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Title: Targeting of the subthalamic nucleus for deep brain stimulation: a survey among Parkinson's disease specialists

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Abstract: Background: Deep brain stimulation (DBS) within or adjacent to the subthalamic nucleus (STN) currently represents the most common stereotactic procedure performed for Parkinson's disease. Better STN imaging is often regarded as a requirement for improving stereotactic targeting. But, remarkably enough, it is unclear whether there is a consensus about the optimal target.
Objective and Methods: To obtain an expert opinion on the site regarded optimal for 'STN stimulation', movement disorder specialists were asked to indicate their preferred position for an active contact on hardcopies of the Schaltenbrand and Wahren atlas depicting the STN in all three planes. This represented an idealized setting and it mimicked optimal imaging for direct target definition in a perfectly delineated STN.
Results: The suggested targets were heterogeneous, although some clustering was observed in the dorsolateral STN and subthalamic area. In particular, in the anterior-posterior direction the intended targets differed to a great extent. Most of the indicated targets are thought to also result in concomitant stimulation of structures adjacent to the STN, including the zona incerta, Fields of Forel, and/or the internal capsule.
Conclusions: This survey illustrates that most sites regarded as optimal for 'STN stimulation' are close to each other, but there appears to be no uniform perception of the optimal anatomical target, possibly influencing surgical results. The anatomical sweet zone for STN stimulation needs further specification since this information is likely to make MRI-based target definition less variable when applied to individual patients.

Response to Reviewers: Author's Revision Letter

Re: REQUEST FOR REVISION; Ms. Ref. No: WNS-16-1481; Title: Targeting of the subthalamic nucleus for deep brain stimulation: a survey among Parkinson's disease specialists

Response to the comments of the reviewers:

Reviewer #1:

* There is very poor concordance between the three planes of the Schaltenbrand and Wahren Atlas with only around 60% overlap between axial / coronal / sagittal views. 1 Much of the observed variability may well be due to these inconsistencies. The authors should mention this limitation in the discussion. They certainly cannot claim that the Schaltenbrand Atlas provides "perfect delineation of the STN."

There is no doubt about this limitation of the Schaltenbrand and Wahren atlas. Insofar we agree that our statement requires clarification. The main limitation is that the authors could not perform actual 3D targeting. Simulated targeting in this survey rather represents 2D targeting in three orthogonal planes. The following has been added to the discussion:

... This survey, however, did not involve true 3D targeting as the plates of the Schaltenbrand and Wahren atlas are known to be incongruent {Nowinski, 2006 #2518}. In commercial stereotactic planning software any target modification in one of the three standard orthogonal planes would be followed by proper adjustments in the other planes. It cannot be ruled out, but it is regarded as unlikely that the variation found in this survey had been overcome by corresponding target adjustments in other planes. ...

We also agree that the statement that the atlas provides "...perfect delineation of the STN..." is ambiguous. We have deleted these words in the abstract and discussion. It was meant that the clear contour of the STN in the Schaltenbrand and Wahren atlas was supposed to mimick perfect imaging in three orthoganal planes with sharp delineation of STN borders that are blurred to a variable extent in current state MRI.

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* I assume that individual participants in Figure 1 have been given the same colour. If so, examination reveals that there are inconsistencies with placement of the active contact within individual participants between the three planes (most likely because of the atlas inconsistencies). It would be interesting to examine the concordance of the coordinates of the three marks within each participant!

It is correct that there have been inconsistencies. Taking the just mentioned limitations of the Schaltenbrand and Wahren atlas into account it is unresolved whether the incongruencies of the atlas or different efforts by the participants for target adjustments are responsible for this.

In the Results section we have added the following statement:

... There were also intrarater differences for x, y, and z coordinates as read from the Schaltenbrand and Wahren atlas. These can be accounted for by inconsistencies within the atlas as well as different efforts of the participants to adjust targets between different atlas planes. However, it is important to note that the inherent coordinate system of the atlas was not to be taken into account but merely the outline of the anatomical structures. ...

In numbers the intrarater deviations for target definition in the three different planes of the atlas were: x, 1.5 / 1.0 mm (mean / median); y, 0.9 / 0.6 mm; z, 0.5 / 0.4 mm. However, since the task did not involve target definition based on (inconsistent) location of the STN within the coordinate system of the Schaltenbrand and Wahren atlas the authors think that providing additional statistics in the manuscript appears expendable and rather misleading.

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* Since a quadripolar lead is most commonly used in DBS surgery, and to avoid the above problems, a more realistic exercise to ascertain the validity of MRI-based targeting would have been to ask the participants to place a DBS lead template within a computerised rotatable stylized 3D atlas of the region (including red nucleus and STN for orientation).

We agree with this suggestion. However, the limitations even with this approach are: (i) one had to decide on an average STN in 3D to be presented; (ii) one had to outline adjacent structures, in particular, fiber tracts, as, for example, authors who assume that pallidothalamic projections conveyed in the Fields of Forel contribute to therapeutic effects should be able to take these into account; (iii) by using an electrode template the angle of an electrode would play a more important role. One had to decide if only the contact supposed to be optimal (as in this survey) or more than one contact of the electrode should be considered for analysis. The latter makes evaluations more complex and the targets less confined.

In spite of all that, we agree that future surveys should preferentially be performed in such a manner. But the authors doubt that such a survey will result in less variability.

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* Despite all these limitations "Average coordinates (x,y,z) did not differ between neurologists and neurosurgeons". Moreover, the standard deviation in each plane is less that the diameter of a DBS lead. There is clear clustering of the vast majority of the selected points within 2 mm of a central point, easily within the volume of activation of a DBS contact. Also, the trajectory of a DBS lead targeting the few outliers would almost certainly lead to a contact coming to rest within the majority cluster."

There is varation in targeting that may be clinically relevant, on the other hand, there are limitations to stereotactic accuracy. We have added the following to the Discussion:
... Despite the fact that targeting was variable it is important to note that the standard deviation in each plane is in the range of the dimensions of electrode contacts of typical DBS leads. Most of the indicated targets cluster within 2 mm of the mean point, and most can be found within the estimated volume of tissue activated as outlined for the mean point. Taking into account that cumulative errors of stereotactic surgery often cannot be kept in the submillimetric range, the variation found in this survey is also similar to the inaccuracy inherent to stereotactic procedures. Furthermore, most of the variation in this survey was found along an anterodorsal to posteromedial direction. This corresponds to usual trajectories chosen for STN electrode implantation by frontolateral approaches. Thus, in clinical practice some of the

variation will be compensated for by the selection of appropriate contacts of multipolar electrodes. ...

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* It is not unusual for more than one contact to provide clinical benefit along a well-placed STN DBS lead, sometimes with minor differences in therapeutic margin between contacts. Some patients also benefit from double monopolar activation. With this in mind, we should contemplate that there may be a "sweet zone" rather than a "sweet spot" within the STN that could also account for some of the observed variability,

We agree with this statement. 'Sweet zone' instead of 'sweet spot is a better term and this has been changed throughout the manuscript. In the manuscript we have also mentioned observations that there might be different 'sweet zones' depending on the symptom to be alleviated.

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* Can the authors comment on whether the neuroscientists represented outliers in the data? If so they should be excluded from analysis, especially since they would not be making clinical decisions on lead placement in patients.

The neuroscientists did not mark the outliers and were not excluded from analysis.

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* The manuscript states: "The anatomical sweet spot for STN stimulation needs further specification before it can be transferred to individual patients for direct MRI-based target definition." Clearly, there is always room for improvement. Routine post implant MRI and correlation of active contact location to long term outcome may lead to further refinement of target selection over time. Would it be possible to ascertain how many of the participants routinely obtain a post op MRI that visualise both lead and STN in patients undergoing DBS at their centre so that they can hone their MRI-based target selection by correlating long term outcome with active contact location?

The position of implanted electrodes may also be checked by coregistration of postoperative CT scans with preoperative MRI. Almost all authors work at institutions examining the location of implanted electrodes with respect to the planned trajectory and individual STN location on a routine basis (authors from three centers did not respond; one of those centers has several highly recognized publications about postoperative imaging).

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* "At present improved STN imaging may not necessarily improve clinical results." Although I generally agree with this statement, improved STN imaging that better delineates the borders of a particular patient's STN and that may allow 3D reconstruction - without the errors of an inconsistent cadaver atlas - may make STN targeting easier even though it may be difficult to prove that it leads to better clinical results given the multitude of variables that affect clinical outcome.

These issues will be addressed below. There is complete agreement with this statement.

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* The manuscript states "MRI-based ('direct') targeting of STN is limited by poorly defined sweet spot" and "This may explain the value of statistical (average) coordinates and why indirect targeting represents a robust approach for STN stimulation." Are the authors proposing a return to indirect targeting? Since the authors have suggested that there is no consensus on the "sweet spot" on the Schaltenbrand Atlas, I fail to understand how there can be consensus on the atlas coordinates to use for indirect targeting in individual patients! This approach would only make sense if the agenda is to insist on correction for anatomical variability with multiple brain tracks during surgery instead of using modern MRI technology to correct for anatomical variability based on the visible target prior to surgery, thereby minimising the number of brain passes.

The authors explicitly do not propose a return to pure indirect or atlas-based targeting. Furthermore, the authors are not aware of centers relying on more indirect targeting. Empirical commissure-based targets are usually modified by selected information from MRI (e.g. laterality of the STN in MRI and other brain and ventricle measurements. The fact that the STN is close to the midcommissural point may explain the merits of starting target definition by the use of empirical coordinates (indirect targeting).

The authors believe that MR imaging is probably the most valuable tool to improve targeting in the future. But pure direct, MRI-based targeting is limited in itself, too. Apart from an ill-defined 'sweet zone' (as demonstrated in this survey), the STN is variably depicted in MRI (not addressed in this survey). For example, the left and right STN may differ in the extent of their visualization even within the same patient (i.e. one large and one small hypointense area in T2-weighted images). This individual asymmetry is usually not confirmed by intraoperative MER (e.g. massive recordings from non-T2 hypointense regions). This explains that solely relying on imaging has its own limitations, but certainly there are centers performing this in a very successful manner.

Taken together, for all the limitations inherent to both approaches pure MRI-based targeting may work as well as MRI-modified indirect targeting does (see below), but this issue has not been the topic of this survey. Our survey indicates that despite some great interest in the matter of MR imaging and increased adoption of direct targeting a patent remedy stating something like "perform this kind of MR imaging and then mark your target exactly as follows" can not be formulated yet.

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Finally, if MRI-based targeting is so "limited", can the authors explain the good clinical results obtained by diverse groups that perform MR-guided and MRI-verified STN DBS surgery? 2 3 Despite limitations, there is much merit in the data collected. However, the authors should not try to extrapolate their findings to discredit a method that has already been shown to have good clinical results.

1. Nowinski WL, Liu J, Arumugam T. Quantification and Visualization of Three-Dimensional Inconsistency of the Globus Pallidus Internus in the

Schaltenbrand-Wahren Brain Atlas. Stereotact Funct Neurosurg. 2006;84(5-6):236-242. doi:10.1159/000096497.
2. Ostrem JL, Ziman N, Galifianakis NB, et al. Clinical outcomes using ClearPoint interventional MRI for deep brain stimulation lead placement in Parkinson's disease. Journal of Neurosurgery. October 2015:1-9. doi:10.3171/2015.4.JNS15173.
3. Foltynie T, Zrinzo L, Martinez-Torres I, et al. MRI-guided STN DBS in Parkinson's disease without microelectrode recording: efficacy and safety. Journal of Neurology, Neurosurgery & Psychiatry. 2011;82(4):358-363. doi:10.1136/jnnp.2010.205542.

There should be no doubt about the fact that direct targeting has been practiced in a very successful manner. However, there is more than one way to perform successful targeting. As explained above there are still limitations to all targeting approaches, indirect, direct and modifications of these.

These three important references have been incorporated into the manuscript.

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Reviewer #2:

It would benefit from knowing the seniority of the rater in terms of DBS experience and years spent practising independently.

All authors have a long-standing clinical and research expertise in the treatment of movement disorder patients with deep brain stimulation. Most of the authors have performed responsible deep brain stimulation for at least 14 years. The range was between 14 and >23 years. More that 10 authors have practiced deep brain stimulation surgery and treatment for more than 20 years. Five authors did not respond, but three of those have publications on deep brain stimulation already in the 1990ies.

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There is little statistical analysis of the data.

The authors think that the relevant statistics have been provided. In the manuscript we addressed whether neurologists or neurosurgeons may have a different perception of the optimal target. Additional statistics, such as intrarater variability, have been provided in this letter (see above). However, as most numbers (coordinates) are based on the incongruent Schaltenbrand and Wahren atlas we think that additional statistics may be rather misleading.

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My main criticism of this study is that it is based upon Schaltenbrand and Warren atlas based targeting alone. Many practitioners target the subthalamic nucleus based on MRI without atlas overlaid and the authors would have a study more applicable to the real world if they give subjects MRI slices to target upon in different sequences such as T2, SWI and FLAIR.

This issue has been addressed above (cf. response to reviewer #1). We agree with this statement, and as already explained the utilization of

specific 3D models would actually represent the preferred method in the future.

At first glance providing MR images to the authors instead of atlas plates (N.B. these were supposed to mimick perfect imaging) had been the better approach. Admittedly this had represented a better real world setting albeit additional variables associated with image selection and image quality had distorted the results: (i) MRI signals supposed to represent the STN may be incongruent between different sequences (e.g. SWI vs T2; e.g. Bot et al., 2016; Polanski et al., 2015). In addition, certain parts of the STN may be more likely to be delineated (e.g. de Hollander et al., 2014). The more such factors will be taken into consideration by informed raters the less the original question, e.g. perception of an optimal site for STN stimulation in an idealized situation is evaluated. (ii) Furthermore, we may suppose the border of the same STN is presented in two different qualities, i.e. in a clear manner (high quality STN) and in a blurred manner (lower quality STN). Rather in the first situation (high quality) than in the latter we will actually assess where raters envision optimal targets. In the latter situation (low quality MRI) also the rater's conclusions drawn from fuzzy information will be assessed. (iii) Last but not least, the human ability to dissolve grey levels differs. This may have some influence on where we see the actual borders of the STN (hardcopies or computer screen? only one window or different windowing allowed?). Thus, to some degree a MRI-based survey would not only assess where participants expect perfect electrode location but also their visual function, knowlegde and other abilities (e.g. windowing).

Taken together, in this survey the authors did not attempt to evaluate targeting in the real world (multifactorial and complex) but simply the degree to which the perception of the optimal target for STN stimulation differs between movement disorder specialists.

Bot M, Bour L, de Bie RM, Contarino MF, Schuurman PR, van den Munckhof P. Can We Rely on Susceptibility-Weighted Imaging for Subthalamic Nucleus Identification in Deep Brain Stimulation Surgery? Neurosurgery. 2016 Mar;78(3):353-60. doi: 10.1227/NEU.0000000000001130.

Polanski WH1, Martin KD, Engellandt K, von Kummer R, Klingelhoefer L, Fauser M, Storch A, Schackert G, Sobottka SB. Accuracy of subthalamic nucleus targeting by T2, FLAIR and SWI-3-Tesla MRI confirmed by microelectrode recordings. Acta Neurochir (Wien). 2015 Mar;157(3):479-86. doi: 10.1007/s00701-014-2328-x. Epub 2015 Jan 18.

de Hollander G1, Keuken MC, Bazin PL, Weiss M, Neumann J, Reimann K, Wähnert M, Turner R, Forstmann BU, Schäfer A. A gradual increase of iron toward the medial-inferior tip of the subthalamic nucleus. Hum Brain Mapp. 2014 Sep;35(9):4440-9. doi: 10.1002/hbm.22485. Epub 2014 Mar 4.

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The authors could also ask respondents what their preferred coordinates for targeting the STN in relation to MCP are and see statistically how much they differ from the atlas or MRI target.

The authors felt that providing such coordinates may be misleading and we request the reviewer to omit these for several reasons: (i) for all limitations of the Schaltenbrand and Wahren atlas the average coordinates as read from the atlas are already presented in the

manuscript; (ii) in many instances MCP-based coordinates used in clinical practice ('indirect targeting') may indicate a target below the actual 'sweet zone' albeit this zone is covered by the trajectory, and in this case the actual location of the stimulated area also depends on the angles chosen which is impossible to be taken into account; (iii) MCP-based coordinates for 'sweet zones' have been published by several groups, and these references have already been included into the manuscript; (iv) providing additional coordinates diverts attention from the main message of the manuscript, i.e. variable targeting within clearly defined anatomy, and leads to overinterpretation of less informative statistics.

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Reviewer #3:

I agree that, "The anatomical sweet spot for STN stimulation needs further specification," but I find the remainder of the authors' conclusion: "before it can be transferred to individual patients for direct MRI-based target definition." to be a non sequitur.

The sentence has been revised as follows: ... The anatomical sweet spot for STN stimulation needs further specification since this information is likely to make MRI-based target definition less variable when applied to individual patients. ...

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Indirect targeting, as the authors assert, "represents a robust approach for STN stimulation." On the other hand, indirect targeting is, by definition, aiming at a target we cannot see and inferring its position based on its spatial relationships to visible landmarks. The success of indirect targeting relies on the assumption that each patient's subthalamic nucleus will be in the same position relative to the anterior and posterior commissures—an assumption that we know to be false. Fortunately, the position of the STN is relatively close to midline and it is not highly variable from patient to patient, so indirect targeting has worked reasonably well. One would expect that the further the position of a given patient's STN deviates from the mean, the higher the likelihood of failure of indirectly targeted STN DBS in that patient.

The authors agree with these remarks. In rare instances the STN may be found in extreme locations and indirect targeting would result in lead malplacement. It has already been pointed out that we are not aware of centers performing pure indirect targeting. There are limitations to all approaches that have already been addressed and which are not the focus of this survey. Our survey data just indicate that even in a perfectly delineated STN (2D) targeting would probably remain variable.

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A related observation is that indirect targeting of the GPI, the position of which is substantially more variable among individuals relative to AC-PC landmarks, produces inconsistent results. My observation when retrospectively analyzing Professor Benabid's early GPI DBS cases, was that those DBS leads that were positioned in the posterior lateral ventral GPI (4 out of 12) produced excellent symptomatic relief, while the remaining 8 leads that were not as optimally positioned produced less

desirable results. When the Professor switched to the less variable STN target, his results were much more consistently positive. I believe his adoption of the STN as the target of choice for PD DBS may have been largely based on a failure of indirect targeting of the GPI. He was meticulous and careful in his stereotactic technique and his indirect targeting was very consistent, but it was based on the false assumption that each patient's brain was the same as the atlas and the imaging available to him at the time was quite poor relative to today's available technology.

The authors agree that variation will increase with targets further away from the commissural reference points. Statistical coordinates may even be of some value for targeting of the GPI. Target definition based on proportional adjustments of statistical targets (e.g. Talairach's method) have their own limitations. Issues concerning individual target adjustments have been discussed since the 1960ies (e.g. Spiegel, Talairach, van Manen, van Buren, Spiegel, Mundinger, Röder and Orthner) and – even with MR imaging – not been solved yet.

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The authors' assertion that "…it is not obvious how advances in imaging technology can be utilized for improved clinical efficacy" is not supported by the data presented in the manuscript and adherence to this belief would likely be counterproductive to the general improvement of DBS targeting and global DBS outcomes. The notion that it might be preferable to aim at a target we cannot see than to augment our aiming strategies by exploiting modern technology to actually visualize the target seems absurd. The authors themselves state at the conclusion of the manuscript that "Improved imaging capabilities together with technological advances, such as multi-segmented electrodes allowing for steering and shaping the electrical field in different directions perpendicular to the electrode, will be useful to narrow down the best site for STN stimulation. It is hoped that with such knowledge DBS may be applied with greater efficacy and reduced side effects." I agree with their final statement, and I suggest that the authors remove the contradictory, unsupported, illogical assertion that improved imaging might well result in worse DBS outcomes. On the contrary, improved imaging, as they have stated, will be one of the most useful tools that will enable us to zero in on the "sweet spot" and reach a consensus on optimal STN targeting.

To clarify our statement we have changed the text in the manuscript as follows: ... it is not obvious how advances in imaging technology can automatically be translated into improved clinical efficacy as there is no consensus on the optimal target yet and different use will be made of superior imaging. ...

To explain this statement we may imagine a specialist who uses a certain but not optimal MRI sequence for elaborate targeting with a close to zero rate for lead malplacement. That is already possible at present (see above). The implementation of a better sequence may have an influence on the way that specialist performs targeting. Let uns assume that surgeon strives for electrode positioning within the sensorimotor region of the STN and ends up with slightly more lateral targeting by using those improved images. Initially he may encounter a higher rate of capsular side effects until he has learned to work with these superior MR images. There is no improvement that comes without potential risks, and

although paradoxical or absurd at first glance, in the beginning he might be less successful than he used to be.

On the other hand, had a "sweet zone" already been defined that specialist could have used this information when implementing the superior MRI sequence and he had performed better. Even by not asssuming this theoretical worst case, that surgeon may simply perform as good as before despite have better images at hand. In other words, it is a fallacy that improved imaging will necessarily improve targeting and clinical results. Reviewer #1 wrote: "At present improved STN imaging may not necessarily improve clinical results." Although I generally agree with this statement... (see above).

Another example would be a specialist succeeding with indirect targeting that is modified based on selected information from MRI (e.g. STN laterality). Although being successful with this method his perception of the anatomical "sweet zone" might be erroneous. If this specialists eventually moves to direct targeting because STN imaging has become almost perfect his results will get worse. On the other hand, this may not have happened if there is a proven recipe how to mark the "sweet zone" in (or at) the STN of an individual patient.

Despite all that the authors regard improved imaging capabilities as one of the key factors for the understanding of differential clinical effects elicited with different electrode locations and eventually improved or more consistent targeting.

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Regarding methodology:
Although the authors' hypothesis is an important one to highlight, the manner in which this study was conducted severely limits the ability to draw a broad conclusion about the heterogeneity of target selection within the STN. Twenty-seven movement disorders specialists marked their preferred target in a predetermined coronal plane (3 mm posterior to the mid-commissural point (MCP)), sagittal plane (12 mm lateral to the MCP) and in four axial planes (0.5, 1.0, 1.5, and 3.5 mm ventral to the MCP). The selection of these particular planes inherently biases the respondent targets. Although the planes chosen can be argued as reasonable representations of "typical" STN DBS placement, as the authors are aware, the STN is represented on many more planes than those chosen. For example, in the 1977 version of the Schaltenbrand and Wahren atlas published by Thieme, the STN is present on sagittal planes ranging from 6.5 to 17 mm lateral to the MCP. The relatively arbitrary restriction for participants to identify a target in the sagittal plane on the 12 mm plate biases the mean coordinate to that plane. Indeed, the mean and median laterality is reported as 12.0 mm (table 1). If given the opportunity, many respondents may have chosen to select a target on the 10.5 mm sagittal plate. Furthermore, a respondent asked to select a target separately in each of three planes, is unlikely to precisely synchronize their point across the planes. For example, the respondent identified by the dark blue dot chose a point significantly more dorsal in the coronal plane (Fig 1A) than in the sagittal plane (Fig 1B). In essence, each of the 27 respondents chose a total of 81 targets (27 respondents * 3 planes, with the exception of three participants who did not mark a target in all three planes, as commented in the last paragraph of page 7). This method introduces intrarater variability in addition to the interrater variability the study was attempting to assess. The pseudo-increased number of targets also artificially increased statistical power.

The preselection of atlas plates for each of the three planes limits 3D assessments. The plates stem from different brains and exhibit well-known inconsistencies. This issue has already been addressed above (cf. reviewer #1). We cannot completely rule out that selected plates have influenced target selection. However, this would mainly be due to a different shape of the STN in different plates, but not because of the stereotactic location of the plate in the atlas. The position of the slice in the Schaltenbrand and Wahren atlas was not to be taken into account by the raters. For example, in the preselected coronal slice the authors just marked their target relative to the borders of the STN (supposed to mimick a perfect image of the STN in a coronal MRI).

Although coordinates were read from the plots and presented in the manuscript this analysis was not the main purpose of this survey. Regarding x, y and z coordinates the location of the preselected plate (e.g. 12 mm lateral for the sagittal plate) was never taken into account. For example, only the x and z coordinates of indicated points were read from this coronal plate. On the other hand, the fact that the average x coordinate (lateral coordinates as read from axial and coronal plates) of all authors was 12.0 mm (mean and median) supports the preselection of a sagittal plate 12 mm lateral to the midline for this survey (in retrospective). Similarly, mean and median y (−1.7 mm) and z (−2.3 mm) coordinates of all authors were close to the preselected coronal (−3 mm) and axial plates (between −0.5 and −3.5 mm) presented to the authors.

The coordinates presented in Table 1 were based on averages calculated for each participant. For each participant one x coordinate representing the average x coordinate as read from coronal and axial plates, one mean y coordinate as read from sagittal and axial plate, and one mean z coordinate as read from coronal and sagittal image was calculted.

The fact that respondents have synchronized their targets to a different degree has been addressed above. Similarly, the limitations of inconsistent atlas plates have been discussed. An important message of this survey is rather that authors have a different perception of how dorsal or lateral they would choose their target relative to a clearly delineated border of the STN.

We agree that these limitations do not allow to make meaningful quantitative assessments of the heterogeneitiy of target selection. But as already pointed out, other surveys (MRI based, use of a different atlas, virtual or real models in 3D, drawings etc.) had their own limitations. Furthermore, as stereotactic coordinates from the atlas were not to be taken into account for the indication of targets we doubt that our method "introduced intrarater variability in addition to the interrater variability" to a significant extent.

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A more impactful study would examine variability in target selection on a digitized atlas in which each plane may be assessed simultaneously (i.e. an atlas in which a respondent chooses one target in a three-dimensional space, rather than three targets in two-dimensional spaces).

The authors agree with this statement. This has already been commented on above.

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As stated above, the conclusion that "MRI-based ('direct') targeting of STN is limited by a poorly defined sweet spot" simply cannot be inferred

from this study. If anything, the study can only conclude that targeting using a two-dimensional atlas produces higher intra and inter rater variability. Overall, the study may merit publication, primarily to highlight the lack of general consensus regarding the appropriate target for STN stimulation, but significant revisions are warranted to highlight the limitations of the method used and to remove the unsupported conclusion that direct targeting is limited by a poorly defined sweet spot.

We will not state that 'MRI-based ('direct') targeting of STN is limited by a poorly defined sweet spot' as this may be misunderstood. We have clarified our statement as follows:

- The anatomical sweet spot zone for STN stimulation requires further specification
- Without specified sweet zone MRI-based ('direct') targeting will remain variable

_____

Also:
The exact instructions given to participants should be clarified.

These are the instructions given to the authors:

Optimal STN targeting

Please imagine the 'ideal world:'

- The patient's brain is 100% congruent with the Schaltenbrand & Wahren atlas
- MR imaging delineates the patient's STN in a perfect manner

Please:
Indicate with a cross ( X ) in the coronal, sagittal, and axial slices of the S&W atlas where the center of the active DBS electrode contact (1.5 mm length) for monopolar / cathodic STN stimulation with 3.5 mA / 60 usec / 130 Hz should be placed.

Please mark:

___ neurologist ___ neurosurgeon ___ other

Email: _____

THANK YOU !!!

_____

There may be, in some cases, a difference between the optimal place to stimulate and the optimal place to position the active electrode because placing the active contact in the center of the "sweet spot" for therapeutic stimulation might result, based on the 3 mm VTA, spread current into the internal capsule with adverse effects.
Therefore, the questions:
Where is the optimal location to stimulate in the STN for therapeutic benefit?

Where is the optimal location to position the active contact for STN stimulation?
Might have different answers…

What was asked for is (cf. Instructions):
"Where is the optimal location to position the active contact for STN stimulation?"

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In the figure legend it is not explicitly stated that in 1D and 1E the 3 mm radius yellow sphere is indicative of the volume of activation, centered at the mean point of the surveyed responses.

This important information was missing. We added the following sentence to the figure legend:
... Yellow spheres in D and E indicate the volume of tissue activated (3 mm radius) centered at the mean target indicated by all participants. ...

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The individual points in figure 1C are extremely difficulty to visualize. Either the resolution of the figure should be increased to allow the reader to zoom in with greater definition, or the individual points should be made larger.

The figure has been revised accordingly (individual points were enlarged).

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In table 1, it is not clear in which group the two clinical neuroscientists are included (neurologists or neurosurgeons).

The two clinical neuroscientists have not been included into this analysis. This has been stated in the manuscript (cf. page 8, first paragraph). We have added this information to the Table legend. ... Both clinical neuroscientists were excluded from this comparison. ...

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A reference for the Shaltenbrand and Wahren atlas used by participants and represented in figure 1 should be present

This reference has been added:
Schaltenbrand G, Wahren W (1977) Atlas for stereotaxy of the human brain, 2nd Ed. Thieme, Stuttgart

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October 30, 2016

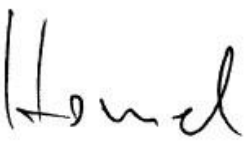
Dear Professor Benzel:

We were delighted to hear that our manuscript entitled *'Targeting of the subthalamic nucleus for deep brain stimulation: a survey among Parkinson's disease specialists*' is considered for for publication in *World Neurosurgery*.

The responses of the reviewers have been very helpful in improving the contents and clarity of the manuscript. All issues raised by the reviewers have been addressed in the 'authors response letter.'

We hope that with these changes our manuscript is acceptable for publication in *World Neurosurgery*.

On behalf of all authors,
Sincerely,



PD Dr. W. Hamel

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Bayer, UCB, zur Rose Pharma, TEVA. Neither L.T. nor any member of his family holds stocks, stock options, patents or financial interests in any of the above mentioned companies or their competitors.

A.M.L. serves as consultant for Boston Scientific, Medtronic Inc., St. Jude Medical, and Aleva Inc. Stocks and stock options as co-founder of Functional Neuromodulation.

**Abbreviations:**

DBS, deep brain stimulation

STN, subthalamic nucleus

MRI, magnetic resonance imaging

PD, Parkinson's disease

# Author's Revision Letter

**Re:** REQUEST FOR REVISION; Ms. Ref. No: WNS-16-1481; Title: Targeting of the subthalamic nucleus for deep brain stimulation: a survey among Parkinson's disease specialists

**Response to the comments of the reviewers:**

## Reviewer #1:

* *There is very poor concordance between the three planes of the Schaltenbrand and Wahren Atlas with only around 60% overlap between axial / coronal / sagittal views. 1 Much of the observed variability may well be due to these inconsistencies. The authors should mention this limitation in the discussion. They certainly cannot claim that the Schaltenbrand Atlas provides "perfect delineation of the STN."*

There is no doubt about this limitation of the Schaltenbrand and Wahren atlas. Insofar we agree that our statement requires clarification. The main limitation is that the authors could not perform actual 3D targeting. Simulated targeting in this survey rather represents 2D targeting in three orthogonal planes. The following has been added to the discussion:

... This survey, however, did not involve true 3D targeting as the plates of the Schaltenbrand and Wahren atlas are known to be incongruent {Nowinski, 2006 #2518}. In commercial stereotactic planning software any target modification in one of the three standard orthogonal planes would be followed by proper adjustments in the other planes. It cannot be ruled out, but it is regarded as unlikely that the variation found in this survey had been overcome by corresponding target adjustments in other planes. ...

We also agree that the statement that the atlas provides *"...perfect delineation of the STN..."* is ambiguous. We have deleted these words in the abstract and discussion. It was

meant that the clear contour of the STN in the Schaltenbrand and Wahren atlas was supposed to mimick perfect imaging in three orthoganal planes with sharp delineation of STN borders that are blurred to a variable extent in current state MRI.

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* *I assume that individual participants in Figure 1 have been given the same colour. If so, examination reveals that there are inconsistencies with placement of the active contact within individual participants between the three planes (most likely because of the atlas inconsistencies). It would be interesting to examine the concordance of the coordinates of the three marks within each participant!*

It is correct that there have been inconsistencies. Taking the just mentioned limitations of the Schaltenbrand and Wahren atlas into account it is unresolved whether the incongruencies of the atlas or different efforts by the participants for target adjustments are responsible for this.

In the Results section we have added the following statement:

... There were also intrarater differences for x, y, and z coordinates as read from the Schaltenbrand and Wahren atlas. These can be accounted for by inconsistencies within the atlas as well as different efforts of the participants to adjust targets between different atlas planes. However, it is important to note that the inherent coordinate system of the atlas was not to be taken into account but merely the outline of the anatomical structures. ...

In numbers the intrarater deviations for target definition in the three different planes of the atlas were: x, 1.5 / 1.0 mm (mean / median); y, 0.9 / 0.6 mm; z, 0.5 / 0.4 mm. However, since the task did not involve target definition based on (inconsistent) location of the STN within the coordinate system of the Schaltenbrand and Wahren atlas the authors think that providing additional statistics in the manuscript appears expendable and rather misleading.

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* *Since a quadripolar lead is most commonly used in DBS surgery, and to avoid the above problems, a more realistic exercise to ascertain the validity of MRI-based targeting would have been to ask the participants to place a DBS lead template within a computerised rotatable stylized 3D atlas of the region (including red nucleus and STN for orientation).*

We agree with this suggestion. However, the limitations even with this approach are: (i) one had to decide on an average STN in 3D to be presented; (ii) one had to outline adjacent structures, in particular, fiber tracts, as, for example, authors who assume that pallidothalamic projections conveyed in the Fields of Forel contribute to therapeutic effects should be able to take these into account; (iii) by using an electrode template the angle of an electrode would play a more important role. One had to decide if only the contact supposed to be optimal (as in this survey) or more than one contact of the electrode should be considered for analysis. The latter makes evaluations more complex and the targets less confined.

In spite of all that, we agree that future surveys should preferentially be performed in such a manner. But the authors doubt that such a survey will result in less variability.

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* *Despite all these limitations "Average coordinates (x,y,z) did not differ between neurologists and neurosurgeons". Moreover, the standard deviation in each plane is less that the diameter of a DBS lead. There is clear clustering of the vast majority of the selected points within 2 mm of a central point, easily within the volume of activation of a DBS contact. Also, the trajectory of a DBS lead targeting the few outliers would almost certainly lead to a contact coming to rest within the majority cluster."*

There is varation in targeting that may be clinically relevant, on the other hand, there are limitations to stereotactic accuracy. We have added the following to the Discussion:

... Despite the fact that targeting was variable it is important to note that the standard deviation in each plane is in the range of the dimensions of electrode contacts of typical DBS leads. Most of the indicated targets cluster within 2 mm of the mean point, and most can be found within the estimated volume of tissue activated as outlined for the mean point. Taking into account that cumulative errors of stereotactic surgery often cannot be kept in the submillimetric range, the variation found in this survey is also similar to the inaccuracy inherent to stereotactic procedures. Furthermore, most of the variation in this survey was found along an anterodorsal to posteromedial direction. This corresponds to usual trajectories chosen for STN electrode implantation by frontolateral approaches. Thus, in clinical practice some of the variation will be compensated for by the selection of appropriate contacts of multipolar electrodes. ...

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* *It is not unusual for more than one contact to provide clinical benefit along a well-placed STN DBS lead, sometimes with minor differences in therapeutic margin between contacts. Some patients also benefit from double monopolar activation. With this in mind, we should contemplate that there may be a "sweet zone" rather than a "sweet spot" within the STN that could also account for some of the observed variability,*

We agree with this statement. 'Sweet zone' instead of 'sweet spot is a better term and this has been changed throughout the manuscript. In the manuscript we have also mentioned observations that there might be different 'sweet zones' depending on the symptom to be alleviated.

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* *Can the authors comment on whether the neuroscientists represented outliers in the data? If so they should be excluded from analysis, especially since they would not be making clinical decisions on lead placement in patients.*

The neuroscientists did not mark the outliers and were not excluded from analysis.

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* *The manuscript states: "The anatomical sweet spot for STN stimulation needs further specification before it can be transferred to individual patients for direct MRI-based target definition." Clearly, there is always room for improvement. Routine post implant MRI and correlation of active contact location to long term outcome may lead to further refinement of target selection over time. Would it be possible to ascertain how many of the participants routinely obtain a post op MRI that visualise both lead and STN in patients undergoing DBS at their centre so that they can hone their MRI-based target selection by correlating long term outcome with active contact location?*

The position of implanted electrodes may also be checked by coregistration of postoperative CT scans with preoperative MRI. Almost all authors work at institutions examining the location of implanted electrodes with respect to the planned trajectory and individual STN location on a routine basis (authors from three centers did not respond; one of those centers has several highly recognized publications about postoperative imaging).

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** "At present improved STN imaging may not necessarily improve clinical results." Although I generally agree with this statement, improved STN imaging that better delineates the borders of a particular patient's STN and that may allow 3D reconstruction - without the errors of an inconsistent cadaver atlas - may make STN targeting easier even though it may be difficult to prove that it leads to better clinical results given the multitude of variables that affect clinical outcome.*

These issues will be addressed below. There is complete agreement with this statement.

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** The manuscript states "MRI-based ('direct') targeting of STN is limited by poorly defined sweet spot" and "This may explain the value of statistical (average) coordinates and why indirect targeting represents a robust approach for STN stimulation." Are the authors proposing a return to indirect targeting? Since the authors have suggested that there is no consensus on the "sweet spot" on the Schaltenbrand Atlas, I fail to understand how there can be consensus on the atlas coordinates to use for indirect targeting in individual patients! This approach would only make sense if the agenda is to insist on correction for anatomical variability with multiple brain tracks during surgery instead of using modern MRI technology to correct for anatomical variability based on the visible target prior to surgery, thereby minimising the number of brain passes.*

The authors explicitly *do not* propose a return to pure indirect or atlas-based targeting. Furthermore, the authors are not aware of centers relying on more indirect targeting. Empirical commissure-based targets are usually modified by selected information from MRI (e.g. laterality of the STN in MRI and other brain and ventricle measurements. The fact that

the STN is close to the midcommissural point may explain the merits of starting target definition by the use of empirical coordinates (indirect targeting).

The authors believe that MR imaging is probably the most valuable tool to improve targeting in the future. But pure direct, MRI-based targeting is limited in itself, too. Apart from an ill-defined 'sweet zone' (as demonstrated in this survey), the STN is variably depicted in MRI (not addressed in this survey). For example, the left and right STN may differ in the extent of their visualization even within the *same* patient (i.e. one large and one small hypointense area in T2-weighted images). This individual asymmetry is usually not confirmed by intraoperative MER (e.g. massive recordings from non-T2 hypointense regions). This explains that solely relying on imaging has its own limitations, but certainly there are centers performing this in a very successful manner.

Taken together, for all the limitations inherent to *both* approaches pure MRI-based targeting may work as well as MRI-modified indirect targeting does (see below), but this issue has not been the topic of this survey. Our survey indicates that despite some great interest in the matter of MR imaging and increased adoption of direct targeting a patent remedy stating something like "perform this kind of MR imaging and then mark your target exactly as follows" can not be formulated yet.

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*Finally, if MRI-based targeting is so "limited", can the authors explain the good clinical results obtained by diverse groups that perform MR-guided and MRI-verified STN DBS surgery? 2 3 Despite limitations, there is much merit in the data collected. However, the authors should not try to extrapolate their findings to discredit a method that has already been shown to have good clinical results.*

*1. Nowinski WL, Liu J, Arumugam T. Quantification and Visualization of Three-*

*Dimensional Inconsistency of the Globus Pallidus Internus in the Schaltenbrand-Wahren Brain Atlas. Stereotact Funct Neurosurg. 2006;84(5-6):236-242. doi:10.1159/000096497.*

*2. Ostrem JL, Ziman N, Galifianakis NB, et al. Clinical outcomes using ClearPoint interventional MRI for deep brain stimulation lead placement in Parkinson's disease. Journal of Neurosurgery. October 2015:1-9. doi:10.3171/2015.4.JNS15173.*

*3. Foltynie T, Zrinzo L, Martinez-Torres I, et al. MRI-guided STN DBS in Parkinson's disease without microelectrode recording: efficacy and safety. Journal of Neurology, Neurosurgery & Psychiatry. 2011;82(4):358-363. doi:10.1136/jnnp.2010.205542.*

There should be no doubt about the fact that direct targeting has been practiced in a very successful manner. However, there is more than one way to perform successful targeting. As explained above there are still limitations to all targeting approaches, indirect, direct and modifications of these.

These three important references have been incorporated into the manuscript.

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**Reviewer #2:**

*It would benefit from knowing the seniority of the rater in terms of DBS experience and years spent practising independently.*

All authors have a long-standing clinical and research expertise in the treatment of movement disorder patients with deep brain stimulation. Most of the authors have performed responsible deep brain stimulation for at least 14 years. The range was between 14 and >23 years. More that 10 authors have practiced deep brain stimulation surgery and treatment for more than 20 years. Five authors did not respond, but three of those have publications on deep

brain stimulation already in the 1990ies.

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*There is little statistical analysis of the data.*

The authors think that the relevant statistics have been provided. In the manuscript we addressed whether neurologists or neurosurgeons may have a different perception of the optimal target. Additional statistics, such as intrarater variability, have been provided in this letter (see above). However, as most numbers (coordinates) are based on the incongruent Schaltenbrand and Wahren atlas we think that additional statistics may be rather misleading.

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*My main criticism of this study is that it is based upon Schaltenbrand and Warren atlas based targeting alone. Many practitioners target the subthalamic nucleus based on MRI without atlas overlaid and the authors would have a study more applicable to the real world if they give subjects MRI slices to target upon in different sequences such as T2, SWI and FLAIR.*

This issue has been addressed above (cf. response to reviewer #1). We agree with this statement, and as already explained the utilization of specific 3D models would actually represent the preferred method in the future.

At first glance providing MR images to the authors instead of atlas plates (N.B. these were supposed to mimick perfect imaging) had been the better approach. Admittedly this had represented a better *real world* setting albeit additional variables associated with image selection and image quality had distorted the results: (i) MRI signals supposed to represent the STN may be incongruent between different sequences (e.g. SWI vs T2; e.g. Bot et al., 2016;

Polanski et al., 2015). In addition, certain parts of the STN may be more likely to be delineated (e.g. de Hollander et al., 2014). The more such factors will be taken into consideration by informed raters the less the original question, e.g. perception of an optimal site for STN stimulation in an idealized situation is evaluated. (ii) Furthermore, we may suppose the border of the *same* STN is presented in two different qualities, i.e. in a clear manner (high quality STN) and in a blurred manner (lower quality STN). Rather in the first situation (high quality) than in the latter we will actually assess where raters envision optimal targets. In the latter situation (low quality MRI) also the rater's conclusions drawn from fuzzy information will be assessed. (iii) Last but not least, the human ability to dissolve grey levels differs. This may have some influence on where we see the actual borders of the STN (hardcopies or computer screen? only one window or different windowing allowed?). Thus, to some degree a MRI-based survey would not only assess where participants expect perfect electrode location but also their visual function, knowlegde and other abilities (e.g. windowing).

Taken together, in this survey the authors did not attempt to evaluate targeting in the real world (multifactorial and complex) but simply the degree to which the perception of the optimal target for STN stimulation differs between movement disorder specialists.

Bot M, Bour L, de Bie RM, Contarino MF, Schuurman PR, van den Munckhof P. Can We Rely on Susceptibility-Weighted Imaging for Subthalamic Nucleus Identification in Deep Brain Stimulation Surgery? Neurosurgery. 2016 Mar;78(3):353-60. doi: 10.1227/NEU.0000000000001130.

Polanski WH1, Martin KD, Engellandt K, von Kummer R, Klingelhoefer L, Fauser M, Storch A, Schackert G, Sobottka SB. Accuracy of subthalamic nucleus targeting by T2, FLAIR and SWI-3-Tesla MRI confirmed by microelectrode recordings. Acta Neurochir (Wien). 2015 Mar;157(3):479-86. doi: 10.1007/s00701-014-2328-x. Epub 2015 Jan 18.

de Hollander G1, Keuken MC, Bazin PL, Weiss M, Neumann J, Reimann K, Wähnert M, Turner R, Forstmann BU, Schäfer A. A gradual increase of iron toward the medial-inferior tip of the subthalamic nucleus. Hum Brain Mapp. 2014 Sep;35(9):4440-9. doi:

10.1002/hbm.22485. Epub 2014 Mar 4.

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*The authors could also ask respondents what their preferred coordinates for targeting the STN in relation to MCP are and see statistically how much they differ from the atlas or MRI target.*

The authors felt that providing such coordinates may be misleading and we request the reviewer to omit these for several reasons: (i) for all limitations of the Schaltenbrand and Wahren atlas the average coordinates as read from the atlas are already presented in the manuscript; (ii) in many instances MCP-based coordinates used in clinical practice ('indirect targeting') may indicate a target below the actual 'sweet zone' albeit this zone is covered by the trajectory, and in this case the actual location of the stimulated area also depends on the angles chosen which is impossible to be taken into account; (iii) MCP-based coordinates for 'sweet zones' have been published by several groups, and these references have already been included into the manuscript; (iv) providing additional coordinates diverts attention from the main message of the manuscript, i.e. variable targeting within clearly defined anatomy, and leads to overinterpretation of less informative statistics.

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**Reviewer #3:**

*I agree that, "The anatomical sweet spot for STN stimulation needs further specification," but I find the remainder of the authors' conclusion: "before it can be transferred to individual patients for direct MRI-based target definition." to be a non sequitur.*

The sentence has been revised as follows: ... The anatomical sweet spot for STN stimulation needs further specification since this information is likely to make MRI-based target definition less variable when applied to individual patients. ...

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*Indirect targeting, as the authors assert, "represents a robust approach for STN stimulation." On the other hand, indirect targeting is, by definition, aiming at a target we cannot see and inferring its position based on its spatial relationships to visible landmarks. The success of indirect targeting relies on the assumption that each patient's subthalamic nucleus will be in the same position relative to the anterior and posterior commissures—an assumption that we know to be false. Fortunately, the position of the STN is relatively close to midline and it is not highly variable from patient to patient, so indirect targeting has worked reasonably well. One would expect that the further the position of a given patient's STN deviates from the mean, the higher the likelihood of failure of indirectly targeted STN DBS in that patient.*

The authors agree with these remarks. In rare instances the STN may be found in extreme locations and indirect targeting would result in lead malplacement. It has already been pointed out that we are not aware of centers performing pure indirect targeting. There are limitations to all approaches that have already been addressed and which are not the focus of this survey. Our survey data just indicate that even in a perfectly delineated STN (2D) targeting would probably remain variable.

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*A related observation is that indirect targeting of the GPI, the position of which is*

*substantially more variable among individuals relative to AC-PC landmarks, produces inconsistent results. My observation when retrospectively analyzing Professor Benabid's early GPI DBS cases, was that those DBS leads that were positioned in the posterior lateral ventral GPI (4 out of 12) produced excellent symptomatic relief, while the remaining 8 leads that were not as optimally positioned produced less desirable results. When the Professor switched to the less variable STN target, his results were much more consistently positive. I believe his adoption of the STN as the target of choice for PD DBS may have been largely based on a failure of indirect targeting of the GPI. He was meticulous and careful in his stereotactic technique and his indirect targeting was very consistent, but it was based on the false assumption that each patient's brain was the same as the atlas and the imaging available to him at the time was quite poor relative to today's available technology.*

The authors agree that variation will increase with targets further away from the commissural reference points. Statistical coordinates may even be of some value for targeting of the GPI. Target definition based on proportional adjustments of statistical targets (e.g. Talairach's method) have their own limitations. Issues concerning individual target adjustments have been discussed since the 1960ies (e.g. Spiegel, Talairach, van Manen, van Buren, Spiegel, Mundinger, Röder and Orthner) and – even with MR imaging – not been solved yet.

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*The authors' assertion that "…it is not obvious how advances in imaging technology can be utilized for improved clinical efficacy" is not supported by the data presented in the manuscript and adherence to this belief would likely be counterproductive to the general improvement of DBS targeting and global DBS outcomes. The notion that it might be preferable to aim at a target we cannot see than to augment our aiming strategies by exploiting modern technology to actually visualize the target seems absurd. The authors*

*themselves state at the conclusion of the manuscript that "Improved imaging capabilities together with technological advances, such as multi-segmented electrodes allowing for steering and shaping the electrical field in different directions perpendicular to the electrode, will be useful to narrow down the best site for STN stimulation. It is hoped that with such knowledge DBS may be applied with greater efficacy and reduced side effects." I agree with their final statement, and I suggest that the authors remove the contradictory, unsupported, illogical assertion that improved imaging might well result in worse DBS outcomes. On the contrary, improved imaging, as they have stated, will be one of the most useful tools that will enable us to zero in on the "sweet spot" and reach a consensus on optimal STN targeting.*

To clarify our statement we have changed the text in the manuscript as follows: ... it is not obvious how advances in imaging technology can automatically be translated into improved clinical efficacy as there is no consensus on the optimal target yet and different use will be made of superior imaging. ...

To explain this statement we may imagine a specialist who uses a certain but not optimal MRI sequence for elaborate targeting with a close to zero rate for lead malplacement. That is already possible at present (see above). The implementation of a better sequence may have an influence on the way that specialist performs targeting. Let uns assume that surgeon strives for electrode positioning within the sensorimotor region of the STN and ends up with slightly more lateral targeting by using those improved images. Initially he may encounter a higher rate of capsular side effects until he has learned to work with these superior MR images. There is no improvement that comes without potential risks, and although paradoxical or absurd at first glance, in the beginning he might be less successful than he used to be.

On the other hand, had a "sweet zone" already been defined that specialist could have used this information when implementing the superior MRI sequence and he had performed better. Even by not asssuming this theoretical worst case, that surgeon may simply perform as good as before despite have better images at hand. In other words, it is a fallacy that improved

imaging will *necessarily* improve targeting and clinical results. Reviewer #1 wrote: *"At present improved STN imaging may not necessarily improve clinical results." Although I generally agree with this statement...* (see above).

Another example would be a specialist succeeding with indirect targeting that is modified based on selected information from MRI (e.g. STN laterality). Although being successful with this method his perception of the anatomical "sweet zone" might be erroneous. If this specialists eventually moves to direct targeting because STN imaging has become almost perfect his results will get worse. On the other hand, this may not have happened if there is a proven recipe how to mark the "sweet zone" in (or at) the STN of an individual patient.

Despite all that the authors regard improved imaging capabilities as one of the key factors for the understanding of differential clinical effects elicited with different electrode locations and eventually improved or more consistent targeting.

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*Regarding methodology:*

*Although the authors' hypothesis is an important one to highlight, the manner in which this study was conducted severely limits the ability to draw a broad conclusion about the heterogeneity of target selection within the STN. Twenty-seven movement disorders specialists marked their preferred target in a predetermined coronal plane (3 mm posterior to the mid-commissural point (MCP)), sagittal plane (12 mm lateral to the MCP) and in four axial planes (0.5, 1.0, 1.5, and 3.5 mm ventral to the MCP). The selection of these particular planes inherently biases the respondent targets. Although the planes chosen can be argued as reasonable representations of "typical" STN DBS placement, as the authors are aware, the STN is represented on many more planes than those chosen. For example, in the 1977 version of the Schaltenbrand and Wahren atlas published by Thieme, the STN is present on*

*sagittal planes ranging from 6.5 to 17 mm lateral to the MCP. The relatively arbitrary restriction for participants to identify a target in the sagittal plane on the 12 mm plate biases the mean coordinate to that plane. Indeed, the mean and median laterality is reported as 12.0 mm (table 1). If given the opportunity, many respondents may have chosen to select a target on the 10.5 mm sagittal plate. Furthermore, a respondent asked to select a target separately in each of three planes, is unlikely to precisely synchronize their point across the planes. For example, the respondent identified by the dark blue dot chose a point significantly more dorsal in the coronal plane (Fig 1A) than in the sagittal plane (Fig 1B). In essence, each of the 27 respondents chose a total of 81 targets (27 respondents * 3 planes, with the exception of three participants who did not mark a target in all three planes, as commented in the last paragraph of page 7). This method introduces intrarater variability in addition to the interrater variability the study was attempting to assess. The pseudo-increased number of targets also artificially increased statistical power.*

The preselection of atlas plates for each of the three planes limits 3D assessments. The plates stem from different brains and exhibit well-known inconsistencies. This issue has already been addressed above (cf. reviewer #1). We cannot completely rule out that selected plates have influenced target selection. However, this would mainly be due to a different *shape* of the STN in different plates, but not because of the stereotactic location of the plate in the atlas. The position of the slice in the Schaltenbrand and Wahren atlas was not to be taken into account by the raters. For example, in the preselected coronal slice the authors just marked their target relative to the borders of the STN (supposed to mimick a perfect image of the STN in a coronal MRI).

Although coordinates were read from the plots and presented in the manuscript this analysis was not the main purpose of this survey. Regarding x, y and z coordinates the location of the preselected plate (e.g. 12 mm lateral for the sagittal plate) was never taken into account. For example, only the x and z coordinates of indicated points were read from this

coronal plate. On the other hand, the fact that the average x coordinate (lateral coordinates as read from axial and coronal plates) of all authors was 12.0 mm (mean and median) supports the preselection of a sagittal plate 12 mm lateral to the midline for this survey (in retrospective). Similarly, mean and median y (–1.7 mm) and z (–2.3 mm) coordinates of all authors were close to the preselected coronal (–3 mm) and axial plates (between –0.5 and –3.5 mm) presented to the authors.

The coordinates presented in Table 1 were based on averages calculated for each participant. For each participant one x coordinate representing the average x coordinate as read from coronal and axial plates, one mean y coordinate as read from sagittal and axial plate, and one mean z coordinate as read from coronal and sagittal image was calculted.

The fact that respondents have synchronized their targets to a different degree has been addressed above. Similarly, the limitations of inconsistent atlas plates have been discussed. An important message of this survey is rather that authors have a different perception of how dorsal or lateral they would choose their target relative to a clearly delineated border of the STN.

We agree that these limitations do not allow to make meaningful quantitative assessments of the heterogeneitiy of target selection. But as already pointed out, other surveys (MRI based, use of a different atlas, virtual or real models in 3D, drawings etc.) had their own limitations. Furthermore, as stereotactic coordinates from the atlas were not to be taken into account for the indication of targets we doubt that our method "introduced intrarater variability in addition to the interrater variability" to a significant extent.

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*A more impactful study would examine variability in target selection on a digitized atlas in which each plane may be assessed simultaneously (i.e. an atlas in which a respondent chooses one target in a three-dimensional space, rather than three targets in two-*

*dimensional spaces).*

The authors agree with this statement. This has already been commented on above.

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*As stated above, the conclusion that "MRI-based ('direct') targeting of STN is limited by a poorly defined sweet spot" simply cannot be inferred from this study. If anything, the study can only conclude that targeting using a two-dimensional atlas produces higher intra and inter rater variability. Overall, the study may merit publication, primarily to highlight the lack of general consensus regarding the appropriate target for STN stimulation, but significant revisions are warranted to highlight the limitations of the method used and to remove the unsupported conclusion that direct targeting is limited by a poorly defined sweet spot.*

We will not state that 'MRI-based ('direct') targeting of STN is limited by a poorly defined sweet spot' as this may be misunderstood. We have clarified our statement as follows:

- The anatomical sweet ~~spot~~ zone for STN stimulation requires further specification
- Without specified sweet zone MRI-based ('direct') targeting will remain variable

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*Also:*

*The exact instructions given to participants should be clarified.*

These are the instructions given to the authors:

## Optimal STN targeting

**Please imagine the 'ideal world:'**

- The patient's brain is 100% congruent with the Schaltenbrand & Wahren atlas
- MR imaging delineates the patient's STN in a perfect manner

**Please:**

Indicate with a cross ( X ) in the *coronal*, *sagittal*, and *axial slices* of the S&W atlas where the center of the active DBS electrode contact (1.5 mm length) for monopolar / cathodic STN stimulation with 3.5 mA / 60 usec / 130 Hz should be placed.

**Please mark:**

___ neurologist ___ neurosurgeon ___ other

**Email:**

_____

**THANK YOU !!!**

_____

*There may be, in some cases, a difference between the optimal place to stimulate and the optimal place to position the active electrode because placing the active contact in the center of the "sweet spot" for therapeutic stimulation might result, based on the 3 mm VTA, spread current into the internal capsule with adverse effects.*

*Therefore, the questions:*

*Where is the optimal location to stimulate in the STN for therapeutic benefit?*

*Where is the optimal location to position the active contact for STN stimulation?*

*Might have different answers…*

What was asked for is (cf. Instructions):

"*Where is the optimal location to position the active contact for STN stimulation?*"

---

*In the figure legend it is not explicitly stated that in 1D and 1E the 3 mm radius yellow sphere is indicative of the volume of activation, centered at the mean point of the surveyed responses.*

This important information was missing. We added the following sentence to the figure legend:

... Yellow spheres in D and E indicate the volume of tissue activated (3 mm radius) centered at the mean target indicated by all participants. ...

---

*The individual points in figure 1C are extremely difficulty to visualize. Either the resolution of the figure should be increased to allow the reader to zoom in with greater definition, or the individual points should be made larger.*

The figure has been revised accordingly (individual points were enlarged).

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*In table 1, it is not clear in which group the two clinical neuroscientists are included (neurologists or neurosurgeons).*

The two clinical neuroscientists have not been included into this analysis. This has been stated in the manuscript (cf. page 8, first paragraph). We have added this information to the Table legend. ... Both clinical neuroscientists were excluded from this comparison. ...

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*A reference for the Shaltenbrand and Wahren atlas used by participants and represented in figure 1 should be present*

This reference has been added:

Schaltenbrand G, Wahren W (1977) Atlas for stereotaxy of the human brain, 2nd Ed. Thieme, Stuttgart

*– Original Article –*

# Targeting of the subthalamic nucleus for deep brain stimulation: a survey among Parkinson's disease specialists

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**Running title:** STN targeting survey

**Key words:** deep brain stimulation, Parkinson's disease, subthalamic nucleus, targeting

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**Abstract**

**Background:** Deep brain stimulation (DBS) within or adjacent to the subthalamic nucleus (STN) currently represents the most common stereotactic procedure performed for Parkinson's disease. Better STN imaging is often regarded as a requirement for improving stereotactic targeting. But, remarkably enough, it is unclear whether there is a consensus about the optimal target.

**Objective and Methods:** To obtain an expert opinion on the site regarded optimal for 'STN stimulation', movement disorder specialists were asked to indicate their preferred position for an active contact on hardcopies of the Schaltenbrand and Wahren atlas depicting the STN in all three planes. This represented an idealized setting and it mimicked optimal imaging for direct target definition in a perfectly delineated STN.

**Results:** The suggested targets were heterogeneous, although some clustering was observed in the dorsolateral STN and subthalamic area. In particular, in the anterior-posterior direction the intended targets differed to a great extent. Most of the indicated targets are thought to also result in concomitant stimulation of structures adjacent to the STN, including the zona incerta, Fields of Forel, and/or the internal capsule.

**Conclusions:** This survey illustrates that most sites regarded as optimal for 'STN stimulation' are close to each other, but ~~that even with perfect delineation of the STN,~~ there appears to be no uniform perception of the optimal anatomical target, possibly influencing surgical results. The anatomical sweet ~~spot~~ zone for STN stimulation needs further specification ~~before it can be transferred to individual patients for direct MRI-based target definition.~~ since this information is likely to make MRI-based target definition less variable when applied to individual patients.

**Introduction**

High-frequency stimulation of the subthalamic nucleus (STN) ameliorates most parkinsonian signs and motor complications and allows for a significant reduction of dopaminergic medication [1-3]. This results in improved quality of life in selected patients suffering from Parkinson's disease (PD) [4-6]. With regard to the surgery itself, avoidance of adverse events and proper targeting represent the most important prerequisites for a successful operation. It is interesting to note the extent to which surgical planning can vary among different surgeons and centers. Laitinen once performed a survey regarding the preferred surgical target for treatment of parkinsonism [7]. The variability of the indicated targets was astonishing considering that the procedure had been conducted on thousands of patients with success.

Present-day STN surgery differs from thalamotomy because in principle, the STN can be visualized and directly targeted. Although direct targeting is still limited by current magnetic resonance imaging (MRI) capabilities, these might be improved by ongoing developments such as higher-field-strength imaging [8]. Assuming that the STN can be delineated in a better manner, it is unclear whether this could lead stereotactic surgeons to define exactly the same target. It is also conceivable that clearer imaging might result in the opposite, i.e. more variable targeting.

To obtain an opinion about the site regarded as clinically optimal for STN stimulation, a panel of movement disorder specialists was asked to indicate their preferred position for an active electrode contact. In contrast to Laitinen's survey [7], not only neurosurgeons but also neurologists and neuroscientists were invited to participate and our survey was limited to a single target (i.e. STN) only. Other targets used in PD patients, in particular the ventrolateral thalamus and globus pallidus, were not considered.

**Methods**

This survey was conducted at an advisory board meeting. Thirty-three movement disorder specialists were asked to mark where the active contact (1.5 mm length) of an STN electrode should be placed. The presupposition was an 'ideal world' in which (i) the patient's brain is congruent with the Schaltenbrand and Wahren atlas [9] and (ii) MR imaging delineates the patient's STN in a perfect manner. With these assumptions, *direct* targeting can be performed without being limited by poor imaging. The active contact was intended to be used for monopolar (cathodic) stimulation with 3.5 mA, 60 µsec, and 130 Hz. Participants were asked to indicate their preferred position with a pencil on paper copies of the Schaltenbrand and Wahren stereotactic atlas. The following planes were used: coronal, 3 mm posterior to MCP; sagittal, 12 mm lateral to midline; axial, 0.5, 1.0, 1.5, and 3.5 mm below the intercommissural plane. Coronal and sagittal slices had been magnified (10 mm on the hardcopy corresponded to 1 mm in the atlas brain). Stereotactic positions of the markings were manually read. Coordinates were visualized in a digitized version of the Schaltenbrand and Wahren atlas using open-source libraries programmed by one of the authors (JAK) using 'coin3D' (https://bitbucket.org/Coin3D/coin/wiki/Home).

**Results**

Twenty-seven movement disorder specialists contributed to this survey. The panel included 13 neurologists, 12 neurosurgeons, and two clinical neuroscientists. Three participants did not mark the target in all the three planes for different reasons, and available data were included. Six other participants of the meeting were also invited to participate but did not respond.

Mean and median stereotactic (x,y,z) coordinates of all participants are presented in Table 1. Average coordinates (x,y,z) did not differ between neurologists and neurosurgeons (both clinical neuroscientists were excluded from this comparison; Student's t test, p >0.5; no correction for multiple comparisons). The maximum deviation between targets indicated by different authors was 5.5 mm in the medial-lateral direction, 6.1 mm in the anterior-posterior direction, and 5.8 mm in the dorsal-ventral (superior-inferior) direction (Table 1).

There were also intrarater differences for x, y, and z coordinates as read from the Schaltenbrand and Wahren atlas. These can be accounted for by inconsistencies within the atlas [10] as well as different efforts of the participants to adjust targets between different atlas planes. However, it is important to note that the inherent coordinate system of the atlas was not to be taken into account but merely the outline of the anatomical structures.

The targets indicated for the placement of the active contact and permanent STN stimulation were variable (Figure 1A–C). The least variation was observed in the coronal plane, where clustering of preferred targets could be observed in the dorsolateral portion of the STN corresponding to its sensorimotor territory (Figure 1A). In the sagittal plane, most participants chose their target in the dorsal (superior) half of the STN (Figure 1B). Despite variation in the anterior-posterior axis, the rostral two-thirds of the STN were preferred (Figure 1B and C). In the axial plane, most authors set their target at or rostral to the anterior border of the red nucleus (Figure 1C). Nevertheless, four authors who defined their target within the atlas slice located 3.5 mm below the intercommissural plane preferred a position clearly posterior to the anterior rim of the red nucleus (Figure 1C). Four authors indicated their target at the dorsal border of the anterior STN or slightly above within the subthalamic area (Figure 1B and C).

Based on the prescribed stimulation parameters, a radius of 3 mm was arbitrarily chosen as a rough approximation for the volume of activated tissue [11,12]. This indicates that radiant from the mean stereotactic coordinates of all participants (cf. Table 1), the upper two-thirds and rostral three quarters of the STN would be stimulated (green area in Figure 1D and E). Some current would also be applied to parts of the fields of Forel and the zona incerta (Figure 1D and E). In addition, current would radiate to the medial border of the internal capsule (Figure 1D and E). In Figure 1F, the dimensions of a usual DBS electrode contact (1.5 mm in length and 1.3 mm in width) placed along typical angles would be projected into a coronal section.

**Discussion**

This survey indicates that there is no consensus on the best site for STN stimulation. The densest cluster was observed in the coronal plane, where the dorsolateral part of the STN was preferred. This corresponds to the region of the STN receiving sensorimotor input from cortical motor areas and the external pallidum [13-18]. The sensorimotor region, at least to a great extent, coincides with the area exhibiting characteristic beta oscillations and enhanced synchronization in PD [19-22]. Nevertheless, a considerable degree of variability remained along the main axis of the STN from antero-superior-lateral to posterior-inferior-medial. Several participants preferred targeting posterior to the anterior rim of the red nucleus, representing a commonly used landmark [23,24]. The ventral STN was avoided by most participants.

Despite the fact that targeting was variable it is important to note that the standard deviation in each plane is in the range of the dimensions of electrode contacts of typical DBS leads. Most of the indicated targets cluster within 2 mm of the mean point, and most can be found

within the estimated volume of tissue activated as outlined for the mean point. Taking into account that cumulative errors of stereotactic surgery often cannot be kept in the submillimetric range, the variation found in this survey is also similar to the inaccuracy inherent to stereotactic procedures. Furthermore, most of the variation in this survey was found along an anterodorsal to posteromedial direction. This corresponds to usual trajectories chosen for STN electrode implantation by frontolateral approaches. Thus, in clinical practice some of the variation will be compensated for by the selection of appropriate contacts of multipolar electrodes.

Direct targeting represents the preferred approach at some centers requiring optimal delineation of the STN (e.g. [25-27]). For this survey, idealized conditions were provided. Thus, the degree of variation among participants cannot be explained by poor target delineation that may occur with suboptimal MR imaging. The Schaltenbrand and Wahren atlas was chosen because it not only provides the highest resolution but also delineates adjacent structures. These could be taken into account for target definition or when estimating current distribution from the indicated targets. This survey, however, did not involve true 3D targeting as the plates of the Schaltenbrand and Wahren atlas are known to be incongruent [10]. In commercial stereotactic planning software any target modification in one of the three standard orthogonal planes would be followed by proper adjustments in the other planes. It cannot be ruled out, but it is regarded as unlikely that the variation found in this survey had been overcome by corresponding target adjustments in other planes.

From the volume of tissue hypothesized to be activated by the predefined stimulation parameters arbitrarily chosen in the upper range of what is clinically used, practically all the indicated targets of this survey resulted in concomitant, albeit weaker, stimulation of structures adjacent to the STN. This included the fields of Forel and the zona incerta located

dorsal and medial to the STN, and possibly conveying (long-lasting) therapeutic effects [28-31]. Furthermore, the medial part of the internal capsule was encroached by STN stimulation from most of the indicated sites. A more lateral position of contacts within the STN was suggested to be associated with improved motor outcome [32]. However, too lateral stimulation bears the risk of tonic muscle contractions, in particular with more posterior targeting of the STN. Moreover, concomitant stimulation of the corticospinal tracts may limit the therapeutic window by worsening bradykinesia, despite good improvement of rigidity [33].

This survey is naturally lacking clinical feedback data. The 'optimal' site for STN stimulation represents a trade-off between beneficial effects and adverse events. Definition of an 'optimal' target is made even more complex by the fact that improvement of particular symptoms may vary depending on the site used for STN stimulation (for example, rigidity versus bradykinesia [34]). Such uncertainties, along with the actual dimensions of electrode contacts, inconsistent delineation of the STN depending on the MRI sequence [35], and the volume of tissue activated by DBS, put the impact of individual anatomical variation of the STN into perspective. This may explain the value of statistical (average) coordinates for targeting of the STN ~~and why indirect targeting represents a robust approach for STN stimulation~~ (e.g. [24]). It is noteworthy that the average target indicated by participants of this survey (cf. Table 1) is close to what has been reported for active contact locations in actual patient cohorts. Based on such studies, the average coordinates for active electrode contacts are: x= 12.1 mm; y= –1.4 mm; z= –1.8 mm [36-49].

Taken together, we found that even in an idealized setting ~~with perfect delineation of the STN~~, targeting among DBS specialists remains variable and there appears to be no uniform perception of the optimal anatomical target. Thus, contrary to the common notion it is not obvious how advances in imaging technology can ~~be utilized for improved clinical efficacy.~~

automatically be translated into improved clinical efficacy as there is no consensus on the optimal target yet and different use will be made of superior imaging. This survey rather suggests that the anatomical sweet ~~spot~~ zone for STN stimulation needs further specification ~~before it can be transferred to individual patients for direct MRI-based target definition.~~ since this information is likely to make MRI-based target definition less variable when applied to individual patients. Improved imaging capabilities together with technological advances, such as multi-segmented electrodes allowing for steering and shaping the electrical field in different directions perpendicular to the electrode [50,51]8, will be useful to narrow down the best site for STN stimulation. It is hoped that with such knowledge DBS may be applied with greater efficacy and reduced side effects.

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**Figure legends**

**Figure 1**

A, D, and F, coronal (3 mm posterior to the midcommissural point, MCP), B and E, sagittal (12 mm lateral to MCP), and C, axial (0.5, 1.0, 1.5, and 3.5 mm below MCP) sections from the Schaltenbrand and Wahren atlas in which participants indicated their preferred target for STN stimulation. Each dot represents the target of an individual participant. Yellow spheres in D and E indicate the volume of tissue activated (3 mm radius) centered at the mean target indicated by all participants. In F, the active contact according to average coordinates of all participants is indicated in red. Structures adjacent to subthalamic nucleus (S.th.) are: Z.i., zona incerta; $H_1$, $H_2$, fields of Forel $H_1$, $H_2$; N.i., substantia nigra; Cp.i.p., posterior limb of internal capsule; Ru, red nucleus.

## Highlights

- There is no consensus among experts on optimal site for STN stimulation
- Most indicated sites would result in concomitant DBS of structures adjacent to STN
- The anatomical sweet ~~spot~~ zone for STN stimulation requires further specification
- Without specified sweet zone MRI-based ('direct') targeting will remain variable
- ~~MRI-based ('direct') targeting of STN is limited by poorly defined sweet spot~~
- At present improved STN imaging may not necessarily improve clinical results

**Table 1. Stereotactic coordinates for image-based planning of STN surgery**

| | x | y | z |
|---|---|---|---|
| Mean | 12.0 | – 1.7 | – 2.3 |
| Median | 12.0 | – 1.7 | – 2.3 |
| Standard deviation | 1.2 | 1.4 | 1.2 |
| Min. | 9.0 | –4.8 | –5.8 |
| Max. | 14.5 | 1.3 | 0 |

Coordinates indicate the distance from the midcommissural point in the Schaltenbrand and Wahren atlas in the lateral (x), anterior-posterior (y), and inferior-superior (z) direction. Average coordinates in mm (± standard deviation; range) for neurologists (nl) and neurosurgeons (ns) were as follows: $x_{nl}$= 12.1 (±0.9; 10 to 13.9); $x_{ns}$= 12.0 (±1.4; 9 to 14.5); $y_{nl}$= –1.4 (±1.4; –4.2 to 1.3); $y_{ns}$= –2.1 (±1.4; –4.8 to 0); $z_{nl}$= –2.1 (±0.7; –3.3 to –0.8); $x_{ns}$= –2.7 (±1.5; –5.8 to –0.3). Both clinical neuroscientists were excluded from this comparison.

## Highlights

- There is no consensus among experts on optimal site for STN stimulation
- Most indicated sites would result in concomitant DBS of structures adjacent to STN
- The anatomical sweet zone for STN stimulation requires further specification
- Without specified sweet zone MRI-based ('direct') targeting will remain variable
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*– Original Article –*

# Targeting of the subthalamic nucleus for deep brain stimulation: a survey among Parkinson's disease specialists

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**Running title:** STN targeting survey

**Key words:** deep brain stimulation, Parkinson's disease, subthalamic nucleus, targeting

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**Abstract**

**Background:** Deep brain stimulation (DBS) within or adjacent to the subthalamic nucleus (STN) currently represents the most common stereotactic procedure performed for Parkinson's disease. Better STN imaging is often regarded as a requirement for improving stereotactic targeting. But, remarkably enough, it is unclear whether there is a consensus about the optimal target.

**Objective and Methods:** To obtain an expert opinion on the site regarded optimal for 'STN stimulation', movement disorder specialists were asked to indicate their preferred position for an active contact on hardcopies of the Schaltenbrand and Wahren atlas depicting the STN in all three planes. This represented an idealized setting and it mimicked optimal imaging for direct target definition in a perfectly delineated STN.

**Results:** The suggested targets were heterogeneous, although some clustering was observed in the dorsolateral STN and subthalamic area. In particular, in the anterior-posterior direction the intended targets differed to a great extent. Most of the indicated targets are thought to also result in concomitant stimulation of structures adjacent to the STN, including the zona incerta, Fields of Forel, and/or the internal capsule.

**Conclusions:** This survey illustrates that most sites regarded as optimal for 'STN stimulation' are close to each other, but there appears to be no uniform perception of the optimal anatomical target, possibly influencing surgical results. The anatomical sweet zone for STN stimulation needs further specification since this information is likely to make MRI-based target definition less variable when applied to individual patients.

**Introduction**

High-frequency stimulation of the subthalamic nucleus (STN) ameliorates most parkinsonian signs and motor complications and allows for a significant reduction of dopaminergic medication [1-3]. This results in improved quality of life in selected patients suffering from Parkinson's disease (PD) [4-6]. With regard to the surgery itself, avoidance of adverse events and proper targeting represent the most important prerequisites for a successful operation. It is interesting to note the extent to which surgical planning can vary among different surgeons and centers. Laitinen once performed a survey regarding the preferred surgical target for treatment of parkinsonism [7]. The variability of the indicated targets was astonishing considering that the procedure had been conducted on thousands of patients with success.

Present-day STN surgery differs from thalamotomy because in principle, the STN can be visualized and directly targeted. Although direct targeting is still limited by current magnetic resonance imaging (MRI) capabilities, these might be improved by ongoing developments such as higher-field-strength imaging [8]. Assuming that the STN can be delineated in a better manner, it is unclear whether this could lead stereotactic surgeons to define exactly the same target. It is also conceivable that clearer imaging might result in the opposite, i.e. more variable targeting.

To obtain an opinion about the site regarded as clinically optimal for STN stimulation, a panel of movement disorder specialists was asked to indicate their preferred position for an active electrode contact. In contrast to Laitinen's survey [7], not only neurosurgeons but also neurologists and neuroscientists were invited to participate and our survey was limited to a single target (i.e. STN) only. Other targets used in PD patients, in particular the ventrolateral thalamus and globus pallidus, were not considered.

**Methods**

This survey was conducted at an advisory board meeting. Thirty-three movement disorder specialists were asked to mark where the active contact (1.5 mm length) of an STN electrode should be placed. The presupposition was an 'ideal world' in which (i) the patient's brain is congruent with the Schaltenbrand and Wahren atlas [9] and (ii) MR imaging delineates the patient's STN in a perfect manner. With these assumptions, *direct* targeting can be performed without being limited by poor imaging. The active contact was intended to be used for monopolar (cathodic) stimulation with 3.5 mA, 60 μsec, and 130 Hz. Participants were asked to indicate their preferred position with a pencil on paper copies of the Schaltenbrand and Wahren stereotactic atlas. The following planes were used: coronal, 3 mm posterior to MCP; sagittal, 12 mm lateral to midline; axial, 0.5, 1.0, 1.5, and 3.5 mm below the intercommissural plane. Coronal and sagittal slices had been magnified (10 mm on the hardcopy corresponded to 1 mm in the atlas brain). Stereotactic positions of the markings were manually read. Coordinates were visualized in a digitized version of the Schaltenbrand and Wahren atlas using open-source libraries programmed by one of the authors (JAK) using 'coin3D' (https://bitbucket.org/Coin3D/coin/wiki/Home).

**Results**

Twenty-seven movement disorder specialists contributed to this survey. The panel included 13 neurologists, 12 neurosurgeons, and two clinical neuroscientists. Three participants did not mark the target in all the three planes for different reasons, and available data were included. Six other participants of the meeting were also invited to participate but did not respond.

Mean and median stereotactic (x,y,z) coordinates of all participants are presented in Table 1. Average coordinates (x,y,z) did not differ between neurologists and neurosurgeons (both clinical neuroscientists were excluded from this comparison; Student's t test, $p > 0.5$; no correction for multiple comparisons). The maximum deviation between targets indicated by different authors was 5.5 mm in the medial-lateral direction, 6.1 mm in the anterior-posterior direction, and 5.8 mm in the dorsal-ventral (superior-inferior) direction (Table 1).

There were also intrarater differences for x, y, and z coordinates as read from the Schaltenbrand and Wahren atlas. These can be accounted for by inconsistencies within the atlas [10] as well as different efforts of the participants to adjust targets between different atlas planes. However, it is important to note that the inherent coordinate system of the atlas was not to be taken into account but merely the outline of the anatomical structures.

The targets indicated for the placement of the active contact and permanent STN stimulation were variable (Figure 1A–C). The least variation was observed in the coronal plane, where clustering of preferred targets could be observed in the dorsolateral portion of the STN corresponding to its sensorimotor territory (Figure 1A). In the sagittal plane, most participants chose their target in the dorsal (superior) half of the STN (Figure 1B). Despite variation in the anterior-posterior axis, the rostral two-thirds of the STN were preferred (Figure 1B and C**)**. In the axial plane, most authors set their target at or rostral to the anterior border of the red nucleus (Figure 1C). Nevertheless, four authors who defined their target within the atlas slice located 3.5 mm below the intercommissural plane preferred a position clearly posterior to the anterior rim of the red nucleus (Figure 1C). Four authors indicated their target at the dorsal border of the anterior STN or slightly above within the subthalamic area (Figure 1B and C).

Based on the prescribed stimulation parameters, a radius of 3 mm was arbitrarily chosen as a rough approximation for the volume of activated tissue [11,12]. This indicates that radiant from the mean stereotactic coordinates of all participants (cf. Table 1), the upper two-thirds and rostral three quarters of the STN would be stimulated (green area in Figure 1D and E). Some current would also be applied to parts of the fields of Forel and the zona incerta (Figure 1D and E). In addition, current would radiate to the medial border of the internal capsule (Figure 1D and E). In Figure 1F, the dimensions of a usual DBS electrode contact (1.5 mm in length and 1.3 mm in width) placed along typical angles would be projected into a coronal section.

**Discussion**

This survey indicates that there is no consensus on the best site for STN stimulation. The densest cluster was observed in the coronal plane, where the dorsolateral part of the STN was preferred. This corresponds to the region of the STN receiving sensorimotor input from cortical motor areas and the external pallidum [13-18]. The sensorimotor region, at least to a great extent, coincides with the area exhibiting characteristic beta oscillations and enhanced synchronization in PD [19-22]. Nevertheless, a considerable degree of variability remained along the main axis of the STN from antero-superior-lateral to posterior-inferior-medial. Several participants preferred targeting posterior to the anterior rim of the red nucleus, representing a commonly used landmark [23,24]. The ventral STN was avoided by most participants.

Despite the fact that targeting was variable it is important to note that the standard deviation in each plane is in the range of the dimensions of electrode contacts of typical DBS leads. Most of the indicated targets cluster within 2 mm of the mean point, and most can be found

within the estimated volume of tissue activated as outlined for the mean point. Taking into account that cumulative errors of stereotactic surgery often cannot be kept in the submillimetric range, the variation found in this survey is also similar to the inaccuracy inherent to stereotactic procedures. Furthermore, most of the variation in this survey was found along an anterodorsal to posteromedial direction. This corresponds to usual trajectories chosen for STN electrode implantation by frontolateral approaches. Thus, in clinical practice some of the variation will be compensated for by the selection of appropriate contacts of multipolar electrodes.

Direct targeting represents the preferred approach at some centers requiring optimal delineation of the STN (e.g. [25-27]). For this survey, idealized conditions were provided. Thus, the degree of variation among participants cannot be explained by poor target delineation that may occur with suboptimal MR imaging. The Schaltenbrand and Wahren atlas was chosen because it not only provides the highest resolution but also delineates adjacent structures. These could be taken into account for target definition or when estimating current distribution from the indicated targets. This survey, however, did not involve true 3D targeting as the plates of the Schaltenbrand and Wahren atlas are known to be incongruent [10]. In commercial stereotactic planning software any target modification in one of the three standard orthogonal planes would be followed by proper adjustments in the other planes. It cannot be ruled out, but it is regarded as unlikely that the variation found in this survey had been overcome by corresponding target adjustments in other planes.

From the volume of tissue hypothesized to be activated by the predefined stimulation parameters arbitrarily chosen in the upper range of what is clinically used, practically all the indicated targets of this survey resulted in concomitant, albeit weaker, stimulation of structures adjacent to the STN. This included the fields of Forel and the zona incerta located

dorsal and medial to the STN, and possibly conveying (long-lasting) therapeutic effects [28-31]. Furthermore, the medial part of the internal capsule was encroached by STN stimulation from most of the indicated sites. A more lateral position of contacts within the STN was suggested to be associated with improved motor outcome [32]. However, too lateral stimulation bears the risk of tonic muscle contractions, in particular with more posterior targeting of the STN. Moreover, concomitant stimulation of the corticospinal tracts may limit the therapeutic window by worsening bradykinesia, despite good improvement of rigidity [33].

This survey is naturally lacking clinical feedback data. The 'optimal' site for STN stimulation represents a trade-off between beneficial effects and adverse events. Definition of an 'optimal' target is made even more complex by the fact that improvement of particular symptoms may vary depending on the site used for STN stimulation (for example, rigidity versus bradykinesia [34]). Such uncertainties, along with the actual dimensions of electrode contacts, inconsistent delineation of the STN depending on the MRI sequence [35], and the volume of tissue activated by DBS, put the impact of individual anatomical variation of the STN into perspective. This may explain the value of statistical (average) coordinates for targeting of the STN (e.g. [24]). It is noteworthy that the average target indicated by participants of this survey (cf. Table 1) is close to what has been reported for active contact locations in actual patient cohorts. Based on such studies, the average coordinates for active electrode contacts are: x= 12.1 mm; y= –1.4 mm; z= –1.8 mm [36-49].

Taken together, we found that even in an idealized setting targeting among DBS specialists remains variable and there appears to be no uniform perception of the optimal anatomical target. Thus, contrary to the common notion it is not obvious how advances in imaging technology can automatically be translated into improved clinical efficacy as there is no consensus on the optimal target yet and different use will be made of superior imaging. This

survey rather suggests that the anatomical sweet zone for STN stimulation needs further since this information is likely to make MRI-based target definition less variable when applied to individual patients. Improved imaging capabilities together with technological advances, such as multi-segmented electrodes allowing for steering and shaping the electrical field in different directions perpendicular to the electrode [50,51]8, will be useful to narrow down the best site for STN stimulation. It is hoped that with such knowledge DBS may be applied with greater efficacy and reduced side effects.

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**Figure legends**

**Figure 1**

A, D, and F, coronal (3 mm posterior to the midcommissural point, MCP), B and E, sagittal (12 mm lateral to MCP), and C, axial (0.5, 1.0, 1.5, and 3.5 mm below MCP) sections from the Schaltenbrand and Wahren atlas in which participants indicated their preferred target for STN stimulation. Each dot represents the target of an individual participant. Yellow spheres in D and E indicate the volume of tissue activated (3 mm radius) centered at the mean target indicated by all participants. In F, the active contact according to average coordinates of all participants is indicated in red. Structures adjacent to subthalamic nucleus (S.th.) are: Z.i., zona incerta; $H_1$, $H_2$, fields of Forel $H_1$, $H_2$; N.i., substantia nigra; Cp.i.p., posterior limb of internal capsule; Ru, red nucleus.

**Table 1. Stereotactic coordinates for image-based planning of STN surgery**

| | x | y | z |
|---|---|---|---|
| Mean | 12.0 | – 1.7 | – 2.3 |
| Median | 12.0 | – 1.7 | – 2.3 |
| Standard deviation | 1.2 | 1.4 | 1.2 |
| Min. | 9.0 | –4.8 | –5.8 |
| Max. | 14.5 | 1.3 | 0 |

Coordinates indicate the distance from the midcommissural point in the Schaltenbrand and Wahren atlas in the lateral (x), anterior-posterior (y), and inferior-superior (z) direction. Average coordinates in mm (± standard deviation; range) for neurologists (nl) and neurosurgeons (ns) were as follows: $x_{nl}$= 12.1 (±0.9; 10 to 13.9); $x_{ns}$= 12.0 (±1.4; 9 to 14.5); $y_{nl}$= –1.4 (±1.4; –4.2 to 1.3); $y_{ns}$= –2.1 (±1.4; –4.8 to 0); $z_{nl}$= –2.1 (±0.7; –3.3 to –0.8); $x_{ns}$= –2.7 (±1.5; –5.8 to –0.3). Both clinical neuroscientists were excluded from this comparison.

Figure(s)
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