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Probabilistic conversion of neurosurgical DBS electrode coordinates into MNI space

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Abstract

In neurosurgical literature, findings such as deep brain stimulation (DBS) electrode positions are conventionally reported in relation to the anterior and posterior commissures of the individual patient (AC/PC coordinates). However, the neuroimaging literature including neuroanatomical atlases, activation patterns, and brain connectivity maps has converged on a different population-based standard (MNI coordinates). Ideally, one could relate these two literatures by directly transforming MRIs from neurosurgical patients into MNI space. However obtaining these patient MRIs can prove difficult or impossible, especially for older studies or those with hundreds of patients. Here, we introduce a methodology for mapping an AC/PC coordinate (such as a DBS electrode position) to MNI space without the need for MRI scans from the patients themselves. We validate our approach using a cohort of DBS patients in which MRIs are available, and test whether several variations on our approach provide added benefit. We then use our approach to convert previously reported DBS electrode coordinates from eight different neurological and psychiatric diseases into MNI space. Finally, we demonstrate the value of such a conversion using the DBS target for essential tremor as an example, relating the site of the active DBS contact to different MNI atlases as well as anatomical and functional connectomes in MNI space.

Introduction

In the field of functional neurosurgery, target locations have been described using coordinates of a defined stereotactic space since 1906 (Clarke and Horsley, 1906). Currently,

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the Schaltenbrand-Wahren atlas for stereotaxy of the human brain (Schaltenbrand et al., 1977) and the Talairach Co-planar stereotactic Atlas of the Human Brain (Talairach and Tournoux, 1988) serve as standards for reporting brain locations with respect to the anterior commissure (AC) and posterior commissure (PC). Both the AC and PC are small structures that can clearly be identified and are considered relatively invariant in their spatial location (Brett et al., 2002). The largest studies of deep brain stimulation (DBS) for a variety of neurological and psychiatric indications have reported electrode locations in ACPC coordinates (Table 1). In contrast to neurosurgery, the neuroimaging field has gradually moved away from the single-subject AC/PC standard to population-based atlases. In 1994, the Montreal Neurological Institute (MNI) matched anatomical images of 305 subjects to the Talairach brain (Collins, 1994), which was iteratively refined to the MNI152 2009 NLIN atlas (Fonov et al., 2009). This MNI atlas space has become the standard for reporting results across thousands of neuroimaging studies.

Given these different coordinate system standards, it is difficult to relate findings in the neurosurgical literature (such as clinical DBS response at a given AC/PC coordinate) to findings in the neuroimaging literature (such as activation or connectivity). Relating these two atlas standards is potentially valuable as there are an increasing number of resources available in MNI space that could lend insight into the effect of stimulation at a given brain location (Fox et al., 2014; Horn and Kühn, 2015; Höflich et al., 2010). These MNI resources include subcortical atlases based on histology (Amunts et al., 2013; Chakravarty et al., 2006; Jakab et al., 2012; Krauth et al., 2010; Morel, 2013; Yelnik et al., 2007), high-field MRI (Keuken et al., 2013; 2014), structural connectivity (Accolla et al., 2014; Behrens et al., 2003) and functional connectivity (Choi et al., 2012; Zhang et al. 2008). Beyond atlases, there are increasingly detailed structural and functional connectome datasets in MNI space (Horn, 2015; Mori et al., 2008; Yeh and Tseng, 2011; Yeo et al., 2011; Setsompop et al., 2013; van Essen et al., 2012) that can be used to investigate the connectivity properties of DBS targets (Fox et al., 2014) or brain lesions (Boes et al., 2015; Laganiere et al., 2016; Fischer et al., 2016; Darby et al., 2016).

There are several potential options for converting AC/PC coordinates from a neurosurgical study into MNI space. By far the best option is to obtain the MRI data from the neurosurgical patients included in the study and directly warp their brains into MNI space. This allows for direct conversion between each patient's AC/PC coordinates and MNI coordinates. Indeed some neurosurgical studies are beginning to use this approach and report results in MNI space (Barow et al., 2014; Hohlefeld et al., 2015; Horn and Kühn, 2015; Merkl et al., 2015; 2013; Neumann et al., 2015a; 2015b; Riva-Posse et al., 2014; Schönecker et al., 2009; Schroll et al., 2015). However, these studies are few relative to the wealth of information in the neurosurigical literature. For example, papers reporting MNI coordinates of DBS sites for Parkinson's disease range from 10–20 patients (e.g. Barow et al., 2014; Neumann et al., 2015), compared to >150 patients for papers reporting AC/PC coordinates (e.g. Caire et al., 2013). Moreover, for most treatment indications, no studies have reported MNI coordinates (Höflich et al., 2010; see Table 1). Obtaining pre and post operative neuroimaging from all these neurosurgical cohorts for direct transformation into MNI space is difficult if not impossible. A conversion tool between AC/PC coordinates and MNI space

that does not require the original MRI scans from the neurosurgical patients themselves would be valuable.

However, transforming between coordinate systems is not straightforward. For example, the MNI brain is substantially larger than average (Allen et al., 2002), whereas the Talairach brain is smaller than average (Figure 1). Talairach-to-MNI conversion tools based on linear (Brett et al., 2002; Lancaster et al., 2007) and nonlinear transforms (Lacadie et al., 2008) were designed to map from *Talairach* to MNI – not from AC/PC coordinates used in functional surgery. Explicitly, surgical coordinates are often reported relative to the patient's midcommisural point (MCP) or even the PC, requiring an initial conversion into AC-based Talairach-coordinates. This additional conversion step requires knowing the AC-PC distance of the cohort, which is rarely reported (for exceptions see Papavassiliou et al., 2004; Ponce et al., 2015). The AC-PC distance varies between Talairach and MNI space, from 19 to 32 mm across single subjects, and from 24.9 to 28.3 mm across different populations (Figure 1; Fiandaca et al., 2011; Lee et al., 2008; Liang et al., 2015; Papavassiliou et al., 2004). Moreover, the exact landmarks used to define the AC and PC themselves vary across centers (Weiss et al., 2003; Figure 1 b).

Here, we present a method that converts AC/PC coordinates to MNI space in a probabilistic fashion. In contrast to the solutions mentioned above, mappings are carried out using the individual anatomy in large cohorts of subjects. We validated our approach using two cohorts of DBS patients, one with Parkinson's disease (PD) with DBS to the subthalamic nucleus (STN) and one with Treatment-resistant Depression (TRD) with DBS to the subcallosal cingulate (SCC; Merkl et al., 2015). We chose the PD cohort because the STN is the most common stereotactic target world-wide and spatially close to the AC and PC. We chose the TRD cohort because the subcallosal cingulate is much further from the AC-PC line, helping test for generalizability of our approach. Following validation, we then use our approach to transform average AC/PC coordinates reported in the neurosurgical DBS literature into MNI space. Finally, we demonstrate how using such a conversion allows one to take advantage of MNI-based atlases and tools such as anatomical and functional connectomes to better characterize DBS locations.

Methods

Subject cohorts and imaging

450 subjects total from five cohorts were used in this study. The reason for including different cohorts was to determine the relative value of using young healthy subjects, age-matched, disease-matched, or disease severity matched cohorts for our probabilistic mapping.

1. *Young*: 32 young healthy subjects were downloaded from the Human Connectome Project database (mean age 31.5 years ± 8.6 SD, 14 female, see acknowledgements; Setsompop et al., 2013). 3 subjects of the original 35 were excluded because they lacked a T2-weighted anatomical image. T2-weighted images had an isotropic voxel size of 0.7 mm and were acquired on the

customized MGH Siemens 3T Connectome scanner. Detailed scanning parameters can be found on the project website (https://ida.loni.usc.edu/).

2. *PD DBS Patients*: 39 PD patients were treated with DBS to the STN (mean age 59.0 years ± 7.9 SD, 14 female). Details regarding this patient cohort are available in supplementary material (S1). T2-weighted images had an in-plane axial resolution of 0.51 × 0.51 mm and a slice thickness of 2 mm. Detailed scanning parameters have been published previously (Horn and Kühn, 2015). Patients in this cohort are referred to as *other DBS patients* when comparing single mappings of one patient to the mapping based on the rest of the group (leave-one-out design).

3. *PD Disease Matched*: 160 PD patients were downloaded from the from the Parkinson's progression markers initiative (PPMI) database PPMI database (mean age 61.3 ± 9.4 SD, 56 female). T2-weighted images had an in plane resolution of 0.94 × 0.94 and a slice thickness of 3 mm. Detailed scanning parameters can be found on the project website (www.ppmi-info.org).

4. *TRD DBS Patients*: 9 patients suffering from treatment-resistant depression (TRD) underwent DBS surgery to the subcallosal cingulate (mean age: 50.11 years ± 12.73 SD, 4 women). Details regarding this patient cohort have been published previously (Merkl et al., 2015). T2-weighted images had an in-plane axial resolution of 0.51 × 0.51 mm and a slice thickness of 2 mm. Detailed scanning parameters have been published previously (Horn and Kühn, 2015). As above, patients in this cohort are referred to as *other DBS patients* when comparing single mappings of one patient to the mapping based on the rest of the group (leave-one-out design).

5. *Age matched*: 564 healthy subjects with a large age range (mean age: 48.12 years ± 16.5 SD, age range 19–86 years, 341 women) were downloaded from the IXI database (http://brain-development.org/ixi-dataset/; Kuklisova-Murgasova et al., 2011). T2-weighted images had a resolution of 0.94 × 0.94 × 1.00 mm. Detailed scanning parameters can be found on the project website. For each AC/PC coordinate from a DBS study, 30 subjects of the 564 were chosen to match the mean age of the DBS patient population. In total, 210 subjects from this dataset were used in the present analysis.

Identifying the AC and PC

In the neurosurgical literature, AC and PC are usually marked manually and the MCP is computed. However this process is a known source of error (Pallavaram et al., 2015; 2008) and would be labor intensive for the 450 subjects in the current analysis. We therefore used a transform to automatically place fiducials of AC, PC and a mid-sagittal point (MSP) within each subject's native space. Literature results suggest that this process is feasible and even favorable compared manual AC/PC mapping (Pallavaram et al., 2015). Still, to confirm this on our data, the AC and PC were manually marked using axial and sagittal views on all subjects of the *Young* and the *DBS patients (PD)* cohorts using 3D Slicer 4.5 (www.slicer.org) by a trained expert. The same fiducials were additionally marked on the

ICBM 2009b nonlinear T2-weighted MNI template. The latter were transformed from MNI into native space using Advanced Normalization Tools (ANTs) SyN registration (Avants et al., 2008) as implemented in Lead-DBS and compared to their manually marked counterparts by computing RMS distance errors and Pearson's correlation coefficients of x-, y- and z-coordinates independently.

Converting DBS electrode coordinates in AC/PC space to MNI

In the *PD DBS and TRD DBS patient* cohorts, electrode contacts could be manually localized in native as well as in MNI space. Thus, these imaging data served as a gold-standard of AC/PC to MNI conversions. Electrode contacts were localized in native space with respect to the MCP (AC/PC coordinates), as per convention in the neurosurgical literature (Weiss et al., 2003). The coordinates of the electrode contact active >12 months after surgery was recorded. Preoperative and postoperative MRIs from each DBS patient were then co-registered and normalized into MNI space using the nonlinear SyN approach as implemented in ANTs/Lead-DBS. The location of the same contact was then directly identified in MNI space as described in (Horn and Kühn, 2015).

Because MRIs from the patients themselves are often unavailable, for example when an AC/PC coordinate comes from the neurosurgical literature, we tested several other approaches for converting AC/PC coordinates to MNI space. The results of each approach were then compared to the gold standard as described above. The first and simplest approach, referred to as *MNI survey*, involved defining the AC, PC, and MCP on the MNI template brain (ICBM 2009b nonlinear T2 asymmetric) then marking a point at the same x, y, and z distances as measured in the patient's brain. The second approach involved converting AC/PC coordinates measured in each patient (defined relative to the MCP) into Talairach coordinates (defined relative to the AC), then transforming these Talairach coordinates to MNI space using either the TAL2MNI (Brett et al., 2002) or TAL2ICBM (Lancaster et al., 2007) transforms. To convert MCP to AC coordinates, we added ½ the average AC/PC distance to the y coordinate. A value of 25.64 mm was used for the average AC/PC distance, derived from a large cohort of 60–69 year old caucasians (Lee et al., 2008).

Note that both the MNI survey and the Talairach to MNI transforms define just a single point in MNI space. However without the patient's own MRI, the exact location of a given AC/PC coordinate in MNI space is unknown and may be better represented as a probabilistic distribution. To create such a distribution, we mapped each AC/PC coordinate to a group of individual subjects in native space, then used a nonlinear warp to determine where that AC/PC coordinate would appear in MNI space. Because individual subjects differ in their anatomy and AC-PC distances, a single point in AC/PC space will be represented as a three-dimensional point cloud in MNI space. The average coordinates from this point cloud represent the center of this distribution (as reported in table 1) and all statistics such as whether the point cloud spreads more in one direction than another were performed on this distribution. However, for visualization purposes, we found it helpful to convert the point cloud to a Gaussian distribution. A 3D Gaussian distribution was fitted to the points using Matlab 2015b (the Mathworks, Natick, MA). This allows us to color code the distribution so the center and spread can be easily visualized. Gaussian distributions were visualized using

Lead-DBS software (figs. 3&4). Different groups of subjects could conceivably be used for this probabilistic conversion. For the PD-DBS patients, we tested the accuracy of our probabilistic transform using a young cohort, age-matched cohort, disease-matched cohort, and disease severity-matched cohort (other PD DBS patients). Probabilistic transforms for the TRD-DBS patients were tested using the young cohort, age-matched cohort, and a disease-severity matched cohort (other TRD DBS patients). Mappings were compared to the gold standard and resulting errors were compared between methods using a one-way ANOVA analysis pairwise multiple comparison post-hoc tests between each pair of approaches using Tukey's Honest Significant Difference procedure. Variance of probabilistic mappings along x-, y- and z-axes was compared using Bartlett's test and F-tests for post-hoc head-to-head comparisons.

Calculation of MNI coordinates for standard DBS targets based on literature findings

AC/PC coordinates of effective DBS contacts defined relative to the MCP were retrieved via literature research for the most common DBS targets. Our list of diseases and DBS targets was largely informed by (Lozano and Lipsman, 2013). However five of eleven diseases were excluded due to lack of human experiments (tinnitus, schizophrenia), target heterogeneity (epilepsy, chronic pain), or target overlap with another disease (anorexia nervosa matches the target used in treatment-refractory major depression). For a detailed description of how DBS targets were selected from literature results for each disease, see supplementary material (S2). Each AC/PC coordinate was converted into MNI space using the above probabilistic mapping approach and a set of age-matched MRIs. X-, y- and z-coordinates of single warps were tested to conform to a Gaussian distribution using the Chi-square goodness-of-fit test. The Gaussian fit illustrated in figs. 2–4 was performed by calculating mu and Sigma from the samples.

MNI resources and connectivity mapping from probabilistic DBS targets

To demonstrate why converting a DBS target previously reported in AC/PC coordinates into MNI space might be useful, we used the DBS target for essential tremor as an example. Thalamic atlases in MNI space were identified via a literature and web search. Some of these atlases needed an additional warp into ICBM 2009b nonlinear space used in this study. For details see supplementary material (S3). The probabilistic DBS target for essential tremor in MNI space was overlapped with these atlases and corresponding atlas structures were identified.

To compute whole-brain connectivity of the MNI-space DBS target for essential tremor, we took advantage of publically available functional and anatomical connectomes in MNI space. Resting-state functional connectivity data came from a database of 1000 subjects (Thomas Yeo et al., 2011). BOLD time series from the probabilistic DBS target for essential tremor in MNI space was isolated from the rs-fMRI data of each subject and correlated to each voxel's time series (Fox et al., 2014). Average R-values across subjects were calculated for each voxel and fMRI mappings were visualized using Surf Ice software (https://www.nitrc.org/projects/surfice/).

Structural connectivity utilized a database of diffusion spectrum and T2-weighted imaging from 32 subjects, part of the Human Connectome Project (HCP) at Massachusetts General Hospital ("MGH HCP Adult Diffusion"; Setsompop et al., 2013; https://ida.loni.usc.edu/login.jsp). Data was processed using a generalized q-sampling imaging algorithm (Yeh et al., 2010) as implemented in DSI studio (http://dsi-studio.labsolver.org). A white matter mask was estimated by segmenting the T2-weighted anatomical images and co-registering the images to the b0 image of the diffusion data using SPM12. In each subject, two-hundred thousand fibers were sampled within this mask. Fibers were transformed into MNI space using Lead-DBS following the approach described in (Horn, 2015; Horn et al., 2013). This was done based on the nonlinear deformation field into MNI space calculated based on T2-weighted images using a diffeomorphic registration algorithm (Ashburner, 2007). Tractography results were displayed using TrackVis software (http://www.trackvis.org/).

Results

To avoid marking the AC and PC locations by hand in all 450 subjects, we first validated an automated method for automatically marking these locations based on non-linear warping of an atlas (Pallavaram et al., 2015). RMS distance errors between manually-marked and automatically-marked coordinates were 0.29 mm (X-Axis), 1.59 mm (Y-Axis) and 1.16 mm (Z-Axis) for the Young cohort (fig. S1). For DBS patients, results were similar (0.53 mm on X-, 1.27 mm on Y- and 1.33 mm on Z-axis). These errors are on par with the voxel-wise resolution of the MRI data itself (0.7 mm isotropic for the *Young* cohort, 0.5 × 0.5 × 2 mm for the *DBS Patient* cohorts). Pearson's correlation coefficients between manually-marked and automatically-marked X-, Y- and Z- coordinates were above 0.99 in both cohorts.

The AC/PC coordinates of active DBS electrode contacts from 51 PD patients and 9 TRD patients were transformed into MNI space using a variety of different methods (Figure 2). Using the MRI from the actual patient (i.e. the gold standard), MNI coordinates for active contact in the PD patients was x = 12.0, y = −12.4, z = −5.7 mm and for the TRD patients was x = ±7.3, y = 25.3, z = −13.1 mm. When attempting to approximate this transform without using the patient's own MRI, the Talairach to MNI transforms (Brett et al., 2002; Lancaster et al., 2007) and marking of coordinates directly on the MNI template (*MNI survey*) resulted in a single point, while the nonlinear transforms using groups of subjects (*Young, PD Age-matched, PD Disease matched, Other DBS patients*) resulted in a probabilistic distribution in MNI space. The error compared to the gold standard was significantly different across different methods for both the PD and TRD cohorts ($p<0.001$).

In PD patients (where the DBS target resides closer to the AC/PC line), the probabilistic methods significantly outperformed the *Tal2MNI* and *Tal2ICBM* methods ($P<0.05$) but not the *MNI survey* method. Surprisingly, the *MNI survey* method actually performed better than the probabilistic mapping using the young cohort, likely because the larger MNI brain better matches lateral displacement of the STN with age (see fig. S2). Amongst the probabilistic methods, there was a trend towards less error using cohorts increasingly similar to the PD DBS patients themselves, however differences were small (< 0.5 mm) and not statistically significant ($P > 0.07$ for all head-to-head comparisons). In TRD patients (where the DBS target is further from the AC/PC line) the probabilistic methods significantly

outperformed the *MNI survey* and *Tal2MNI* methods (P>0.05) but not the *Tal2ICBM* method. There was no difference between the three probabilistic methods (*Young* vs. *Age Matched* vs. *other TRD DBS patients*).

Although the *MNI survey* method performed well in the PD DBS group and the *Tal2ICBM* method performed well in the TRD DBS group, only the probabilistic method performed well in both groups. Furthermore, the variance of probabilistic mappings was significantly different in x-, y- and z-directions ($\chi 2 = 52.1$, $p<0.001$ for PD, $\chi 2 = 10.4$, $p<0.006$ for TRD, based on *Age matched* cohort). In PD variance along the x-axis was significantly higher than along y- ($F = 0.26$, $p<0.001$) and z- axes ($F=0.17$, $p<0.001$). In TRD, variance along the z-axis was significantly lower than for x- ($F=0.21$, $p<0.003$) and y-axes ($F=0.36$, $p<0.05$). Using different cohorts for probabilistic mappings yielded comparable results. This illustrates that depending on the DBS target, variance of the probabilistic mapping approach yields differently shaped non-spherical probability maps in MNI space.

Based on the above results, we next used probabilistic mapping with age-matched cohorts to convert previously reported AC/PC DBS electrode coordinates into probabilistic MNI coordinates across a variety of different diseases (Figure 3, Table 1). X-, y- and z-coordinates were normally distributed across warps from the age-matched cohort at the 5% significance level. Single warps are superimposed as Asterisks over a fitted Gaussian distribution is visualized, for each target.

Once DBS targets are mapped in a probabilistic fashion into MNI space, they can be combined with a number of MNI-based neuroimaging resources. As an example, the DBS target for Essential Tremor (conventionally the ventral intermediate nucleus, VIM, of the thalamus) is illustrated in figure 4. The DBS target was overlaid on five thalamic atlases available in MNI space (figure 4A). The Chakravarty atlas showed the target in the anterior portion of the ventral posterior lateral nucleus (VPLa), whereas the Morel atlas showed it in the ventral posterior medial nucleus (VPM). Both nuclei are directly adjacent to the ventral part of the ventral lateral posterior nucleus (VLpv) which (in Hirai & Jones nomenclature) corresponds to the VIM (in Walker nomenclature) or Vimi (in Hassler nomenclature; Macchi and Jones, 1997). Thalamic parcellations based on anatomical connectivity (Behrens et al., 2003), showed the DBS target in premotor and primary motor zones of the thalamus, while parcellations based on functional connectivity showed it between motor and sensory (Zhang et al., 2008) or in thal-5 zone (Joliot et al., 2015). Finally, the VIM DBS target could be related to histological MNI-based resources such as the BigBrain dataset (Amunts et al., 2013).

Beyond atlases, connectome datasets are also widely available in MNI space and can be used to compute the anatomical and functional connectivity profiles of DBS targets. Our probabilistic DBS target for essential tremor was functionally connected to the motor network and cerebellum (fig. 4B, left) and structurally adjacent to the cerebellothalamocortical pathway (fig. 4B, right).

Discussion

There are three main findings from this study. First, we presented and validated a conversion tool to map from AC/PC coordinates to MNI space in a probabilistic fashion by taking individual anatomical variation into account. Second, we used this tool to identify MNI coordinates for classical DBS targets defined in the literature. Finally, we demonstrate the utility of integrating DBS lead locations with MNI-based resources, using the DBS target for essential tremor as an example. Implications of each finding and its limitations will be discussed in turn.

Although there are existing well-validated tools for converting Talairach coordinates to MNI space (Laird et al., 2010; Lancaster et al., 2007), the current method provides two advantages. First, it was designed and tested for accuracy using DBS electrode positions, overcoming unique challenges like converting MCP to AC-based coordinates. Second, our method is probabilistic, incorporating anatomic variability into the transform. Rather than identify a single point in MNI space, our method returns a weighted distribution which significantly varies in the x, y, and z directions and better reflects the most likely location of an electrode contact in MNI space.

The one instance in which our probabilistic approach failed to perform well was using a young cohort to convert STN DBS coordinates. In this case, directly measuring the coordinates on the MNI template was more accurate, likely due to a more lateral STN in elderly patients (Keuken et al., 2013) matching the STN position in the larger MNI brain (fig. S2). This problem resolved when using an age-matched rather than the young cohort for probabilistic mapping. No approach significantly out-performed probabilistic mapping with an age-matched cohort, justifying it's use across diseases (Table 1). However, there was a trend towards more accuracy with better-matched MRIs, and these coordinates may be refined in future work using cohorts matched to each specific disease population. Similarly, our method was validated for STN DBS for Parkinson's disease and SCC DBS for treatment resistant depression. The use of two different DBS populations is a strength of this study, but other diseases with greater changes in anatomy (e.g. Alzheimer's) may benefit more from transforms better matched to the DBS patient population. A potential limitation is the low number of patients within the SCC cohort (N=9).

There have been prior attempts to identify MNI coordinates of some of the DBS electrode locations investigated here (Höflich et al., 2010). In most cases this was done using manual visual transformation to an MNI atlas (Höflich et al., 2010). Direct transformation of each DBS patient's MRI into MNI space is the gold-standard for identifying MNI coordinates of DBS electrode locations, but this is rarely done in the neurosurgical literature. For example, all of the DBS clinical trials included in table 1 reported coordinates in AC/PC space, but not in MNI space. Comparing MNI coordinates from these prior studies (utilizing our probabilistic transform) to gold standard MNI coordinates identified using the current PD and TRD cohorts, the two match well.

Probabilistic mapping may be seen as a further advantage to bridge the gap between studies of the functional neurosurgery literature and neuroimaging (Fox et al., 2014), because

resulting maps may be used to analyze the spatial positions based on anatomical atlases and their structural and functional connectivity in a probabilistic manner (by applying them as weighted seeds to standardized connectomes in MNI space). This was demonstrated using the ET DBS target. Using this method, the VIM target defined by (Papavassiliou et al., 2004) and colleagues resided within the ventral posterior medial nucleus based on both Morel and Chakravarty atlases (nuclei defined in Jones nomenclature (Macchi and Jones, 1997)). The VPM nucleus resides directly adjacent to the VLpv nucleus which in Jones nomenclature corresponds to the VIM in Hassler/Walker nomenclatures.

Functional connectivity of the VIM DBS target was analyzed previously in a study by Fox and colleagues (Fox et al., 2014). However, in that study the DBS target was defined anatomically (VLpv ≈ VIM/v.im.i nucleus defined by the Chakravarty atlas) rather than based on the location of effective DBS electrode contacts. As such, the results of the present study differ slightly from this prior work: there are stronger correlations with primary motor cortex and weaker correlations with the superior frontal gyrus. These new results align better with prior work showing that functional connectivity from primary motor cortex (and cerebellum) aligns well with thalamic DBS targets (J. S. Anderson et al., 2011). The current results illustrate that using actual DBS electrode locations instead of anatomically defined ROIs as seed regions in connectivity experiments may make a difference. This is especially important given the increasing interest of the DBS research community in connectivity analyses (Accolla et al., 2016; Henderson, 2012; Vanegas Arroyave et al., 2016).

Regarding structural connectivity, the VLp (≈ VIM) nucleus of the thalamus was initially defined as the large-celled cerebellar recipient zone by Jones (Krack et al., 2002; Macchi and Jones, 1997; its ventral part best corresponds to the VIM based on other nomenclatures). The fiber bundle connecting the cerebellar nuclei to the thalamus has been referred to as the dentatothalamic tract, dentatorubrothalamic tract, or cerebellothalamocortical pathway and matches the present results based on connectivity with the thalamic DBS target. Interestingly, most fibers in this pathway are thought to decussate between the thalamus and cerebellum, with only a minority of fibers staying uncrossed (Chan-Palay, 1977; Meola et al., 2015; R. Wiesendanger and M. Wiesendanger, 1985). Whether the predominantly uncrossed tracts identified here are due to the exact position of the electrode with the thalamus (Meola et al., 2015; 2016) or a limitation of DTI requires further work. Either way, this demonstrates the type of analyses that can be performed once the MNI coordinates of DBS electrode positions are known.

It should be noted that the ideal way to convert AC/PC coordinates to MNI space is by using MRI data from the patients themselves. Unfortunately, obtaining MRIs from prior studies – especially if multiple studies or large cohorts are concerned – can be difficult if not impossible. In these cases, probabilistic transformation using a surrogate cohort as described here may be useful. Our data shows, that closely matching the original cohort by age, disease and even disease severity does improve results (although only age-matching improved results significantly). Thus, we argue that matching the original cohort as closely as possible is important.

One other limitation is that often, the explicit methodology of defining the AC and PC fiducials is not reported in original studies (see. fig. 1; Weiss et al., 2003). Here, we incorporated the most common approach, i.e. defining the posterior border of the AC and the anterior of the PC. However, our algorithm should be modified if surgeons in an original study of interest used a different approach for marking the AC and PC.

Conclusions

We introduced a method for converting stereotactic AC/PC coordinates to MNI space in a probabilistic fashion that incorporates anatomic variability. Our method was validated using two cohorts of DBS patients, appears superior to alternative methods, and works well using transforms derived from healthy subject MRIs. We used this method to convert stereotactic coordinates of common DBS targets into MNI space, providing a resource for future studies. Finally, we use the DBS target for essential tremor as an example to illustrate the value of integrating DBS lead locations with MNI-based resources. The methodology and code will be made available within the open source toolbox Lead-DBS (www.lead-dbs.org).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Conversion tool between MNI space (used in neuroimaging) and AC/PC coordinates (used in neurosurgical literature)
- Approach validated using deep brain stimulation electrodes in Parkinson's Disease and Treatment-resistant Depression
- Deep brain stimulation target definitions within MNI space across eight diseases
- Characterization of deep brain stimulation target for Essential Tremor using multiple subcortical atlases and standardized structural and functional connectomes

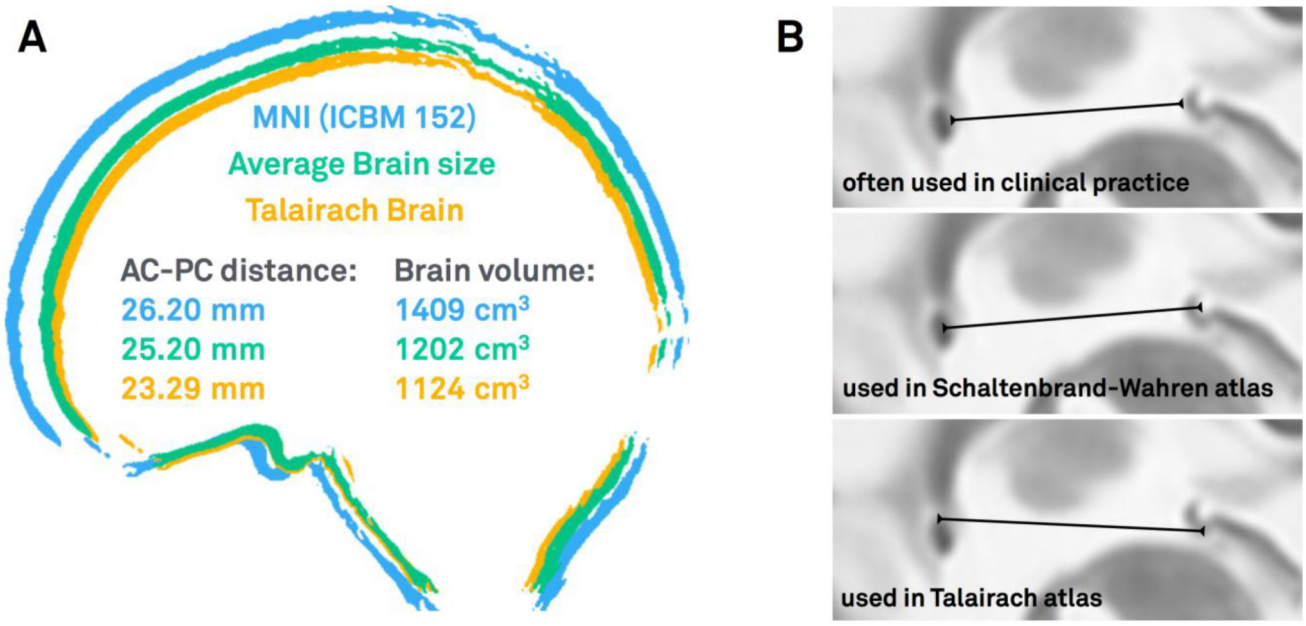

Figure 1.

a) Schematic illustrating differences in size of an average brain, the MNI brain and the Talairach brain (data from Allen et al., 2002; Lee et al., 2008). b) Different ways to measure AC/PC distance and place fiducials for the AC-PC line (see Weiss et al., 2003). The upper case was used in this study, the other two used in reference atlases often used in neurosurgical literature (Schaltenbrand et al., 1977; Talairach et al., 1988).

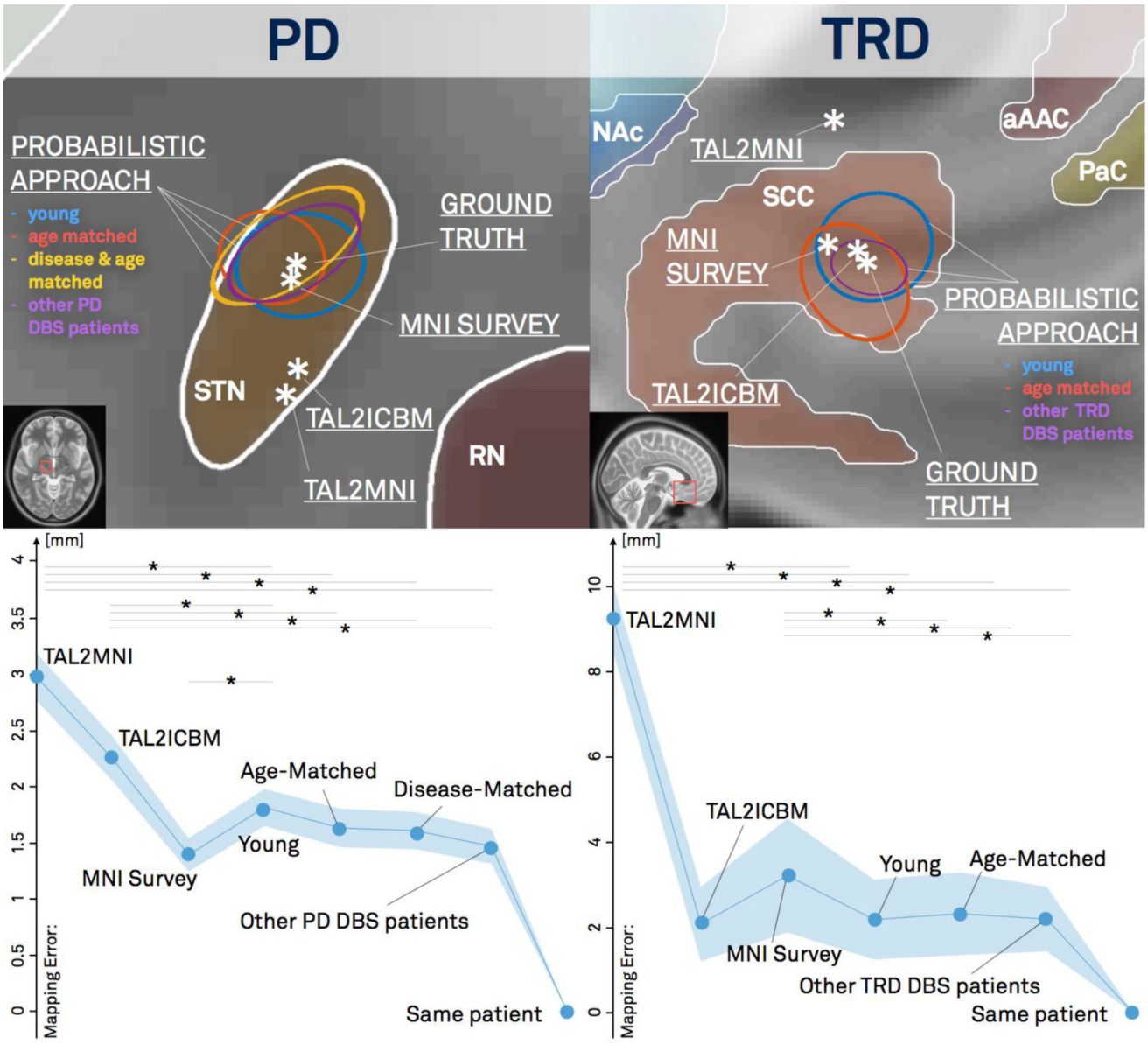

Figure 2.

Mapping of active contacts of two DBS cohorts into MNI space using different approaches. Left: cohort of 39 PD patients (target STN). Right: cohort of 9 patients with treatment-refractory major depression (target SCC). For PD, Young, age-matched, disease-matched and disease-severity matched cohorts were available. In case of the depression cohort, the Young, age-matched and original cohort were compared. The upper panels show mappings from group average coordinates of active contacts for both DBS cohorts. The lower panels show mapping errors (compared to the gold standard of manually localized DBS electrode contacts) when active cohorts of all patients were mapped independently. In PD, the probabilistic methods significantly outperformed all methods except the *MNI survey* method, whereas in TRD, they outperformed all methods except the *Tal2ICBM* method (stars indicate $p<0.05$).

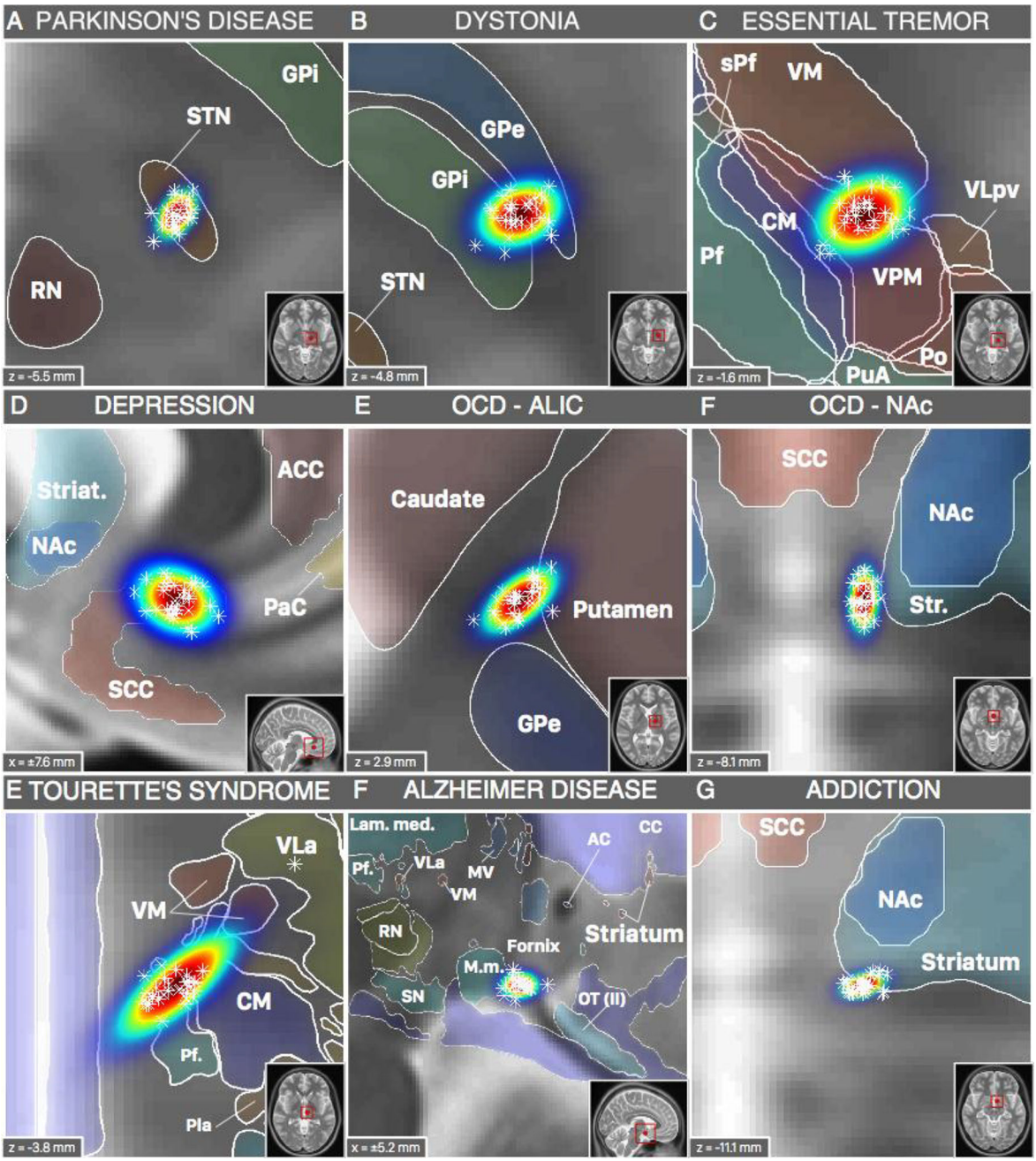

Figure 3.

Spatial location of probabilistic DBS targets (table 1) in synopsis with structural brain atlases available in MNI space. Parkinson's disease (STN; A) and Dystonia (GPi; B) targets shown with structures defined by DISTAL atlas (Ewert and Horn, 2016). Essential tremor target (VIM; C) shown with Morel atlas structures. Depression (SCC; D), OCD (NAc; F) and Addiction (NAc; G) targets shown with structures from the Harvard-Oxford atlas (Desikan et al., 2006) and the striatum ROI from the ATAG atlas (Keuken et al., 2014). OCD target in the ALIC shown with structures defined by the ATAG atlas (Keuken et al., 2014). DBS targets for Tourette's syndrome (CM/Pv/VOI; E) and Alzheimer's disease (Fornix; F)

shown with structures from the Chakravarty atlas (Chakravarty et al., 2006). For abbreviations see (Chakravarty et al., 2006; Krauth et al., 2010); thalamic nuclei were labeled using Jones nomenclature whenever possible (Macchi and Jones, 1997) and Hassler nomenclature for nuclei not defined in Jones nomenclature (Hassler et al., 1965; Schaltenbrand et al., 1977).

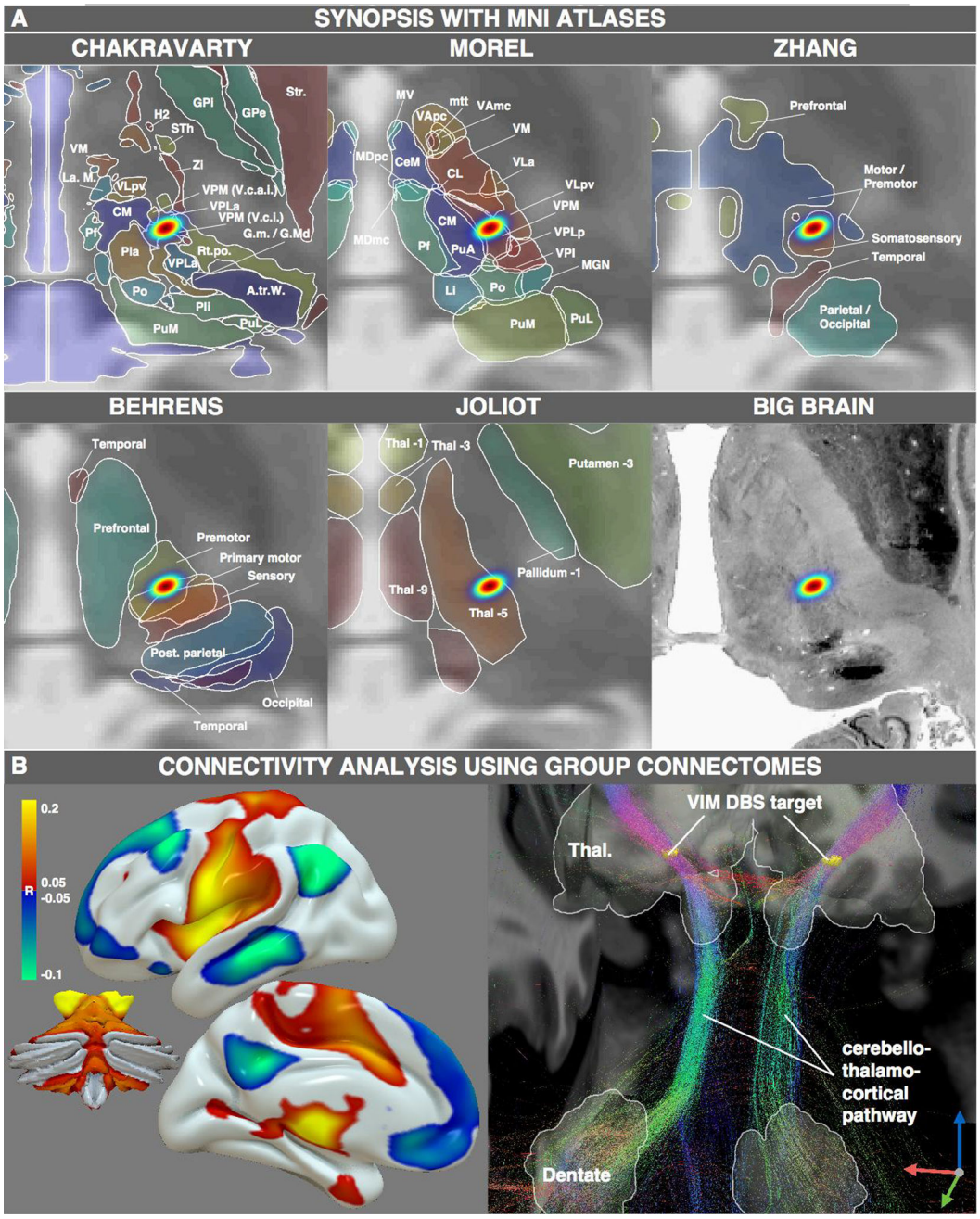

Figure 4.

MNI resources that may be used once the DBS target is available in standard space. A) synopsis of the VIM DBS target with five structural atlases available in MNI space. B) Functional (left) and structural (right) connectivity analysis seeding from the VIM DBS target.

Table 1

AC/PC and transformed MNI coordinates for common DBS targets. AC/PC coordinates are specified as lateral to, anterior to, and below the reference point (MCP or AC). All coordinates are listed as X, Y, then Z. Mean ages are reported as mean age ± standard deviation (age range). Mappings were performed on an age matched sample of the IXI dataset.

Disease	DBS Target	Reference	Number of patients	Mean age of cohort (yrs)	AC/PC coordinates	Relative to	MNI coordinates	MNI standard deviations
Parkinson's disease	STN	(Caire et al. 2013)	171	59	± 12.02	MCP	± 12.58	± 0.60
					− 1.53		− 13.41	± 0.71
					1.91		− 5.87	± 0.71
Dystonia	GPi	(Starr et al. 2006)	23	32 ± 15	± 20.0	MCP	± 22.37	± 1.15
					5.8		− 5.57	± 0.91
					0.5		− 4.97	± 0.84
Essential tremor	VIM (Thalamus)	(Papavassiliou et al. 2004)	37	66.2 ± 13.6	± 12.8	MCP	± 13.05	± 0.96
					− 5.7		− 18.38	± 0.80
					− 0.8		− 2.01	± 0.64
Treatment-resistant depression *	Subcallosal cingulate	(Hamani et al. 2009)	20	50.11 **	± 5.6	MCP	± 7.35	± 0.95
					34.2		23.75	± 2.14
					3.0		− 11.60	± 1.79
Obsessive-compulsive disorder	NAc	(Franzini et al. 2010)	2	37 ± 5.6 (33 – 41)	± 3	MCP	± 3.78	± 0.44
					16		5.08	± 0.91
					2		− 7.79	± 0.30
	ALIC	(Nuttin et al. 2003) (Anderson & Ahmed 2003)	6	35 ***	± 14.00	AC	± 15.29	± 1.04
					6.0		8.08	± 0.92
					− 6.0		1.57	± 0.86
Tourette's syndrome	CM/Pv/VOI (Thalamus)	(Ackermans et al. 2011)	8	40.33 (35 −48)	± 5.0	MCP	± 5.54	± 1.15
					4.0		− 15.81	± 1.05
					0.0		− 3.25	± 0.50
Alzheimer's disease	Fornix	(Ponce et al. 2015)	42	68.2 ± 7.8 (48.0 -	± 4.4	MCP	± 4.94	± 0.47
				79.7)	9.8		− 1.52	± 1.06
					7.2		− 13.98	± 0.75
Addiction	NAc	(Müller et al. 2009)	3	37.7 ± 2.1 (36 – 40)	± 6.5	AC	± 7.66	± 0.66

Disease	DBS Target	Reference	Number of patients	Mean age of cohort (yrs)	AC/PC coordinates	Relative to	MNI coordinates	MNI standard deviations
					2.7		3.61	± 0.39
					4.5		− 10.35	± 0.49

*for TRD, DBS coordinates have been reported directly within MNI space in {RivaPosse 2014cea} – see discussion

**The age of the cohort in Hamani et al. 2009 could not be retrieved. The mean age of the study by Merkl et al. 2013 was used instead

***The age of the cohort in Nuttin et al. 2003 could not be retrieved. The mean age from Anderson & Ahmed 2003 was used instead.