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LETTER TO THE EDITOR

Reply: Thalamotomy for tremor normalizes aberrant pre-therapeutic visual cortex functional connectivity

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Sir,

We thank Tuleasca and colleagues for their insightful comments on our study that compared the distinct neural network signatures identified with functional imaging analysis for dystonic tremor (DT) and essential tremor (ET). We chose to compare these tremor disorders as these entities are frequently confused in the clinical setting. In our experimental paradigm, we examined the effect of visual feedback on grip-force tremor and how that relates to blood oxygen level-dependent (BOLD) activity and functional connectivity in the two tremor disorders. We found increased visual feedback led to similar force tremor exacerbation; however, the functional activation abnormalities (termed $BOLD_{\Delta}$) in the cortical and subcortical regions were different between dystonic and essential tremor. More importantly, the seed-based functional connectivity (termed FC_{Δ}) from the sensorimotor cortex/inferior parietal lobule, globus pallidus internus, ventral intermediate nucleus, and dentate nucleus in dystonic tremor was strikingly far more impaired within the cortical, subcortical and cerebellar regions in dystonic tremor compared to essential tremor (DeSimone *et al.*, 2019). Our study highlights the importance of the visual network in essential tremor generation, which is consistent with previous studies by our group and other investigators (Tuleasca *et al.*, 2017, 2018*a*; Archer *et al.*, 2018; Benito-Leon *et al.*, 2019). Additionally, our imaging analysis extends the involvement of a widespread visually sensitive functional network to dystonic tremor, which is a novel insight for understanding the pathogenesis. While we are just beginning to understand the neural network signatures for dystonic tremor, future multimodal studies at a molecular, structural and functional level similar to those performed by Tuleasca *et al.* and other groups in essential tremor will further parse out the critical differences between these two disorders. Furthermore, the effects of therapeutic intervention such as deep brain stimulation (DBS) or thalamotomy procedures on tremor suppression and the corresponding change in the network behaviour similar to studies performed in essential tremor (Tuleasca *et al.*, 2017, 2019) will add clarification to their exact role in pathogenesis. Ultimately, these advances will contribute to the development of a robust diagnostic framework and focused treatments for the two disorders.

Dystonic tremor versus essential tremor

Functional perspective

A few years ago, the Movement Disorders Society officially designated tremor as a part and parcel symptom of dystonia (Albanese *et al.*, 2013). Dystonic tremor is defined as a tremor manifesting in a body part affected with dystonic features. Despite these efforts, owing to clinical resemblance dystonic tremor is frequently misdiagnosed as essential tremor. While behavioural studies have provided some clues for tremor distinction (DeSimone *et al.*, 2019), there is

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limited knowledge on disorder-specific brain deficits that can reliably differentiate these two disorders. In our previous studies, we learned visuomotor processes influenced the amplitude of tremor and force error in essential tremor; the current study evidenced similar overlapping findings in the dystonic tremor cohort. We agree with Tuleasca and colleagues who draw attention in their letter to converging pieces of evidence in support of a widespread dysfunction of a visually sensitive functional network underlying tremor generation in essential tremor. What remains less understood is the detailed role of the visuomotor network in the pathogenesis of dystonic tremor.

We found the BOLD activity change in response to visual feedback was reduced in essential tremor compared to the dystonic tremor cohort when examined across many brain regions including the sensorimotor cortex, inferior parietal lobule, cingulate cortex, medial premotor cortex, and lingual gyrus (DeSimone *et al.*, 2019). Dystonic tremor versus healthy control comparisons also revealed different activation patterns in many cortical regions of the brain, including middle and medial frontal gyri, cingulate gyrus, and cerebellar lobule I–IV. As pointed out in the letter, a recent resting state functional MRI study in a cohort of spasmodic dysphonia with and without tremor found that compared with healthy controls, there was abnormal hyperexcitability of the premotor-parietal-putaminal circuitry likely related to deficient connectivity and thus the aberrant flow of information between these regions (Battistella and Simonyan, 2019).

Visual network FC_{Δ} was impaired in dystonic tremor relative to controls for all seed locations, whereas essential tremor demonstrated reduced visual network FC_{Δ} for seed locations in the sensorimotor cortex/inferior parietal lobule and dentate nucleus. Furthermore, visual cortex FC_{Δ} was significantly reduced for the dystonic tremor group compared to the essential tremor group for seed locations in the sensorimotor cortex/inferior parietal lobule, ventral intermediate nucleus, and dentate nucleus. In line with our task-based functional MRI analysis, Tuleasca *et al.* (2019), report resting state functional MRI findings in essential tremor cohort analysed before and after patients receive thalamotomy surgery. The authors used a co-activation pattern analysis to understand how a specific seed region in the brain interacts in a time-varying manner with the rest of the brain. They found the co-activation patterns involving the visual network, particularly the extrastriate visual areas normalize when the tremor severity is controlled with thalamotomy surgery. The current treatment interventions for dystonic tremor are noted to significantly overlap with essential tremor, e.g. DBS and focused ultrasound thalamotomy targeted to the ventral intermediate nucleus (Fasano *et al.*, 2017), but what remains to be seen is the short-term and long-term relationship between tremor control and the pathogenic networks.

Structural perspective

While our study focused on neural signatures from a functional perspective, Tuleasca *et al.*, in their previous work involving essential tremor, found structural changes in the visual regions of the brain. They implemented voxel-based morphometry analysis to track the longitudinal effects of ventral intermediate nucleus radiosurgery on the grey matter volume (Tuleasca *et al.*, 2017). They found higher baseline grey matter volumes in Brodmann area 19 (visual cortex region) were associated with higher improvements in tremor scores. In another voxel-based morphometry study, they found that a decrease in grey matter density at 1 year in the occipital cortex after ventral intermediate nucleus radiosurgery was related to improvements that are more significant in the hand tremor score (Tuleasca *et al.*, 2018*b*).

For a long time dystonia was regarded as a disorder purely affecting brain function. With the advent of voxel-based morphometry, many studies in dystonia uncovered distinct structural abnormalities in the grey matter of the cortical and subcortical regions (Lehericy *et al.*, 2013). Furthermore, diffusion tensor imaging has shown changes in the white matter fibre tracts in many forms of dystonia (Colosimo *et al.*, 2005). We agree our study does not address the structural changes in dystonic tremor; however, a well designed imaging study combining structural and functional aspects of the pathogenic networks with parallel monitoring of treatment response is the next promising step to pursue.

Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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Competing interests

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