**Thalamotomy for tremor normalizes aberrant pretherapeutic visual cortex functional connectivity**

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**Running title:** Visual brain regions in essential tremor

Dear Editor,

DeSimone *et al*. ([DeSimone *et al.*, 2019](#_ENREF_8)) discuss network-level connectivity as a critical feature for distinguishing dystonic tremor (DT) from essential tremor (ET). The experimental paradigm tested how the exacerbation of grip force tremor between low and high gain visual feedback conditions related to changes in blood oxygenation level-dependent (BOLD) amplitude (termed BOLDΔ)and in functional connectivity (termed FCΔ). Task-based functional magnetic resonance imaging (fMRI) was acquired, and BOLDΔ as well as FCΔ with selected seed regions were quantified at the whole-brain level. The overall conclusion of DeSimone and co-authors was that dystonic and essential tremor were characterized by distinct BOLD and FC abnormalities in higher-level cortical and visual regions, as well as in the cerebellum in the latter FC case ([DeSimone *et al.*, 2019](#_ENREF_8)). In particular, deficits in the visual functional circuitry were a recurrent feature: compared to controls, ET FCΔ with the visual cortex was reduced for somatomotor cortex, ventral intermediate nucleus of the thalamus, and dentate nucleus seeds. Further, those alterations were generally stronger in ET than in DT patients.

The current paper by DeSimone *et al*. ([DeSimone *et al.*, 2019](#_ENREF_8)) offers new insights with regards to two major aspects, both with potential clinical implications. Firstly, differentiating between ET and DT is of crucial medical importance, as the former acts differently in its natural history and response to interventional procedures, such as deep-brain stimulation (DBS). Insights from functional neuroimaging studies have, in fact, up to now, suggested the cerebellum as an important node within the pathological abnormal activity ([Lehericy *et al.*, 2013](#_ENREF_11)). In the current paper, DeSimone *et al*. ([DeSimone *et al.*, 2019](#_ENREF_8)) suggest that DT and ET were characterized by distinct functional activation abnormalities in cortical regions, but not in the cerebellum. Recently, Battistella *et al*. ([Battistella and Simonyan, 2019](#_ENREF_3)) employed independent component analysis (ICA) and dynamic causal modeling (DCM) of the resting-state fMRI (rs-fMRI) network in DT as compared with healthy controls (HC). The authors suggested that abnormal hyper-excitability of the premotor-parietal-putaminal circuitry might be explained by altered information transfer between these regions due to underlying deficient connectivity. Moreover, identification of some brain regions involved in processing of sensorimotor information in preparation for movement execution was considered suggestive for complex network disruption well before the dystonic behavior is produced by the primary motor cortex. All these circuitry abnormalities might have therapeutic implications. In fact, recent evidence suggested that phase-specific DBS is more effective than conventional DBS for ET, but with smaller and inconsistent positive effects in DT ([Cagnan *et al.*, 2017](#_ENREF_6)). Recently, MRI-guided focused ultrasound thalamotomy has emerged as a promising and less invasive alternative to DBS for disabling DT ([Fasano *et al.*, 2017](#_ENREF_9)). How DBS as compared with lesioning techniques and their respective technical nuances and radiobiological effect affects this network-level connectivity in DT remains to be elucidated by further studies.

Secondly, the findings by DeSimone et al. ([DeSimone *et al.*, 2019](#_ENREF_8)) add to recent evidence ([Archer *et al.*, 2017a](#_ENREF_1)) of a widespread visually-sensitive functional network, including extrastriate areas V3 and V5, that would relate to tremor severity in patients with ET. They are also consistent with several studies from other groups ([Tuleasca *et al.*, 2017b](#_ENREF_20); Benito‐León *et al.*, 2018; [Tuleasca *et al.*, 2018a](#_ENREF_14), [b](#_ENREF_15); [Tuleasca *et al.*, 2018d](#_ENREF_17); [Tuleasca *et al.*, 2018e](#_ENREF_18); [Verger *et al.*, 2018](#_ENREF_21)). We have recently published two voxel-based morphometry (VBM) ([Tuleasca *et al.*, 2017a](#_ENREF_19); [Tuleasca *et al.*, 2017b](#_ENREF_20)) and several rs-fMRI reports ([Tuleasca *et al.*, 2017a](#_ENREF_19); [Tuleasca *et al.*, 2017b](#_ENREF_20); [Tuleasca *et al.*, 2018a](#_ENREF_14), [b](#_ENREF_15); [Tuleasca *et al.*, 2018e](#_ENREF_18)), in which we provide evidence of the association of a widespread visually-sensitive structural and functional network with ET, which is affected by thalamotomy. We coined the term “cerebello-thalamo-visuo-motor network” to describe these observations. We used different methodologies to analyze rs-fMRI data, including data-driven multivariate analysis through ICA ([Calhoun *et al.*, 2001](#_ENREF_7); [Beckmann *et al.*, 2005](#_ENREF_4)) to conduct whole-brain analyses without prior assumptions ([Tuleasca *et al.*, 2018a](#_ENREF_14)), or seed-to-voxel FC, considering as a region-of-interest (ROI) the targeted thalamus by means of ventro-intermediate nucleus thalamotomy for drug-resistant ET ([Tuleasca *et al.*, 2018b](#_ENREF_15), [c](#_ENREF_16)). Interestingly, our findings converged towards parts of the extrastriate visual system as being involved in tremor generation and further arrest after thalamotomy. They were further supported by recent 18-F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) studies, where metabolism in the right temporo-occipital area was reported reduced in patients who alleviated less to thalamotomy, as opposed to the others, and this was predictive for future clinical response after this type of interventional study (sensitivity: 89%; specificity: 71%; [Verger *et al.*, 2018](#_ENREF_21)). More recently, Benito-Léon *et al. (Benito‐León et al., 2018)* discussed anatomical changes in brain areas controlling movement sequencing in patients with essential tremor (ET). The authors elegantly combined cortical thickness measures from MRI with neurophysiological studies. They suggested the posterior parietal cortex role, including its potential major interactions with the extrastriate cortex, in terms of thinning of the right lingual gyrus, suggesting dysfunction of the visual associative cortex in ET. Benito-Léon *et al.* concluded that there is an impaired visual-motor integration accompanied by structural changes in these areas.

As moment-to-moment variations of FC were not yet explored in ET, we deployed a recently proposed approach, termed co-activation pattern (CAP) analysis, to explore how a specific seed region interacts with the rest of brain in time-varying manner during resting-state ([Liu and Duyn, 2013](#_ENREF_12)). To investigate this ([Tuleasca *et al.*, 2019](#_ENREF_13)), we studied a subpart of the right extrastriate cortex (Brodmann area 19- including V3, V4 and V5) as a unique ROI in HC, pretherapeutic ET patients, and further after thalamotomy by radiosurgery. This choice was related to our previously published findings ([Tuleasca *et al.*, 2018a](#_ENREF_14); [Tuleasca *et al.*, 2018e](#_ENREF_18)), and further confirmed by task-based reports ([Archer *et al.*, 2017b](#_ENREF_2)). We extracted a set of whole-brain network patterns, termed CAPs, which are repeatedly expressed over time in HC and pretherapeutic ET subjects at moments when the studied ROI turns active. We also determined, by frame assignment, how frequently each CAP was expressed in ET patients following interventional therapy (*i.e.*, after thalamotomy). For all three cases, we thus gathered occurrences for each CAP, where larger values reflect a more frequently expressed CAP throughout the resting-state session. We correlated CAP occurrences, and their changes upon thalamotomy, with tremor severity using clinically relevant scores.

In our view, the findings from our report ([Tuleasca *et al.*, 2019](#_ENREF_13)) nicely complement the ones reported by DeSimone *et al*. ([DeSimone *et al.*, 2019](#_ENREF_8)). Our analysis suggested a novel perception for identifying mechanisms of moment-to-moment brain activity and, subsequently, linking their temporal features to clinically functional properties, an important next step towards systems-level models (Karahanoğlu and Van De Ville, 2017). Three relevant CAPs were revealed: cerebello-visuo-motor (CAP1), thalamo-visuo-motor (CAP2), and basal ganglia and extrastriate cortex (CAP3; see Figure 1). Their relative occurrences in the combined pool of HC and pretherapeutic ET data were comparable (p>0.05; CAP1, 38.6%; CAP2, 32.6%; CAP3, 28.8%). Across those two conditions, CAP1 showed decreased pretherapeutic occurrences as compared with HC, while it was the opposite for CAP2 and CAP3. For all CAPs, occurrences after SRS-T came back to the HC level (p>0.05; see Figure 2 for boxplot representations).

Several aspects warrant for further discussion. Firstly, a conventional seed-based FC analysis actually aggregates what is in fact a complex, dynamic balance between cerebello-visuo-motor, thalamo-visuo-motor and basal ganglia circuitries, each reflected by one CAP. Secondly, these circuitries might have distinct roles in tremor generation and further arrest, as we will see below. Thirdly, the only decreased pretherapeutic FC in ET patients as compared with HC was the one in CAP1, the cerebello-visuo-motor network. This includes parts of the extrastriate system also reported by DeSimone *et al*. ([DeSimone *et al.*, 2019](#_ENREF_8)). The findings based on rs-fMRI, as deployed by our group ([Tuleasca *et al.*, 2019](#_ENREF_13)), and those on task-based fMRI, as deployed by DeSimone *et al*. ([DeSimone *et al.*, 2019](#_ENREF_8)), are consistent in this sense. A boxplot representation of occurrences for CAP1 (Figure 2A) revealed lower occurrences in pretherapeutic ET (median 19, range [8,67]) as compared with HC (median 38, range [15,78]; p=0.02), which increased back to similar values as the HC after thalamotomy (median 32, range [15,62]; pHC,posttherapeuticET=0.47; ppretherapeuticET,posttherapeuticET=0.03; pAnova<0.001). Oppositely, in CAP2, occurrences were increased in pretherapeutic ET (median 25, range [10,44]) as compared to HC (median 17, range [4,43]; p=0.02; Figure 2B), and further decreased to similar values as the HC at 1 year after thalamotomy (median 19, range [2,26]; pHC,posttherapeuticET=0.96; ppretheraoeuticET,posttherapeuticET=0.003; pAnova<0.001). Similarly to CAP2, in CAP3 there was an increase in pretherapeutic ET occurrences (median 23, range [10,42]; Figure 2C) as compared to HC (median 13, range [4,24]; p=0.004), and a further decrease to similar values as the HC at 1 year after thalamotomy (median 13, range [3,30]; pHC,posttherapeuticET=0.78; ppretherapeuticET,posttherapeuticET=0.01; pAnova<0.001). When analyzing how these different CAPs would relate to tremor generation and further arrest after thalamotomy, pretherapeutic ET clinical scores correlated with the abnormal increase in occurrences of the thalamo-visuo-motor network (CAP2, also including the targeted thalamus; Figure 2B), suggesting a compensatory pathophysiological trait. Moreover, the improvement in tremor scores after thalamotomy was more related to changes within the basal ganglia and extrastriate cortex (CAP3, Figure 2C). Our conclusion was that there is a functionally relevant balance between the cerebello-visuo-motor, thalamo-visuo-motor and basal ganglia brain circuitries. Our findings ([Tuleasca *et al.*, 2019](#_ENREF_13)) suggest further explanations for the results of DeSimone *et al*. ([DeSimone *et al.*, 2019](#_ENREF_8)). In particular, our rs-fMRI report provides complementary evidence of a widespread visually sensitive functional network in ET, which is involved in tremor generation and further arrest after thalamotomy.

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**Figure legends:**

**Figure 1:** Illustration of the 3 CAPs, from 1 to 3 (left to right)

**Figure 2:** Illustration of the number of occurrences, as boxplots, for each CAP, in ET, HC and post-thalamotomy states, with associated p-values (A, B, C); correlation between pretherapeutic clinical scores and the number of occurrence for CAP2 (activities of daily living, B); correlation between posttherapeutic tremor score on the treated hand and difference in occurrences between posttherapeutic and pretherapeutic states for CAP3 (C)

**Funding:**

Constantin Tuleasca gratefully acknowledges receipt of a ‘Young Researcher in Clinical Research Award’ (Jeune Chercheur en Recherche Clinique) from the University of Lausanne (UNIL), Faculty of Biology and Medicine (FBM) and the Lausanne University Hospital (CHUV)

Thomas Bolton and Dimitri Van de Ville gratefully acknowledge the Bertarelli Foundation

**Acknowledgments:** The authors would like to thankLausanne, Marseille and Paris-South University Hospitals and the University of Lausanne, Faculty of Biology and Medicine (FBM).

**Conflict of interest:** The authors have no conflict of interest to report.