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THE INDIVIDUAL VARIABILITY OF THE DENTATO-RUBRO-THALAMIC TRACT IN THE PLANNING OF STEREOTACTIC OPERATIONS IN PATIENTS WITH TREMOR

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Background. Stereotactic operations on the ventral-intermediate nucleus of the thalamus (Vim) and the posterior subthalamic area (PSA) are used for the surgical treatment of tremor. Since these structures are invisible in standard magnetic resonance imaging (MRI) regimes, indirect stereotactic guidance is mainly used during operations. MRI tractography allows taking into account the individual variability of the target structures for tremor, visualizing the target directly, but this technique has not yet entered the routine practice of preparing operations.
Aim. The aim of the work is to study the variability of the position of the dentato-rubro-thalamic tract (DRT), determined according to MRI tractography data, in relation to the main reference points for indirect stereotactic guidance, as well as to the visible landmarks on MRI in FGATIR mode, to assess the validity of the currently used methods of preparing operations in patients with tremor.
Materials and methods. Probabilistic MRI tractography of DRT based on the HARDY protocol was performed in 34 patients. Additionally, 3D T1 tomograms were obtained with axial slices with an isotropic voxel size equal to 1 mm, as well as FLAIR sagittal slices with a thickness of 1.12 and a pitch of 0.56 mm. Eleven patients additionally underwent a series of MRI sections according to the FGATIR program with a thickness of 1 mm, without an intersectional gap.
Results. A significant variability of the DRT position has been established both in the coordinate system of the anterior and posterior commissures, and in relation to standard targets for indirect stereotactic guidance. In addition, a visible interhemispheric asymmetry of the position of the tracts was revealed. The smallest degree of deviation from the tract was noted for the trajectories of deep brain stimulation electrodes implanted in the caudal zona incerta (cZI) at the level of the maximum diameter of the red nuclei. A high degree of correspondence between the tract and the target zone of prelemniscal radiations (Raprl) was also established on tomograms in the FGATIR mode.
Conclusions. The standard target points for the indirect targeting of Vim targets and the cerebello-thalamic tract in PSA give a deviation of more than 2 mm from DRT in almost half of patients. During the use of cZI as a standard target for indirect guidance in the treatment of tremor, the DRT is located at the zone of stereotactic impact at the level of the 2nd or 3rd contact of the electrode in 76.5 % of cases. FGATIR mode allows visualizing the structure of Raprl, with stereotactic guidance on which the effect on the DRT can be achieved in 86.4 % of cases.

Keywords: stereotactic guidance, surgical treatment of tremor, magnetic resonance tractography, dentato-rubro-thalamic tract, deep brain stimulation, Vim-thalamotomy, cerebellothalamic tractotomy

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BACKGROUND

Stereotactic functional interventions (deep brain stimulation (DBS) and stereotactic destructions) on the ventral intermediate nucleus (Vim) of the thalamus and in the posterior subthalamic area (PSA) are effective treatment methods for tremor [1, 2]. Notably, good results were demonstrated not only in patients with Parkinson's disease and essential tremor, but for other types of tremor (posttraumatic, dystonic, Holmes tremor, in multiple sclerosis, etc.) [3]. However, the target structures are indistinguishable in standard preoperative magnetic resonance imaging (MRI) sequences, and in most cases stereotactic atlases are used for indirect guidance during surgery. As reference points for indirect guidance the anterior and posterior commissures, 3rd ventricle, internal capsule as well as intracerebral structures distinguishable in MRI – red and subthalamic nuclei are used [4, 5].

Due to individual variability of brain structure, indirect stereotactic guidance is always supplemented by intraoperative neurophysiological techniques (microelectrode recording, electrostimulation, test heating or cooling at the target points) with correction of stereotactic instrument position in patient's brain after test actions. Repeat introduction of the instrument into the brain can increase injury rate and risk of complications.

According to current knowledge, pathophysiology of tremor is caused by pathological synchronization of impulses from neurons organized into the cerebello-thalamo-cortical pathway [6]. Stereotactic intervention (destruction or stimulation) in structures participating in the pathway's functioning leads to desynchronization of neural activity and stops tremor. Multiple published articles show the possibility of using preoperative visualization of the dentato-rubro-thalamic tract (DRT) through which pathological activity of the cerebello-thalamo-cortical pathway is realized for direct labeling of the above-noted stereotactic targets (Vim and PSA). This serves as the rationale for using MRI tractography for direct stereotactic guidance to the target structures and increased surgical accuracy with decreased injury rate [4, 5, 7].

Routine use of tractography in planning of stereotactic surgeries is hindered by significant increase in time and complexity of preoperative preparation, high requirements for equipment (MRI machines and working stations for tract calculations) [5, 8], necessity of highly qualified specialists for tract construction, as well as insufficient development of the tractography method for stereotactic guidance. On the other hand, new articles have been published on the possibility of using some programs of structural MRI as alternatives to tractography for direct stereotactic guidance to the target structures for treatment of tremor [5, 9].

Aim of the study is to investigate variability of DRT position using probabilistic MRI tractography data in relation to the main reference points for indirect stereotactic guidance as well as to the structures visible in FGATIR MRI for evaluation of currently used techniques of stereotactic surgeries in patients with tremor.

MATERIALS AND METHODS

Data from 34 patients aged between 43 and 69 years (mean age 59 years), including 19 men and 15 women, were analyzed. All patients underwent MRI during preparation for stereotactic intervention (in 31 patients due to Parkinson's disease, in 3 due to cervical dystonia).

Philips Achieva 3.0T MRI system was used. For tractography, diffusion tensor images per the HARDY protocol were obtained with angular resolution 32, voxel size 1.75 × 1.75 × 1.75 mm, phase coding AP, b-factor 1000 s/mm^2. In planning of diffusion image sections in the axial direction, incline of 20–40° backwards depending on the patient's anatomy was used to exclude the negative effect of artefacts from the nasal airways. to prevent movement artifacts associated with hard to control tremor or dyskinesia in patients, images were obtained with neck immobilization using a plastic Schanz collar. Additionally, T1-weighted anatomical images of the brain in axial sections were obtained with voxel size 1 mm, as well as FLAIR sagittal sections with 1.12 mm thickness and 0.56 mm pitch. Eleven patients also underwent FGATIR MRI to obtain sagittal sections with 1 mm thickness without intersectional gap.

Reconstruction of the tracts was performed using probabilistic tractography as it allows to better reconstruct spatial path of the white matter fibers [5] per the constrained spherical deconvolution (CSD) protocol [10] for fiber orientation distribution (FOD) evaluation. The SSST-CSD (Single-tissue CSD) algorithm was applied. Cloud calculations were performed on the server of the N.P. Bekhtereva Institute of the Human Brain with CPU AMD Ryzen Threadripper 3970 with 32 central processor cores and base frequency 3.7 Hz and software 3D-Slicer 4.10, MRtrix 3, FSL 6.0, ANTS, ITKSNAP 3.6.0 [8]. Typical reconstruction trajectory based on a whole-brain tractogram in accordance with anatomical knowledge of fiber pathways was the following: tracts exit from the contralateral dentate nucleus of the cerebellum, medially pass next to the red nucleus and end near the Vim of the thalamus [11]. Therefore, intersecting DRT was constructed comprising the main (2/3) part of the cerebello-thalamo-cortical pathway fibers in contrast with the non-intersecting DRT traversing from the dentate nucleus of the cerebellum positioned ipsilaterally to the thalamus and comprising 1/3 of the fibers [12].

Hereafter spatial matching of the probabilistic tractography data to the coordinate system of the anterior and posterior commissures of the patient's brain constructed using 3D scanning of T1-weighted images was performed. Analysis of the tract locations in relation to the stereotactic coordinate system and patient's cerebral structures was performed using the Medtronic StealthStation S7 station (USA) and Cranial software where three-plane reconstruction of all images, image alignment in built-in stereotactic planning software and subprogram StealthMerge and measurement of the coordinates in the coordinate system of the anterior and posterior commissures were performed. In total, positions of 68 DRTs were analyzed (in the right and left hemispheres of 34 patients included in the study).

RESULTS

Position of the DRT geometric center ("axis") and its variability relative to the stereotactic targets were evaluated at 3 anatomical levels:

1) "zero" horizontal level of the stereotactic coordinate system at the level of the anterior and posterior commissures where localization of the stereotactic target Vim was performed [1, 3, 5];
2) horizontal level 2 mm lower than the anterior and posterior commissures where stereotactic planning for cerebellothalamic tractotomy in the subthalamic zone was performed [11];
3) horizontal section at the level of maximum red nuclei diameter where stereotactic localization of the caudal

Table 1. *Coordinates of the center of the dentato-rubro-thalamic tract on magnetic resonance imaging slices in the coordinate system of the anterior and posterior commissures, mean ± SD, mm*

Horizontal level	Coordinates of tracts in both hemispheres			Coordinates of the tracts of the right hemisphere			Coordinates of the tracts of the left hemisphere		
	X	Y	Z	X	Y	Z	X	Y	Z
"Zero"	14.1 ± 2.5	–5.6 ± 1.7	0	13.8 ± 2.6	–5.7 ± 1.8	0	14.3 ± 2.4	–5.5 ± 1.4	0
2 mm below the level of commissures	11.2 ± 1.8	–6.7 ± 1.6	–2	10.9 ± 2.1	–6.7 ± 1.6	–2	11.4 ± 1.9	–6.6 ± 1.5	–2
The level of the maximum diameter of the red nuclei	7.8 ± 2.4	–8.1 ± 1.5	–5.0 ± 0.6	8.0 ± 1.3	–7.8 ± 1.6	–5.0 ± 0.6	7.6 ± 3.2	–8.4 ± 1.3	–5.0 ± 0.6

Table 2. *Distances of the dentato-rubro-thalamic (DRT) centers from the wall of 3rd ventricle and the posterior commissure of the brain at the "zero" horizontal level, and also distances of the DRT centers from the 3rd ventricle at a horizontal level 2 mm below the plane of the anterior and posterior commissures, mean ± SD, mm*

Structure	Tracts in both hemispheres	Tracts of the left hemisphere	Tracts of the right hemisphere
Wall of the 3rd ventricle at the "zero" level	10.9 ± 1.9	11.0 ± 2.2	10.8 ± 2.2
Posterior commissure at the "zero" level	7.2 ± 1.6	7.2 ± 1.4	7.1 ± 1.8
Wall of the 3rd ventricle at the level 2 mm below the intercomissural line	9.3 ± 1.5	9.4 ± 1.4	9.1 ± 1.7

zona incerta (cZI), one of the stereotactic targets in PSA surgeries in patients with tremor, was performed [2].

Table 1 shows the results of measurement of the DRT center coordinates at different horizontal levels in the coordinate system of the anterior and posterior commissures.

As evident from the Tables 1, 2, at the "zero" horizontal plane level, mean value of tract coordinates reasonably approximates the Vim coordinate taken from the stereotactic atlas (X = 14, Y = –5.5, Z = 0) (for all 3 coordinates the differences are statistically insignificant, p >0.05). For the position of the "standard" target point per the most common technique of indirect stereotactic localization of the Vim nucleus – 11 mm outside the 3rd ventricle wall and 1/4 of the intercommissure distance (6–7 mm) anteriorly from the posterior commissure – there are no statistically significant differences in relation to the distance from the 3rd ventricle (p = 0.9527). However, there is a small but statistically significant anterior offset of the tract from this point by on average 0.7 mm (p = 0.00132). At the level 2 mm below the anterior and posterior commissure plane, mean values of DRT position were located outward and behind the target point of the cerebellothalamic tract (CTT) recommended for cerebellothalamic tractotomy (8 mm laterally from the 3rd ventricle wall and 5–6 mm behind the middle of the intercommissure distance) [11], and this difference was statistically significant (p <0.0001 for both coordinates).

Additionally, high variability in DRT position was observed. Even in the same patient, position of the tract (compared to the symmetrical point in the opposite hemisphere) differed by 2.3 ± 1.2 mm on average at the level of "zero" horizontal plane, by 2.1 ± 1.1 mm at the level 2 mm below it, and by 1.6 ± 1.1 mm at the level of maximal size of the red nuclei. At the same time, there was no significant difference in the position of the left and right tracts for all coordinates at all levels (p >0.05).

Evaluation of clinical significance of tract variability was performed based on the level of offset of its center from the "standard" target points. Significant for stereotactic surgery was deviation of the tract center by more than 2 mm from the target point as this difference between the target point and real electrode position is considered threshold for deciding on the necessity of correcting electrode position during surgeries for implanting DBS systems [13]. The distance between individual electrodes in the BenGun system for intraoperative microelectrode recording is also 2 mm. Additionally, the resulting error of the majority of stereotactic frames (including instrumental error, tomography error, intraoperative brain shift, etc.) is also within this value [14].

Analysis of individual position of 68 DRTs in patients at the «zero» level showed that in case of Vim guidance using an atlas, only in 28 (41.7 %) cases the tracts were located within 2 mm radius from the target point (Fig. 1, *a*) (target point at the horizontal section is not located at the center of a circle with 2 mm radius but a little behind considering the fact that stereotactic trajectory from the frontal approach has a slope of 55–70° relative to the anterior and posterior commissure plane [15]). Using the recommended "standard" target point Vim calculated in relation to the 3rd ventricle wall and posterior commissure, tracts were located within 2 mm from it in 35 (51.5 %) cases (Fig. 1, *b*).

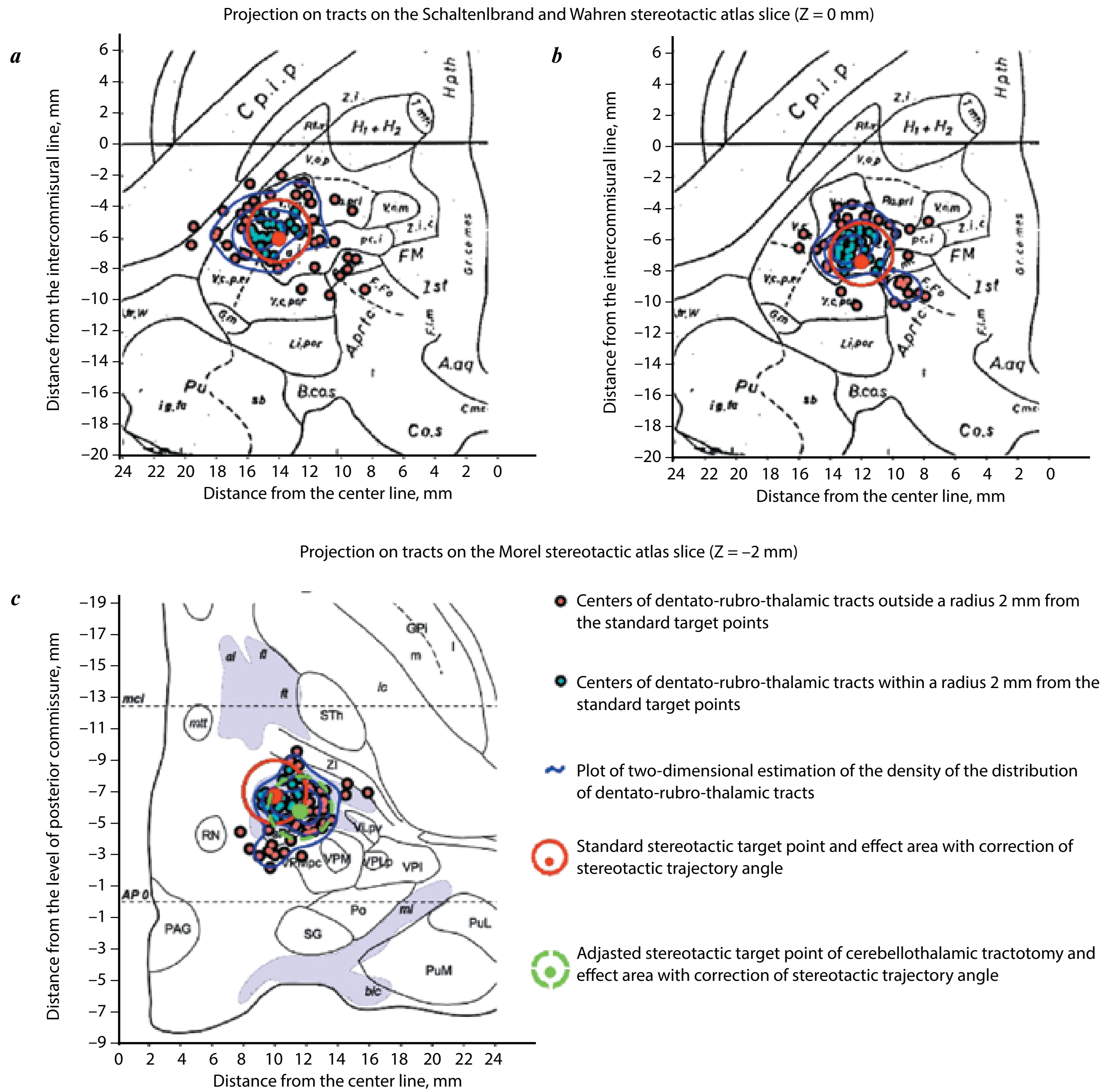

Fig. 1. *Variability of the dentato-rubro-thalamic (DRT) location at the "zero" horizontal level, expressed in stereotactic coordinate system (a) and in relation to stereotactic landmarks – the wall of the 3rd ventricle and the posterior commissure (b). Coordinates of the standard ventral-intermediate nucleus (Vim) target point: X = 14, Y = –5.5, Z = 0 (a); X – 11 mm laterally to the wall of the 3rd ventricle, Y = 1/4 of the distance between the anterior and posterior commissures anteriorly from the posterior commissure, Z = 0 (b). Variability of the location of the DRT on a horizontal level 2 mm below the plane of the anterior and posterior commissures, relative to the wall of the 3rd ventricle and the middle of the intercomissural line (c). Coordinates of the target point of cerebellothalamic tract (CTT) for cerebellothalamic tractotomy according to M.N. Gallay (indicated in red): X – 8 mm laterally to the wall of the 3rd ventricle, Y – 5.5 mm posteriorly from the middle of the intercomissural line, Z = –2. Coordinates of the corrected target point (green): X – 9.3 mm laterally to the wall of the 3rd ventricle, Y – 6.7 mm posteriorly from the middle of the intercomissural line, Z = –2*

At the level 2 mm below the commissures using the "standard" CTT target for cerebellothalamic tractotomy, tract centers were located within 2 mm from the target point in 24 (35.3 %) cases. However, if at this level the "standard" target is moved into the target point located 9.3 mm laterally from the 3rd ventricle wall and 6.7 mm anteriorly from the intercommissure distance (in accordance with the mean DRT coordinates, see Table 1), then the number of tracts located within 2 mm area from the target point increases to 42 (61.8 %) (Fig. 1, *c*).

At level of maximal red nuclei diameter, the distance from the cZI target to the DRT center was 3.7 ± 1.0 mm, and almost in all patients it was outside 2 mm area around the target point. The cZI position on the horizontal MRI section at this level was determined using the Blomstedt method as a point at the border of 1/3 and 2/3 transversal interval connecting the posterior part of the subthalamic nucleus and the external part of the red nucleus at its maximal diameter [2, 16]. Additionally, evaluation of the distance from the tract to the trajectory of DBS electrode introduction into the cZI target modeled taking into account common principles (burr hole within 1.5 cm from the coronal suture, entry point is located on the gyrus ridge, trajectory should not transect the lateral ventricles and cerebral sulci) was performed [2, 7, 15]. It was determined that at the level of "zero" horizontal plane, the distance from the DRT center to the electrode is 2.5 ± 1.4 mm on average, on the level 2 mm below the "zero" horizontal plane it is 1.8 ± 1.1 mm. The minimal distance to DRT for all trajectories at all levels is 1.6 ± 1.0 mm. Among 68 trajectories, only in 18 cases the minimal distance to the tract was above 2 mm, while in 52 (76.5 %) cases it was within this value (Fig. 2) which explains high effectiveness of the target described in literature.

Additionally, in 11 patients who underwent FGATIR MRI, coordinates of the center of the wing-shaped hypointense signal located laterally relative to the upper part of the red nucleus in its middle zone were determined. According to some authors [9, 17], this area corresponds to prelemniscal radiations (Raprl) in the PSA structure, including DRT fibers, and is also a stereotactic target in surgical treatment of tremor [18]. Coordinates of the DRT center at the level corresponding to the level of the center of hypointense signal zone (between 0 and 2.8 mm below the plane of the anterior and posterior commissures) were also determined. Difference between these points in patients was statistically insignificant ($p > 0.05$ for all coordinates) and insignificant in value (1.3 ± 1.1 mm). Nineteen (86.4 %) of 22 tracts of the right and left hemispheres in this patient group were located within 2 mm from the center of the hypointense zone (Fig. 3). Blend–Altman plots and standard deviations for the targets are presented in Fig. 4.

DISCUSSION

Among all stereotactic targets, structures of the thalamus and subthalamic zone are practically the only targets which are hard to visualize using MRI and are subject to indirect stereotactic guidance. However, there are quite a lot of studies searching for MRI programs allowing to locate these targets directly. In contrast to T1- and T2-weighted images, the use of sequences weighted by proton density allows to accurately locate the lateral border of the thalamus (including Vim nuclei) and prevent unwanted introduction of an instrument into the internal capsule. However, the

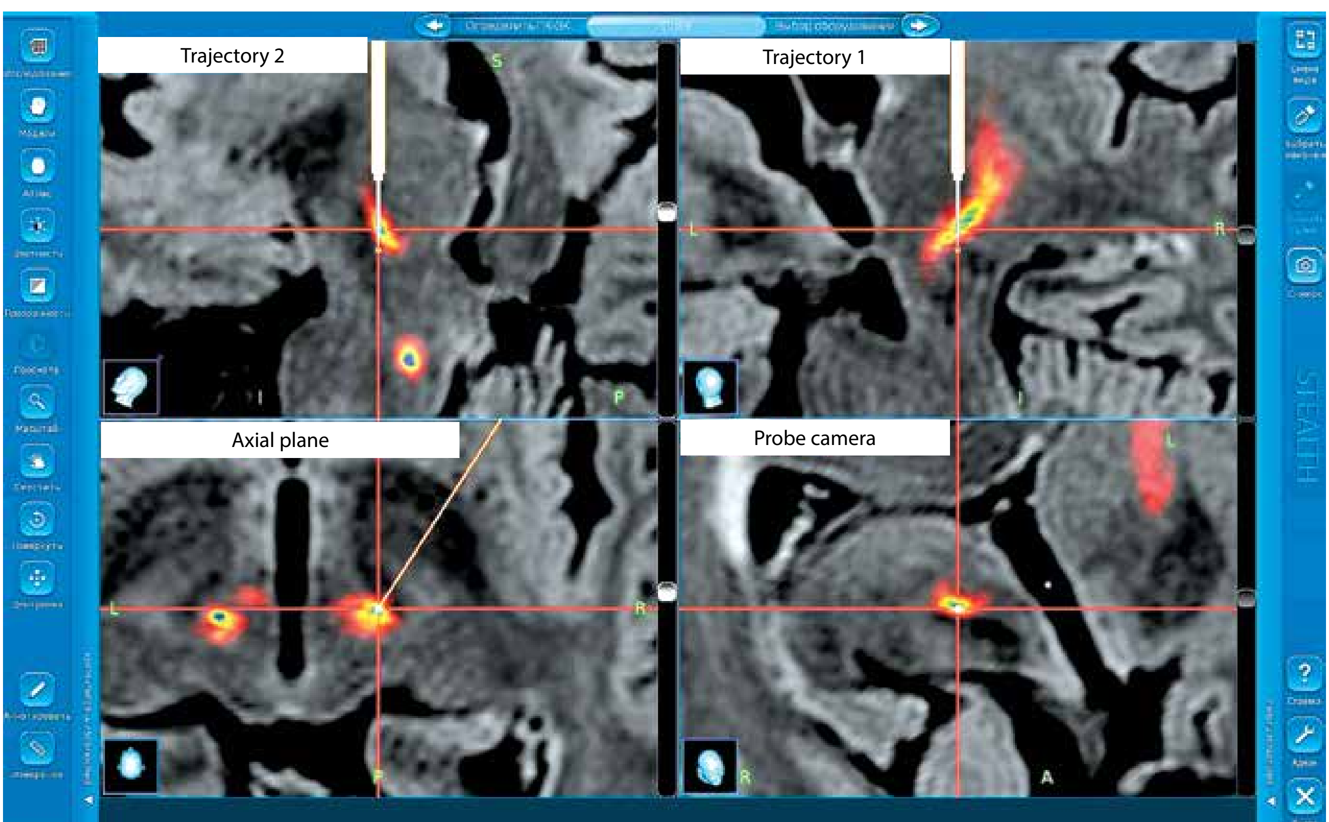

Fig. 2. *FLAIR magnetic resonance imaging with the superposition of the probabilistic magnetic resonance tractography of dentato-rubro-thalamic tract (DRT). Screenshot from the Medtronic StealthStation S7 navigation station. Simulation of the trajectory of the deep brain stimulation electrode inserted into the caudal zona incerta (cZI) target point. At a distance of 2–5 mm from the target point, the electrode is closely attached to the DRT in most patients*

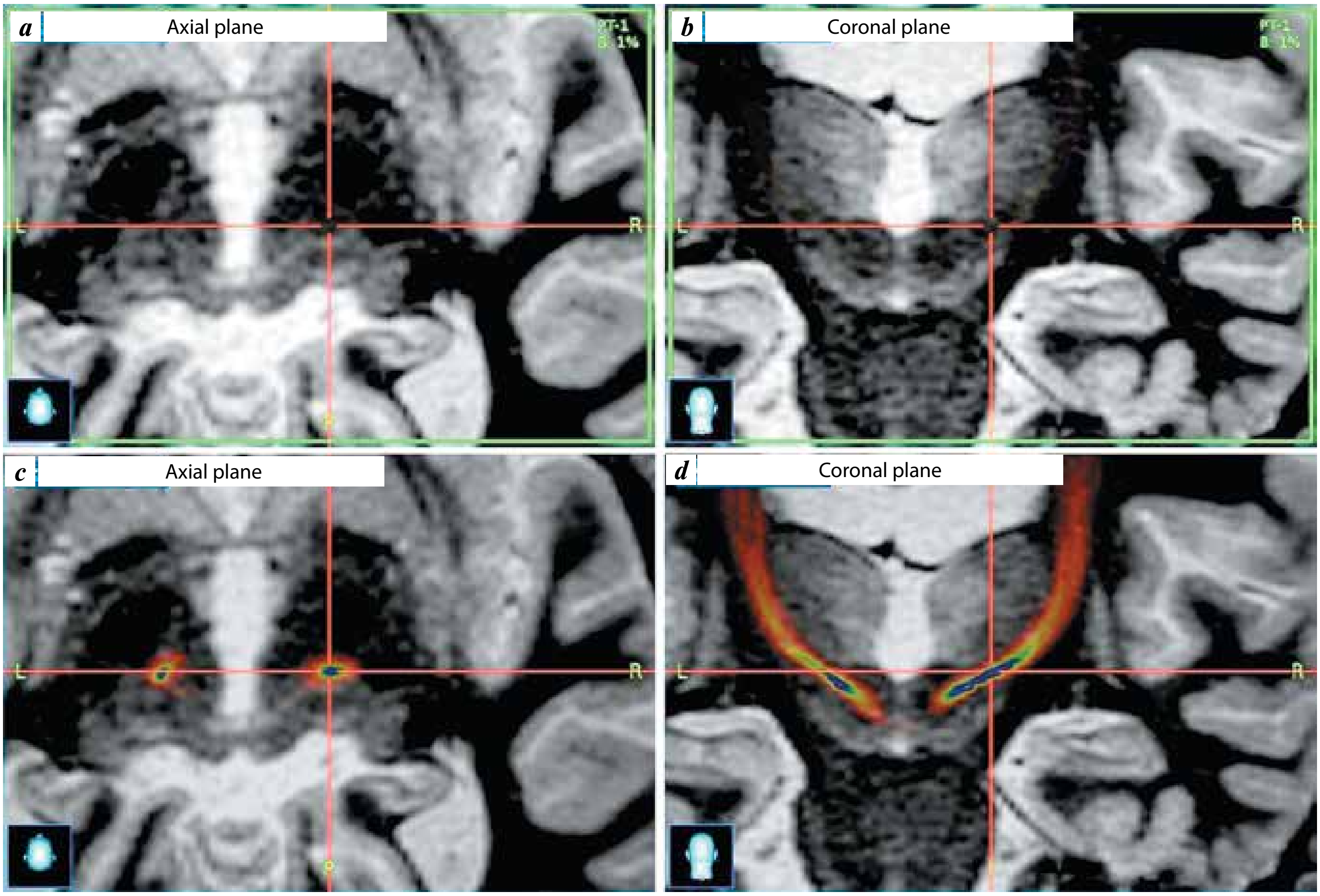

Fig. 3. *Magnetic resonance imaging (MRI) of the brain in FGATIR mode, the window of the Cranial Medtronic StealthStation S7 program: structural MRI (a, b) and the superimposition of dentato-rubro-thalamic tract (DRT) MRI tractography on structural MRI (c, d); MRI reconstruction in the axial plane (a, c) and in the coronal (b, d). The hypointensive zone laterally to the upper parts of the red nucleus corresponds to the passage of the DRT. The crosshair corresponds to the center of the hypointensive zone*

borders between thalamic nuclei are not visible in tomography images despite histological examinations confirming morphological differences between them [19]. Supposedly, in contrast to, for example, the globus pallidus, individual thalamic nuclei are not separated by white matter plates [9]. Other sequences (SWI, STIR, T2-weighted images using high-field MRI, etc. [5, 9]) were also proposed, but they did not achieve widespread use. Presumably, these techniques are too complicated and there is insufficient number of studies proving their clinical advantage compared to standard technique of indirect Vim localization [5].

Due to studies demonstrating the role of cerebello-thalamo-cortical pathway in pathophysiology of tremor, currently the main concept states that the effect of stereotactic treatment of tremor is achieved through direct interaction with the DRT at the Vim or PSA level [5, 6, 20]. Therefore, visualization of this tract should underlie stereotactic guidance to the target in patients with tremor. In recent years, the role of MRI tractography in surgery preparation in this patient group is being actively investigated [4–8, 15, 20–25]. Many articles consider deterministic and probabilistic tractography. Some authors claim that probabilistic tractography is more accurate compared to deterministic as the latter considers only one direction of diffusion for every voxel which can lead to errors during reconstruction of intersecting, branching or neighboring tracts [5, 13]. At the same time, probabilistic tractography based on more complex algorithms requires long calculations (12–32 h compared to 11–18 min for deterministic tractography) and is more sensitive to motion artifacts [5, 13]. We used additional immobilization and calculations based on cloud technologies which allowed to perform quicker and more accurate reconstruction of tract pathways.

Previously it was shown that the effect of DBS on tremor directly depends on the distance between the active contact of the electrode and DTR [5, 7, 21]. However, techniques of stereotactic planning using tractography did not enter wide practice due to the above-mentioned reasons. Therefore, the problem of tract variability in relation to commonly used stereotactic targets is important. In this study, we did not investigate the effectiveness of DRT surgery; we only aimed to evaluate the significance of its individual variability. Only some articles state the stable position of DRT relative to the Vim standard target point [20, 22]. The majority of authors point to wide variability of tracts relative to both the target taken from the atlas and standard

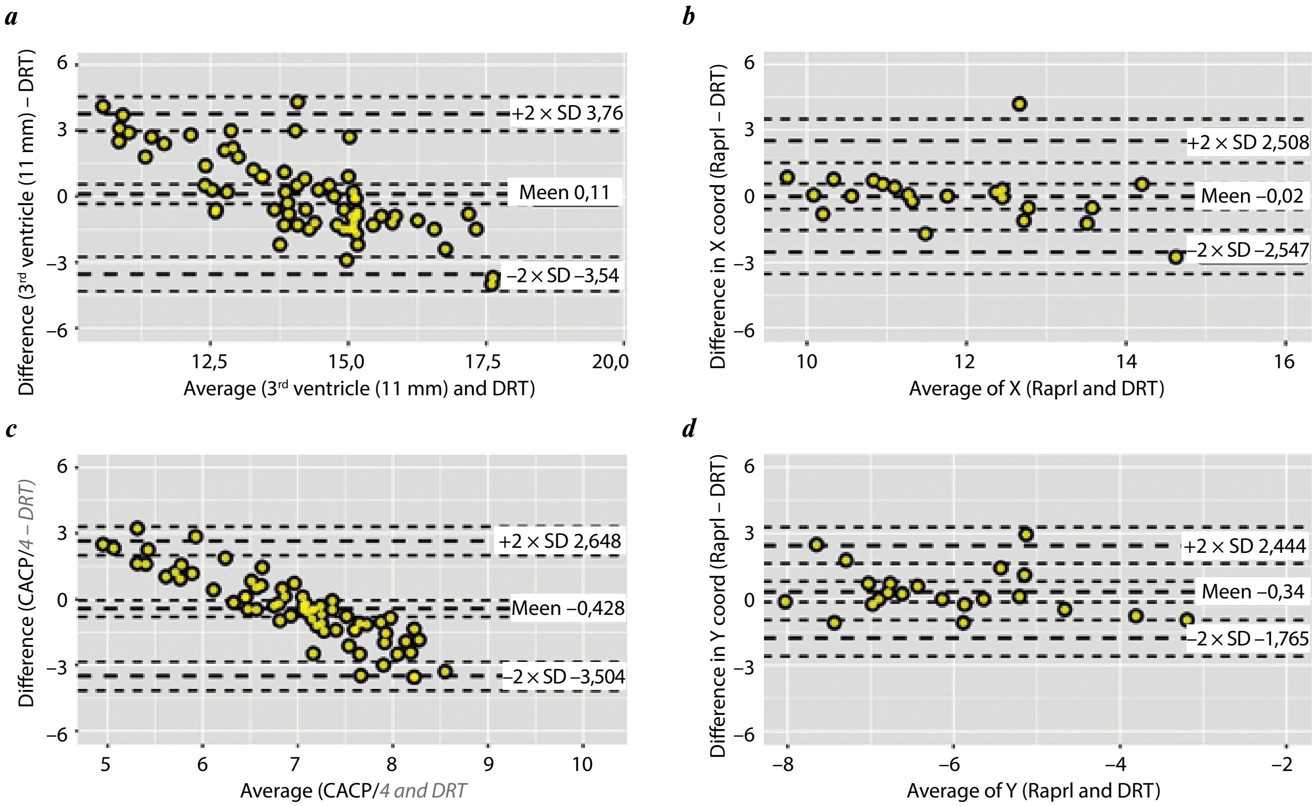

Fig. 4. *Blend–Altman plots: comparison of the position of the stereotactic coordinates of the dentato-rubro-thalamic tract (DRT) with the most commonly used target for indirect localization ventral intermediate nucleus (Vim) (11 mm lateral to 3rd ventricle, 1/4 of the distance between anterior and posterior commissure anterior to the posterior one) (a, b), and the target point calculated from the center of maximum hypointensity signal in the subthalamic region (Raprl) on FGATIR magnetic resonance images (c, d). The variability indices for the target point Raprl are significantly lower*

target point calculated relative to the 3rd ventricle and posterior commissure. The reason for this, for example, can be more lateral location of the thalamic structures in cases of 3rd ventricle expansion. However, this is not observed in atrophy of the thalamus when ventricular expansion happens *"ex vacuo"*. Additionally, in increased distance between the anterior and posterior commissure, the border between the ventral caudal thalamic nucleus and Vim can move posteriorly and not anteriorly [15]. F. Ferreira et al. note the interhemispheric asymmetry of the tracts, and in the left hemisphere the tracts are reliably located posteriorly and laterally reflecting function asymmetry of the hemispheres in healthy individuals [13]. In our study we also observed asymmetry of the tracts in all patients, but displacement vector was not unidirectional. Supposedly, F. Ferreira et al. studied healthy subjects while in our study we used images from patients with neurodegenerative diseases which better reflects experience of preparation for stereotactic surgeries.

Results of our study, as well as others, show high variability of DRT position in relation to the standard targets of preparation for stereotactic surgeries in patients with tremor. Considering that the possibility of using MRI tractography (especially probabilistic) in preparation for stereotactic surgeries remains debatable, the search for new MRI programs for direct target visualization is very important. In this context, FGATIR mode might be promising as it allows to visualize the Raprl structure, one of the links in the cerebello-thalamo-cortical pathway through which pathological tremor system is realized and which is also used for treatment of tremor by some authors along with the Vim and cZI targets [18, 25]. Apart from DRT, Raprl also includes fibers connecting the orbitofrontal cortex, mesencephalon, globus pallidus, subthalamic nucleus, brainstem structures, and reticular formation [18, 24].

Hypointense MRI signal in the Raprl zone in the posterior subthalamic area laterally from the red nucleus can be caused by merging of intersecting and non-intersecting DRTs which leads to local increase of myelinization in this zone [24]. Our study confirms the high degree of correspondence between this directly visualized in MRI structure and presence of DRT on this level. Therefore, this MRI sequence can be useful in planning stereotactic surgeries to treat tremor. However, further research evaluating the clinical effect of interventions based on this technique of stereotactic guidance is needed.

CONCLUSIONS

Probabilistic MRI tractography data show that the use of standard techniques of indirect stereotactic guidance to the Vim and CTT structures during DRT surgeries can be achieved in no more than 61.8 % of cases.

Among the techniques of indirect stereotactic guidance in patients with tremor, the highest DRT involvement can be achieved using the Blomstedt technique with introduction of DBS electrodes in the caudal zona incerta. If the electrode is introduced into the standard cZI target point, DRT will be located in the intervention zone proximally at a distance of 2–5 mm (which corresponds to the 2nd or 3rd electrode contact) in 76.5 % of cases.

FGATIR MRI allows to visualize the Raprl structure located in the posterior subthalamic area at the depth between 0 and 2.8 mm below the intercommissure plane. Stereotactic guidance to this target allows to manipulate DRT in 86.4 % of cases. Further research on the role of this MRI sequence in preparation of stereotactic surgeries in patients with tremor is needed.

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A.I. Kholyavin: development of the research concept, writing the text of the article;
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