Author's response to reviews

Title: Transcranial sonography for diagnosis of Parkinson's disease

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Author's response to reviews: see over
Dear Editor-in-Chief,

thanks for your helpful comments concerning our submission, “Transcranial sonography for diagnosis of Parkinson’s disease”.
We have revised the manuscript according to the reviewer comments.
The reviewer comments I would like to answer as follows:

Reviewer 1:
1) Especially the differentiation between patients with IPD and other parkinsonian disorders like multiple system atrophy, progressive supranuclear palsy, drug induced parkinsonism and vascular parkinsonism can be difficult. Unfortunately, in this study only patients with IPD and healthy controls are studied.
2) Secondly, the authors only included patients that were already diagnosed with IPD. However, this does not resemble the situation in clinical practice, where the neurologist would want to used TCS to reach a diagnosis in patients with a clinically unclear parkinsonism.

Reply:
Aim of this study was to calculate sensitivity and specificity of TCS for diagnosis of IPD using a SONOS 5500 ultrasound device. Therefore diagnosis of IPD had to be save by clinical parameters applying United Kingdom brain bank criteria. We agree that the differentiation between IPD and other Parkinsonian disorders can be difficult. But this differentiation was not topic of this study.

Reviewer 1:
1) Not all of the subjects that were investigated and that were described in the methods are handled in the results and discussion (i.e. inter-observer reliability, Perdue pegboard test, Webster gait test, echogenicity of raphe, red nuclei, thalamus, caudate, lenticular nuclei, width ventricles). Please remove these items from the methods or discuss the results shortly.

Reply:
Interobserver reliability is reported in RESULTS p6 l22 and DISCUSSION p9 l20.
Results of Pegboard and Webster gait test are presented in RESULTS p7 ll12-15, p8 ll2-7 and in DISCUSSION p10 ll10-19 and TABLE 3.

Echogenicity of raphe, red nuclei, thalamus, caudate, lenticular nucleus and width of ventricles are documented in RESULTS p8 ll8-15, TABLE 3 and now included in DISCUSSION p10 ll19-23.

Reviewer 1:
The abbreviation TCS is not explained in the last sentence of the abstract.

Reply:
This is now included in the first sentence of the ABSTRACT.

Reviewer 1:
page 3 (Until now studies using the same ultrasound machine only involved small subjects groups..... )
One study of Vlaar et al is not mentioned. In BMC neurol 2008 nov (9:8:42) Vlaar
et al used SONOS 5500 in their TCS study. They included a mixed group of patients and found lower diagnostic accuracy.

Reply: This study is now included and discussed.

Reviewer 1:
In which time period were the subjects included?

Reply:
The subjects were included from December 2005 to August 2007.

Reviewer 1:
Since the size of the SN size changes with age one would prefer similar age groups for both the IPD group and the control group. In this study the mean age of the IPD patients was 66 (range 62-71). The mean age of the control group is not mentioned, only the range (20-79 years).

Reply:
This study was further designed to clarify the influence of age or life circumstances on the echogenicity of SN in healthy and IPD individuals. Therefore we included at least 30 individuals without CNS disorders per decade from age 20 to 79. “Unfortunately” we could not include many IPD patients with young disease onset. The mean age and percentiles of the control group are presented in p6 ll15-16 of RESULTS and as well presented in TABLE 1. In our opinion the influence of age is negligible in this topic because SN size differs significantly between groups. As reported in table 1 the SN size even of the oldest NCD group (70-80 y) is 0.14 cm$^2$ (0.05; 0.15) and therefore far away from a cut-off of 0.2 cm$^2$.

Reviewer 1:
Unfortunately the three investigators were not blinded. Since the age distribution of both groups was so different, the investigators could have assumed that everyone aged below 62 would be healthy.

Reply:
The limitations of this study by not blinding are discussed in p10 ll2-3 and p11 l6. In this submission as described in METHODS the mean and 25$^{th}$ and 75$^{th}$ percentiles are reported. The range of age of IPD patients was 38 to 85 years. We did not know before how many young onset IPD patients we would be able to include in this study. We agree that results might be influenced by the age difference. This possible bias is now mentioned in the DISCUSSION.

Reviewer 1:
Table 1 Inter-observer difference
The difference in means of the SN area of both groups, and the standard deviation, is extremely small. Is this caused by the fact that almost all healthy controls had a SN area of 0 cm$^2$?

Reply:
The mean and 25th and 75th percentiles of SN area of the control group differentiated by age decade are presented in TABLE 1. Only 3 NCD individuals had a SN size of 0 cm$^2$, predominantly a small SN was detectable.

Reviewer 1:
In how many of the IPD patients did the observers come to another conclusion (cut-off point of 0.2cm$^2$)? Hier klopt nog iets niet, door die koppeling met het cut-off point

Reply:
The conclusion of the observers concerning group assignment differed in 5 subjects (2 controls and 3 IPD patients). Please rewrite the second question in English as we don’t understand Dutch.

Reviewer 1:
In table 1. Number of individuals tested by both investigators. In the methods
the authors mentioned three observers.

Reply:
This seems to be a misconception. As mentioned in METHOD p5 l20-22: “The whole measurement of SN was repeated by two independent investigators, blinded to the results of each other- one of them an experienced sonographer (SM, ES) and the other a well trained student (PM, KS).” SM investigated 80% of individuals.

Reviewer1:
page 10, first sentence.
….since this is the basis to advocate TCS as the method of choice in the
diagnostic workup…
Please include the shortcomings of this study (not a mixed patient group, already
diagnosed patients, ……).

Reply:
See first author comment.
The limitation of this study is now included p11 l6, p10 l2-3.

Reviewer 2:
(1) The control group is significantly younger than the patient group (difference of median age 17 years, no overlap of quartiles) and the authors found a significant positive correlation between age and areas of SN echogenicity. Therefore, in ROC analysis sensitivity and specificity of SN echogenicity for iPD diagnosis may be overestimated. This needs to be addressed in the discussion.

Reply:
There is a small overlap in quartiles (see RESULTS p6 l12+l16). This limitation is now mentioned.
This study was designed to clarify the influence of age or life circumstances on the echogenicity of SN in healthy and IPD individuals. Therefore we included at least 30 individuals without CNS disorders per decade from age 20 to 79. “Unfortunately” we could not include more young onset IPD patients.
In our opinion the influence of age is negligible in this context because SN size differs significantly between groups. As reported in table 1 the SN size even of the oldest NCD group (70-80 y) is 0.14 cm² (0.05; 0.15) and therefore far away from a cut-off of 0.2 cm².

Reviewer 2:
The authors conclude from their data that the method is not substantially
influenced by the device used, implying that the cutoff value for SN
hyperechogenicity can be applied to all ultrasound systems. However, although
the data strongly support TCS as a valuable diagnostic tool, this generalisation
needs to be qualified, since no comparison of ultrasound systems has been
performed neither in this nor in previous studies.

Reply:
Unfortunately formal studies comparing different devices are still lacking. Nevertheless based on our results in a large cohort of individuals and considering that in other studies using the same or different ultrasound devices similar scoring criteria concerning SN area were established the hypothesis that the sonographic method is not substantially influenced by the ultrasound device seems acceptable. This is now changed in the discussion.
Reviewer 2:
Figure 2 shows very low echogenicity of the substantia nigra, which is the typical finding in restless legs syndrome and therefore does not constitute a normal finding in a healthy adult. Please replace the figure by another one showing normal SN echogenicity (i.e. SN area 0.13 cm²) and mark the SN as done in figure 3.

Reply:
Figure 2 is now changed.

Reviewer 2:
p6, ll 7/8: What does “combined measurements of left and right side” mean? Average of both sides? Was a correction for multiple comparisons performed?

Reply: Average of both sides. (Most results were recalculated using left, right or largest SN sizes without significant difference.) A correction for multiple comparisons was performed where appropriate using Bonferroni analysis.

Reviewer 2:
p7, ll 5-8: Please add the “area under the curve” (AUC) to the results of ROC analysis.

Reply:
AUC is included now.

Reviewer 2:
p7, ll 21-24. The listing states no correlation of age and SN echogenicity in the NCD group. Please clarify.

Reply:
This correlation is stated, see p7 ll7-8, p10 l10: “In NCD group SN size increased with age (Spearman Rho=0.17, p<0.02), but individuals with SN size > 0.2 cm² did not significantly differ in age from individuals with SN size <0.2 cm² (Mann-Whitney-U p>0.5).”

Reviewer 2:
p9, l 7: “collective” is a germanism, “cohort” might fit better.
p9, l 20: It should read “probably” and “due to the small sample size”.

Reply:
These words are changed now.

Reviewer 2:
Table 1 does not give supplementary information and might therefore be omitted.

Reply:
We think by including this table results might be easier comprehensible but we now omitted TABLE 1.

I hope that the manuscript is now suitable for publication in BMC Neurology. We look forward to your decision.

Sincerely,
Sabine Mehnert.