Transcranial sonography as early indicator for genetic Parkinson's disease

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Abstract— **Early diagnosis of Parkinson's disease (PD) is of immense importance, since clinical symptoms do not occur until substantial parts of the brain stem have been irreparably damaged. Recent work suggests that by means of transcranial sonography (TCS) it is possible to determine the formation of monogenic forms of parkinsonism at a very early state. In TCS images, the mesencephalon shows a distinct hyperechogenic pattern in about 90% of patients with PD, despite its normal appearance on CT and MRI scans. At present, this pattern is manually segmented and the region size is used as an early PD indicator. In order to remove investigator dependence inherent to manual segmentation, we develop and validate semi-automatic features to serve as risk factors for PD manifestation. We show in a clinical study that some of the features correlate significantly with the presence of specific genetic mutations causing PD.**

Keywords— **Early Diagnosis, Investigator Independence, Parkinson's Disease, Substantia Nigra, Transcranial Sonography.**

I. Introduction

Early diagnosis of Parkinson's disease (PD) is of immense importance, since clinical symptoms do not occur until substantial parts of the substantia nigra (SN) neurons in the brain stem have been irreparably damaged. Furthermore, large parts of the population are affected by this disease [1] and although PD is currently regarded as incurable, the symptoms can be alleviated by the administration of drugs. Neuroprotective drugs could shelter neurons of the SN when used at the beginning of the disease in the preclinical state [2]. Therefore a technology to detect early SN damage is needed for the identification of individuals at risk for PD.

For some forms of parkinsonism such an early indicator exists in the form of specific genetic mutations that are likely to lead to a clinical manifestation [3]. These mutations can be detected by genetic tests. However, such tests are time-consuming and expensive and the part of the population showing this genetic characteristic is comparably small. Hence, genetic tests are not well-suited to serve as a screening procedure. A faster and less expensive method for identifying individuals without genetic mutations could help, since then only doubtful results would have to be tested genetically.

Recent work suggests that by means of transcranial sonography (TCS) it is possible to determine the formation of idiopathic PD as well as monogenic forms of parkinsonism at a very early state [4, 5]. In ultrasound (US) images of the mesencephalon, the substantia nigra shows a distinct hyperechogenic pattern on TCS in about 90% of patients with PD, despite its normal appearance on CT and MRI scans [6, 7]. This SN hyperechogenicity is associated with a significant reduction of 18-Fluorodopa (FDOPA) uptake in the striatum measured with positron emission tomography (PET) [8]. A positive correlation was found between the echogenicity and the concentration of iron and ferretin in the SN [9].

However, this finding is based on manual evaluation of examined images. Nevertheless, the fact that this phenomenon occurs with the use of US as imaging method is very promising, since US is fast, cheap, and tolerable to immobile patients compared to other clinical imaging methods. To develop and validate an early, observer-independent PD indicator, an automatic or at least semiautomatic algorithm for analysis of brain stem TCS images is necessary.

II. Methods

The mesencephalon in the transverse view is a butterfly-shaped structure. In each "wing", the substantia nigra exists as a line-shaped structure in the middle of the mesencephalon area (see Fig. 1). The ultrasound examination is performed from the temporal acoustic bone window in a standardised axial mesencephalic imaging plane (landmark: butterfly-shaped brainstem). Due to a decreased signal-to-noise-ratio with increasing insonation depth, only the closer (ipsilateral) half of the mesencephalon is analysed, which requires acquiring two images per individual.

In the images, the mesencephalon can be identified as a dark butterfly-shaped structure with the SN lying in the middle part of each wing. In about 90% of healthy subjects, the maximal area of SN hyperechogenicity in an axial imaging plane is below the threshold of 0.2 cm^2, whereas in more

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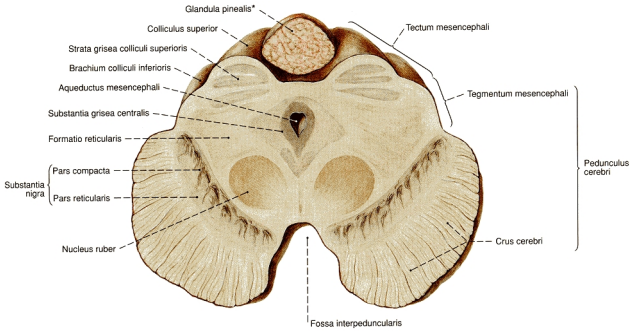


Fig. 1: Location of the substantia nigra in the mesencephalon (transverse view). The SN is located in the two darker, line-shaped regions [10].

than 90% of PD affected persons the SN appears as a bright region interrupted by speckle noise with an area of more than 0.2 cm^2 [11]. Fig. 2 shows two TCS images of a healthy subject and a PD patient. In the former, the SN is not identifiable in the mesencephalic area, whereas the SN appears as a bright spot in the image of the PD patient.

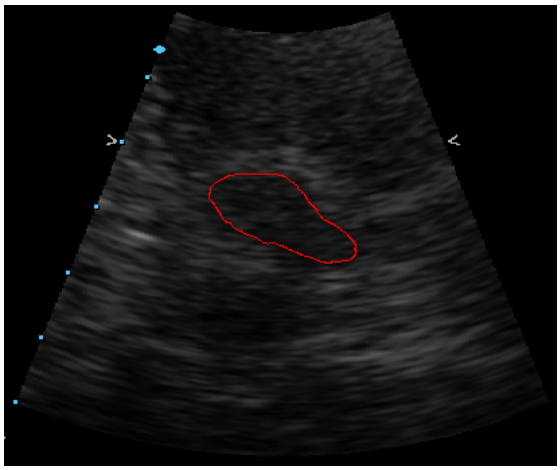
Currently, the resulting ultrasound images are subject to manual analysis only. The examiner segments the substantia nigra if in his opinion it is distinguishable from the remaining mesencephalon. The resulting diagnostic parameter is the size of the (altered) SN given in cm^2. Due to varying acoustic bone windows, different levels of training of involved physicians and since the person segmenting the images is not blinded to the clinical status of the patient, this process is highly investigator-dependent.

A. Automatic feature extraction

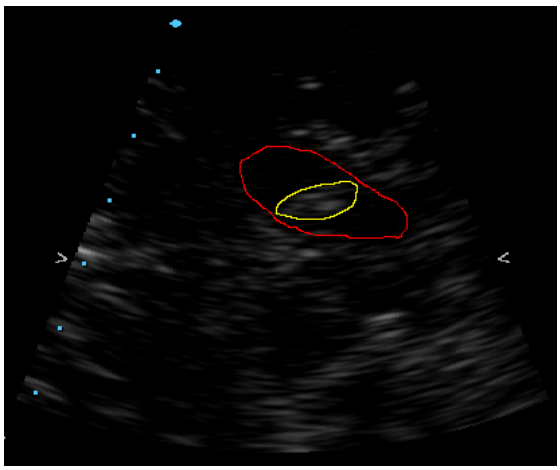
First steps to reduce observer-dependence were to segment the substantia nigra automatically [12]. This approach has not proven to be very fruitful, mainly due to an unreliable ground truth or inconsistent segmentation criteria. Hence, the automatic SN segmentation is abandoned for the time being.

Our approach reduces investigator dependence by having the examiner segment the ipsilateral mesencephalon wing, which is closer to the US probe. The structure and variability of the mesencephalon does not depend on whether the person suffers from PD or not. In addition, the mesencephalon is also better identifiable and discriminable from the surrounding tissue compared to the SN, since it is a mostly dark structure in light surroundings. Hence, we expect a decreased inter- and intra-observer variability in manually segmenting this region of interest (ROI). Furthermore, by segmenting the whole ipsilateral mesencephalon, we use all the information given in the ROI, especially in the close surroundings of the SN.

On the segmented ROIs the moment of inertia and the seven Hu moments ϕ_i were calculated [13]. The (physical)



(a) The mesencephalon is a homogeneous region with the substantia nigra not identifiable in a healthy subject.



(b) The substantia nigra is visible as a bright spot (marked in yellow) in the mesencephalon of a PD affected subject.

Fig. 2: Manually segmented upper half of the mesencephalon (red) in healthy (top) and PD affected subjects (bottom).

moment of inertia is adapted to image processing by interpreting intensity values as inertia values and represents the distribution of gray level values in the ROI. It varies strongly between an uniform and a centrical distribution and is calculated as

$$I = \sum_x \sum_y \left((x-\overline{x})^2 + (y-\overline{y})^2 \right) \cdot f(x,y) \qquad (1)$$

with $f(x,y)$ being the image intensity at pixel (x,y), whereas $\overline{x}$ and $\overline{y}$ are the coordinates of the centre of gravity of the ROI, which are calculated as

$$\overline{x} = \frac{m_{10}}{m_{00}} \qquad \text{and} \qquad \overline{y} = \frac{m_{01}}{m_{00}}. \qquad (2)$$

The zero- and first-order moments m_{pq} are calculated as [14]

$$m_{pq} = \sum_x \sum_y x^p \cdot y^q \cdot f(x,y). \quad (3)$$

The Hu moments were used to characterise the ROIs because of their invariance to translation, rotation and scaling. The latter are influences which can be ascribed to the investigator and are to be removed. As the gold standard for SN image analysis area of SN (aSN) was measured by a human expert blinded to the genetic status of the studied subjects.

III. Validation Study

A clinical study has been conducted to evaluate whether these features can be used as an early PD indicator and/or a genetic mutation indicator. The study consisted of 14 healthy controls (Group 1: 6 female, mean age: 50.6 ± 12.5 years) and 10 heterozygous Parkin mutation carriers without signs and symptoms of PD (Group 2: 5 female, mean age: 36.9 ± 5.9 years). After giving informed consent, all 24 study subjects underwent a detailed neurological examination by a member of the local movement disorders team, including assessment of the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn-Yahr stage. PD was defined according to the United Kingdom Parkinson's Disease Brain Bank Criteria, except that positive family history for PD was not considered an exclusion criterion.

To investigate differences in the both groups regarding the different features, the Mann-Whitney test was calculated, rendering exact two-sided p-values. To describe the diagnostic value of the features which showed significant differences between the two groups, receiver operating characteristic (ROC) curves were plotted. Specifically, we calculated the sensitivity and the specificity of the different features regarding mutation status at every possible cut-off and plotted the resulting sensitivity values against (1 - specificity) values. To account for threefold testing, resulting nominal p-values were adjusted according to the procedure by Holm-Bonferroni [15]. Adjusted p-values below 0.05 were considered significant.

A. Results

From the 10 healthy Parkin mutation carriers we could analyse 19 images of the mesencephalon of each side. In one subject image quality was too poor because of insufficient ultrasound penetration through the temporal acoustic bone window. Insonation problems were present in 8 investigations in the control group leading to 20 images of the mesencephalon half which could be used for further analysis. We evaluated the image segments as described in the section IIIn the univariate statistics we found significant differences of both moment of inertia and the first Hu moment ϕ_1 (see Table 1). Mean values of aSN and the remaining Hu moments were not significantly different comparing both groups.

Table 1: Area of SN (aSN), moment of inertia, and Hu-moments (ϕ_i) for mutation carriers and controls (mean $\pm$ SD, * significant on local alpha).

Feature	Group 1 (n=20)	Group 2 (n=19)	p-Value
aSN	415.6 ± 230.6	590.5 ± 312.1	0.07
Inertia	$24 \pm 10 \cdot 10^7$	$9.4 \pm 4.5 \cdot 10^7$	$< 0.0001^*$
ϕ_1	$0.9 \pm 0.6 \cdot 10^{-2}$	$2.0 \pm 1.4 \cdot 10^{-2}$	0.0005^*
ϕ_2	$0.8 \pm 1.3 \cdot 10^{-4}$	$12.4 \pm 28.7 \cdot 10^{-4}$	0.0039
ϕ_3	$1.9 \pm 2.7 \cdot 10^{17}$	$2.0 \pm 2.6 \cdot 10^{17}$	0.92
ϕ_4	$2.1 \pm 3.0 \cdot 10^{16}$	$2.2 \pm 2.9 \cdot 10^{16}$	0.92
ϕ_5	$-3.9 \pm 9.4 \cdot 10^{33}$	$-3.8 \pm 8.3 \cdot 10^{33}$	0.92
ϕ_6	$1.4 \pm 3.7 \cdot 10^{14}$	$1.3 \pm 3.2 \cdot 10^{14}$	0.32
ϕ_7	$-0.4 \pm 1.3 \cdot 10^{23}$	$-0.9 \pm 3.9 \cdot 10^{23}$	0.92

To calculate limits for separation between Parkin mutation carriers and controls we used receiver operator characteristics (ROC) calculations. Limits for separation of Parkin mutation carriers and control subjects for the best features inertia and Hu1-moment showed high sensitivities and moderate specificities (see Fig. 4). The limit for the moment of inertia is $16.7 \cdot 10^7$ and the limit for the Hu1-moment is $1.2 \cdot 10^{-2}$. Fig. 3 shows the 39 examinations in a plot of these two features versus each other. It is clear to see that the two groups can be separated reasonably well.

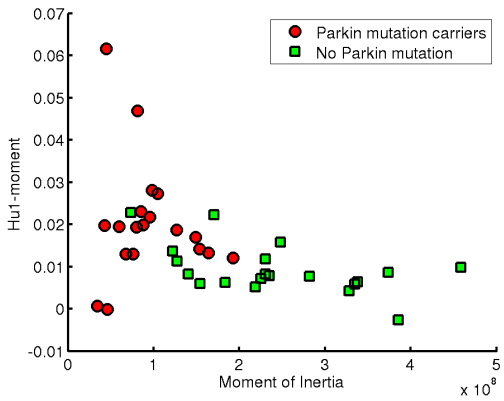


Fig. 3: The 39 examinations of both groups in a plot of the two best features versus each other.

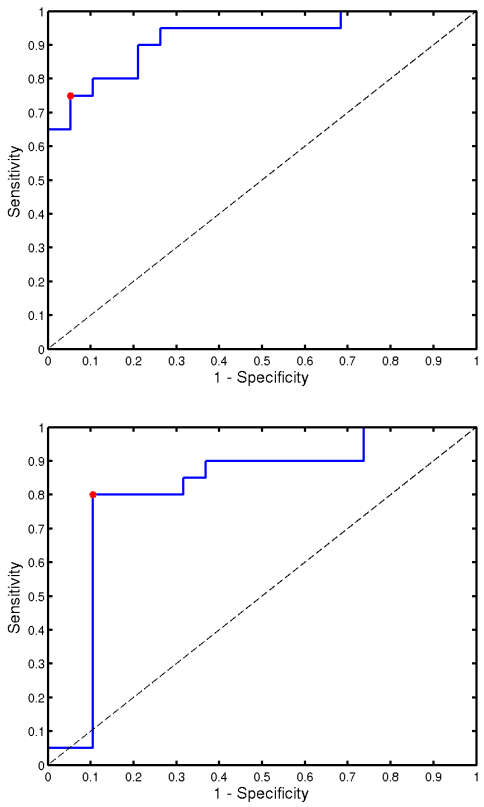


Fig. 4: ROC curves of the moment of inertia (top) and ϕ_1 (bottom).

IV. Conclusions

This analysis is the first study to separate mutation status of Parkin mutation carriers by image characteristics other than the area of substantia nigra. We found both the moment of inertia and Hu1-moment as capable parameters to separate control subjects from parkin mutation carriers. This finding is exceptionally important because both clinical findings with respect to Parkinson's disease and area of substantia nigra could not separate both groups. A high value of inertia for control subjects is plausible because it indicates a more homogeneous dissemination of bright spots in the mesencephalon. The interpretation of a high Hu1-moment in controls is less palpable. It is an abstract measure which due to its invariance to affine transformations uncovers the relevant information.

The analysis of the TCS images is performed by an investigator independent algorithm. This is the second aspect of special interest, because the analysis of substantia nigra hyperechogenicity was performed in all studies published by now either with the area of substantia nigra or a qualitative score, which are both investigator dependent.

There are a few limitations of our present study. First the number of subjects evaluated is small, but for a statistical analysis sufficient. Second, the number of drop outs for the analysis of controls was high (8 out of 24). This is an unexpected high number of acoustic window failures which is normally lower than 10%. Third, manual segmentation of the ipsilateral mesencephalic brain stem is still a source of investigator dependence, which we plan to eliminate in the future by a semi-automatic segmentation algorithm.

In conclusion, this work helps to separate different genetic defined populations with respect to Parkinson's disease which could not be separated by clinical or standard ultrasound imaging procedures. Further studies are necessary to validate the method for other genetic forms of monogenic PD and the usefulness in clinical routine.

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