Deep brain stimulation of the STN was introduced as a treatment for advanced Parkinson disease in 1993. Patients who initially showed a good response to levodopa but suffer from on-off fluctuations after a prolonged medication regimen have been shown to benefit from STN DBS. The beneficial effects of STN DBS on the motor symptoms of Parkinson disease have been described in long-term follow-up studies, but unwanted stimulation-induced side effects can occur. These side effects have been described as cognitive deterioration and behavioral changes and have been reported in approximately 40%–50% of patients. It is hypothesized that these side effects are the result of direct stimulation of or current spread to the nonmotor parts of the STN.

In addition to a large dorsolateral motor part, the STN has 2 other functional subterritories, namely a small ventromedial limbic part and a cognitive part intermediate in position and size. Precise targeting of the dorsolateral (motor) part of the STN is of great importance for 2 reasons: first of all, to obtain the best possible effect on motor symptoms, and second, to minimize the undesirable side effects on cognition and behavior. Yet, the operative technique of targeting the STN has not been standardized, and the authors of this review aimed to summarize the current state of the art concerning MR imaging–based targeting techniques for STN DBS in patients with Parkinson disease.

The authors reviewed 70 publications on MR imaging–based targeting techniques for identifying the subthalamic nucleus (STN) for deep brain stimulation in patients with Parkinson disease. Of these 70 publications, 33 presented quantitatively validated results. There is still no consensus on which targeting technique to use for surgery planning; methods vary greatly between centers. Some groups apply indirect methods involving anatomical landmarks, or atlases incorporating anatomical or functional data. Others perform direct visualization on MR imaging, using T2-weighted spin echo or inversion recovery protocols.

The combined studies do not offer a straightforward conclusion on the best targeting protocol. Indirect methods are not patient specific, leading to varying results between cases. On the other hand, direct targeting on MR imaging suffers from lack of contrast within the subthalamic region, resulting in a poor delineation of the STN. These deficiencies result in a need for intraoperative adaptation of the original target based on test stimulation with or without microelectrode recording.

It is expected that future advances in MR imaging technology will lead to improvements in direct targeting. The use of new MR imaging modalities such as diffusion MR imaging might even lead to the specific identification of the different functional parts of the STN, such as the dorsolateral sensorimotor part, the target for deep brain stimulation.

Abbreviations used in this paper: AC = anterior commissure; DBS = deep brain stimulation; FSE = fast spin echo; IR = inversion recovery; MCP = midcommissural point; MER = microelectrode recording; MPRAGE = magnetization prepared rapid acquisition gradient echo; PC = posterior commissure; STIR = short tau inversion recovery; STN = subthalamic nucleus; TSE = turbo spin echo.

This article contains some figures that are displayed in color online but in black and white in the print edition.
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STN DBS including the imaging method for primary targeting of the STN still varies greatly between centers. Magnetic resonance imaging is one of the most frequently used modalities, alone or in combination with CT or ventriculography. Most DBS procedures also involve a secondary targeting step using intraoperative assessments, such as MER or macrostimulation, to adapt the position of the electrodes to the clinical goals.

The aim of this paper is to review the multitude of available methods and give a systematic overview of techniques for primary targeting of the dorsolateral part of the STN. This review discusses both indirect and direct targeting procedures, as well as comparative studies. The overall focus of the review is on MR imaging, because this modality is most widely used. The next section of this paper will summarize indirect and direct targeting methods using MR imaging. Subsequently, the results of the systematic review will be presented. Finally, the advantages and drawbacks of the targeting techniques will be discussed.

Summary of Targeting Methods

Methods for targeting the dorsolateral STN can be classified as either direct or indirect. Indirect methods rely on contextual information, while direct methods focus on visualizing the STN itself on preoperative images.

Indirect Targeting

Indirect targeting can rely on 2 types of contextual information—patient-specific landmarks or generic atlas information adapted to the patient’s anatomy.

The gold standard in indirect targeting using anatomical landmarks involves the AC and PC. Once one has localized the AC, PC, and the midcommissural point, the stereotactic coordinates of the STN follow from fixed distances based on classical atlases such as the Schaltenbrand-Wahren brain atlas, as can be seen in Fig. 1. The second most widely used landmark is the red nucleus (Fig. 2). Less widespread methods include the use of the nigrocapsular angle (as explained in Fig. 3), the supramammillary commissure, the postmammillary commissure, and the line connecting the mammillary bodies and the PC.

Furthermore, regions of interest can also be determined by mapping an anatomical and/or functional atlas onto the patient’s MR imaging (see Fig. 4). Anatomical atlases incorporate information about the position of brain structures. The most popular ones are the Talairach-Tournoux atlas, the Schaltenbrand-Wahren atlas, and the Montreal Neurological Institute atlas. Functional atlases consist of point sets that are collected during MER, postoperative imaging or neurological assessments.

Direct Targeting

Direct targeting involves the use of specific MR imaging protocols that enable direct visualization of the STN, avoiding the need to employ contextual information.

Fig. 1. Diagram showing AC-PC line–based targeting in a sagittal plane. After the AC and PC are identified, the midcommissural point (MCP) is determined. From there, the STN position can be calculated using fixed distances (often 12 mm lateral, 3 mm inferior, and 3 mm posterior) based on an atlas.

An often used method is the T2-weighted FSE MR imaging protocol, on which the STN shows as a hypointense area (see Fig. 5). Another popular technique for direct visualization is the IR protocol (see Fig. 6). Still subject to more research are the use of relaxation time maps and susceptibility-weighted (T2*) imaging (see Fig. 7), together with special postprocessing methods to reduce signal loss and enhance contrast.

Systematic Review

In order to present a review on the different targeting methods, we performed a thorough search for papers on STN targeting. The criteria that we used are briefly outlined below.

Search Strategy

First, we searched PubMed and ScienceDirect for papers published between January 1999 and January 2011, using the terms “targeting,” “magnetic resonance imaging,” “MRI,” or “visualization” in combination with “subthalamic nucleus” or “STN.” Second, we explored the bibliographies of relevant publications until no further additional studies were found. Papers were selected if they provided qualitative descriptions or quantitative results of direct or indirect MR imaging–based STN targeting methods. Language other than English was an exclusion criterion.

We included 70 publications, of which 33 studies quantitatively validated results of patient trials. The quantitative results are reported in Tables 1–4. The details extracted from the studies for this purpose included the following: number of subjects, targeting techniques used (landmark, MR imaging protocol, atlas, registration method), validation method, outcome, and the main conclusion.

Indirect Targeting

Anatomical Landmarks. Publications on landmark-
Magnetic resonance imaging for STN visualization

Based targeting presenting quantitative results can be found in Table 1. After the ventriculography-based study by Schuurman et al. in 1999,\(^7\) one of the first MR imaging–based studies was presented by Starr et al.\(^8\) Their AC-PC line–based targets differed 1–1.5 mm from directly visualized STNs. Due to the variability in manual selection of the AC-PC line,\(^6\) the need for automated methods became apparent. Ardekani and Bachman\(^5\) used an atlas-based automatic analysis method, and the resulting landmarks were very close (within 1 mm) to points determined manually. A similar study by Pallavaram et al.\(^6\) yielded more accurate targets than achieved by manual selection.

The first studies on red nucleus–based targeting were presented by Aziz et al.\(^7\) and Bejiani et al.\(^8\) The latter reported selection of the central electrode in 19 of 24 cases. However, authors of other studies, based on best response\(^2\) and anatomical relationships,\(^2\) have stated that the red nucleus is not reliable enough. To solve this, Liu et al.\(^6\) used the red nucleus and the substantia nigra, but they did not report quantitative results. Pollo et al.\(^6\) exploited the AC-PC line, red nucleus, thalamus, internal capsule, substantia nigra, and midline, resulting in a mean target in the inferior STN.

Regarding less widespread methods, according to Giller et al.,\(^3\) the use of the nigrocapsular angle was justified by the higher visibility of the internal capsule and substantia nigra on MR imaging. Lee et al.\(^5\) proposed the supramammillary commissure, which lacked reliability. Toda et al.\(^3\) used the postmammillary commissure and selected the central electrode in 81% of cases. Finally, Rijkers et al.\(^7\) suggested the line connecting the mammillary bodies and PC, although this remains to be validated.

**Brain Atlas Registration.** Table 2 summarizes the papers found on atlas-based STN targeting that presented quantitative results. Ortega et al.\(^6\) digitized the anatomical Talairach-Tournoux atlas, registered it nonlinearly, and compared the resulting targets with recorded microelectrode positions, obtaining good results. However, Nowinski et al.\(^6\) demonstrated inconsistency of the 3 planes for an anatomical atlas in the STN region, restricting the use of the atlas in 3D.

Sánchez-Castro et al. collected MR imaging data with visible STNs to use as a brain atlas.\(^1\) Duay et al.\(^3\) increased the speed of the registration algorithm and showed that the targeting variability is comparable to that of an expert, with a registration error similar to those reported by Sánchez-Castro et al.\(^7\) Bardinet et al.\(^3\) combined 2 kinds of anatomical information, namely histological and MR imaging data, into a human basal ganglia atlas (see also Yelnik et al.\(^1\)). After atlas registration, the resulting STN coordinates correlated well with MER and postoperative MR imaging. The authors improved the registration step, enabling a better match with individual patient anatomy (error < 1 mm).\(^8\)

With respect to functional atlases, Nowinski et al.\(^6\) investigated the differences in spatial position between the anatomical and functional STN. The anatomical STN was derived from the Schaltenbrand-Wahren atlas,\(^7\) while the functional STN was constructed from ventriculography, MER, and radiographic data, and neurological assessment of 184 patients with Parkinson disease.\(^5\) The anatomical and functional STN correlated well.

D’Haese et al.\(^2\) developed a targeting method using MER and optimal electrode contacts determined postoperatively and showed that automatic target prediction is feasible. Pallavaram et al.\(^6\) extended this, achieving a bet-

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**Fig. 2.** Diagram showing red nucleus–based targeting in an axial plane. The center of the STN lies on the same line as the anterior boundary of the red nucleus (RN).

**Fig. 3.** Diagram showing targeting based on the nigrocapsular angle, in a sagittal plane. The STN lies in the corner that is formed by the descending internal capsule (IC) and the substantia nigra (SN).
ter correlation of the electrophysiological maps with the underlying anatomy. Guo et al. compared 6 methods using functional data, including a brain atlas, MER data, and a collection of previous targets. The combination of all data performed best, followed by the previous targets and the MER data. All 3 methods provided a more accurate estimation than techniques solely dependent on anatomy. The authors used these results to construct probabilistic maps for STN DBS trajectory planning.

Direct Targeting

**T2-Weighted MR Imaging.** As can be seen in Table 3, a multitude of papers have reported validated results of T2-weighted MR imaging for direct STN identification. Starr et al. showed that direct targeting is possible on T2-weighted FSE MR imaging, leading to consistent electrode placement in the dorsolateral STN. Bejjani et al. selected the central track for implantation in 19 of their 24 cases. Egidi et al. reported even slightly better results: their visualized target track was chosen in 85% of cases. Dormont et al. examined postmortem tissue and showed that the hypointense signal reported by these first studies correlates with the presence of iron and corresponds anatomically to the STN. They noted, however, that the most posterior part of the STN was not visible in any of the cases.

In addition, research has been done on the correspondence between MR imaging–based and landmark-based STN coordinates. Zhu et al. and Richter et al. concluded that MR imaging is needed, because atlas-based coordinates suffer from interpatient variability in STN size and position. Littlechild et al. and Slavin et al. both reported that the STN target varies considerably in relation to the midcommissural point, again suggesting that direct visualization on MR imaging enables more accurate targeting than the atlas-based method. Ashkan et al. confirmed this, finding a significant difference between the atlas target and the STN as visualized on MR imaging. They found that the latter is on average 1.7 mm more medial, 0.7 mm more anterior, and 0.7 mm more ventral than the atlas target.

A substantial interindividual variability of STN size, orientation, and position and a significant difference between MR imaging– and atlas-based coordinates in 66 patients was also demonstrated by Patel et al. Davies and Daniluk and colleagues found similar variation, based on series of 60 and 62 patients. In the latter series, the lateral coordinate of the STN varied by as much as 5.8 mm and the anteroposterior size of the STN varied by 8 mm, implying that the use of atlas-based targeting may result in failure to identify the STN during MER.

Patel et al. validated direct targeting on axial and coronal MR images. In a first series, they used macrostimulation for target adjustment; subsequently target verification was based on preoperative MR imaging only. The latter method yielded a mean error of only 0.3–0.4 mm. Together with a follow-up study on the improvement of activities of daily living and the motor score, this led to the conclusion that targeting based on T2-weighted MR imaging is safe and effective.
Inversion Recovery MR Imaging. Researchers have also investigated IR methods for direct visualization of the basal ganglia. Starr et al. identified the globus pallidus internus, while Benabid et al. depicted the globus pallidus internus and the thalamus. The protocols they used were not suitable for visualizing the STN. Although many research groups have tried to improve upon these results, no quantitative studies on this subject are available yet.

Kitajima et al. proposed the STIR method and compared this to T2-weighted FSE MR imaging. The upper and lateral STN margins were depicted more clearly by FSE, while fast STIR was superior with respect to the visibility of the lower margin and provided a better contrast between the STN and substantia nigra. In addition, Taoka et al. developed 2 sets of guidelines that facilitate identification of the STN on STIR images, the so-called “Suke-roku sign” and the “dent internal-capule sign.” Ishimori et al. investigated phase-sensitive IR and showed that the STN position on IR MR imaging differs by at most 2 mm from the coordinates found with AC-PC line–based targeting—comparable to the results obtained with T2-weighted images.6

Susceptibility-Weighted MR Imaging. Apart from T2-weighted and IR MR imaging, it is also possible to acquire T2*-weighted (susceptibility-weighted) MR images, and T2* imaging is even more sensitive to local iron deposits, as occur in the STN among other areas. Dormont et al. established the correlation of these iron deposits and the hypointensities on T2*-weighted MR imaging, while Slavin et al. applied this to 3T data. Taoka et al. also visualized the iron content of the STN using T2*-weighted MR imaging. They compared the results with STIR MR imaging and found that the posterior STN parts were not visible on the T2*-weighted images, leading to the conclusion that a combination with STIR might be more useful to target the STN.

Bonny et al. generated multiple images with increased T2*-weighting to maximize the contrast between the STN and surrounding structures. Elolf et al. used multiple gradient echoes to add contrast to conventional T1-weighted MR imaging. Wu et al. used a steady-state free precession MR imaging method, facilitating the visualization of midbrain nuclei with a heavy T2*-weighting and relatively short echo time. However, none of these studies presented quantitative results on STN targeting.

To enhance T2*-weighted images, Volz et al. presented a method to reduce signal loss, resulting in good contrast. Another applicable technique is susceptibility-weighted imaging, a method that uses the phase data. Young and Chen exploited this technique to produce T2* contrast additive to the T1 or T2 contrast intrinsic to the imaging protocol, thus improving the contrast between the nuclei of interest. Rauscher et al. and Vertinsky et al. also performed postprocessing with phase images, giving rise to a better visibility of the STN and even of the subthalamic fasciculus. However, for these methods again, the STN position as identified on MR imaging has not been validated.

Relaxation-Time Maps Derived From MR Imaging. Apart from T1-, T2- or T2*-weighted acquisitions, it is also possible to map the true relaxation time for each
voxel by performing multiple MR acquisitions with different parameters. Bonny et al.12 already reconstructed T2* maps from their measurements in 2001. Helms et al.45 used T2* maps for improved delineation of iron-rich structures, in particular the STN and substantia nigra. Lebel et al.51 investigated T2* mapping of the basal ganglia at 4.7 T, and obtained increased spatial resolution and sensitivity to iron content.

Guo et al.36 were the first to introduce relaxation-time maps for T1 and T2 into their DBS targeting application.37,39 They compared the centers of basal ganglia nuclei based on the relaxation-time maps with the coordinates derived from the Schaltenbrand-Wahren atlas and the actual surgical targets in 15 patients who underwent surgery. As the mean displacement was 3.21 ± 0.80 mm, these results indicated the potential of the relaxation-time maps for DBS targeting.

High Field Strength MR Imaging. Following the example of Lebel et al.,51 more studies have recently been published on direct visualization of the STN and other basal ganglia using MR imaging scanners with high field strengths. Aboesch et al.1 acquired susceptibility-weighted MR imaging data at 7.0 T and showed that the superior resolution and contrast at this field strength dramatically improved delineation of the STN. Cho et al.19 also visualized the STN using T2*-weighted scans obtained with a 7-T MR imaging unit, and in addition imaged the substantia nigra in 9 healthy controls and 8 patients with Parkinson disease, revealing distinct morphological changes due to this disorder.20

Comparative Studies

Much research has been done on the comparison of direct and indirect targeting. Table 4 summarizes the comparative papers that presented quantitative results.

Studies That Favor Indirect Targeting. Zonenshayn et al.103 investigated STN targeting using 4 different methods, namely: 1) coronal MR imaging, 2) the STN center on a Schaltenbrand-Wahren atlas, 3) targeting based on the AC-PC line, and 4) a composite target based on all 3 methods. The results were compared with the final target (found with help of MER). The combination of 3 methods appeared to be best, while the use of MR imaging as a sole method gave the worst result. Cuny et al.23 also compared 3 methods. The first technique was direct identification on T2-weighted MR imaging (see Table 1). The second and third methods both involved indirect targeting based on the AC-PC line, determined by ventriculography or MR imaging, respectively. The most effective contact was taken as the gold standard. The authors concluded that indirect targeting based on MR imaging worked best, while direct targeting gave the worst outcome.

Andrade-Souza et al.3 investigated direct targeting using coronal MR imaging, indirect targeting using the AC-PC line, and a technique using the red nucleus as a landmark. The implantation was optimized using MER, while the most effective contact was identified using postoperative MR imaging. After comparing the mean distances between the targets and optimal contact, the authors concluded that indirect targeting based on MR imaging worked best, while direct targeting gave the worst outcome.

In further research, Andrade-Souza et al.4 compared 2D T2-weighted axial and 3D reconstruction MR imaging. They found that indirect and direct targets based on 3D reconstruction more closely approximate the optimal contact than targets chosen using 2D MR imaging. However, both indirect targets were better than the direct targets.

Studies That Favor Direct Targeting on MR Imaging. Starr et al.82 performed MR imaging and MER to target the STN. They used a combination of indirect AC-PC line–based targeting and direct targeting on T2-weighted MR imaging. The authors managed to visualize the STN directly for 92% of procedures, which supports the choice for direct imaging instead of AC-PC line–based methods for STN targeting. The reliability of indirect methods as compared with direct targeting was also investigated by...
Magnetic resonance imaging for STN visualization

Schlaier et al. They determined STN targets in 5 different ways: 1) direct targeting using axial T2-weighted MR imaging, 2) direct targeting on coronal T2-weighted MR imaging, 3) indirect targeting using an axial atlas slice, 4) indirect targeting on a coronal atlas slice, and 5) indirect targeting using AC-PC references. Direct targeting seemed more reliable than atlas-based targeting, due to large interpatient variability in the STN coordinates as derived from MR imaging. Ashkan et al. confirmed these results on variability in STN position. Their direct target differed on average 0.7–1.7 mm in all 3 directions.

Although the results of all studies described showed superior reliability for direct targeting, the finding was not validated with intra- or postoperative information. Koike et al. did use the identified STN thickness during MER and clinical parameters, namely the effect of DBS on the disease and on the medication dose, as evaluation parameters. They compared direct targeting on T2-weighted FSE MR imaging to the conventional indirect AC-PC line–based method. The results showed a significantly larger mean STN thickness (indicating a longer electrode track through the STN and thus better target-
ing) in the direct targeting group, and clinical parameters also displayed larger improvements in the direct targeting group.

Although all studies mentioned previously in this section used 1.5-T MR imaging, Acar et al.² investigated the benefit of direct targeting on 3.0-T MR images over traditional AC-PC line–based targeting using 1.5-T MR images. They calculated Euclidean distances between the directly and indirectly determined coordinates in 3 dimensions, resulting in mean differences between the two locations of 0.45 mm, 0.72 mm, and 0.98 mm in the x, y, and z axes, respectively. According to the authors, MR imaging has advanced to the extent that direct targeting of the STN is no longer imprecise.

### Discussion

In this paper we reviewed indirect and direct STN targeting methods based on MR imaging. The most common indirect methods use either landmarks such as the AC-PC line⁴⁻⁶,⁹,¹⁸,¹⁹,²⁶ and the red nucleus⁵,¹⁰,²³,²⁷ or atlases built from anatomical⁵,⁸,¹⁸,³¹,⁷⁶ and/or functional¹⁰,²⁴,³⁷,³⁹,⁵⁹,⁶³ information. These methods are applicable in all cases but are not very patient specific. Direct methods already in use clinically comprise T2-weighted FSE¹⁰,²⁹,³²,⁸³ and IR MR imaging.¹⁷,⁴⁸,⁸⁶ These techniques can account for interpatient variability,⁶,²⁶,⁵⁵,⁶⁷,⁸⁰ but have drawbacks of their own, including low contrast and technical issues,⁴⁴ such as a long acquisition time,¹⁰,⁶⁶,¹⁰² required reformatting of images, and the need for preparatory T1-weighted sequences used to plan the acquisition of T2-weighted sequences.¹⁰,⁸²

The comparative studies presented do not provide us with a straightforward conclusion on the best STN targeting protocol. Earlier publications tend to favor indirect methods, mainly based on the AC-PC line, while authors of more recent studies are more inclined to prefer direct visualization. Most publications reported the use of 1.5-T MR imaging, and the majority of hospitals still use this field strength, so the recent preference for direct targeting is not likely to be due to 3-T MR imaging. The phenomenon might be caused by advances in MR imaging at 1.5 T, with respect to contrast, noise, and distortion, resulting in a targeting method that is more specific than AC-PC line–based targeting. Due to continuous progress in MR imaging technology, improvements in direct targeting are still anticipated.

Although it seems that the future of STN targeting will be focused on patient-specific direct methods, it is nevertheless important to keep in mind the limitations of STN visualization on anatomical MR imaging. Often only the anterior STN is visible as a hypointense region.²⁹ In addition, the contrast between the STN and surrounding structures is not optimal, hindering identification of the STN boundaries.³³,⁴⁵,⁴⁸ Furthermore, the question remains whether the visualized STN coincides with the functional target for DBS (often determined by MER).⁴⁰,⁴³,⁵⁵ Promising new methods such as relaxation-time maps and susceptibility-weighted imaging, as well
TABLE 3: Summary of direct studies using T2−weighted MR imaging and relaxation-time maps

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Pts</th>
<th>MRI Protocol</th>
<th>Validation Method</th>
<th>Outcome</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starr et al., 1999</td>
<td>6</td>
<td>coronal T2−weighted FSE MRI, 1.5 T</td>
<td>MER</td>
<td>coordinates close to AC−PC−based values; initial MER track passed through the STN in every case</td>
<td>Direct visualization facilitates reliable targeting of the STN, but MER mapping remains necessary.</td>
</tr>
<tr>
<td>Starr, 2002</td>
<td>44</td>
<td>coronal T2−weighted FSE MRI, 1.5 T</td>
<td>MER &amp; postop MRI</td>
<td>STN directly visualized on MRI in 92% of cases; MER used to adapt target intraoperatively</td>
<td>Combined approach leads to consistent electrode placement in the dorsolateral STN.</td>
</tr>
<tr>
<td>Bejjani et al., 2000</td>
<td>12</td>
<td>coronal T2−weighted spin-echo MRI, 1.5 T</td>
<td>MER &amp; optimal contact position</td>
<td>central track selected for 19 of 24 electrodes</td>
<td>MRI targeting is useful for STN stimulation but should be combined w/ MER.</td>
</tr>
<tr>
<td>Egidi et al., 2002</td>
<td>13</td>
<td>axial T2−weighted spin-echo MRI, 1.5 T</td>
<td>MER &amp; postop MRI</td>
<td>targeted track chosen for 22 of 26 electrodes</td>
<td>1.5-T MR images are highly effective for STN targeting.</td>
</tr>
<tr>
<td>Littlechild et al., 2003</td>
<td>25</td>
<td>axial T2−weighted MRI, 1.5 T</td>
<td>MER &amp; optimal contact position</td>
<td>sig variation in target position (4−5 mm); mean distance btw target &amp; electrode 1.7 mm</td>
<td>The STN varies in position &amp; can be accurately targeted from MRI alone.</td>
</tr>
<tr>
<td>Slavin et al., 2006</td>
<td>13</td>
<td>T2−weighted FSE MRI in 3 directions, 3.0 T</td>
<td>MER</td>
<td>variation in target position ~2 mm; all tracks pass through STN</td>
<td>3 T MRI enables accurate direct visualization of the STN.</td>
</tr>
<tr>
<td>Patel et al., 2002</td>
<td>26, 19†</td>
<td>axial &amp; coronal T2−weighted MRI, 1.5 T</td>
<td>macrostimulation, intraop MRI</td>
<td>mean target error of 0.3 mm mediolat &amp; 0.4 mm AP</td>
<td>MRI-directed targeting of the STN through guide tubes is accurate &amp; allows direct verification &amp; corrections as necessary.</td>
</tr>
<tr>
<td>Guo et al., 2005</td>
<td>15</td>
<td>T1 &amp; T2 maps, 1.5 T</td>
<td>atlas coordinates, actual surgical targets</td>
<td>mean displacement 3.21 ± 0.80 mm</td>
<td>The results indicate the potential capability of this system to accurately identify the STN.</td>
</tr>
</tbody>
</table>

* AP = anteroposterior.
† The authors performed a first series of 26 cases using intraoperative macrostimulation as the control method and a subsequent series of 19 patients with MR imaging−based verification.

as imaging at 7 T, have not been validated yet in large clinical studies. Besides, technical issues strongly influence the MR imaging procedure and quality. Examples are the MR compatibility of the stereotactic frame, image artifacts due to patient movement, and magnetic field distortion, although distortion can be controlled reasonably for the midbrain. Because of these issues, further research into STN localization methods, both direct and indirect, seems necessary.

The comparative studies that have validated the targeting with the most effective contact location also have their limitations. The conclusions of Cuny et al.,23 Andrade-Souza et al.,3,4 and Breit et al.,13 that indirect targeting is more relevant for electrode placement, should thus be considered with care. Because the primary targeting in these studies was indirect, the final contact, even after intraoperative adjustment, was close to the original indirect target. In addition, analyzing indirect versus direct targeting according to the optimal contact only emphasizes differences between the final position and the primary targets. This bias would of course also exist if primary targeting were to be performed using a direct method. Caire et al.37 also compared STN localization methods based on the AC−PC line and 1.5-T MR imaging, revealing significant differences in all 3 dimensions. Instead of drawing conclusions about which targeting method is more suitable, the authors stated that apparently it would be better to conclude that the indirect AC−PC line−based target does not coincide with the center of the STN as visualized on anatomical MR imaging. Moreover, various follow-up42,50,54,75 and postmortem84 studies state that the best clinical target is located in the dorsolateral part of the STN and the area just superior to the STN (zona incerta, field of Forel).

The results from several papers show that stimulating the dorsolateral motor part of the STN is more effective than stimulating the center.7,42,50,54,75,84 As conventional direct targeting on anatomical MR imaging cannot distinguish the dorsolateral STN due to lack of contrast, it is useful to further investigate the use of other MR imaging−based methods to facilitate specific targeting of this area of the STN. Examples of techniques that have not yet proven their clinical utility but might aid in STN localization are the use of landmarks such as the nigrocapsular angle,44 the mammillary commissures,32,91 and the line connecting the mammillary bodies.73 In addition, a fast-developing line of research focuses on susceptibility-weighted MR imaging and T2* mapping to improve the
TABLE 4: Summary of studies comparing indirect and direct methods

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Pts</th>
<th>Methods</th>
<th>Validation Method</th>
<th>Outcome</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zonenshayn et al., 2000</td>
<td>15</td>
<td>coronal MRI (T2-weighted/IR), atlas, AC-PC, combination</td>
<td>final target based on MER</td>
<td>distance between MRI/final target: 2.6 ± 1.3 mm; distance between composite/final target: 1.3 ± 1.1 mm</td>
<td>Combination of 3 targeting methods offers best correlation with the final target.</td>
</tr>
<tr>
<td>Cuny et al., 2002</td>
<td>14</td>
<td>T2-weighted MRI, AC-PC w/ ventriculog, AC-PC w/ MRI</td>
<td>most effective contact</td>
<td>distance between AC-PC (MRI)/best contact: 2.6 ± 1.2 mm; distance between direct/best contact: 3.9 ± 1.9 mm</td>
<td>Indirect targeting based on MRI works best; direct targeting gives worst outcome.</td>
</tr>
<tr>
<td>Andrade-Souza et al., 2005³</td>
<td>14</td>
<td>coronal MRI, AC-PC, RN-based targeting</td>
<td>optimal contact (MER &amp; postop MRI)</td>
<td>distances to optimal contact: MRI: 4.7 mm; AC-PC: 3.4 mm; RN: 3.2 mm</td>
<td>RN is a reliable marker to approximate the optimal contact position.</td>
</tr>
<tr>
<td>Breit et al., 2006</td>
<td>30</td>
<td>coronal T2-weighted MRI, AC-PC based on ventriculog</td>
<td>most effective contact</td>
<td>mean targeting error 4.1 ± 1.7 mm for MRI &amp; 2.4 ± 1.1 mm for AC-PC</td>
<td>AC-PC using ventriculog is more accurate than direct targeting on MRI.</td>
</tr>
<tr>
<td>Castro et al., 2006</td>
<td>39</td>
<td>coronal T2-weighted IR MRI, anatomical atlas based on direct targets</td>
<td>comp in MRI coordinate system</td>
<td>best atlas registration method (B-splines): avg error 1.72 ± 0.48 mm</td>
<td>Automatic STN targeting is possible &amp; as accurate as current expert methods.</td>
</tr>
<tr>
<td>Andrade-Souza et al., 2005⁴</td>
<td>14</td>
<td>axial T2-weighted MRI, 3D reconstr (both direct &amp; indirect)</td>
<td>optimal contact (MER &amp; postop MRI)</td>
<td>distances to optimal contact: 2D MRI direct: 4.7 mm; 3D reconstr direct: 3.5 mm; 2D MRI indirect: 3.4 mm; 3D reconstr indirect: 2.6 mm</td>
<td>3D reconstruction leads to a better approximation of the optimal contact; indirect methods are better than direct targets.</td>
</tr>
<tr>
<td>Starr, 2002</td>
<td>44</td>
<td>coronal T2-weighted FSE MRI, AC-PC</td>
<td>comp in atlas coordinate system</td>
<td>in 34% the STN lies &gt;1 mm more lateral than 12 mm &amp; in 40% the STN lies &gt;1 mm lower than 4 mm</td>
<td>Direct targeting accounts better for interpatient variability than indirect targeting.</td>
</tr>
<tr>
<td>Schlaier et al., 2005</td>
<td>14</td>
<td>axial/coronal T2-weighted MRI &amp; atlas, AC-PC</td>
<td>comp in atlas coordinate system</td>
<td>all STN coordinates displayed a range of 4–5 mm</td>
<td>Direct targeting is more reliable due to large interpatient variability.</td>
</tr>
<tr>
<td>Ashkan et al., 2007</td>
<td>29</td>
<td>axial T2-weighted MRI, AC-PC</td>
<td>comp in atlas coordinate system</td>
<td>direct: 1.7 mm more medial, 0.7 mm more anterior, 0.7 mm more ventral</td>
<td>Direct targeting is more accurate due to variability in STN position.</td>
</tr>
<tr>
<td>Koike et al., 2008</td>
<td>44</td>
<td>T2-weighted FSE MRI (using RN), AC-PC</td>
<td>MER &amp; clinical parameters</td>
<td>direct group: longer track through STN &amp; larger clinical improvement</td>
<td>Direct targeting with single-track recording can be standard for DBS.</td>
</tr>
<tr>
<td>Acar et al., 2007</td>
<td>20</td>
<td>axial T2-weighted FSE MRI (3T), AC-PC (1.5T)</td>
<td>comp in atlas coordinate system</td>
<td>mean distances were 0.45 mm, 0.72 mm &amp; 0.98 mm in x, y, z directions</td>
<td>Direct targeting is no longer impractical and/or imprecise.</td>
</tr>
<tr>
<td>Caire et al., 2009</td>
<td>22</td>
<td>coronal T2-weighted TSE MRI, AC-PC</td>
<td>comp of STN center coordinates</td>
<td>sig differences in coordinates in all 3 directions</td>
<td>MRI- &amp; AC-PC–based targets do not coincide.</td>
</tr>
</tbody>
</table>

* Reconstr = reconstruction.

It is unlikely, however, that this improved contrast would give rise to identification of the dorsolateral STN specifically.

In addition to trying to identify the dorsolateral STN, possibilities of dividing the STN functionally and identifying the motor part should also be investigated. Modalities such as functional or diffusion-weighted MR imaging could yield features that facilitate separation of the motor part of the STN. Diffusion-weighted MR imaging sensitizes the MR acquisition to water diffusion in specific directions. The diffusion profile in a voxel can be fitted as an ellipse (diffusion tensor imaging) or a higher order shape (high angular resolution diffusion imaging). By analyzing these profiles in the STN itself, it has been shown that different parts of the STN in a rat brain could be separated visually and automatically. Recently, Coenen et al. also published a case study on diffusion tensor imaging–based fiber anatomy in the STN region, to help identification of the tremor suppression target. Apart from the primary targeting based on (MR) imaging, there are other parts of the surgical “pipeline” that influence the clinical outcome of a DBS procedure and should not be ignored. The most important are the type of stereotactic frame, the selection of the trajectory (this can be done manually or automatically), registration of different imaging modalities, intraoperative brain shift, intraoperative electrode adjustment, and postoperative parameter estimation. In striving for the best possible re-
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sults of DBS, all these factors should be given appropriate attention.

Conclusions

This review gave a systematic overview of studies on noninvasive STN targeting. The studies either presented a single indirect or direct targeting method, or compared different techniques. Because each method has been shown to have its own benefits but also specific drawbacks, it is not possible to reach a straightforward conclusion on which targeting technique should be used. Therefore, identification of the dorsolateral and motor part of the STN remains an open question, although it is expected that future advances in MRI technology will help to find an answer to this question.

Disclosure

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References

24. D’Haese PF, Cetinkaya E, Konrad PE, Kao C, Dawant BM:
27. Danish SF, Jaggi JL, Moyer JT, Finkel L, Baltuch GH: Con
28. Davies KG, Daniluk S: Stereotactic targeting of the subtha
29. Dormont D, Ricciardi KG, Tandé D, Parain K, Menuel C,
30. Dormont D, Seidenwurm D, Galanaud D, Cornu P, Yelnik J,
32. Elolf E, Bockermann V, Gringel T, Knauth M, Dechent P,
33. Elolf E, Bockermann V, Gringel T, Knauth M, Dechent P,
34. Giller CA, Babcock EE, Mendelsohn DB: Use of sagittal im
37. Hamani C, Richter EO, Andrade-Souza Y, Hutchinson W, Si
38. Hamani C, Richter EO, Andrade-Souza Y, Hutchinson W, Si
40. Hamani C, Richter EO, Andrade-Souza Y, Hutchison W, Si
41. Hamani C, Saint-Cyr JA, Fraser J, Kaplitt M, Lozano AM: Th
42. Hamel W, Fietzek U, Morsocha A, Schrader B, Herzog J, We
44. Hariz MI, Krack P, Melvill J, Jörgensen JV, Hamel W, Hira
46. Hamels S, Sauner D, Maarouf M, Poggenborg J, Lachner K, S
47. Ishimori T, Nakano S, Mori Y, Seo R, Togami T, Masuda T, e
48. Ishimori T, Nakano S, Mori Y, Seo R, Togami T, Masuda T, e
49. Kojke Y, Shima F, Nakamizo A, Miyagi Y: Direct localizat
52. Lee C, Young B, Sanders MF: The role of the supramammil
53. Littlechild P, Varma TRK, Eldridge PR, Fox S, Forster A, Flech
55. Littlechild P, Varma TRK, Eldridge PR, Fox S, Forster A, Flech
56. Liu X, Rowe J, Nandi D, Hayward G, Parkin S, Stein J, et a
57. Luders HO, Dujardin J, Talairach J: Variability in the STN si
58. Luschei SE, Sailas D, Mangelson DL, Davis V: Rat striatum a
59. Luschei SE, Sailas D, Mangelson DL, Davis V: Rat striatum a
60. Luschei SE, Sailas D, Mangelson DL, Davis V: Rat striatum a
61. Luschei SE, Sailas D, Mangelson DL, Davis V: Rat striatum a
62. Luschei SE, Sailas D, Mangelson DL, Davis V: Rat striatum a
63. Luschei SE, Sailas D, Mangelson DL, Davis V: Rat striatum a
64. Luschei SE, Sailas D, Mangelson DL, Davis V: Rat striatum a
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