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Author's response to the Letter to editor

# Complexities of connectivity-based DBS targeting: Rebirth of the debate on thalamic and subthalamic treatment of tremor

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In response to our recent work on thalamic segmentation in deep brain stimulation (DBS) for essential tremor (Middlebrooks et al., 2018), Dr. Akram and colleagues shared their insights and expertise on the subject of thalamic segmentation. The authors first highlight the challenge inherent to a "common language" of thalamic regions that is further compounded by recent advances in functional neuroimaging. We fully agree with the authors that traditional atlases can often oversimplify thalamic anatomy while the ground truth has been shown to be much more complex. Therefore, one aim of our study was to provide reproducible regions-of-interest for supplementation of surgical targeting given the inability to reliably identify such divisions with traditional structural imaging (Middlebrooks et al., 2018). The methodology of "hard segmentation" itself is undeniably an oversimplification of thalamic anatomy as there is certainly overlap between the microscopically defined regions. Indeed, we find from the raw probability data that even within subjects there is considerable overlap between connectivity between cortical regions. We do not propose that these segments defined by connectivity measures have a high correlation with historically defined histologic anatomy. In fact, we firmly believe that this model will ultimately be replaced with more sophisticated modeling of thalamic connectivity that also accounts for the inherent overlap of connectivity within the thalamus. However, such data is yet to be developed and presents additional challenges in clinical implementation, whereas the segmentation model provides more readily understandable definitions in current clinical practice. Additionally, it is intriguing that the authors discredit the validity of the segmentation model despite their prior publication (cited in their response) having a paragraph designated to highlighting the existing validation of this model that their group was the first to publish (Akram et al., 2018; Behrens et al., 2003).

We also do not dispute the clinical benefit achieved with dentato-rubro-thalamic tract (DRT) stimulation; however, the authors assertion that this is a proven sole thalamic target for tremor benefit is problematic given the benefit shown with stimulation within multiple additional surrounding regions including the posterior subthalamic area (e.g., prelemniscal radiations and caudal zona incerta) (Bot et al., 2018; Plaha et al., 2008) and ventralis oralis nucleus (Foote and Okun, 2005; Foote et al., 2006). In fact, Bot et al. recently highlighted the improved tremor control with posterior subthalamic area stimulation when directly compared to Vim stimulation by placing an electrode across both targets in multiple patients (Bot et al., 2018). Importantly, they also found a higher incidence of gait disturbance with Vim stimulation, a known common occurrence with Vim DBS (Bot et al., 2018; Earhart et al., 2009; Pahwa et al., 2006). While likely multifactorial, the rare occurrence of this phenomenon in our patient group may also highlight the potential benefit of stimulation outside of the Vim/DRT region; however, this could also be confounded by selection of unilateral Vim implants (Mitchell et al., 2018). While the basis of these gait effects is currently not well known, they are potentially related to increased modulation of cerebellar and/or internal capsule connections. The combination of these studies, amongst many others, highlights the complexity of tremor control within and around the thalamus.

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The primary limitation of all existing data remains the lack of comparative testing within these multiple targets. As originally highlighted by our group, there is a lack of substantial variability in stimulation regions within individual studies that is primarily driven by the retrospective nature of these studies and the variation in surgical methodology. For instance, our study had preferential SMA/PMC overlap compared to M1 that is undoubtedly a product of surgical placement guided by intraoperative microelectrode recording (Middlebrooks et al., 2018). Others, such as Akram et al. had more ventral targets of stimulation that all lie ventral to the thalamus and did not directly compare these ventral thalamic regions that are currently discussed. Others have also found contradictory results, such as stimulation within the SMA region of the ventral thalamus (Pouratian et al., 2011), as well as the lack of correlation between tremor improvement and DRT stimulation with multiple fiber tracking methods (Nowacki et al., 2018). Therefore, the purpose of our paper is also to highlight the therapeutic response achieved with our surgical method that is statistically driven as opposed to many other existing studies that only present observational evidence (Akram et al., 2018; Pouratian et al., 2011). The study of Bot et al. is a great example of how such crossover-type studies can provide a great deal of insight into the differences between these multiple therapeutic targets (Bot et al., 2018).

Akram et al. also erroneously charge that we imply modulation of cerebellar outflow to the SMA/PMC region; however, we have explicitly stated in our manuscript that pallidal-receiving neurons to SMA/PMC via the ventralis oralis region is the proposed mechanism of action for tremor control in this secondary treatment target (Foote and Okun, 2005; Foote et al., 2006; Mehanna et al., 2014; Oyama et al., 2011; Yu et al., 2009). The basis of this mechanism is supported by other studies highlighting the known connectivity between these regions from both human DTI studies and primate studies (Hyam et al., 2012; Wiesendanger and Wiesendanger, 1985). We believe these prejudicial conclusions drawn from our data by Akram et al. are a misrepresentation of the conclusions discussed in our manuscript.

Lastly, the authors also re-iterate many of the limitations of the technique that we had previously discussed on our manuscript regarding the methodology of DTI and limitations of retrospective surgical data. These limitations are well known and extensively described in DTI literature, yet they have not prevented DTI from already drastically changing patient care, such as in brain tumor surgery (Osipowicz et al., 2016; Wu et al., 2007). As is the case with application of DTI surgical planning in brain resection, caution must be exercised when relying on such data for treatment planning due to these known limitations of the technique. Such is the basis for our original recommendation that additional studies are needed to understand the role of DTI in DBS surgery better. We respect the opinion of Dr. Akram and colleagues that our findings, as well as that of other groups, adds ambiguity to the application of connectivity measures in DBS planning; however, such ambiguity is also rampant in structural and electrophysiologic targeting. The tradeoff between long-term tremor control and reduction of side effects remains the “holy grail” of DBS therapy. We remain confident that the continued evolution of MRI-based connectivity measures will play a major role in achieving this goal, but is no substitute for multidisciplinary patient selection, surgical expertise, and diligent device programming.

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