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LETTER TO THE EDITOR

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

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Sir,

DeSimone *et al.* (2019) discuss network-level connectivity as a critical feature for distinguishing dystonic tremor from essential tremor. 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 $BOLD_{\Delta}$) and in functional connectivity (termed FC_{Δ}). Task-based functional MRI was acquired, and $BOLD_{\Delta}$ as well as FC_{Δ} 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 functional connectivity abnormalities in higher-level cortical and visual regions, as well as in the cerebellum in the latter functional connectivity case (DeSimone *et al.*, 2019). In particular, deficits in the visual functional circuitry were a recurrent feature: compared to controls, essential tremor FC_{Δ} with the visual cortex was reduced for somatomotor cortex, ventral intermediate nucleus of the thalamus, and dentate nucleus seeds. Although task functional connectivity of visual regions was affected in both disorders relative to controls, the magnitude of the effects in visual regions were generally stronger for the dystonic tremor-control comparison. Also, compared to controls, visual cortex functional connectivity was affected for all seeds in dystonic tremor, whereas visual cortex functional

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connectivity was affected in sensorimotor cortex/inferior parietal lobule and dentate nucleus seeds for essential tremor. Furthermore, when comparing dystonic and essential tremor, the functional connectivity of visual regions was reduced in dystonic tremor for all seed locations (with the exception of globus pallidus internus).

The paper by DeSimone *et al.* (2019) offers new insights with regards to two major aspects, both with potential clinical implications. First, differentiating between essential and dystonic tremor 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). DeSimone *et al.* (2019) suggest that essential and dystonic tremor were characterized by distinct functional activation abnormalities in cortical regions, but not in the cerebellum. Recently, Battistella and Simonyan (2019) used independent component analysis (ICA) and dynamic causal modelling of the resting-state functional MRI (rs-fMRI) network in dystonic tremor as compared with healthy control subjects. The authors suggested that abnormal hyperexcitability 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 of complex network disruption well before the dystonic behaviour is produced by the primary motor cortex. All of these circuitry abnormalities may have therapeutic implications. In fact, recent evidence suggested that phase-specific DBS is more effective than conventional DBS for essential tremor, but with smaller and inconsistent positive effects in dystonic tremor (Cagnan *et al.*, 2017). Recently, MRI-guided focused ultrasound thalamotomy has emerged as a promising and less invasive alternative to DBS for disabling dystonic tremor (Fasano *et al.*, 2017). How DBS compared with lesioning techniques and their respective technical nuances and radiobiological effect affects this network-level connectivity in dystonic tremor remains to be elucidated by further studies.

Second, the findings by DeSimone *et al.* (2019) add to recent evidence (Archer *et al.*, 2017*a*) of a widespread visually-sensitive functional network, including extrastriate areas V3 and V5, that would relate to tremor severity in patients with essential tremor. They are also consistent with several studies from other groups (Tuleasca *et al.*, 2018*a*, *b*, *d*, *e*, *f*; Benito-León *et al.*, 2018; Verger *et al.*, 2019). We have recently published two voxel-based morphometry (Tuleasca *et al.*, 2017*a*, 2018*f*) and several rs-fMRI reports (Tuleasca *et al.*, 2017*a*, 2018*a*, *b*, *e*, *f*), in which we provide evidence of the association of a widespread visually-sensitive structural and functional network with essential tremor, which is affected by thalamotomy. We coined the term 'cerebello-thalamo-visuo-motor network' to describe these observations. We used different methodologies to analyse rs-fMRI data, including data-driven multivariate analysis through ICA (Calhoun *et al.*, 2001; Beckmann *et al.*, 2005) to conduct whole-brain analyses without prior assumptions (Tuleasca *et al.*, 2018*a*), or seed-to-voxel functional connectivity, considering as a region of interest the targeted thalamus by means of ventro-intermediate nucleus thalamotomy for drug-resistant essential tremor (Tuleasca *et al.*, 2018*b*, *c*). 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)-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.*, 2019). More recently, Benito-Léon *et al.* (2018) discussed anatomical changes in brain areas controlling movement sequencing in patients with essential tremor. 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 essential tremor. Benito-Léon *et al.* (2018) concluded that there is an impaired visual-motor integration accompanied by structural changes in these areas.

As moment-to-moment variations of functional connectivity were not yet explored in essential tremor, we used a recently proposed approach, termed co-activation pattern (CAP) analysis, to explore how a specific seed region interacts with the rest of the brain in a time-varying manner during resting state (Liu and Duyn, 2013). To investigate this (Tuleasca *et al.*, 2019), we studied a subpart of the right extrastriate cortex (Brodmann area 19, including V3, V4 and V5) as a unique region of interest in healthy control subjects, pre-therapeutic essential tremor patients, and further after thalamotomy by radiosurgery. This choice was related to our previously published findings (Tuleasca *et al.*, 2018*a*, *e*), and further confirmed by task-based reports (Archer *et al.*, 2017*b*). We extracted a set of whole-brain network patterns, termed CAPs, which are repeatedly expressed over time in healthy controls and pre-therapeutic essential tremor subjects at moments when the studied region of interest turns active. We also determined, by frame assignment, how frequently each CAP was expressed in essential tremor 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.

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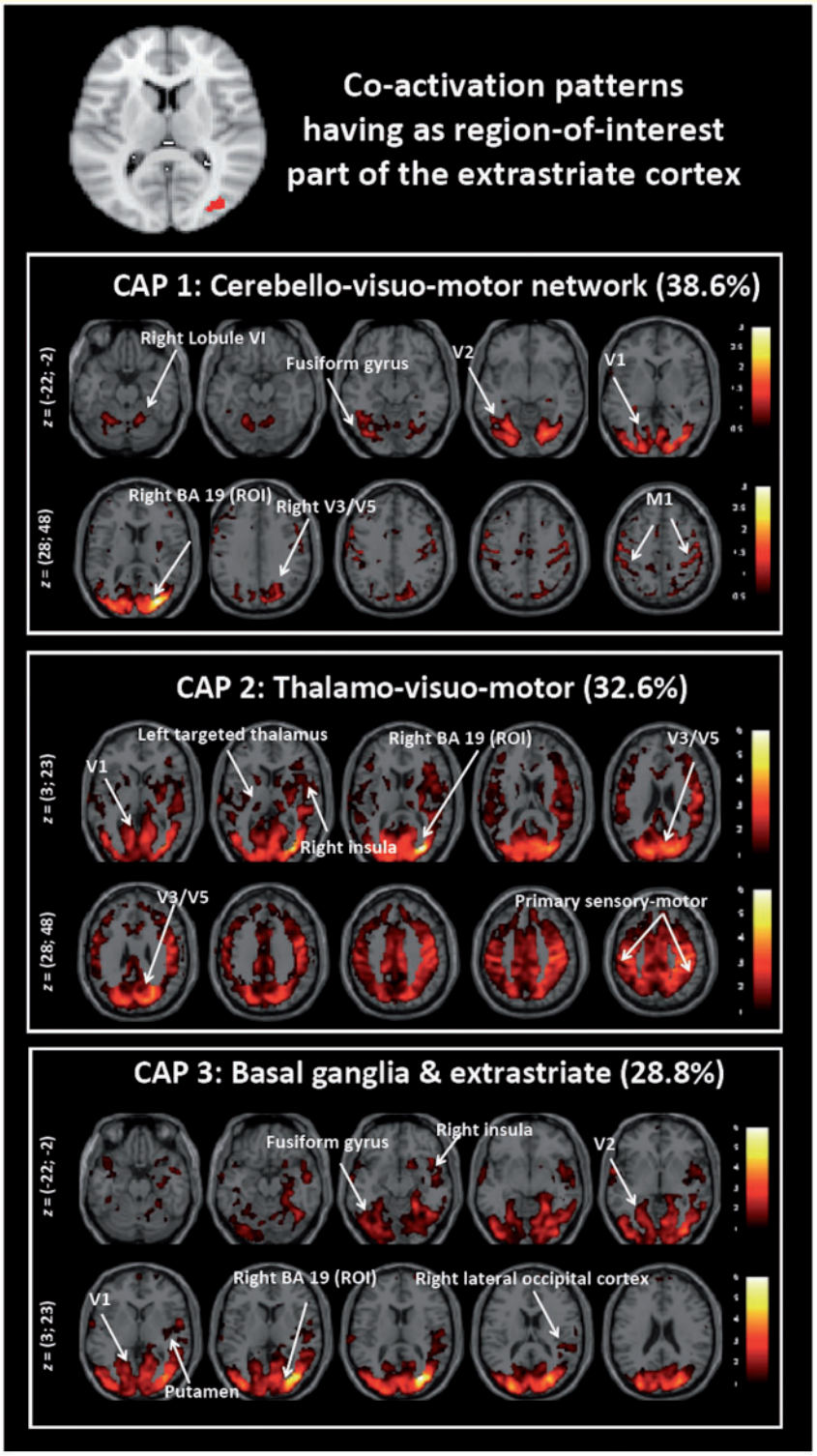

Figure 1 Illustration of the three CAPs, from 1 to 3 (*left* to *right*). Figure modified from Tuleasca *et al.* (2019). ROI = region of interest.

In our view, the findings from our report (Tuleasca *et al.*, 2019) nicely complement those reported by DeSimone *et al.* (2019). 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 (CAP_1), thalamo-visuo-motor (CAP_2), and basal ganglia and extrastriate cortex (CAP_3) (Fig. 1).

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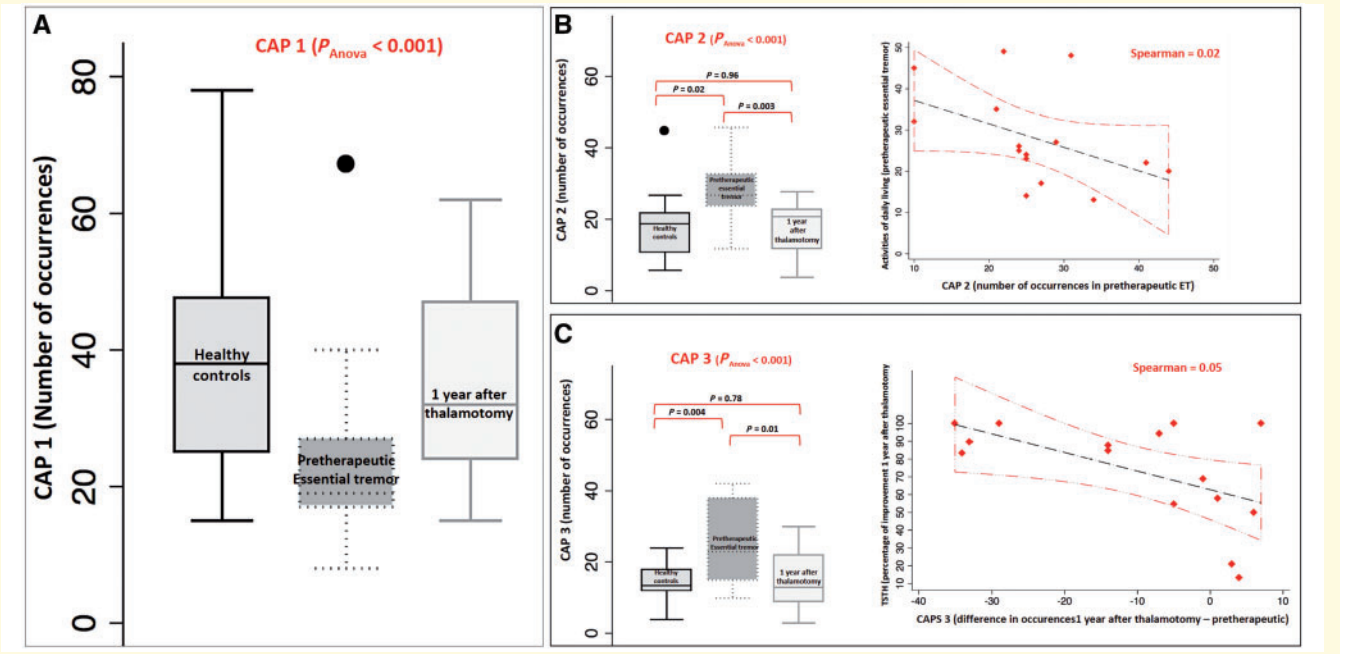

Figure 2 CAPs–13 in essential tremor, control subjects and post-thalamotomy states. Illustration of the number of occurrences, as boxplots, for each CAP, in essential tremor, control subjects and post-thalamotomy states, with associated *P*-values (**A**–**C**). (**B**) Correlation between pre-therapeutic clinical scores and the number of occurrences for CAP2 (activities of daily living). (**C**) Correlation between post-therapeutic tremor score on the treated hand and difference in occurrences between post-therapeutic and pre-therapeutic states for CAP3. Figure modified from Tuleasca *et al.* (2019).

Their relative occurrences in the combined pool of control subjects and pretherapeutic essential tremor data were comparable ($P > 0.05$; CAP_1, 38.6%; CAP_2, 32.6%; CAP_3, 28.8%). Across those two conditions, CAP_1 showed decreased pre-therapeutic occurrences as compared with control subjects, while it was the opposite for CAP_2 and CAP_3. For all CAPs, occurrences after stereotactic radiosurgery thalamotomy came back to the healthy control level ($P > 0.05$) (Fig. 2 for boxplot representations).

Several aspects warrant further discussion. First, a conventional seed-based functional connectivity 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. Second, these circuitries may have distinct roles in tremor generation and further arrest, as described below. Third, the only decreased pretherapeutic functional connectivity in essential tremor patients as compared with control subjects was the one in CAP_1, the cerebello-visuo-motor network. This includes parts of the extrastriate system also reported by DeSimone *et al.* (2019). The findings, based on rs-fMRI, as carried out by our group (Tuleasca *et al.*, 2019), and those on task-based functional MRI, as carried out by DeSimone *et al.* (2019), are consistent in this sense. A boxplot representation of occurrences for CAP_1 (Fig. 2A) revealed lower occurrences in pre-therapeutic essential tremor (median 19, range 8–67) compared with controls (median 38, range 15–78; $P = 0.02$), which increased back to similar values as the healthy controls after thalamotomy (median 32, range 15–62; $P_{HC,posttherapeuticET} = 0.47$; $P_{pretherapeuticET,posttherapeuticET} = 0.03$; $P_{Anova} < 0.001$). Conversely, in CAP_2, occurrences were increased in pre-therapeutic essential tremor (median 25, range 10–44) as compared to controls (median 17, range 4–43; $P = 0.02$) (Fig. 2B), and further decreased to similar values as the controls at 1 year after thalamotomy (median 19, range (2–26); $P_{HC,posttherapeuticET} = 0.96$; $P_{pretheraoeuticET,posttherapeuticET} = 0.003$; $P_{Anova} < 0.001$). Similarly to CAP_2, in CAP_3 there was an increase in pre-therapeutic essential tremor occurrences (median 23, range 10–42) (Fig. 2C) compared to control subjects (median 13, range 4–24) ($P = 0.004$), and a further decrease to similar values as the controls at 1 year after thalamotomy (median 13, range 3–30); $P_{HC,posttherapeuticET} = 0.78$; $P_{pretherapeuticET,posttherapeuticET} = 0.01$; $P_{Anova} < 0.001$). When analysing how these different CAPs would relate to tremor generation and further arrest after thalamotomy, pre-therapeutic essential tremor clinical scores correlated with the abnormal increase in occurrences of the thalamo-visuo-motor network (CAP_2, also including the targeted thalamus) (Fig. 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 (CAP_3) (Fig. 2C). Our conclusion was that there is a

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functionally relevant balance between the cerebello-visuo-motor, thalamo-visuo-motor and basal ganglia brain circuitries. Our findings (Tuleasca *et al.*, 2019) suggest further explanations for the results of DeSimone *et al.* (2019). In particular, our rs-fMRI report provides complementary evidence of a widespread visually sensitive functional network in essential tremor, which is involved in tremor generation and further arrest after thalamotomy.

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

The authors report no competing interests.

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