

Cerebello-cortical networks in orthostatic tremor

This scientific commentary refers to ‘Orthostatic tremor: a cerebellar pathology?’ by Gallea *et al.* (doi:10.1093/brain/aww140).

There is no tremor as clinically uncontroversial as orthostatic tremor with its unique symptom of shaking in the legs and trunk at a pathognomonic frequency of 13–20 Hz. It is present only during standing and absent while sitting, but rare patients can trigger orthostatic tremor with isometric contraction of limb muscles. The presenting complaint of the patient is a feeling of unsteadiness in the standing position, despite an unremarkable neurological examination. Later in the disease, a quarter of patients have sudden falls. The tremor is hardly visible unless the patient presents with subharmonics but it is regularly palpable and can be auscultated with a normal stethoscope (helicopter sign). The diagnosis is confirmed with EMG from at least one leg muscle (Deuschl *et al.*, 1998). The cause of orthostatic tremor is unknown. Rare symptomatic causes have been proposed in patients with cerebellar atrophy or lesions in the pons or midbrain together with orthostatic tremor (Vetrugno *et al.*, 2013). An autoimmune aetiology has also been proposed because of concomitant Graves’ disease, stiff person syndrome or simply because immunoglobulins were helpful in selected patients (Hassan *et al.*, 2016). In this issue of *Brain*, Gallea and co-workers present

anatomical and functional connectivity data suggesting that orthostatic tremor may be a cerebellar pathology (Gallea *et al.*, 2016).

Metabolic imaging studies of orthostatic tremor have shown intact serotonergic and dopaminergic pathways (Trocello *et al.*, 2008) and further biochemical analyses have been fruitless. A few peculiar observations are associated with this condition. The first is that all muscles of the body tremble at the main tremor frequency and only during stance. While for other tremors the coherence between different muscles changes over time, there is a high coherence between all muscles in orthostatic tremor including facial muscles (Koster *et al.*, 1999). In particular, homologous muscles of both sides are highly coherent even over extended time periods (Muthuraman *et al.*, 2013). This is so far the best argument for a central generator. The presumed oscillator must reside in a brain region with strong connections to brainstem and spinal motor nuclei. Indeed, electric current stimulation of the posterior fossa, but not over the motor cortex, can reset the rhythm of orthostatic tremor. This finding has been interpreted as evidence for a brainstem oscillator (Wu *et al.*, 2001), but ultimately the location or neuronal network responsible for orthostatic tremor is still unknown.

A further important clinical feature is the presenting complaint of unsteadiness. A severe sensory symptom like this is unknown for other tremors.

It was first attributed to the increased postural sway; however, the oscillatory disruption of proprioceptive afferents in the legs is more likely to be responsible (Fung *et al.*, 2001). Attempts to identify the cerebral network underlying the tremor by analysing coherence between tremor EMG and high density EEG revealed a bilateral coherence between the muscles and a cerebello-thalamo-cortico-cortical network (Muthuraman *et al.*, 2013). This initially bilateral representation separated abruptly into two contralateral projecting networks ~ 15 s after standing up. This is the time frame in which most patients report unsteadiness, suggesting that decoupling of sensory information may be related to this feeling. Finally, evidence from a few cases suggests that deep brain stimulation (DBS) can improve orthostatic tremor, but not to the same extent as for other tremors, and sometimes with a reduction in the effect over time. Beyond these limited insights, the cerebral network involved and the exact pathophysiological mechanisms that lead to orthostatic tremor are not understood. A multimodal approach addressing the structural and functional deficiencies in these patients may be needed.

In this issue of *Brain*, Gallea and co-workers examine the structural and functional defects in 17 patients with orthostatic tremor using such a multimodal approach (Gallea *et al.*, 2016). This is the largest functional study of orthostatic tremor to date. First, the authors used MRI and

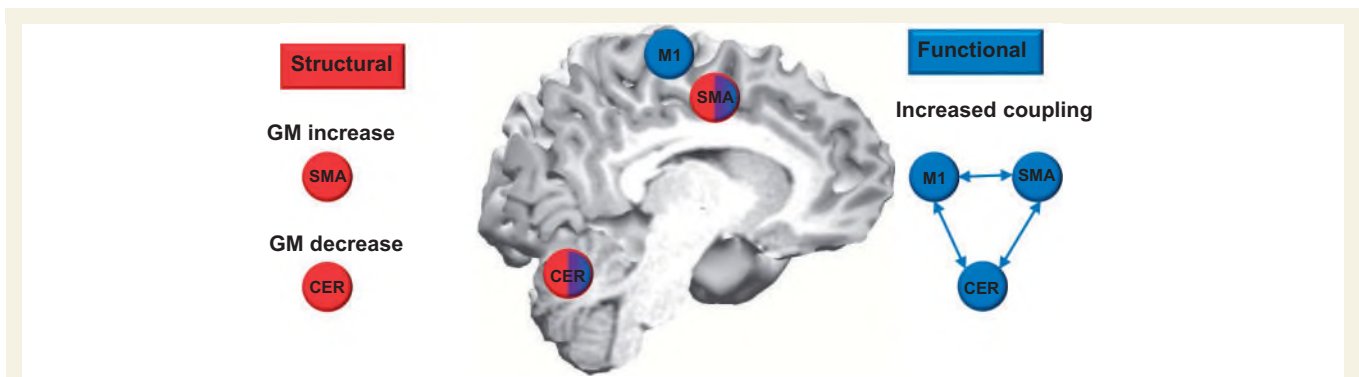


Figure 1 Hypothetical schema for cerebello-cortical structural and functional network. Involvement in orthostatic tremor. M1 = primary sensory motor area; SMA = supplementary motor area; Cer = cerebellum; GM = grey matter.

voxel-based morphometry to track the structural abnormalities in patients with orthostatic tremor in comparison to healthy controls. The areas of interest were confined to regions involved in voluntary control of the limbs and posture. Second, the authors addressed functional differences using functional MRI and the analysis of low frequency fluctuations in the above-mentioned network. Resting state functional MRI was analysed to identify functional abnormalities of resting brain activity. A clinical examination with the Fullerton Advanced Balance rating scale (FAB) and EMG recordings during standing were performed to quantify the severity of symptoms. The EMG signals were analysed for peak frequency, area and width, which reflect the tremor characteristics and frequency dispersion. The clinical and neurophysiological parameters were meticulously correlated with the structural and functional correlates of the depicted network. Manipulation of cerebellar activity through repetitive transcranial magnetic stimulation (TMS) during separate sessions over 5 days in half of the patients partially reversed the pathological activity in the cerebello-thalamo-cortical network and led to an improvement of tremor symptoms.

One of the innovations of this study is the detailed analysis of the regional changes within the cerebellum. The structural networks analysis revealed a bilateral decrease in grey matter

volume in cerebellar lobule VI, which correlated negatively with disease duration and positively with clinical severity. Furthermore, a bilateral increase of grey matter volume in supplementary motor areas (SMA) correlated positively with disease duration and electrophysiological tremor characteristics from EMG. An increase in grey matter volume was also found bilaterally in the cerebellar vermis. Analysis of the functional networks revealed an analogous synchronization between cerebellum and SMA. Importantly, the coupling in the cerebello-cortical network was associated with higher tremor severity and longer duration of standing (Fig. 1). The previous hypothesis that the orthostatic tremor network comprises two strong and separated cerebello-thalamic-cortical networks may provide a tentative explanation for this (Muthuraman *et al.*, 2013): on the basis of EMG/EEG coherence, one would expect concordant structural and functional MRI changes in all constituents. Indeed, the findings of Gallea *et al.* in the functional connectivity domain, taking into account cerebellar lobules IX, VI and the bilateral superior vermis, are consistent with a primary cerebellar defect leading to the emergence of an oscillator. Functional connectivity bilateral to lobule IX correlated with motor scores and psychological scores. In addition, the functional connectivity between lobule IV and SMA and M1, and the correlation between

tremor frequency peak and connectivity measures support this hypothesis. That the mostly opposing cerebellar changes are dependent on tremor severity measured with the electromyogram might indicate that the cortical MRI changes are secondary, and could reflect compensatory mechanisms of the cerebellar vermis. The authors reassessed the results with repetitive TMS manipulations showing that the functional connectivity between cerebellum and premotor or motor cortex can be therapeutically reduced. This finding in particular highlights the functional relevance of this study and may open up new avenues for therapeutic interventions.

As pointed out by Gallea *et al.*, certain limitations must be taken into consideration when interpreting the findings, namely that the measurements were made in the absence of tremor and the temporal resolution of functional MRI limited the ability to resolve the 13–18 Hz rhythm. Finally, the repetitive TMS did not include sham stimulation so a placebo effect cannot be completely ruled out.

The authors do not delve too deeply into their complex pattern of findings. Indeed, additional assumptions need to be made to arrive at an interpretation. Assuming that a decrease in grey matter is related to the disease process itself, and that an increase in grey matter reflects a compensatory strategy, one could interpret the current findings as suggesting that the lateral cerebellum is

Glossary

Fullerton advanced balance rating scale (FAB): a valid, well-defined multi-item balance assessment tool designed to assess balance in higher functioning older adults.

chiefly involved in the disease process while the structural changes in the SMA and vermis reflect compensatory mechanisms. Other hypotheses are certainly possible. It remains unknown whether the lateral cerebellum is primarily affected in orthostatic tremor and how this could lead to a synchronization of the motor output to all muscles. It is widely accepted that all tremors are generated by a cerebello-thalamo-cortical network (Schnitzler *et al.*, 2009). The current study may have identified some of the compensatory mechanisms in orthostatic tremor. In the past, the search was always for an oscillating pacemaker underlying the tremor, while nowadays the focus is shifting to changes in networks with the view that loss of segregation in oscillating networks is pathophysiologically more important (Rivlin-Etzion *et al.*, 2006). While for parkinsonian tremor the loss of segregation of the basal ganglia loops seems to be critical, the current findings in orthostatic tremor may be interpreted as a loss of segregation in cerebello-thalamo cortical loops. The voxel-based morphometry changes and functional MRI correlations seen here might be augmented by the addition of coherence studies with EEG/MEG to address the starting point and time

course of the oscillations. This is an exciting field of neuroscience and this paper represents a step towards a better understanding of orthostatic tremor and tremors in general.

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