LETTER TO THE EDITOR

Visually-sensitive networks in essential tremor: evidence from structural and functional imaging

Constantin Tuleasca,1,2,3,4 Jean Régis,5 Elena Najdenovska,2 Tatiana Witjas,6 Nadine Girard,7 Jean-Philippe Thiran,3,4,8 Meritxell Bach Cuadra,2,3 Marc Levivier1,4 and Dimitri Van De Ville9,10

1 Centre Hospitalier Universitaire Vaudois (CHUV), Neurosurgery Service and Gamma Knife Center, Lausanne, Switzerland
2 Medical Image Analysis Laboratory (MIAL) and Department of Radiology-Center of Biomedical Imaging (CIBM), Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
3 Signal Processing Laboratory (LTS 5), Ecole Polytechnique Fédérale de Lausanne (EPFL), Switzerland
4 University of Lausanne, Faculty of Biology and Medicine, Lausanne, Switzerland
5 Stereotactic and Functional Neurosurgery Service and Gamma Knife Unit, CHU Timone, Marseille, France
6 Neurology Department, CHU Timone, Marseille, France
7 AMU, CRMBM UMR CNRS 7339, Faculté de Médecine and APHM, Hopital Timone, Department of Diagnostic and Interventionnal Neuroradiology, Marseille, France
8 Centre Hospitalier Universitaire Vaudois, Department of Radiology, Lausanne, Switzerland
9 University of Geneva, Faculty of Medicine, Switzerland
10 Medical Image Processing Laboratory, Ecole Polytechnique Fédérale de Lausanne (EPFL), Switzerland

Correspondence to: Constantin Tuleasca, MD, MD-PHD candidate
Centre Hospitalier Universitaire Vaudois, Neurosurgery Service and Gamma Knife Center
Rue du Bugnon 44-46, BH-08, CH-1011, Lausanne, Switzerland
E-mail: constantin.tuleasca@gmail.com

Correspondence may also be addressed to: Dimitri Van De Ville
E-mail: dimitri.vandeville@epfl.ch

Sir,

Archer et al. (2018) provide new evidence of a widespread visually-sensitive functional network, including extrastriate areas V3 and V5, which relates to tremor severity in patients with essential tremor. They obtained right-hand force measurements during functional MRI of a grip-force task while they manipulated visual feedback. The authors conclude that the severity of tremor is exacerbated by increased visual feedback, suggesting that designers of new computing technologies should consider using lower visual feedback to reduce tremor in essential tremor. Furthermore, the network-level characterization of essential tremor would not solely be confined to the cerebello-thalamo-cortical pathway (Kelly and Strick, 2003). Likewise, in the light of this evidence, surgical targeting for drug-resistant tremor should be refined in the future, while the current two main sites are thalamic ventro-intermediate nucleus (VIM) (Fox et al., 1991; Benabid et al., 1996; Witjas et al., 2015; Elias et al., 2016) and posterior subthalamic area (PSA) (Blomstedt et al., 2010).

We have recently published two voxel-based morphometry (VBM) reports (Tuleasca et al., 2017b, 2018b) and one resting-state functional MRI report (Tuleasca et al., 2018a), in which we provide evidence of the implication of a widespread visually-sensitive structural and functional network in essential tremor, which is affected by thalamotomy. The clinical studied parameter was tremor score on right treated hand, from the standard Fahn-Tolosa-Marin tremor rating scale (Fahn et al., 1988). Archer et al. (2018) cited one of our VBM studies (Tuleasca et al., 2017b), in which we reported that grey matter density changes in a larger occipital cluster, including Brodmann area (BA) 19, V4, V5 and parahippocampal place area, relate to tremor arrest after VIM radiosurgery. However, this mention follows a
suggest that the structural changes that we observed were ered by Benabid deep brain stimulation targeting the VIM, originally pioneered by Witjas in part the effect of a stereotactic radiofrequency thalamotomy (Fig. 1) (Schuurman et al., 2000), with an additional considered neuromodulatory effect (Regis et al., 2010; Tuleasca et al., 2017a). Radiosurgery of the VIM (Fig. 1) is one of the minimally invasive alternatives to open standard stereotactic procedures for tremor (Witjas et al., 2015). Unlike radiosurgery, another possibility, modern high-focused ultrasound (HIFU, Fig. 1) (Elias et al., 2016), produces a controlled thermoablation, with immediate clinical and radiological effect. In another VBM study (Tuleasca et al., 2018b), we showed that pretherapeutic grey matter density in right extrastriate cortex BA 18 was predicting tremor score on right treated hand improvement 1 year after VIM radiosurgery, to account for the delayed and progressive clinical effect.

In addition, we have investigated essential tremor patients using resting-state MRI (Tuleasca et al., 2018a), acquired before and 1 year after VIM radiosurgery. We used data-driven multivariate analysis (i.e. independent component analysis; Calhoun et al., 2001; Beckmann et al., 2005) to conduct whole-brain analysis without prior assumptions. Statistical investigation was implemented in SPM12 as an ANOVA flexible factorial model, on each separate component, by using individual subject-level maps, to take into account time point (pre-therapeutic versus 1 year after VIM radiosurgery), clinical response (≤50% versus >50% improvement of the tremor score on right treated hand), as well as the interactions between. Bonferroni correction was used to deal with number of models (n = 20). We then reported corrected P-values using conventional cluster-level family wise error (FWE) correction. For relevant interconnectivity values, there was no influence of age or disease duration (P > 0.05).

We found two networks, which presented statistically significant interconnectivity with visual clusters. One network reflected the interaction between time (pre- and 1 year post-therapeutic) with clinical effect; this included bilateral motor network, frontal eye-fields and left cerebellum lobule VI [the former as in the report of Archer et al. (2018)], of which network interconnectivity strength with right visual BA 19 related to tremor arrest after VIM RS [FWE = 0.001, Fig. 2A, top, upper part, adapted from Tuleasca et al. (2018a)]. Both pretherapeutic interconnectivity (Fig. 2A, middle), as well as difference between 1 year and baseline, related to tremor score on right treated hand improvement after VIM radiosurgery. Furthermore, patients who alleviated less presented negative pretherapeutic interconnectivity (which increased to median positive values 1 year later), while those who alleviated more, had already positive pretherapeutic values (which decreased to a median of 0, 1 year later) (Fig. 2A, bottom). The second network reflected the time effect independently of the clinical one; this included reminiscent of the salience network, which showed altered interconnectivity with right fusiform gyrus and V5 (FWE = 0.000, Fig. 2B, top). For this former network, opposite results as compared with the previous one were observed. Overall interconnectivity values decreased from slightly positive to the opposite slightly negative values (Fig. 2B, middle). Furthermore, patients who alleviated less presented slightly positive pretherapeutic interconnectivity (which decreased to median of slightly negative symmetric, close to 0, 1 year later), while those who alleviated more, had pretherapeutic negative median values (close to 0, which slightly increased to a median of 0, 1 year later) (Fig. 2B, bottom). We concluded, based on the previous, that VIM radiosurgery seems to bring interconnectivity in the visual areas back to normal for all patients, but the ones who had this region more functionally integrated pretherapeutically had much larger benefit.

Our findings suggest further explanation of the result of Archer et al. (2018). In particular, our resting-state functional MRI report provides complementary evidence of a widespread visually-sensitive functional network in essential tremor. Moreover, it is a cerebello-visuo-motor network that is responsible for tremor arrest after VIM radiosurgery. This is explanatory for a more prominent physiological role, rather than a simple, individual, adaptive trait. We suggested that interconnectivity between these networks have a prone role in sensory guidance of

---

**Figure 1** Artistic representation of the current surgical treatments for tremor targeting the VIM. Left to right: VIM electrical stimulation; VIM radiofrequency thalamotomy; VIM radiosurgery; VIM high focused ultrasound.
movements of hands and fingers, and further in movement control (Tuleasca et al., 2018a). We hypothesized that the input from the visual to the contralateral motor network could be calibrated by the corpus callosum, by the basal ganglia (caudate and claustrum) or by the cerebellum, based also upon previously published data (Glickstein, 2000).

Currently, three different views on essential tremor are under debate: abnormal oscillations within the tremor network, progressive cell loss in the frame of a neurodegenerative disorder or a localized GABAergic dysfunction (Gironell et al., 2012; Sharifi et al., 2014). We do believe that these recent findings provided both by Archer et al. (2018) and by our group (Tuleasca et al., 2018a) open...
new gates in understanding of the pathophysiology of essential tremor. As we suggested, they might have clinical implications for interventional studies, such as thalamotomy.

The discussion of the appropriate target for tremor remains opened, although the VIM or the PSA are classically considered. In both our VBM reports published earlier (Tuleasca et al., 2017b, 2018a), we proposed that if indeed the visual networks are involved in tremor arrest, this raises the question of a requirement to potentially recruit them in the surgical targeting. This issue remains to be debated and should be discussed in the frame of further studies, with larger cohorts, reproducing both findings from structural (VBM) and functional (task-based and resting-state) MRI. Furthermore, randomized controlled trials should provide evidence for a targeting refinement, including parts of visual areas, as we advocated, for standard electrical stimulation and/or VIM radiosurgery or HIFU.

Ultimately, this might lead to eventual safer, less expensive and more effective methods of neuro-enhancement and further turn decades of hard work into real-life benefits.

Acknowledgements
Lausanne and Marseille University Hospitals.

Funding
The work was supported in part by the Swiss National Science Foundation (SNSF-205321-157040); in part by the CHU Timone, Marseille, France; and in part by the Centre d’Imagerie BioMédicale (CIBM) of the Universities of Lausanne and Geneva, the Ecole Polytechnique Fédérale de Lausanne, the Centre Hospitalier Universitaire Vaudois, the Hôpitaux Universitaires de Genève, and the Leenaards and Jeantet Foundations.

References


