Stimulation sweet spot in subthalamic deep brain stimulation-myth or reality? A critical review of literature

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Short title : Stimulation sweet spot in subthalamic deep brain stimulation-myth or reality?

Number of Tables: 5

Number of figures: 3

Manuscript words count: 4140

Abstract word count: 236

Keywords:

Parkinson's disease
Deep Brain Stimulation
Subthalamic Nucleus
Volume of Tissue Activated
Sweet spot

Conflict of interest: none

Funding source: none

ABSTRACT:

Introduction: While deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been extensively used for more than 20 years in Parkinson's disease (PD), the optimal area of stimulation to relieve motor symptoms remains elusive.

Objective: We aimed at localizing the sweet spot within the subthalamic region by performing a systematic review of the literature.

Method: PubMed database was searched for published studies exploring optimal stimulation location for STN DBS in PD, published between 2000 and 2019. A standardised assessment procedure based on methodological features was applied to select high quality publications. Studies conducted more than 3 months after the DBS procedure, employing lateralised scores and/or stimulation condition, and reporting the volume of tissue activated or the position of the stimulating contact within the subthalamic region were considered in the final analysis.

Results: Out of 439 references, 24 were finally retained, including 21 studies based on contact location and three studies based on VTA. Most studies (all VTA-based studies and 13 of the 21 contact-based studies) suggest the superior-lateral STN and the adjacent white matter as the optimal site for stimulation. Remaining contact-based studies were either inconclusive (5/21), favoured the caudal zona incerta (1/21) or suggested a better outcome of STN stimulation compared to adjacent white matter stimulation (2/21).

Conclusion: Using a standardised methodological approach, our review supports the presence of a sweet spot located within the supero-lateral STN and extending to the adjacent white matter.

Highlights:

The optimal area of stimulation to improve motor symptoms with STN-DBS in Parkinson's disease remains a matter of debate.

Most studies selected in our work suggest an optimal stimulation area within the supero-lateral STN subthalamic nucleus and the adjacent white matter.

Averaged coordinates of the reported active contacts corresponded to the supero-lateral and posterior subthalamic nucleus.

Future improvements in VTA prediction models, as well as better consideration for non-anatomical factors influencing the DBS outcome might further improve the delineation of this sweet spot.

Introduction

Deep Brain Stimulation (DBS) of the Subthalamic nucleus (STN) is a well-established approach for the management of motor fluctuations in Parkinson's disease (PD) (1–6). Whilst this treatment benefits most patients, divergences in outcomes exist (7). This has brought attention to factors that might potentially explain the divergence (7,8), such as electrode placement and the volume of tissue activated (VTA) by stimulation (7,9,10).

The identification of an optimal stimulation area or 'sweet spot' within the subthalamic region is crucial in surgical planning. This, combined with the emergence of new programming strategies based on VTA prediction, might help reducing programming time (11,12), as well as avoiding subtle or delayed onset side effects (13). Nevertheless, despite the extensive use of this concept in the literature for over twenty years, its exact location remains elusive. A systematic review aiming to address this issue (10) found large discrepancies between studies, leaving the question unanswered. Potential reasons underlying this heterogeneity include the variability in the strategies used to localise the stimulation site, the active contact positions or the location and boundaries of the STN (10). A recent survey of movement disorders specialists aiming at identifying the theoretical best contact location on atlas slices also demonstrated disagreement between experts (9).

While contact-based studies have been the mainstay of this exploration, recent advances in VTA modelling has brought novel insights into this field (14,15), that can be exploited to explore the effect of different stimulation settings on the stimulation volume. A growing number of studies using this newly available strategy as a way to identify the best location of stimulation for motor outcome have been released over the last few years, prompting an update of the available evidence. Furthermore, ever since the increased reliance on visualization platforms as a tool to assist with DBS programming, the identification of the stimulation 'sweet spot' as well as 'sour spots' (for side effects) has become of great relevance to the programming clinician and not just the operating neurosurgeon. In this work, we aim to review the existing literature and apply strict methodological criteria to identify the ideal stimulation location in the STN for the treatment of PD motor symptoms. Given the increasing use of imaging software as a promising tool to assist with DBS programming, this work was a primarily focused on studies involving imaging-defined STN.

Material and methods

A comprehensive review of the literature was conducted over the period of August to December 2019 using Medline (Pubmed) and the Cochrane Library. The search strategy included the terms (active contact) or (most effective contacts) or (sweet spots) or (localization) or (location) or volume of tissue activated) and (subthalamic nucleus) and covered the period between 01/2000 and 12/2019. No language restrictions were applied. Papers were excluded if they were not relevant to the search topic. Of the subsequent included papers, a manual search of bibliographies was conducted to identify additional articles that may have been missed on the initial search. Data regarding connectivity pattern associated with the optimal stimulation area (7,16), or with the beta oscillation source (7), were considered as beyond the scope of this review and therefore excluded.

Articles included were then categorised according to the method used to describe the best stimulation spot (contact location or volume of stimulation).

For studies based on contact position, the time interval between stimulation setting and clinical assessment served to differentiate the ones assessing the outcome in the short-term (contact testing and clinical assessment performed the same day) from long-term studies. Long-term studies based on contact location were further categorised between those simply reporting the position of the optimal contact as defined through clinical care and the ones further exploring the relationship between contact position and motor outcome (either through group comparison or by mapping the clinical effect of stimulation within the STN). In the text, studies falling into the first category will be mentioned as "active contact localisation studies" while the ones relying on motor outcome to statistically determine the best stimulation area will be mentioned as "motor outcome/contact location association studies".

Within each category, articles were individually reviewed using methodological criteria selected from a consensus between authors based on their deemed impact on study outcome. These included: number of patients, timing between DBS implantation and assessment, STN segmentation (imaging, atlas, MER) and lead visualisation methods (planar X rays, fluoroscopy, CT scan, MRI scan). Specific attention to these elements was emphasised in view of previous studies suggesting that imaging modality for lead detection, as well as the method to define individuals STN boundaries might influence the main findings (17–19). When atlas-based segmentation was used, the method employed (type of co-registration or transposition strategy) was noted. Similarly, when group-based analysis was performed from individual coordinates or scans, the normalisation method (transposition onto a common space) was examined. For studies assessing the motor outcome in relation to stimulation location, the method of evaluation, including the type of motor assessment, medication status during motor assessment (ON, OFF or not described), and lateralisation (total or lateralised score, under unilateral or bilateral stimulation) were recorded. For VTA based studies we also reviewed VTA

models (FEM-based or heuristic, adapted to individual electrodes' impedances or not). Main results concerning optimal stimulation sites were noted, as well as contact or stimulation coordinates, and information regarding active contact distribution within the STN area, when available.

In order to warrant comparability between studies, we defined selection criteria based on the above-mentioned features to focus the review analysis on high-quality studies. Studies enrolling less than 12 patients, early stimulation settings assessment (<3 months from surgery), without STN segmentation or based on planar X rays for lead detection were consequently excluded from main results analysis. Since motor assessment relying on non-lateralized score reflects the average effect from both contacts locations on motor outcome, we purposely focused on studies using lateralized score and/or unilateral stimulation.

While this work focused on providing conclusions regarding the stimulation sweet spot on imaging, studies relying on MER-based STN segmentation and otherwise fulfilling methodological criteria were included but considered separately for further comparisons.

Results

Studies

Among the 439 articles identified, we selected 55 that fulfilled the initial selection criteria (figure 1). One article could not be accessed online (20) and another four, based on connectivity profile (7,16), beta oscillation signal (7,21), or exclusively studying freezing of gait and falls (22), were considered as beyond the scope of this review, and excluded. Following a review of the remaining 50 articles, 11 additional studies were identified and included in the present work and 61 (10 VTA based and 51 contact based) studies were finally used in this review.

DBS contact location

Nineteen studies reported distribution of contacts 'location (two short-term and 17 long-term, see Figure 1)**.** The proportion of contacts in various subthalamic areas is presented in (Table 1)**.** Six studies (31.5%) had most contacts within the STN**,** four (21%) a majority at the superior border**,** while 6 (31.5%) had a roughly equal distribution between areas (inside/outside STN or inside/superior border/above the STN, see figure 2). Three studies (15.8%) had most contacts above the STN (table 1)**.**

Excluded studies after methodological assessment

Six out of 10 VTA based studies were excluded with the following reasons: insufficient number of participants included (14,23,24), interval of time between surgery and stimulation assessment not

reported (24), non-lateralised motor assessment with bilateral stimulation (25–28) motor assessment reported ON medication (27,28) and the absence of true VTA modelling with the use a common predefined VTA size, regardless of individual stimulation settings (therefore not considering the effect of stimulation parameters in the resulting volume of stimulation) (26).

Thirty-two/51 studies were excluded. Among those, eight short-term studies were excluded due to: insufficient number of participants included (29–32) assessment of bilateral stimulation with total UPDRS-III (32–34), stimulation procedure being performed ON medication (31,34), variable/insufficient time from DBS implantation (29,32,32) or time from surgery not being mentioned (31). Additionally, lead detection was based on planar X-rays in two studies (32,32) and not clearly described in one (35); and 24 long-term studies were excluded due to: insufficient number of patients included (36–39), absence of STN segmentation (39–44), and use of planar X-rays for contact location (9,37,42,45–47), lead localisation method not described and absence of contact location (20), motor assessment performed ON medication (48–50), medication status not specified (51) and use of bilateral motor scores to analyse bilateral stimulation (25,39,52–56) (supplementary Table 1-4).

VTA

Out of ten VTA based studies reviewed, three fulfilled the methodological criteria (15,57,58) (Table 2). All three studies utilized voxel analysis to identify the optimal stimulation area to the supero-lateral STN (15,57,58) and adjacent ZI/H2 white matter, beyond the superior limit of the STN (15,57).

Contact based study using short term assessment

Eleven/51 contact-based studies included short-term assessment of deep brain stimulation (Table 3). Following methodological evaluation, three/11 studies using MRI location of the STN were retained (59–61). Among the three selected studies, STN segmentation was based on an atlas, with the Mai atlas being registered linearly to patients scan using landmarks as described and validated using the centre of the red nucleus as determined by experts in Videen et al. (19).

McNeely et al. and Gourisankar et al. both compared the effect of ventral (inferior) and dorsal (superior) stimulation on motor outcomes and did not observe a significant difference apart from rigidity being improved by ventral stimulation in Gourisankar's work (59,61). Eisenstein et al. and Gourisankar et al. also used a voxel-based analysis, weighting voxels according to the distance from the stimulating contact. The former did not identify a specific area associated with global motor improvement, although some lateralised symptoms were associated with specific stimulation spots (right hand bradykinesia with stimulation of the STN/ZI interface i.e superior border, and left hand tremor was associated with the STN/SN interface) (60). Gourisankar et al. further reported

improvement associated with the stimulation of the STN (rigidity), the superior STN (bradykinesia, tremor) and the adjacent ZI (total UPDRS-III) (61).

Contact-based studies using long term assessment

Twenty-six/40 studies fell into the motor outcome/contact location association studies category while the remaining 14 were active contact localisation studies (table 4).

Of 14 active contact localisation studies, two using MRI location of the STN fulfilled the methodological criteria (62,63), while six additional MER-based studies were selected (64–69) (Table 4). Regarding the studies based on imaging-defined delineation of the STN, Vergani et al. reported a balanced contact distribution between the ZI/Forel's field H2 and the STN (62), while Connolly et al. reported that most optimal stimulation contacts were localised within the supero-lateral STN (63). Using MER-defined STN, Saint Cyr et al. described the optimal stimulation area as being in an area extending from the antero-superior STN to the adjacent white matter (ZI/ Forel's field H2) (64). Zheng et al. reported the best contact location as anteriorly and superiorly to the superior STN boundary (68), while the remaining four MER-based studies described the superior limit of the STN as being the optimal stimulation location (65–67,69).

Eight motor outcome/contact location association studies using imaging-based location of the STN (17,70–76) (Table 5) as well as two additional comparative MER-based studies (8,41) met the methodological criteria. While Welter et al; (73) and Chazeron et al; (74) also compared total UPDRS-III with bilateral contact location, they only considered pairs of contact with similar locations, limiting the confusion of incongruent contact locations when interpreting the motor outcome, therefore these two studies were included. Most of the eight studies tended to advantage the STN (73,74), and more precisely, the antero-superior STN (antero-superior STN (71), anterior-supero-lateral STN (75) and antero-lateral STN (72). Two studies did not observe any effect associated with stimulation placement (17,76), although Weise et al. (17) concluded that most contacts were located within the superior half of the STN which also represented half of all contacts location in the study from Mostofi. et al. (Table 5). One study supported caudal ZI over STN stimulation (70). When considering MER-based studies, Verhagen et al. reported the postero-lateral STN as an optimal stimulation location (8). Conversely, Bot et al., by comparing the position of stimulation contacts associated with poor, satisfying and optimal responses to an electrophysiology-defined superior border of the STN did not find statistically significant differences (41).

Coordinates

Stimulation contact coordinates in relation to the AC-PC line were reported in 16 (14 contact-based studies and two VTA-based studies) of the 24 (21+3) studies which satisfied the methodological

review. A total of nine/16 studies, which did not indicate any normalisation of AC-PC based coordinates, were excluded (17,41,66–71,76). Of note, in one of those studies the caudal ZI was selectively targeted (70).

Among the seven/16 remaining studies, the coordinate correction system (based on template dimension) varied significantly. Methods included AC-PC based correction (Saint Cyr et al. correction with AC-PC length of 23mm (64)) and co-registration to common spaces, namely MNI space in Dembek et al. and Akram et al. (15,57), Mai atlas in Gourisankar et al. and Eisenstein et al. (61), Schaltenbrand and Wahren atlas in Vergani et al. (62), and a digitised version of the Morel Atlas using averaged dimension of all patients in Garcia-Garcia et al. (75). AC-PC lengths could be obtained either from the article directly or from available characteristics of common spaces for the seven studies and was used to normalise x, y and z coordinates to a common AC-PC length of 23.29mm (supplementary table 5). For three studies (15,60,61) which expressed the antero-posterior (y) coordinate from another origin than the mid-commissural point, medio-lateral (x) and supero-inferior (dorso-ventral, z) coordinates were kept unchanged and antero-posterior coordinates were converted to MCP based coordinates from the AC-PC length for comparability (supplementary table 5). Corrected average MCP based coordinates ranged from 9mm (57) to 11.9mm (64) laterally, -0.8mm (62) to -5.1mm (61) posteriorly and from 0 mm (15) to -2.9mm inferiorly to MCP (61). Averaged values were x: 10.5mm (±1), y: -2.5mm (±1.5), z: -1.7mm (±0.9) (based on 448 contacts). Those averaged coordinates correspond to the supero-lateral and posterior STN on the MNI template (MNI coordinates: x: 11.6mm ±1mm, y:-13.1mm±1.6mm, z:-6.7mm±1mm, Figure 3, supplementary table 5).

Discussion

In this review, we extensively screened the literature contributing to the knowledge of the 'best' stimulation area for STN-DBS in PD, selecting only high-quality studies through a predefined set of standardized criteria. Our findings suggest the supero-lateral STN and its adjacent superior white matter as the most relevant candidate areas to achieve optimal motor outcome. This is supported by three rigorous VTA based studies as well as 14 contact-based studies. These results are in accordance with a previous review on best stimulation placement (10). The important role of the supero-lateral STN and the adjacent white matter tracts is further supported by the predominance of active contacts located within these regions (17,76) (Table with distribution of contacts). Our findings are also in agreement with previous histological (77) and physiological studies (78) conducted on primates as well as imaging studies (79) in humans (80). Local field potential recording studies measuring beta oscillatory activity, a marker of the best stimulation area (21) also concurs with this.

Differentiating between the superior STN and the adjacent white matter when attempting to define the optimal stimulation area, has been the focus of major attention in the recent literature (14,24,73,74). In our review, two of the three VTA based studies (15,57) and seven (62,64–69) contact-based studies suggested a positive effect of stimulation located in the ZI/H2 region including some reporting minimal or no overlap between the optimal stimulation area and the supero-lateral STN (15,68). The overall variability when opposing these two areas, might be explained by methodological differences including the use of MER to define STN boundaries (24). Indeed, Weise et al. reported a mean difference of 2.8mm in the length of the electrodes placed within the STN, when comparing MRI based and MER based STN delimitation. This resulted in conflicting findings between MRI and MER based segmentation, with 14% and 50% of active contacts being located beyond the superior border of the STN respectively (17). Further supporting this view, most reviewed studies describing a majority of contact within the STN used a MRI-based definition of the STN, while in two out of three studies describing a majority of contact above the superior limit of the STN, the superior boundary was defined by MER (Table 1).

Among other factors, overestimation of the volume of the STN on MRI (especially when using susceptibility imaging), MR image distortion in absence of adequate correction, but also error in the location of the superior border of the STN with MER resulting from brain-shift, or due to suboptimal trajectory angle missing the most superior part of the STN, might contribute to the observed discrepancy between MRI and MER.

Noteworthy, the variety of motor symptoms associated with PD, could further explain the extension of the optimal stimulation area from the superior-lateral STN to the adjacent ZI/H2 area. Indeed, several authors have reported that the different motor features of PD might respond optimally to

different stimulation area, albeit with conflicting results. According to Cintas et al., the best contact was common for both akinesia and rigidity in only 41% of cases (65). Moreover, Gourisankar et al. describes that tremor and bradykinesia were better improved by stimulation of the superior STN, while rigidity responded to the stimulation of the whole STN, and possibly more within its inferior part (61). Furthermore, some authors have also suggested different mechanisms underlying tremor control between proper STN stimulation and ZI stimulation (36). Other studies bring more moderate conclusions with some degree of overlap between symptom specific sweet spots. For Butson et al. (14), bradykinesia and rigidity both responded to the stimulation in a shared area (white matter superior to STN, but with the area associated with improvement in bradykinesia more restricted than for rigidity), while Akram et al. (57) found a common area for tremor, rigidity and bradykinesia within the supero-lateral STN with some further extension medially and posteriorly for rigidity and bradykinesia. This is reinforced by Dembek et al suggesting a significant overlap in the sweet spot for rigidity and akinesia (15).

Assessment timing might also influence the resulting optimal stimulation area, as illustrated in the study from Dembek et al (15). Based on short-term motor assessment the authors described the sweet spot as mostly overlapping within the ZI/H2 area, while the long-term benefits of DBS were predicted by the degree of overlap between the VTA and the whole STN.

In view of the above observations, we believe the current literature cannot discriminate between the supero-lateral STN and its adjacent white matter tracts, which might be considered as a unit rather than two distinct targets. This hypothesis is further supported by the presence of relevant fibres tracts within the ZI/Forel's field H2 region, including afferent fibres from the motor cortex (hyperdirect pathway), and the lenticular fasciculus afferent from the globus pallidus, which have been proposed as playing a critical role in the symptoms of PD (14,15,38,57,70,81).

When considering the extensive literature, inter-individual variability of motor outcomes was suggested by several studies. Indeed, this was directly described by Maks et al (24), who observed different outcomes associated with the same area of stimulation and by Schlaier et al. (50), who noted that, despite an overall better outcome associated with the stimulation of the supero-lateral STN, some patients performed better with the stimulation located in other parts of the STN. Additionally, an important dispersion was observed for contact coordinates within studies, even when considering those which employed normalisation methods: Saint Cyr et al. SD z axis 1,76mm, SD y axis 1,98mm (56 contacts) (64), Garcia-Garcia et al. SD y axis 1.93 (61 contacts) (75). This inter-individual variability might explain the limited results of purely model based programming approach (11,13), and while the precise reason for this heterogeneity remains to be explored, this might challenge the concept of a uniform sweet post applicable to all PD patients, regardless of clinical, imaging or genetic

characteristics. Inter-individual differences in STN size, shape, functional organisation and connectivity profile will surely need further consideration and dedicated investigations.

To our knowledge, our study is also the first critical review of recent VTA-based studies, which potentially provide a superior understanding of the anatomical-stimulation correlation of outcomes. Indeed, contact-based strategies only bring an indirect estimate of the most suitable stimulation spot for STN DBS, as the location of the active contact does not comprehensively explore the entire subthalamic area volume exposed to stimulation, but only the electrode trajectory. Hence, the position of the optimal contact is universally associated to the lead trajectory, thus binding the position of the stimulation along the antero-posterior, medio-lateral and supero-inferior axis. Therefore, one cannot rule out that an apparent better outcome with superior stimulation is not actually driven by an associated lateral or anterior position along the lead trajectory. Conversely, VTA models, when combined with voxel-based analysis, allow the exploration of smaller or larger volumes. This, along with the possibility to predict the spread of stimulation resulting from directional contacts will undoubtedly improve the definition of the optimal stimulation area (15,58). These two factors might explain why all selected studies based on VTA prediction reached similar conclusions as opposed to more discrepant findings from contact-based studies. However, VTA approaches also carry important limitations. Indeed, most models are based on predicting the depolarisation of a myelinated axon of a predefined diameter and electric properties and oriented perpendicular to the direction of the electric field vector (82). Therefore, they only provide partial information about the effect of stimulation on surrounding neural elements. While some models have been validated against EMG recording for the prediction of the stimulation of the pyramidal tracts coursing within the internal capsule, the ability of such models to predict the effect of the stimulation on other tracts such as the hyper direct pathway or the neuronal bodies within the STN remains to be demonstrated (23,82). Furthermore, such methods provide a binary representation where every voxels located within the VTA are considered as being equally affected by the stimulation, regardless of the position of this voxel within this volume (15,57,58). This could potentially limit the accuracy of voxel-based analysis. Despite those inherent limitations, constant progress such as the inclusion of tissue anisotropy (14,23,24), tissue inhomogeneity (15,58), axon characteristics (83) as well as stimulation conditions beyond simply stimulation amplitude (84) will allow further improvements in the reliability of this approach.

Although our approach accounts for the differences of mainstream methodological contributions to localizing stimulation within the STN area, other aspects of the process, such as co-registration accuracy, the use of templates and landmarks, differences in rater segmentation expertise, imaging quality, and VTA modelling differences are important in the interpretation of the results. While most studies involved a limited number of participants (median 25 patients), which restricts the interpretation of the reported findings, very small sample-based studies were excluded (less than 12

patients, corresponding to less than 20% of all studies) in order to limit this potential bias. A further confounding point is the inclusion of studies with an array of evaluation timing. Although the value of the short effect in predicting long-term outcomes remains unclear, we decided to keep studies that tested the short-term effect of stimulation for a number of reasons. Firstly, it is worth mentioning that the magnitude of the benefit from DBS might vary between patients due to factors independent of the stimulation area (7). Therefore, a given outcome can represent, depending on the patient, either the optimal effect (best possible effect), or to the contrary a suboptimal effect, which could be improved by moving the stimulation towards another area. In this respect, while the majority of studies based on long-term outcomes compared groups of patients, short-term studies provide direct comparison of different contact positions/VTAs within the same patient, thus accounting for inter-individual variability. Secondly, two studies that reassessed the effect of each contact during follow-up, reported an overall agreement between the best acute stimulation contact and the contact used for chronic stimulation (47,65).

While we have explored stimulation positions in detail here, previous studies assessing the correlation between adequate stimulation placement and motor outcomes only suggested moderate associations (8,15,72,75). These values were comparable to the ones reported by Horn et al. (7), who, could predict 26% of the variance in the observed motor improvement by combining connectivity data and VTA modelling. This, in association with the finding of an improvement in model predictability of outcomes when clinical factors were combined to connectivity-based model, highlights the necessity for adding relevant clinical and biological/genetic data to current imaging aspects for future prediction models.

To conclude, this critical review of literature incorporates the growing use of VTA-based approaches and introduces a standardised methodological method to approach the extensive and highly heterogeneous literature about the optimal stimulation area within the STN region. Our finding supports the presence of a sweet spot located within the supero-lateral STN and extending to the adjacent ZI/Forel's field H2. These findings could serve as a basis for a necessarily more tailored approach to reach the best possible outcome from STN DBS in PD patients. The contribution of individual factors, such as disease phenotype and the functional organisation of the STN, will warrant more attention in future work.

Authors' Role:

AdR: organisation and execution of the review, data collection and writing; TW: organisation, review and critique; NV: organisation, review and critique; FF: execution of Figure 3; HA: review and

critique; TF: review and critique; LZ: review and critique; PL: conception of the research project, review and critique

Financial Disclosure:

AdR's fellowship position has been financially supported by a grant from Boston Scientific. TW's fellowship was funded by two grants from the "APTES" and the "Fondation Planiol" organizations and received research grants from the Revue Neurologique and travel funding from LVL Medical.

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Figures Legends

Figure 1: Flow chart

Figure 2: distribution of contacts location

Figure 3: MNI space representing the average coordinates of the optimal stimulation contact / area for each of position of the seven studies reporting corrected coordinates. The supero-inferior (Z), anterior-posterior (Y) and medial-lateral (X) coordinates of the slices from the MNI space are indicated. Each plot represents a study are plotted on a common MNI space (red, Gourisankar et al.; pink, Akram et al.; bright blue, Saint-Cyr et al.; dark blue, Garcia-Garcia et al; green, Eisenstein et al.; yellow, Vergani et al.; orange, Dembek et al).