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Letter to the editor

Connectivity derived thalamic segmentation: Separating myth from reality

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Letter to the Editor,

We read with interest the paper by Middlebrooks et al. [October 2018] titled "Structural connectivity-based segmentation of the thalamus and prediction of tremor improvement following thalamic deep brain stimulation of the ventral intermediate nucleus" (Middlebrooks et al., 2018), which described hard-segmentation of the thalamus, performed in 40 patients with essential tremor who had received ventrointermedialis (Vim) deep brain stimulation (DBS), using connectivity to 7 cortical regions.

Meaningful in-vivo segmentation of the human thalamic nuclei continues to be a challenge in the field of neuroimaging. This is mainly due to the lack of contrast between these nuclei on conventional MRI (Lemaire et al., 2010), potentially a consequence of the lack of distinct anatomical borders between these structures in the first place (Ilinsky et al., 2018). Complicating things further, the disparities between the various histological and cytochemical classification systems have led to a diverse range of grouping and naming conventions (Hassler, 1950; Hirai and Jones, 1989; Ilinsky et al., 2018).

In the last decade, connectivity based segmentation, utilising diffusion MRI (dMRI), has emerged as a promising approach of segmenting the thalamic nuclei in-vivo (Behrens et al., 2003). This approach has stirred significant interest in the field of functional neurosurgery as the thalamic targets for the treatment of tremor are not visible on conventional MRI. Since the publication of the study by Behrens et al. in 2003 (Behrens et al., 2003), several studies have set out to replicate these results using hard-segmentation algorithms to form boundaries between thalamic nuclei (Kim et al., 2016; Middlebrooks et al., 2018; Pouratian et al., 2011). Although the results of these studies show similar patterns of segmentations, they all have individual inconsistencies. This can be explained by: the high variability in dMRI acquisition and processing; the known susceptibility to geometrical distortion leading to registration inaccuracies; and the variability in the cortical seed region of interest definition. Furthermore, tractography has inherent limitations related to the laterality of the seed region whereby medially located regions of interest (i.e. the supplementary motor area - SMA) will have stronger connectivity to the thalamus when compared to a more laterally located region (i.e. the cortical hand area). This can result in an erroneously large thalamic-SMA region.

It is concerning that these thalamic nuclei, constructed with diffusion connectivity to cortical areas and demarcated with a hard-segmentation algorithm, differ in their neuroanatomical orientation, shapes, and relative sizes when compared to a ground truth model (Ilinsky et al., 2018). The biggest differences are seen in the lack of overlap between the nuclei and in the mediolateral orientation which is almost perpendicular to the midsagittal plane as opposed to the expected 45° orientation (Ilinsky et al., 2018).

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These inaccuracies in diffusion connectivity-based segmentation may not be significant for illustration purposes but are detrimental when using these maps in surgical targeting where a good outcome hinges on millimetric accuracy. Therefore, in order to rely on these computational models in surgery, multiple validation methods are required (e.g. the overlapping of the M1-thalamic segment with the cerebellar input into the thalamus (Akram et al., 2018)). Moreover, the findings from these models must comply with established anatomical and neurophysiological wisdom; when this is not the case, findings should be dismissed.

The paper by Middlebrooks et al. contains numerous methodological limitations, several of which are alluded to by the authors. The most pertinent weaknesses include the use of a hard-segmentation algorithm, the reliance on retrospective legacy diffusion data, the lack of reverse phase-encode directional acquisition pairs to address susceptibility distortion and potential errors introduced during CT/MR fusion.

Moreover it is suggested that, during DBS, a larger volume of tissue activation (VTA) in the SMA/ Premotor cortex (PMC) but not the M1 area is associated with a significant improvement in tremor scores (Middlebrooks et al., 2018). This position clashes with the observation that a smaller, not a larger, VTA is required when the DBS electrode is in the “sweet spot”. The manuscript subsequently implies that the modulated thalamic sweet spot connects the cerebellar outflow to the SMA/ PMC and not the M1. This conclusion is at odds with the majority of previously published studies that used diffusion connectivity (Akram et al., 2018; Hyam et al., 2012; Klein et al., 2012; Tian et al., 2018; Wintermark et al., 2014), with established knowledge from non-human primate studies (Percheron et al., 1993; Sakai et al., 2000), and with numerous anatomical and neurophysiological studies (Hellriegel et al., 2012; Raethjen and Deuschl, 2012; Schell and Strick, 1984). A Magnetoencephalography (MEG) study, published in the same issue of this journal, shows that Vim DBS evoked cortical responses localized especially in the sensorimotor cortex, not the SMA/ PMC (Hartmann et al., 2018). These points must be duly considered before accepting the conclusions presented by Middlebrooks et al.

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