

## Transcranial echoscopy for diagnostic of Parkinson disease: technical constraints and possibilities

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### Abstract

Parkinson disease (PD) is one of the most common neurodegenerative disorders. The aim of this study is to review the main problems of transcranial echoscopy (TCE) by the pilot clinical investigations and to analyze opportunities and possible technical solutions for improvement of diagnostic of Parkinson disease using ultrasound applications. TCE is subjective enough yet, and strongly dependent on experience of physician.

The suggestions for standardization of TCE are presented in this paper. The influence of temporal bone should be taken into account, because defocusing effects of the skull bone drastically decrease the quality of obtained brain images and these distortions are dependent on individual features of a subject.

**Keywords:** transcranial echoscopy, phased array transducer, hyperechogenicity, frequency range, acoustic window, amplitude aberration, phase aberration, dynamic focusing, defocusing effect.

### Introduction

Nowadays Parkinson disease (PD) is one of the most common neurodegenerative disorders. The Parkinson's disease incidence rate is 4.5–19 per 100 000 population per year making 0.3 – 1.311 million cases per year worldwide [3]. This neurodegenerative disorder affects body movements and is defined by symptoms such as muscle rigidity, resting tremors, loss of facial expression. Decreased level of neurotransmitter dopamine in the brain is the main physiological reason of PD.

Diagnosis of PD is typically based on clinical criteria: medical history and neurological examination of a patient. However sometimes it is difficult to differentiate PD from other neurological conditions, especially in early stages of disease. Single photon emission tomography (SPECT) and positron emission tomography (PET) are used for diagnosis of PD, but these techniques are inefficient due to costs and radiation to a patient, furthermore the results of nuclear tomographic imaging are insufficient for diagnosis of PD. Both methods are still used as investigational tools but not for the routine diagnosis of PD. Computer tomography (CT) is not suitable for such neurological applications, because CT is inefficient tool for visualization of soft tissue. Midbrain could be visualized by magnetic resonance imaging (MRI), but view of inner structures of midbrain, which indicates PD, can not be achieved.

Transcranial B - mode echoscopy (TCE) was proposed as a diagnostic technique for supporting the clinical diagnosis of PD in 1995 [1]. The confirmation of PD diagnosis is based on finding hyperechogenicity in the area of midbrain (Fig. 2) called mesencephalic substantia nigra (SN). Neurotransmitter dopamine is produced in this region. This abnormality and PD relation was confirmed

and described by Becker et al [1]. Later investigations showed that hyperechogenicity may be related to iron metabolic changes. Animal studies in rats revealed a dose dependent increase of the echogenicity after intracerebral injection of iron and iron-releasing substances [2]. The transcranial echoscopy is harmless to apply and quick to do, furthermore early stage of PD can be diagnosed using TCE. That is especially important, because clinical symptoms do not occur until substantial parts of the substantia nigra neurons in the brainstem have been irreparably damaged [1]. The treatment can be applied for suspension of loss of dopaminergic neurons, if PD is diagnosed in an early stage. The main disadvantage of TCE is a poor image quality and this makes the PD diagnostic more subjective. Only experienced physician can identify brain structures, which are region of interest in the ultrasound images. The quality of images is poor because the brain is enclosed by skull bone and ultrasound waves have difficulties penetrating through the bone, because of attenuation.

### TCE scanning method

Scanning generally is performed using phased array ultrasound transducers, in the frequency range (2 – 5)MHz. The relatively thin preauricular temporal bone is conventionally used as an acoustic window for brain ultrasound applications [4]. The physician presses an ultrasound probe to the temporal bone of a patient which lies in supine position. Usually midbrain can be detected when the axial scanning plane is parallel to orbito - metal (marked as letter A in Fig. 1.) line of a skull. When the transducer is correctly positioned butterfly - shaped midbrain structure can be seen in a registered B - scan image. Echogenic areas of midbrain SN and red nuclei (Fig. 2.) should be identified in properly obtained images.

Initial assessment of neurological condition of a patient is performed estimating the size of SN area, manually marked by an expert.

Previous investigators [1, 2, 6] recommended to interpret larger than  $0.25 \text{ cm}^2$  SN area as hyperechogenic. Size of the SN area is evaluated in both sides of midbrain, performing scanning via both opposite - located preauricular temporal bones respectively. Other brain structures can be assessed tilting the transducer  $15 - 20^\circ$  upwards (marked as letter B and C in Fig. 1.) [1]. Images obtained in these scanning planes are useful for differentiation of neurological diseases.

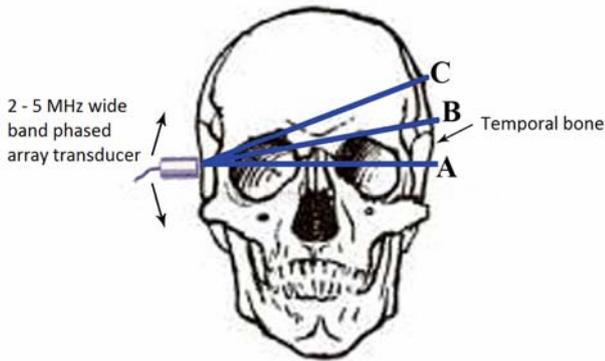


Fig. 1. TSC scanning scheme

Pilot clinical examinations were made applying scanning method described in previous section. TCE ultrasound images of few healthy subjects and affected of PD were obtained and compared by an expert at Neurology clinic at Lithuanian University of Health Sciences.

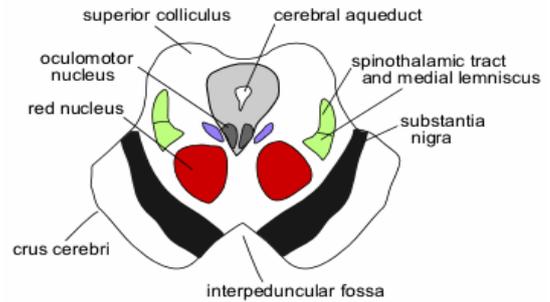


Fig. 2. Anatomy of cross-section of midbrain [5]

The aim of study was to take a look at a specificity of such scanning procedure and to ascertain that TCE is effective method for PD diagnostic. Scanning was performed using PA2-5 wide band phased array transducer ( $f_0=3.5 \text{ MHz}$ , band with:  $1.3 - 4 \text{ MHz}$ , footprint  $20 \times 14 \text{ mm}$  (128 elements)) driven by the ultrasound scanner Voluson730 (General Electric Medical Systems).

**Pilot clinical investigations**

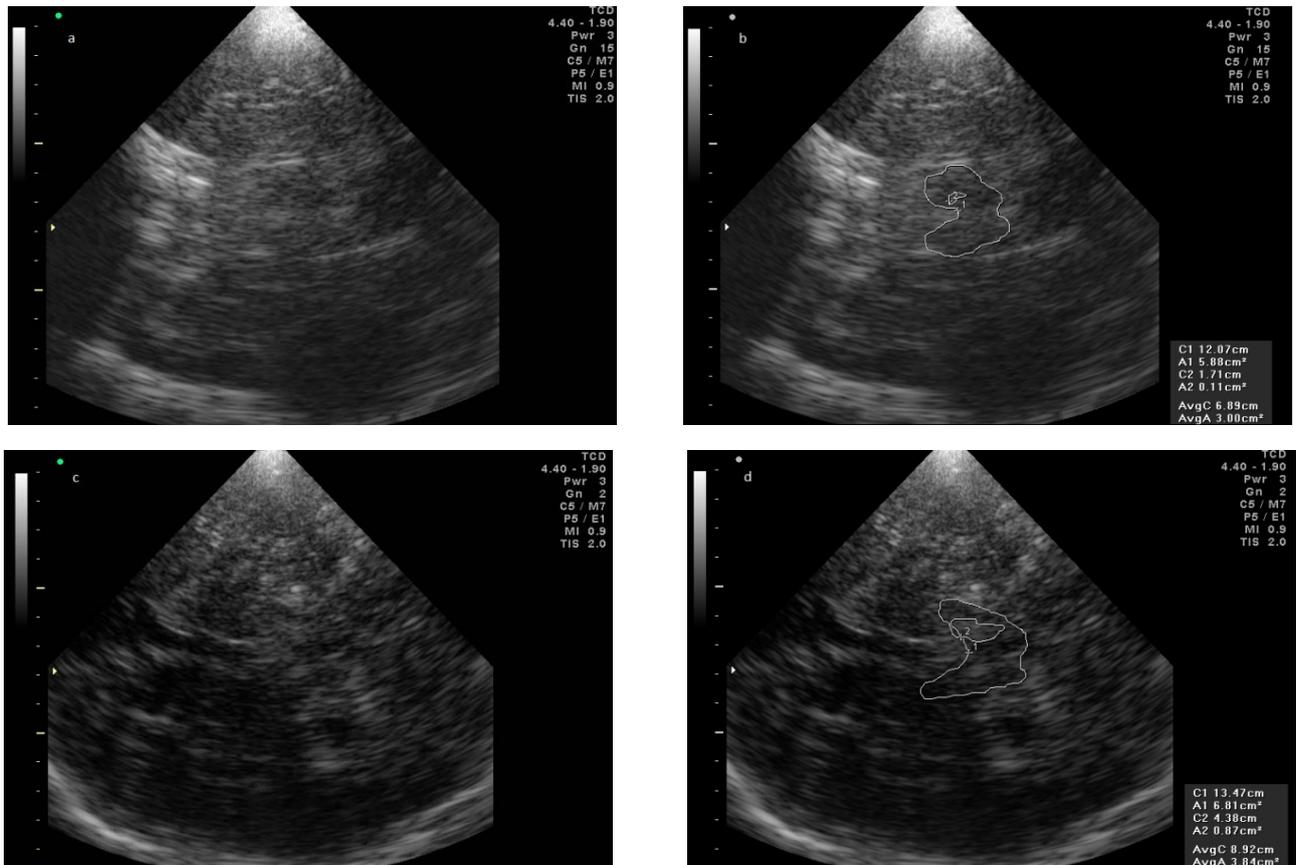


Fig. 3. TCE images: healthy subject (a); same image (a) with expert marked butterfly shaped midbrain cross-section and SN area (size of marked SN area  $0.11 \text{ cm}^2$ ) (b); PD affected subject (c); same image (c) with expert marked butterfly shaped midbrain cross-section and SN area (size of marked SN area  $0.87 \text{ cm}^2$ )

The examination showed that the sizes of specialist marked echogenic SN areas for PD affected subjects were significantly larger. The size of the SN area for healthy subjects was  $<0.15 \text{ cm}^2$ , while PD affected  $>0.43 \text{ cm}^2$ . Few of obtained images are shown in Fig. 3. The size of the SN area of PD affected patient is about 8 times larger than a healthy subject in this case. This shows that TCE could be useful tool for PD diagnostic. However there are a lot of shortcomings, which make TCE examination subjective and related on the experience of physician, who performs TCE scanning and analyzes obtained images. The main challenges for a physician are detection of midbrain (correct placement of ultrasound probe) and identification of brain structures in low resolution images.

### Technical constraints

Regarding performed examination and earlier studies [1, 2, 6], a poor quality of TCE images should be noticed. Only experienced physician can identify brain structures and interpret them correctly in obtained images. Axial resolution of TCE images is limited because scanning is performed in a relatively low frequency range (1 – 4 MHz) of ultrasound waves, but otherwise ultrasound could not penetrate through bone. Even lower frequency range ultrasound waves are affected by defocusing effects of the skull bone: absorption, diffusion and refraction of ultrasounds [7]. Several studies [7, 12, 13] were performed for evaluation of inhomogeneous aberration effects of the skull bone. Few adaptive focusing methods were developed for correction of phase and amplitude aberration of the wave front: time reversal, dynamic focusing, and the spatio-temporal inverse filter, but those techniques require the presence of active sources in the focal plane and thus cannot be used directly for medical imaging [7]. There is no commercial ultrasonic scanner oriented to transcranial applications so far, usually an ultrasound transducer appropriate for abdominal, cardiologic applications is also used for neurological examination.

Other problem of TCE is limitation because of acoustic window. Up to 20% of population have inappropriate acoustic window for transcranial ultrasound applications. Ultrasound waves cannot penetrate through the temporal bone sufficiently enough for analysis of brain structures. Investigation performed by scientists of University of California [11] proved that the thickness of the temporal bone as measured on the bone window of the CT scan is directly related to the quality of the temporal acoustic window. Transmission of the ultrasound beam through the cranium may depend on the structure of the skull as well as the thickness. In homogenous matrix structure of the middle layer of a bone must have higher chance of attenuation and scattering of the ultrasound than a homogenous structure [10]. Earlier studies [10, 11] showed that osteoporosis is one of the important causes affecting the changes of features of temporal bone. The bone mineral density is reduced then, and increment of inhomogeneity causes a higher risk of ultrasound scattering during penetration through the bone. So, acoustic window failure is most common in women and in

the aged population, because these groups are the mostly affected by osteoporosis.

### Possibilities for improvement of diagnostic

Previous studies showed a lot of technical limitations and possibilities for improvement diagnostic of PD using TCE, but sadly diagnostic of PD is still very subjective and competence - dependent. Our investigations will be performed using a conventional ultrasound scanner so there is no possibility to apply adaptive focusing methods. Defocusing effects of the skull bone can be reduced choosing optimal transducer scanning position, and defining patient - dependent scanning mode parameters.

It takes time and requires skills to place an ultrasound probe on the appropriate acoustic window for transcranial examination. Optimizing the probe position results in improved image sensitivity and limited aberration [4]. Influence of defocusing effects depends on the structure and thickness of the temporal bone. Features of skull bone could be estimated using the same transducer as in TCE examination, but a coupling layer (as an example: balloon filled by ultrasound transmission gel) must be used, because the temporal bone is in the transducer dead zone during conventional examination. Therefore evaluation of individual patient acoustic window features could be useful for finding of the optimal transducer position and determination of patient - dependent scanning mode parameters. TCE examination is not standardized yet and relationship between features of acoustic window and scanning parameters still undefined.

There were few attempts [8, 9] to apply automatic or semi-automatic image processing methods for segmentation of midbrain and SN area. These methods gave poor results, because of a low resolution of TCE images. Ultrasound images are the most complicated with regards to image processing, because generally clear boundaries of an object cannot be distinguished in such type images. The best segmentation results could be achieved using shape - based methods (ex.: atlas segmentation), because frequently we have a prior information about anatomic shape (in this case butterfly - shape) of an object. Qualitative segmentation of TCE images could give opportunity to perform 3D freehand ultrasound scanning. 3D image could be reconstructed from series of B - scans recording position and orientation of transducer, while the transducer is manipulated over the acoustic window (temporal bone).

It should be noticed that clinical interpretation of TCE images is ambiguous. Measurements of the size of SN area are performed ignoring the fact that area is obtained from a single scanning plane. So it is difficult to say which part of midbrain is visible in the cross - section. One of the possible options is to measure size of the SN area relatively to the size of the whole midbrain. Another option is to determine the size and the shape of a midbrain with respect to temporal window position. This could be done by the magnetic resonance imaging: finding the position of the medial cross - section of a midbrain in MRI scans, or analyzing by MRI the obtained three - dimensional view of a brain.

## Discussion

Transcranial echoscopy may become a powerful tool for diagnostic of neurological disorders. Early stages of PD can be diagnosed using TCE. Unfortunately this examination is subjective enough yet. The experienced physician is necessary for examination of a patient and analysis of obtained poor resolution ultrasound images.

Standardization of examination should be done in order to improve the quality of diagnostic. Firstly the influence of temporal bone should be taken into account, because defocusing effects of the skull bone drastically decrease the quality of obtained brain image and these distortions are dependent on individual features of a subject. Enhancement of the quality should be a direction to automatic analysis of brain structures in TCE images. That could give an opportunity to perform 3D freehand ultrasonic scanning of a brain.

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## Transkranijinė echoskopija Parkinsono ligos diagnostikai atlikti: techninės problemos ir galimybės

### Reziumė

Darbo tikslas – apžvelgti pagrindines transkranijinės smegenų struktūros echoskopijos problemas ir išnagrinėti technologinius sprendinius, kurie leistų pagerinti Parkinsono ligos diagnostikos patikimumą. Straipsnyje analizuojami techniniai transkranijinės echoskopijos ribojimai, atsirandantys dėl tyrimo per kaukolės kaulus specifikos, – ribota skiriamoji geba, skenuoti tinkamo lango savybės ir kt.

Pateikiami siūlymai dėl tyrimų standartizavimo, ultragarsinio keitiklio pozicionavimo, optimalių skenavimo režimo parametrų nustatymo atsižvelgiant į temporalinio kaulo storį. Aptariamos galimybės pagerinti diagnostikos kokybę taikant pažangius vaizdų apdorojimo metodus.

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