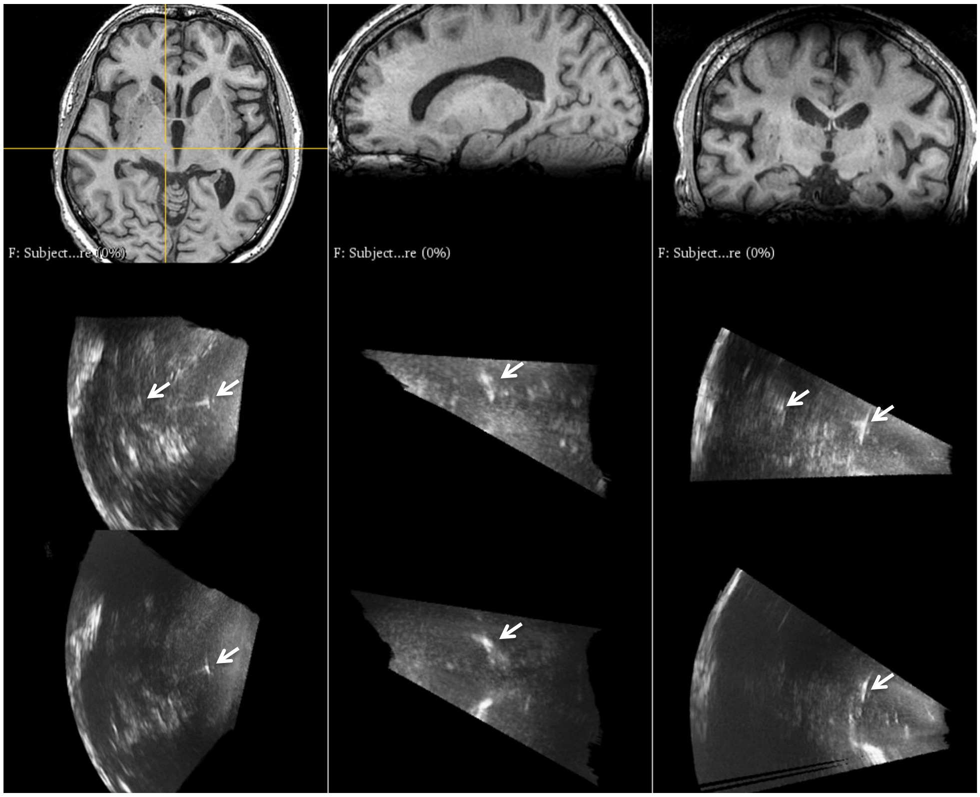

Fig. 3 Qualitative comparison of image quality at 2.5 (*middle row*) and 3.5 MHz (*bottom row*) of subject #4. For better anatomical context, we also provide a corresponding MRI cross section (*top row*). *White arrows* mark electrode wire echoes in axial/sagittal/coronary views (*left*/*middle*/*right column*)

the fact that ultrasound energy absorption increases with frequency, resulting in worsened penetration depth, especially due to scanning through the skull bone. Overall, the anatomic visibility at 3.5 MHz decreases more strongly towards the opposite skull bone, noticeably more than at 2.5 MHz. This is particularly visible in the coronary cross section. Figure 3 also shows a good example of a ring-down artefact at the electrode wire echo (and its 3D reconstruction). This artefact was also reported by Walter in [19].

In Fig. 4, we show different scenarios of visibility of anatomy and electrode echoes under different bone window conditions. All images in this figure pane were scanned at 2.5 MHz. The top row shows an example from the subject that had to be excluded, showing an insufficient bone window quality for electrode localisation. As mentioned, this is a general limitation of TCUS imaging in around 10 % of subjects [3], which also translates to the 3D-TCUS case. The middle row shows a useful bone window quality, with clearly visible anatomic structures, but visible blurring. This can happen due to dephasing and defocussing of the US beam when passing through the bone window, due to the four- time higher speed of sound in bone. Compared to that, different thickness and geometry of the bone window can lead to much sharper resolution of electrode and anatomic structures, as observed in the lower row. Both ipsi- and contra-lateral electrodes are imaged quite sharply in the axial view.

Finally, in Fig. 5, we give a qualitative impression of the registration quality achieved with our two-step approach, for the same subject and cross sections as in the bottom row of Fig. 4. Registration of 3D-TCUS with the pre-operative T1-MRI (top row) and with post-operative CT (bottom row) is shown in form of a two-channel overlay. In the following, we report quantitative results, giving an impression of both registration quality and electrode localisation accuracy.

Quantitative results

In our quantitative evaluation, we first give RMSE errors in Table 2 for point-pair distances after ICP-based skin-surface registration and after rigid point-pair matching, to give a baseline accuracy for US-MRI registration. Overall, the registration accuracy lies on the order of 5.3 mm after ICP-based skin-surface registration and 3.2 mm after point-pair matching. This can be considered as a baseline for the electrode tip localisation accuracy. It is important to note that certain anatomic targets in DBS surgery, such as the STN, have a size on the order of 4 mm. Our RMSE errors lie above that, which

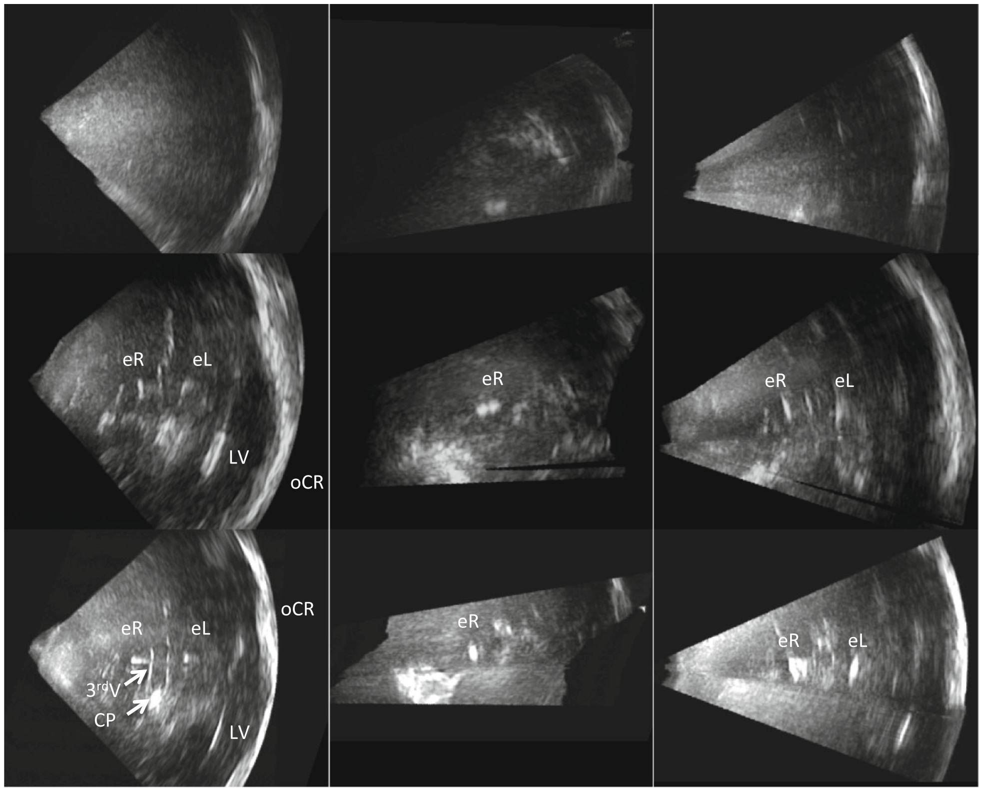

Fig. 4 Qualitative comparison of bone window qualities at 2.5 MHz. *Top row* shows the excluded subject with insufficient bone window quality. *Middle* and *bottom rows* show subjects #3 and #8 with sufficient bone windows, but different focussing quality. Anatomical labels highlight echoes of right electrode (eR), left electrode (eL), lateral ventricles (LV), bone echo at the opposite cranium (oCR), third ventricle (3rd V) and the corpus pineale (CP, pineal gland)

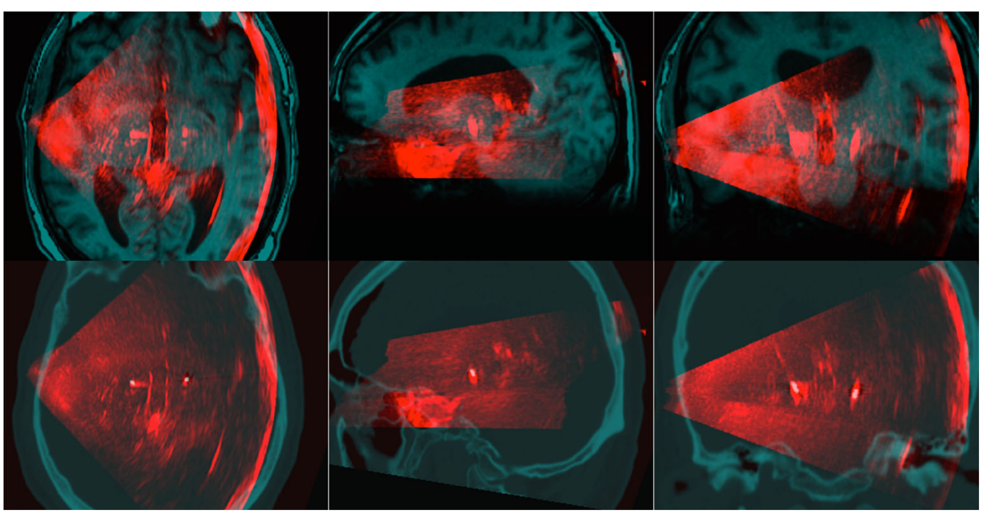

Fig. 5 Qualitative validation of registration quality. Two-channel overlay of pre-op-MRI/post-op-CT (*top/bottom row*) in cyan channel and registered 3D-TCUS in red channel for subject #4, same cross sections as in Fig. 4 *bottom row*. Slices are centred on the left electrode tip marked in CT

would rule out the usability of 3D-TCUS for DBS surgery, however, we will discuss this point in "Discussion" section.

Next, we analyse the electrode tip localisation accuracy and precision (repeatability) in 3D-TCUS in Table 3, which shows electrode tip distance between the tagged L/R electrode tip distance in CT and the tagged L/R tips in multiple 3D-TCUS sweeps. We report Table 3 in a way that allows us to analyse:

1. *Whether there is a systematic error in accuracy between L/R scans:* such an error could emerge from bad 3D Freehand US calibration or from a systematic shift of the reference target at the forehead. With 4.76 mm ipsi-lateral mean distance for scans from the left side and 4.32 mm from the right side, there seems to be no significant systematic error present.
2. *The accuracy and precision of tip localisation for ipsi- and contra-lateral side:* Ipsi-lateral localisation is slightly more accurate (mean all mean 4.76/4.32 mm vs. 4.38/5.96 mm) and slightly more precise (mean all SD 1.81/1.88 mm vs. 0.90/3.12 mm) for the ipsi-lateral side vs. the contra-lateral side.
3. *Whether 3D-TCUS tip localisation accuracy depends significantly on the scan frequency:* We would expect better accuracy at the higher frequency, due to better resolution. However, looking only at L/R ipsi-lateral mean distances at 2.5 MHz (5.54/4.11 mm) and 3.5 MHz (4.43/5.30 mm), there is no clear tendency towards better accuracy at 3.5 MHz.
4. *Whether 3D-TCUS tip visibility depends significantly on the scan frequency:* We would expect a higher percentage of tips visible at 2.5 MHz rather than 3.5 MHz, because 2.5 MHz provides better penetration of the skull and insonification of brain tissue. For the ipsi-lateral electrodes, visibility is always 100 %, irregardless of scan frequency. For the contra-lateral side, L/R percentages of tips visible at 2.5 MHz (87.5/79.1) are slightly higher on average than at 3.5 MHz (56.3/95.9).

In summary, based on our cohort and our system set-up, the numbers suggest that (a) it is not necessary to scan at the higher frequency of 3.5 MHz, because accuracy does not significantly increase, but chances for good visibility of the contra-lateral electrode slightly decrease, and (b) it is recommendable to perform scans from each side to achieve optimal electrode localisation, since ipsi-lateral localisation tends to be more accurate and precise.

Table 2 Point-pair RMSE distances after ICP-based skin- surface registration and after rigid point-pair matching

#	After ICP	After point-pair matching
1	4.68	3.31
2	4.42	3.08
3	3.63	2.44
4	5.33	2.95
5	4.85	3.91
6	5.21	1.51
7	5.89	2.73
8	8.73	5.63
Mean	5.34	3.20
SD	1.43	1.13

Discussion

Several points of discussion can be drawn from the presented qualitative and quantitative results. Most importantly, we have to reconsider the original question in mind, namely whether 3D-TCUS could be a viable intra-operative imaging modality for DBS keyhole neurosurgery.

At first glance, our feasibility study presented here suggests that this is not the case. The target areas in DBS surgery, such as STN, have a size on the order of 4 mm [10]. Our study yields electrode tip localisation errors on the order of 4.8 mm, which is not acceptable for DBS surgery. However, the RMSE distance of anatomical point pairs is still on the order to 3.2 mm on average, despite manual refinement. In

Table 3 Accuracy of electrode tip distances between CT (1 tag) and 3D-TCUS sweeps (4–6 tags) reported as RMSE mean in mm (SD in mm)/percentage of sweeps in which the tip was visible, for each side (ipsi- and contra-lateral)

Side	L		R	
Subject	Ipsi (L)	Contra (R)	Ipsi (R)	Contra (L)
1	7.07 (1.56)/100	3.58 (1.13)/100	6.75 (2.38)/100	12.04 (6.83)/100
2	2.87 (0.85)/100	3.66 (2.06)/100	2.50 (1.52)/100	4.97 (1.77)/50
3	2.78 (0.49)/100	2.55 (0.00)/100	5.78 (2.30)/100	7.21 (3.12)/100
4	3.00 (0.87)/100	1.97 (0.78)/25	3.56 (1.70)/100	3.96 (3.44)/100
5	6.59 (4.19)/100	3.57 (0.50)/50	4.42 (2.19)/100	3.68 (1.59)/100
6	7.49 (3.79)/100	10.85 (0.73)/50	2.00 (1.02)/100	3.61 (2.34)/100
7	3.27 (0.71)/100	4.21 (0.66)/75	4.83 (1.37)/100	6.17 (2.52)/60
8	6.65 (3.44)/100	6.72 (4.59)/100	8.19 (7.72)/100	6.70 (5.40)/100
Mean	4.97 (1.99)/100	4.64 (1.31)/72.5	4.75 (2.53)/100	6.04 (3.38)/88.8
@2.5 MHz	5.54 (1.87)/100	5.06 (1.10)/87.5	4.11 (2.60)/100	7.76 (2.68)/79.1
@2.5 MHz	4.43 (1.40)/100	5.25 (1.94)/56.3	5.30 (2.18)/100	5.11 (1.74)/95.9

The standard deviation (SD) represents precision of tip tagging in 3D-TCUS this study, we could not yet incorporate very recently proposed image-based US-MRI registration methods such as [6,9], which report, e.g. "an accuracy of 2.51 mm, precision of 0.85 mm and capture range of 15 mm" [9]. The capture range makes such methods applicable to our scenario, and we will evaluate their usability in upcoming future work.

TCUS is a difficult imaging modality, even for a human observer. Additionally, in roughly 10 % of subjects, the TCUS technique cannot be used [3]. However, suitable candidates can be very easily identified prior to surgery. During scanning, electrode tip localisation is not easy. Volumetric 3D acquisition facilitates the examination and makes it more objective. Nevertheless, it still requires an experienced sonographer and careful adjustment of the 3D-TCUS transducer positioning on the bone window to achieve optimal visibility of the deep brain areas. Once an optimal bone window has been found, it is necessary to tilt the transducer face carefully to achieve a good sweep, since the US coupling gel makes it easy to slip away from the narrow bone window.

Our numbers, as well as our observations during acquisition of the dataset, suggest that it is probably advisable to scan the left and right side of the brain separately, to achieve optimal visibility of the left/right electrode. This would be compatible with the DBS workflow. Switching the burr-hole involves a repositioning of the stereotactic targeting array to the new coordinates, which should leave enough time for an assistant in the operating room (OR) to reposition the TCUS transducer as well.

It is important to note that we performed our experiments outside of the OR. However, as Walter reports [19], intra-operative TCUS scanning is more challenging due to additional OR instrumentation and time pressure, both obstructing the search for an optimal bone window. Some form of mechanic support, mechanical actuation or maybe even robotic support could help in quickly finding and maintaining an optimal positioning of the transducer on the bone window during surgery. In case of robotic support, performing real-time 3D sweeps in regular intervals to monitor the DBS electrode tip during insertion could be another possibility.

All these ideas rely on a very good registration between 3D-TCUS and MRI. In this work, we used a two-step registration approach that is sufficient to assess the basic feasibility 3D-TCUS, but it has to be improved significantly before final conclusions can be made. As mentioned above, image-based registration would likely yield better results than our surface- and point-pair-based registration methods. Also, due to uncertainty of our point clouds, we chose to only employ a rigid registration model in our experiments. However, due to brain shift, it is very likely that the correct registration model should be a deformable transformation, an issue that we have only touched briefly so far. Several studies suggest that brain shift in DBS surgery usually only occurs in direction of gravitation. Still, authors conclude that, e.g. brain shift of up to 4 mm is comparable to the size of the targets in deep brain stimulation surgery and should not be ignored [10]. In the light of these challenges, the results in our study still render 3D-TCUS as a potential intra-operative imaging technique. Brain shift can also happen post-operatively, which is often referred to as "delayed brain shift" [19]. After surgery, the brain swelling usually retracts, which can cause a slight dislocation of the electrode tip called "electrode migration" [5]. 3D-TCUS could provide a non-invasive and cost-effective tool for monitoring of such dislocations.

Future work therefore should focus on improved imaging quality in TCUS, which would also result in improved 3D-TCUS quality. Improvements could be made by compensating the defocussing and dephasing effects in TCUS, which requires US acquisition manipulation at the hardware level, often referred to as phase aberration correction [13]. Apart from improving the image itself, one aim is to improve US-MRI registration using image-based approaches [6,9], which we will try in upcoming future work. The benefits of 3D-TCUS during intra-operative neurosurgery are significant, creating an interesting motivation for the community to investigate into more advanced acquisition methods such as robot-assisted US imaging during neurosurgery, such as DBS electrode implantation.

Conclusion

In this work, we have investigated the relevance and feasibility of using non-invasive 3D-TCUS for intra-operative imaging during keyhole DBS neurosurgery. We acquired a novel dataset comprising eight subjects with fully registered pre-operative T1-MRI, post-operative CT and post-operative 3D-TCUS image volumes. We gave an impression on image quality of TCUS images and 3D reconstruction, depending on the TCUS base frequency, including certain US image artefacts that can occur, such as ring-down, reverberation or depth-related attenuation. Quantitatively, we reported an average, ipsi-lateral electrode tip localisation accuracy on the order of 4.8 mm (precision 2.3 mm), given the baseline accuracy of our registration method (RMSE 3.2 mm). We relate these results with the workflow of DBS surgery and conclude that 3D-TCUS is not yet ready for intra-operative usage. However, it bears high potential and poses challenging and interesting research problems to the community, which could potentially result in a highly useful technique for deep brain surgery in future.

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

References

1. Avants BB, Tustison NJ, Song G, Cook PA, Klein A, Gee JC (2011) A reproducible evaluation of ANTs similarity metric performance in brain image registration. Neuroimage 54(3):2033–2044
2. Berg D, Behnke S, Seppi K, Godau J, Lerche S, Mahlknecht P, Liepelt-Scarfone I, Pausch C, Schneider N, Gaenslen A, Brockmann K, Srulijes K, Huber H, Wurster I, Stockner H, Kiechl S, Willeit J, Gasperi A, Fassbender K, Gasser T, Poewe W (2013) Enlarged hyperechogenic substantia nigra as a risk marker for Parkinson's disease. Mov Disord 28(2):216–219
3. Berg D, Seppi K, Behnke S, Liepelt I, Schweitzer K, Stockner H, Wollenweber F, Gaenslen A, Mahlknecht P, Spiegel J, Godau J, Huber H, Srulijes K, Kiechl S, Bentele M, Gasperi A, Schubert T, Hiry T, Probst M, Schneider V, Klenk J, Sawires M, Willeit J, Maetzler W, Fassbender K, Gasser T, Poewe W (2011) Enlarged substantia nigra hyperechogenicity and risk for Parkinson disease: a 37-month 3-center study of 1847 older persons. Arch Neurol 68(7):932–937
4. Besl PJ, McKay ND (1992) A method for registration of 3-d shapes. IEEE Trans Pattern Anal Mach Intell 14(2):239–256. doi:10.1109/34.121791
5. Bilger A, Dequidt J, Duriez C, Cotin S (2011) Biomechanical simulation of electrode migration for deep brain stimulation. Med Image Comput Comput Assist Interv (MICCAI) 14(Pt 1):339–346
6. De Nigris D, Collins D, Arbel T (2012) Fast and robust registration based on gradient orientations: case study matching intra-operative ultrasound to pre-operative mri in neurosurgery. In: Abolmaesumi P, Joskowicz L, Navab N, Jannin P (eds) Information processing in computer-assisted interventions. Lecture notes in computer science, vol 7330. Springer, Berlin, pp 125–134. doi:10.1007/978-3-642-30618-1_13
7. D'Haese PF, Pallavaram S, Li R, Remple MS, Kao C, Neimat JS, Konrad PE, Dawant BM (2012) CranialVault and its CRAVE tools: a clinical computer assistance system for deep brain stimulation (DBS) therapy. Med Image Anal 16(3):744–753
8. Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, Fillion-Robin JC, Pujol S, Bauer C, Jennings D, Fennessy F, Sonka M, Buatti J, Aylward S, Miller JV, Pieper S, Kikinis R (2012) 3D slicer as an image computing platform for the quantitative imaging network. Magn Reson Imaging 30(9):1323–1341
9. Fuerst B, Wein W, Muller M, Navab N (2014) Automatic ultrasound-MRI registration for neurosurgery using the 2D and 3D LC(2) metric. Med Image Anal 18(8):1312–1319
10. Khan MF, Mewes K, Gross RE, Skrinjar O (2008) Assessment of brain shift related to deep brain stimulation surgery. Stereotact Funct Neurosurg 86(1):44–53
11. Lasso A, Heffter T, Rankin A, Pinter C, Ungi T, Fichtinger G (2014) PLUS: open-source toolkit for ultrasound-guided intervention systems. IEEE Trans Biomed Eng 61(10):2527–2537
12. Letteboer MM, Willems PW, Viergever MA, Niessen WJ (2005) Brain shift estimation in image-guided neurosurgery using 3-D ultrasound. IEEE Trans Biomed Eng 52(2):268–276
13. Lindsey BD, Nicoletto HA, Bennett ER, Laskowitz DT, Smith SW (2014) 3-D transcranial ultrasound imaging with bilateral phase aberration correction of multiple isoplanatic patches: a pilot human study with microbubble contrast enhancement. Ultrasound Med Biol 40(1):90–101
14. Plate A, Ahmadi SA, Pauly O, Klein T, Navab N, Botzel K (2012) Three-dimensional sonographic examination of the midbrain for computer-aided diagnosis of movement disorders. Ultrasound Med Biol 38(12):2041–2050
15. Starr PA (2002) Placement of deep brain stimulators into the subthalamic nucleus or Globus pallidus internus: technical approach. Stereotact Funct Neurosurg 79(3–4):118–145
16. Unsgaard G, Rygh OM, Selbekk T, Muller TB, Kolstad F, Lindseth F, Hernes TA (2006) Intra-operative 3D ultrasound in neurosurgery. Acta Neurochir (Wien) 148(3):235–253
17. Vlaar AM, de Nijs T, van Kroonenburgh MJ, Mess WH, Winogrodzka A, Tromp SC, Weber WE (2008) The predictive value of transcranial duplex sonography for the clinical diagnosis in undiagnosed parkinsonian syndromes: comparison with SPECT scans. BMC Neurol 8:42
18. Walter U (2010) Transcranial sonography-assisted stereotaxy and follow-up of deep brain implants in patients with movement disorders. Int Rev Neurobiol 90:274–285
19. Walter U (2012) Intra- and post-operative monitoring of deep brain implants using transcranial ultrasound. Perspect Med 1(1–12), 344–348. doi:10.1016/j.permed.2012.02.012. http://www.sciencedirect.com/science/article/pii/S2211968X12000198. New trends in neurosonology and cerebral hemodynamics an update
20. Walter U, Kirsch M, Wittstock M, Muller JU, Benecke R, Wolters A (2011) Transcranial sonographic localization of deep brain stimulation electrodes is safe, reliable and predicts clinical outcome. Ultrasound Med Biol 37(9):1382–1391
21. Walter U, Wolters A, Wittstock M, Benecke R, Schroeder HW, Muller JU (2009) Deep brain stimulation in dystonia: sonographic monitoring of electrode placement into the globus pallidus internus. Mov Disord 24(10):1538–1541