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Neuropsychiatric deep brain stimulation for translational neuroimaging

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ARTICLE INFO

Article history:
Accepted 16 April 2013
Available online 28 April 2013

Keywords:
Deep brain stimulation
Functional neuroimaging
Gilles de la Tourette syndrome
Positron emission tomography
Magnetic resonance imaging
Obsessive–compulsive disorder
Treatment-resistant depression

ABSTRACT

From a neuroimaging point of view, deep brain stimulation (DBS) in psychiatric disorders represents a unique source of information to probe results gained in functional, structural and molecular neuroimaging studies in vivo. However, the implementation has, up to now, been restricted by the heterogeneity of the data reported in DBS studies. The aim of the present study was therefore to provide a comprehensive and standardized database of currently used DBS targets in selected psychiatric disorders (obsessive–compulsive disorder (OCD), treatment-resistant depression (TRD), Gilles de la Tourette syndrome (GTS)) to enable topological comparisons between neuroimaging results and stimulation areas. A systematic literature research was performed and all peer-reviewed publications until the year 2012 were included. Literature research yielded a total of 84 peer-reviewed studies including about 296 psychiatric patients. The individual stimulation data of 37 of these studies meeting the inclusion criteria which included a total of 202 patients (63 OCD, 89 TRD, 50 GTS) was translated into MNI stereotactic space with respect to AC origin in order to identify key targets. The created database can be used to compare DBS target areas in MNI stereotactic coordinates with: 1) activation patterns in functional brain imaging (fMRI, phMRI, PET, MET, EEG); 2) brain connectivity data (e.g., MR-based DTI/tractography, functional and effective connectivity); 3) quantitative molecular distribution data (e.g., neuroreceptor PET, post-mortem neuroreceptor mapping); 4) structural data (e.g., VBM for neurelastic changes). Vice versa, the structural, functional and molecular data may provide a rationale to define new DBS targets and adjust/fine-tune currently used targets in DBS based on this overview in stereotactic coordinates. Furthermore, the availability of DBS data in stereotactic space may facilitate the investigation and interpretation of treatment effects and side effect of DBS by comparing these to neuroimaging results. The present study thus improves comparability between functional, structural and molecular data in standard stereotactic space gained in neuroimaging studies with surgical targets for DBS, which is among other possible implications of crucial importance for the definition of new targets for effective DBS.

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Introduction

Deep brain stimulation (DBS) is a reversible neurosurgical method that enables individual and adjustable electrical stimulation of brain structures. Since its introduction it has become an established treatment for some otherwise treatment-resistant movement disorders, such as Parkinson’s disease (PD) (Chao et al., 2007; Kumar et al., 1998), essential tremor and dystonia (Eller, 2011). The positive clinical outcomes in neurological disorders, the potential reversibility, and its low adverse effect profile, compared with ablative methods, led to the application of DBS as a treatment for otherwise treatment resistant psychiatric disorders such as obsessive–compulsive disorder (OCD), Tourette’s syndrome (GTS) and treatment resistant depression (TRD). Since then, first experimental attempts of using DBS have also been made for other intractable disorders including drug addiction (Luigjes et al., 2012; Voges et al., 2012), chronic pain (Nguyen et al., 2011), refractory epilepsy (Pereira et al., 2012), morbid obesity (Taghva et al., 2012), disorders of consciousness (Sen et al., 2010), and self-mutilating behavior (Kuhn et al., 2008).

Current target selection for DBS relies on two main sources of evidence: brain lesioning and neuroimaging data. Earlier target selection was based on experience with ablative methods which arose from approaches such as prefrontal lobotomy and capsulotomy established in the early 20th century. These methods were continuously refined to more selectively target fibers potentially involved in the pathophysiological processes of the respective disorder. Furthermore, the experience with DBS in movement disorders such as PD has lent further evidence for possible targets by analyzing behavioral side effects of...
the applied procedures (Mallet et al., 2002). In more recent years the emergence of neuroimaging techniques, which could provide information about pathophysiological mechanisms has added substantial knowledge in this regard, and emerged as a second, more neurobiologically substantiated, source of evidence.

In OCD, for example, the choice of the anterior limb of the internal capsule as a target region was primarily based on clinical experience with anterior capsulotomy for refractory OCD (Mindus et al., 1994); the ventral capsule/ventral striatum was considered based on positive results following gamma knife capsulotomy at the ventral region of the anterior limb of the internal capsule in OCD patients (Greenberg et al., 2003); and the choice of the nucleus subthalamicus as a target was based on the observation that the stimulation of this area in PD patients led to improvement of comorbid OCD symptoms (Mallet et al., 2002). The selection of these targets, which arose from functional neurosurgery in neurological and psychiatric disorders, was accompanied or followed by supportive basic neuroscientific results. The currently most established concept of dysfunctional cortico-striato-thalamo-cortical pathways fits well into this context. Studies comparing OCD patients and healthy volunteers using positron emission tomography (PET) have shown hyperactivity in these functional pathways in OCD. Moreover, heightened activity of the orbitofrontal cortex and the nucleus caudatus have been described during symptom provocation in OCD patients in functional magnetic resonance imaging (fMRI) and PET studies (Lawrence et al., 2007; Mataix-Cols et al., 2004; Schienle et al., 2005; Whiteside et al., 2004b). Although this pathophysiological approach might oversimplify the neurobiological underpinnings, and leaves aside the complex interplay between transmitter systems and structural/functional conditions, it may well serve as a rationale for the current performance of DBS in these areas. This fact is underpinned by neuroimaging studies which propose functional normalizations of these areas with pharmacological and non-pharmacological treatment options (Saxena and Rauch, 2000). On the other hand, target areas have been primarily selected on the basis of neuropathological theories of the disorder; for instance the inferior thalamic peduncle based on the substantial involvement of this region in OCD, and the nucleus accumbens because of its involvement in the reward system and motivational processes which might add to OCD-symptomatology (Fige et al., 2011; Greenberg et al., 2010).

Ablative methods used to treat depression, such as anterior capsulotomy (Meyerson and Mindus, 1988; Talairach et al., 1949), anterior cingulotomy (Bailey et al., 1973), subcaudate tractotomy (Bridges et al., 1994; Knight, 1969), and limbic leucotomy (Richardson, 1973), have been widely replaced by DBS of subgenual part of the anterior cingulate cortex (sgACC), ventral striatum/capsula interna, nucleus accumbens and lateral habenula (epithalamus) (Bewernick et al., 2010; Broadway et al., 2012; Durant et al., 2010; Grubert et al., 2011; Guinjoan et al., 2010; Hamani et al., 2009; Holtzheimer et al., 2012; Jimenez et al., 2005, 2007; Kennedy et al., 2011; Lozano et al., 2008, 2012; Machado et al., 2009; Malone et al., 2009; Mayberg et al., 2005; McNeely et al., 2008; Pugidemont et al., 2012; Sartorius et al., 2009; Schlaepfer et al., 2008). The choice of some of these targets was based on experience with the efficacy of ablative procedures; however the involvement of these brain regions is also supported by neuroimaging data. For instance, the choice of DBS of the subgenual cingulate as described by Mayberg and colleagues was based on converging evidence from neuroimaging studies which linked this region to sadness in healthy volunteers (Mayberg et al., 1999; Seminowicz et al., 2004), as well as to depressive symptoms and treatment response in patients with major depression (Dougherty et al., 2003; Nobler et al., 2001). As anatomical studies reinforce the important role of this area, given its connections to orbital and prefrontal regions as well as other cingulate areas, it was decided to target this specific region in DBS treatment of TRD (Mayberg et al., 2005). The same applies for the nucleus accumbens and lateral habenula with neuroimaging studies demonstrating their implication in processes which are dysfunctional in depression, particularly reward processing (Epstein et al., 2006; Gorwood, 2008; Hikosaka et al., 2008; Matsumoto and Hikosaka, 2007; Sartorius and Henn, 2007; Tremblay et al., 2005; Wang et al., 2011).

In GTS different targets have been established but definite choices will need further evaluation of implicated neuronal circuits in neuroanatomical and neuroimaging studies. Furthermore the great number of patients suffering from comorbidities complicates the definition of a distinct neuronal network as target. Currently used targets are sub-sections of the thalamus, the internal pallidum and the internal capsule/nucleus accumbens (Ackermans et al., 2011; Dehning et al., 2008; Ducek et al., 2009; Kaido et al., 2011; Martinez-Fernandez et al., 2011; Neuner et al., 2009, 2010; Porta et al., 2009; Servello et al., 2008, 2010; Vernaleken et al., 2009; Welter et al., 2008). The choice of these specific regions was mainly based on positive clinical outcomes after DBS in these areas in GTS and other related diseases, and on the fundamental implication of basal ganglia dysfunction and cortico-striatal-thalamo-cortical circuits in GTS (Bohlhalter et al., 2006; Graybiel and Rauch, 2000; Mink, 2001a,b; Peterson et al., 1998).

In spite of some agreement on the stimulation targets, a comprehensive standardized database going beyond mere description of targeted brain regions onto the more precise depiction of these areas in standardized stereotactic space is still lacking. The fact that current data is heterogeneous and that the description of targets varies between studies makes it more difficult to relate this unique data source to neuroimaging data in the respective disorders and the associated treatments. Although a number of reviews have focused on deep-brain stimulation in psychiatric disorders there is a lack of data providing the means to facilitate a synergy of neuroimaging and DBS data. In the present study we provide a database of target regions in Montreal Neurological Institute (MNI) standard space (as implemented e.g. in SPM) in order to provide a tool for comparison between studies and the possibility to bring these areas in relation to existing literature. Therefore this database is a tool to allow comparability of coordinates of DBS target areas in MNI space with functional neuroimaging results. The embedding of DBS target coordinates in a neuroimaging framework will be relevant for a number of neuroimaging techniques and allow the comparison with activation patterns in functional brain imaging, using fMRI, pharmacological (phMRI), PET and EEG; effective connectivity using MR-based diffusion-tensor imaging (DTI) and tractography; quantitative molecular distribution data, using neuroreceptor PET, and post-mortem neuroreceptor mapping as well as structural data. This combination might be advantageous in both directions as the wealth of structural, functional and molecular data may provide a rationale to define new DBS targets and adjust/fine-tune currently used targets in DBS. Furthermore, the availability of DBS data in stereotactic space may facilitate the investigation and interpretation of treatment and side effect associated with DBS treatment by comparing it to neuroimaging results. For the present study only treatment resistant OCD, GTS and depression have been considered since other psychiatric disorders with potential relevance for DBS treatment such as drug addiction lack adequate sample sizes, which restricts the application of statistical calculations and a standardized description in general. For the sake of simplicity and following the nomenclature used in the analyzed articles, the analyzed disorders are referred to as TRD, OCD and GTS. However, for all three disorders treatment-resistance to pharmacological and non-pharmacological treatment is a requirement for consideration of DBS.

Materials and methods

Study search and selection

We performed a comprehensive PubMed/MEDLINE search with the combination of the following keywords: “dbs” and “deep brain...
stimulation” in association with “depression”, “tourette” and “obsessive compulsive disorder”. Original articles and case reports on human subjects that emerged from this search until August 2012 were included. Studies had to be published in the English language in peer-reviewed journals. Unpublished data were not sought and reviews were excluded except for reviews of case reports. Conference contributions and poster abstracts were excluded as well except those which gave additional information to subsequently published peer-reviewed articles. In a second step the electronic search was screened by hand for relevant studies and additional articles. Furthermore, search results were limited to papers that primarily investigated DBS on patients with the abovementioned psychiatric disorders. Papers on movement disorders, e.g. Parkinson disease or dystonia, were excluded. The remaining studies were arranged into three groups according to the disorder.

### Stereotactic data definition

Individual target locations usually referring to coordinates based on patient-specific MRI pictures and corresponding to the tip position of the electrode leads were collected from the methodological section of each article as published by the authors and postoperative data was taken when available. Authors of articles without precise stereotactic definition were contacted to provide missing information about the target coordinates. In cases without a response, an estimated coordinate was defined that visually matched most accurately the figure shown in the respective publication, or the information provided in the text or in related-literature. Various anatomical hubs which constitute key targets due to the concentration of coordinates within a given proximity were identified. All studies were categorized into one or more hubs.

A main issue of available DBS data was the fact that most of the reported target-coordinates did not refer to standard space but were based on individual brains which may diverge significantly to the standard MNI brain. Furthermore, the divergence of origins and orientation depending on the used coordinate system complicated the integration into one data set. In order to overcome these issues, a new methodological approach was established and validated also (see Supplementary Fig. 1). As comprehensive MRI data was lacking, the “normalization” procedure in this study had to be based on manual transfer of targets into MNI space. Prior to application of this procedure onto DBS data, the consistency of manual delineation with the normalization procedure using SPM was calculated for in-house MRI data of healthy volunteers. Then, in a second step, state-of-the-art normalization of the MR images depending on the used coordinate system complicated the integration into MNI space. Based on reported target coordinates, individual postoperative coordinates and MR images provided in the papers or by personal communication with the authors target points were transferred onto the single-subject MNI brain as established in the validation step. Again this operational step was carried out by the same 3 raters independently. Inter-rater variability and mean values were calculated and coordinates were double checked for anatomic plausibility. Only articles including original structural MR images or the description of target areas in relation to established brain atlases (e.g., Schaltenbrand and Wahren, 1977) were considered for the calculation of mean values. Furthermore, only target points showing a total pooled group size of a minimum of 8 patients were statistically analyzed and are reported below. For this procedure an inter-rater reliability of ICC = 0.97 (p < 0.001), 95% CI (0.97, 0.98) was calculated.

### Analysis

In the next step we attempted to identify identical patients that appeared in follow-up studies or subsequent publications by both carefully comparing patients’ profiles as well as article descriptions. Identical patients were counted once for each target and excluded from the main target calculation. See Supplementary Tables 1a, 2a and 3a for further details. Then the average coordinate location was calculated for each anatomical hub with respect to the number of patients included (weighted average). Statistical analyses on the descriptive data have been carried out in an approximate manner due to the fact that the data was heterogeneous and quite often missing for certain variables, patients or time-points.

### Results

In total 84 peer-reviewed publications were included: 31 on OCD, 19 on TRD and 34 on GTS. Descriptive data of the study subjects are presented by disorder in Supplementary Tables 1a, 2a and 3a (e.g., sex, age of onset and at DBS treatment, baseline and follow-up scores, follow-up time, treatment response, and major adverse events). Given the heterogeneity of the data, descriptive data is reported in an approximate manner. Due to insufficient pooled sample size or the lack of structural MR images included in the articles only 37 peer-reviewed publications could be used for the calculation of mean DBS targets. However these 37 studies covered the majority of patients, namely 202 of the total of 268 patients (63 OCD patients, 89 TRD patients, 50 GTS patients).

### Characteristics of DBS study population

Altogether, studies used for the calculation of demographic data included 296 patients, excluding case-series with follow-up publications: 119 with OCD, 100 with TRD, and 77 with GTS. Most of the studies included one or few patients as case-reports, and some studies were case-series reporting a further follow-up, or new data on previously published cases together with additional new cases. Among OCD and TRD patients, males and females were about equally present (58% vs. 42%, and 44% vs. 56%, respectively), while among GTS patients the
majority were males (81% vs. 19%). Regarding comorbidity, a diagnosis of OCD was reported in about one fifth of the patients with GTS, a diagnosis of MDD was present in about one third of the patients with OCD, while other comorbid symptoms were present among patients with TRD. The mean age of onset of the disorder was reported to be about 17 years for OCD, about 27 years for TRD, and about 7 years for GTS patients. The mean age at DBS treatment was about 37 years in OCD, about 49 years in TRD, and about 31 years in GTS studies. The longest follow-up time was about 19 months in OCD and TRD, and about 23 months in GTS studies.

The most common measures used to assess treatment-outcome were: for OCD the Yale–Brown Obsessive Compulsive Scale (Y–BOCS); for TRD the Hamilton Depression Rating Scale (HAM-D), Beck Depression Inventory (BDI), or the Montgomery–Åsberg Depression Rating Scale (MADRS); and for GTS the Yale-Global Tic Severity Scale (Y-GTSS). Baseline scores described severe symptoms of the disorders among the patients, with average scores of about 33 in Y–BOCS, about 29 in HAM-D, and about 83 in Y-GTSS. The average decrease in total scores at the latest follow-up was of about 43% on the Y–BOCS among patients with OCD, about 66% on the HAM-D among patients with TRD, and about 52% on the Y-GTSS among patients with GTS. Responders to DBS treatment, as defined and reported in each study, were about 79% among patients with OCD and about 65% among patients with TRD, while remittance from TRD was achieved by about 62% of the patients. Excluding short-lasting or transitory effects, a number of major adverse effects were reported, and varied from infections at the site of the pulse generator, sedative effects, motor problems, mood and behavior changes, to worsening of the symptoms. For a detailed description of

![Fig. 1. Transaxial illustration of centers of DBS stimulation targets currently applied in psychiatric disorders. Centers represent average locations estimated from individual target locations. Only articles including original MR images or the description of target areas in relation to established brain atlas (e.g. (Mai et al., 1997; Schaltenbrand and Wahren, 1977) were considered for the calculation of mean values. Furthermore, only target points showing a total pooled group size of a minimum of 8 patients were reported. ALIC, anterior limb of the internal capsule; GPi, globus pallidus internus; NC/Nacc, nucleus caudatus, nucleus accumbens; SGC, subgenual cingulate cortex. VS/VC, ventral striatum, ventral capsule; OCD (orange), obsessive compulsive disorder; TRD (green), treatment resistant depression, and GTS (blue), Tourette syndrome. See Table 1 for more details.](image-url)
characteristics of the study population see Supplementary Tables 1a, 2a and 3a.

**Main DBS targets of the database**

We created a database of MNI stereotactic coordinates of the DBS targets which in the original publications were reported mainly using measurements in original unnormalized brains or as MRI figures (Fig. 1, Table 1). There were 3 main targets for DBS in OCD: anterior limb of internal capsule, a nucleus accumbens/ventral capsule/ventral striatum/caudate complex and the nucleus subthalamicus; 2 main targets for DBS in TRD: subgenual cingulate cortex/subcallosal cingulate and a nucleus accumbens/ventral capsule/ventral striatum complex, and 2 main targets for DBS in GTS: thalamus and globus pallidus internus. Other reported target regions which could not be integrated in the analysis were the inferior thalamic peduncle for OCD, the lateral habenula and the inferior thalamic peduncle for TRD and the anterior limb of the internal capsule and the nucleus accumbens for GTS. Comparing normalized, weighted coordinates it became clear that targets in TRD and OCD for the ventral striatum/ventral limb of the capsule interna/ncl. accumbens complex show a large degree of correspondence. A more specific role was evident for the ACC/sgACC and the lateral habenula which was stimulated in TRD only as well as the internal pallidum for GTS. The analysis of the data also revealed large differences in the experience with various targets as the number of reported patients ranges from one (lateral habenula and interthalamic peduncle for TRD and Ncl. subthalamicus for GTS) to 78 patients (Ncl. caudatus/Ncl. accumbens/Ventral striatum/ventral anterior limb of the capsula interna for OCD). Results further emphasize the importance of the report of exact stimulation parameters as several targets show high proximity. It is therefore likely that postoperative stimulation parameters have a significant effect, leading to stimulation of fibers with different anatomical and functional connections (Table 1, Fig. 1). For a detailed description of mean DBS targets for the specific studies see Supplementary Tables 1b, 2b and 3b.

**Application of DBS data in relation to neuroimaging results**

**DBS coordinates and molecular distribution patterns of neuroreceptors**

In view of the wide use of antidepressants which block the serotonin transporter or serotonin uptake, as well as of the multitude of neuroimaging studies showing an influence of serotonin transporter genotype on structural and functional alterations in the brain of depressed patients, Figs. 2 and 3 depict the targets used in DBS for TRD in relation to the serotonin transporter (5-HTT) and serotonin-1A (5-HT1A) receptor as defined by positron emission tomography with the radioligand [11C]DASB and [carbonyl-11C] WAY-100635, respectively. The comparison of mean standardized values of currently used DBS targets shows high spatial coherence with high BPND values of the 5-HTT receptor (Fig. 2). High BPND values are evident in the raphe nuclei, hypothalamus and striatum. Based on our own data, several areas relevant for DBS show significant differences in 5-HTT BP between responders and non-responder after 3 weeks of SSRI treatment, namely the sgACC, the habenulae and the striatum (Lanzenberger et al., 2012).

A spatial connection can be also seen for the 5-HT1A receptor, the main inhibitory serotonin receptor in the brain. High BPND are evident in the cingulate cortex, the raphe nuclei and the hippocampus. During treatment with electroconvulsive therapy in depressive patients, a global cerebral reduction of the 5-HT1A receptor has been observed (Lanzenberger et al., 2013). Data was extracted from results of our research group, entirely published in (Lanzenberger et al., 2012, 2013).

**DBS coordinates and functional brain activation**

DBS is hypothesized to impact dysfunctional neuronal circuits, and thereby lead to normalization and clinical response. One of these major functional networks is the reward system, which was shown to be affected in TRD and OCD. Functional activations during reward processing can be probed by specific fMRI tasks in order to delineate implicated brain regions. One possible fMRI task is the monetary incentive delay task, which was developed by Knutson et al. (Knutson et al., 2001). In healthy volunteers, anticipation of reward leads to a robust

**Table 1** Summary of standardized coordinates of the main DBS targets in OCD, TRD and GTS extrapolated from 84 peer-reviewed articles including about 296 patients. 68 articles reported unique patients (see Table 1 and supplementary tables for more details). 37 peer-reviewed publications which provided MR images were included for the calculation of mean DBS targets reported below. These 37 studies covered the majority of patients, namely 202 (63 OCD patients, 89 TRD patients, 50 GTS patients).

<table>
<thead>
<tr>
<th>Target region</th>
<th>MNI (x/y/z) mm</th>
<th>Patient N.</th>
<th>N. of studies</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior limb of the capsula interna (ALIC)</td>
<td>$-12 \pm 4/10.6 \pm 3.7/-2.5 \pm 1.3$</td>
<td>10</td>
<td>3</td>
<td>Anderson and Ahmed, 2003; Chang et al., 2010, Nuttin and Gabrieli, 2003</td>
</tr>
<tr>
<td>Caudate nucleus (NC), Nucleus accumbens (NAcc), Ventral striatum (VS)/ventral internal capsule (VC)</td>
<td>$-11.2 \pm 3.6/10.6 \pm 3.7/-2.5 \pm 1.3$</td>
<td>37</td>
<td>10</td>
<td>Dueck et al., 2009; Martinez-Fernandez et al., 2011</td>
</tr>
<tr>
<td>Nucleus subthalamicus (STN)</td>
<td>$-7.7 \pm 0.6/8.9 \pm 0.6/-5.3 \pm 0.5$</td>
<td>16</td>
<td>1</td>
<td>Aouizerate et al., 2004, 2009; Baker et al., 2007; Haq et al., 2010; Okun et al., 2004, 2007; Sturm et al., 2003</td>
</tr>
<tr>
<td>TRD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgenual cingulate (sgACC), subcallosal cingulate (scACC)</td>
<td>$-4.6 \pm 0.6/26.1 \pm 3.3/-8.1 \pm 0.9$</td>
<td>60</td>
<td>5</td>
<td>Guinjoan et al., 2010; Hamani et al., 2009; Holtzeimer et al., 2012; Lozano et al., 2012; Puigdemont et al., 2012</td>
</tr>
<tr>
<td>Nucleus accumbens (NAcc), Ventral striatum (VS)/ventral internal capsule (VC)</td>
<td>$-7.3 \pm 1.4/6.2 \pm 1.3/-4.5 \pm 0.8$</td>
<td>29</td>
<td>4</td>
<td>Bewernick et al., 2010; Lojan et al., 2012; Malone et al., 2009; Schlaepfer et al., 2008</td>
</tr>
<tr>
<td>GTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>$-6.3 \pm 0.9/-13.1 \pm 1.4/-0.3 \pm 0.1$</td>
<td>42</td>
<td>10</td>
<td>Ackermanns et al., 2011; Bajwa et al., 2007; Houeto et al., 2005; Kaido et al., 2011; Maciunas et al., 2007; Marcerglia et al., 2010; Savica et al., 2012; Servello et al., 2008; Vandewalle et al., 1999; Vermaelen et al., 2009; Visser-Vandewalle et al., 2003</td>
</tr>
<tr>
<td>Globus pallidus internus (GPI)</td>
<td>$-19.5 \pm 4.3/-3 \pm 0.3/-4.5 \pm 0.4$</td>
<td>8</td>
<td>4</td>
<td>Dehnig et al., 2008; Diederich et al., 2005; Ducru et al., 2009; Martinez-Fernandez et al., 2011</td>
</tr>
</tbody>
</table>
activation of the ventral striatum, the ACC and the insula (Fig. 4). Interestingly, main targets for DBS in TRD and OCD are located in the ventral striatum, emphasizing the concordance of neuroimaging results and DBS performance. The duality of potential application of neuroimaging results on DBS data can be illustrated by means of functional activation during this reward task. On a group level, the fact that anticipation of reward clearly leads to an activation of the ventral striatum serves as neurobiological underpinning for the performance of DBS in psychiatric disorders which are known to be associated with dysfunctional reward processing such as depression. On the other hand, the application on a single-subject level shows the large future potential of neuroimaging in the clinical performance of DBS. If subdividing the result gained on a group level into distinct individual activation patterns, the large variability both of location and intensity of activation becomes evident (Fig. 4). Thus, in some individuals, the activation pattern will match the theoretical location and intensity of activation, while in others this effect will be small or absent or spatially shifted due to individual variability.

Discussion

DBS has emerged as a well-tolerated and efficacious treatment option for otherwise treatment-resistant patients suffering from neuro-psychiatric disorders such as GTS, OCD and TRD. From a neuroimaging point of view, DBS further represents a unique possibility to analyze functional networks in the brain which can then be related to data obtained in clinical neuroimaging studies in psychiatric patients. However, up to now, data has been restricted by the heterogeneity of the anatomical localization and description methods of targets in DBS studies. This might be explained by an incongruence between the primary purpose of the reported DBS studies and the demands for the integration into a neuroimaging framework. As the history of functional neurosurgery is controversial, and DBS is a relatively new procedure for psychiatric indications, the requirements for DBS are high and the major focus of previous studies has been to report efficacy and adverse events. On the other hand, the neuroimaging community depends on very precise and standardized reports of targeted structures and also applied parameters. The analysis performed in the current study was intended as a first step toward a standardized and comprehensive representation of this data in MNI space for DBS treatment in OCD, TRD and GTS. A database of standardized target coordinates aims to serve the purpose to improve the comparability of targets in DBS studies with molecular, functional and structural data of neuroimaging studies.

In recent years pooling neuroimaging data of small sample sizes which investigate similar questions has become popular. One of the most widely used algorithms for coordinate-based meta-analysis of neuroimaging data, especially functional MRI data, is Activation likelihood estimation (ALE). In the ALE algorithm activations are not treated as single points but as spatial probability distributions centered at the given coordinate (Eickhoff et al., 2012). The combination of activation probabilities results in these ALE maps. We considered the application of ALE for the present set of DBS data, however due to the nature of the algorithm, which requires statistical outcomes (e.g. T-values) to run, we instead computed average coordinates without the statistical approach. From a neuroimaging point of view, a major limitation of most of the published studies on DBS is that data is reported inconsistently and incompletely. Furthermore, postoperative coordinates when available mostly refer to individual MRI data and cannot be transferred into standard space using state-of-the art normalization techniques. In order to facilitate a direct comparison with neuroimaging data a standardized...
description of the methods and results would be needed. In this study overcoming this issue was attempted by integrating all available information reported in the papers and manually transferring them into MNI space after validation of this technique using in-house MRI data of healthy volunteers. As the deviation of individual to standard values is probably particularly relevant in regions where only a small number of patients is available, statistical analysis was restricted to target regions exceeding a total number of eight reported patients. This approach is naturally imperfect and shows a number of weaknesses compared to the possibility to base the meta-analysis on pre- and postoperative original MRI datasets. Therefore providing original structural MRI data along with the article for the neuroimaging community is strongly recommended (e.g. in the supplementary material or as an online link using frequently used formats for MRI data).

Furthermore, in the context of DBS the exact site and mechanism of action is strongly influenced by the defined stimulation parameters (frequency, amplitude, pulse width and duration). Especially in subcortical regions, where areas with different anatomical and functional connections are spatially close, the exact parameters would be strongly needed for interpretation in the context of neuroimaging data. The exact mechanisms of action of DBS seem to depend on a number of different factors. As summarized by Kringelbach et al., effects of DBS are influenced by intrinsic and extrinsic parameters such as anatomical and physiological properties as well as geometric configuration of the tissue, and applied stimulation parameters (Kringelbach et al., 2007). However, in the published articles, the position of the electrode tip is, for example, often reported instead of the exact coordinates of the active electrode contacts. A detailed description of the stimulation settings should be provided, since stimulation parameters such as pulse rate, amplitude and width, interact with the anatomical position of the electrodes and their characteristics. Recently, Butson and colleagues have suggested a probabilistic stimulation atlas to identify the optimal target and stimulation set-up by combining clinical outcomes with computational models of the volume of tissue activated based on the tissue electrical properties (Butson et al., 2011). Although in this paper the probabilistic atlas was created for Parkinson patients, a
Fig. 4. The VS/VC stimulation site in relation to task-specific activation in fMRI. Neuronal activation during a reward task at 7T in 26 healthy volunteers. Triplanar view of activation during the anticipation of reward vs. baseline assessed by ANOVA in SPM 8. The crossbar indicates the ventral striatum at $-7.3/6.2/-4.5$ (x/y/z) mm, the color table shows the corresponding t-values ($p < 0.001$, uncorrected, $T > 3.9$). In the group analysis (a) high task-induced activation can be observed in the striatum, the insula and the ACC. Concordantly, the striatum and the sgACC are well established targets in OCD and TRD. On the individual level the striatum activation can be both strong (b) and weak (c).
similar approach would be interesting for psychiatric indications. Indeed, the precise definition of the target and stimulation parameters would permit the investigation of effects of DBS on different anatomical sub-structures within a target region, and adjust DBS treatment to the patient’s specific symptoms and side effects. The fact that data is heterogeneously reported further restricts more sophisticated statistical analysis of published data such as ALE, which is standard in other fields of psychiatric research. Therefore, the present study is intended as a first step toward a standardization of available data and stress the need for the development of standardized reports of all relevant information in future DBS studies. A limitation of the present paper is that only selected disorders have been considered for the database. Other disorders which might have a potential for DBS treatment, such as addiction, have been excluded due to low sample size numbers.

The approach of providing a standardized database of target areas for DBS which is pursued in this paper of course neglects the fact that the brain architecture shows a high interindividual variability. In fact, in a study evaluating interindividual variability of the anatomical position of the subthalamic nucleus in Parkinson’s disease patients showed a significant deviation of the “real” subthalamic nuclei position compared to an established stereotactic atlas (Daniiluk et al., 2010). However, a standardized description of results is necessary in order to relate these results to neuroimaging data, and to facilitate an evidence-based rationale for personalized usage of this information, which will be the future gold standard for neurosurgical procedures.

In the last years it has become clear that brain areas are functionally subdivided which may add to the importance of a standardized description of the targeted regions, and potentially explain differences observed in treatment outcomes. Distinct functional subdivisions have been defined for the thalamus, cingulate cortex and prefrontal areas based on neuroimaging methods such as DTI. Only recently attempts were made to integrate this information in practical clinical performance of DBS. A retrospective DTI study in patients undergoing thalamus-stimulation for tremor control detected a favorable clinical outcome in patients with stimulation in thalamic regions with highest connectivity with the premotor cortex instead of those directly connected to the motor cortex as a-priori hypothesized by the authors (Pouratian et al., 2011). In TRD, Johansson et al. defined two distinct functional subregions within the ACC. When this information was applied to data from depressive patients, it was shown that clinically-successful stimulation lies within the subgenual region that exhibits strongest connections to the nucleus accumbens, amygdala, hypothalamus and orbitofrontal cortex (Johansen-Berg et al., 2008). In a number of cases this important information might be lost due to incomplete description of data, which restricts the comparison to basic scientific results.

Future neuroimaging application in DBS might go one step further than the standardized description of target areas toward surgical planning based on individual functional architecture of the brain. Thus, a potential direct application of neuroimaging in the field of DBS might be individual planning of DBS based on task specific activations, functional connectivity or tractography. Our neuroimaging results suggest that not every target might be suitable for every patient as highlighted by large interindividual variability of activation during a reward task in healthy volunteers.

As neurosurgical techniques are far more established in neurological disorders, such as epilepsy or PD, an orientation toward results in this field of research seems reasonable. In fact, the integration of functional imaging has already been implemented for surgical planning and prediction of side effects of anterior temporal lobe resection for refractory temporal lobe epilepsy. Results of published studies thus point toward a predictive potential of preoperative fMRI activation during verbal and visual memory encoding for postoperative memory decline (Bonelli et al., 2010; Powell et al., 2008). Furthermore, preoperative tractography of structures at risk, such as the optic radiation, for epilepsy surgical planning was evaluated with positive results (Winston et al., 2011, 2012). Similar approaches have been evaluated for other neurosurgical indications, such as surgical intervention in oncological patients (Roessler et al., 2005). This data emphasizes the potential of neuroimaging to add to an optimization of neurosurgical techniques with regard to maximization of efficacy and prediction of side effects.

The relevance of neuroimaging for DBS becomes clear by summarizing present concepts of mechanisms of action of DBS. Firstly, several studies propose that DBS would have a modulatory impact on dysfunctional networks by leading to changes of neurotransmitter levels and alterations of neural activity in efferent regions (Anderson et al., 2003; Kringle临bach et al., 2007; McIntyre et al., 2004; Vitek, 2002; Windels et al., 2000). Secondly, it has been hypothesized that DBS might provoke changes on a neurotransmitter level (Hamani et al., 2010, 2012). These aspects can be evaluated in-vivo by means of functional neuroimaging techniques such as fMRI and PET. As a matter of fact relating present PET and DBS data shows that several target regions used in DBS for TRD overlap with regions of serotonin transporter binding as defined by positron emission tomography with the radioligand \(^{11}C\text{DASB}\) (Lanzenberger et al., 2012; Meyer et al., 2001, 2004a, 2004b; Savli et al., 2012). Response vs. non-response to SSRI treatment is associated with clear differences in serotonin receptor binding in the sgACC and the habenulae, regions which are successfully used as DBS-targets in a number of studies (Broadway et al., 2012; Holtzheimer et al., 2012; Lozano et al., 2008, 2012; Mayberg et al., 2005; McNeely et al., 2008; Sartorius et al., 2010; Spindelegger et al., 2009). Electroconvulsive therapy, which is known to be a highly effective treatment strategy for treatment-refractory patients was recently shown to be associated with marked global decrease in 5-HT\(_{1A}\) receptor binding (Lanzenberger et al., 2013). These effects were again evident in the sgACC which has a high density of 5-HT\(_{1A}\) receptors. Concerning overlapping regions between dysfunctional brain areas in depression and DBS target regions a recent meta-analysis shows deviating activation pattern in the pregenual ACC and the thalamus in depressed patients during resting-state as well as the subgenual and pregenual anterior cingulate cortex during emotion processing (Fitzgerald et al., 2008). During symptom provocation in OCD patients’ neural activation was detected in the striatum and the thalamus as reported in a meta-analysis including 8 fMRI studies (Rotge et al., 2008). Concordantly, an overlap of DBS target regions and alterations in neural activation have been reported in a meta-analysis comparing PET and SPECT data between OCD patients and healthy volunteers. In this study significant differences between these two groups were shown for the head of the caudate and the thalamus among others (Whiteside et al., 2004a). These results further emphasize the importance of integrating molecular and functional neuroimaging studies into the concept of DBS in order to further understand its mode of action.

Conclusion

In conclusion, current results emphasize the importance of the combination of DBS data and neuroimaging results and their complementary potential. The nurturing relationship between DBS and neuroimaging results might consist in validation of currently used targets, the development of new potential targets as well as direct applications for individual surgical planning. Thus, a multidisciplinary approach is strongly needed in order to facilitate the dissemination of gained results for future advancement of research in the area of neuroimaging and for optimization of clinical standards. The present database is therefore intended as a first step in this direction as it provides standardized values for currently used target areas in the main fields of applications in psychiatry. Examples illustrating current interlacing of neuroimaging and DBS results, based on our own functional imaging results and those of others, highlight the importance and great value of this data for both the verification of theories gained.
in neuroimaging studies in-vivo and the improvement of patient management. Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2013.04.065.

Acknowledgment
This research was partly funded by grants from the Austrian National Bank (OE1B 13219), the Brain and Behavior Research Foundation, (NARSAD, http://bbrfound.org/), USA, by the research cluster MAN-BIOPSY between the Medical University and the University of Vienna (FA103FC001), Austria, and by the Swedish Council for Working Life and Social Research (FAS: 2011-0627). We thank Sebastian Ganger, MSc, Andreas Hahn, MSc PhD, and Georg Kranz, MSc, for their support in generating the figures and the native speaker Marie Spies for the English proofreading.

Conflict of interest
None of the authors has a conflict of interest with regard to the manuscript.

References


