Mechanisms of deep brain stimulation for essential tremor

Although essential tremor is often thought of as benign, it can be disabling to the point of justifying invasive deep brain stimulation (DBS). However, the mechanisms by which thalamic and subthalamic stimulation suppress tremor are poorly understood.

In this issue of *Brain*, Groppa *et al*. (2014) quantified the performance of seven patients with essential tremor in a reaching task to determine the DBS target structures associated with therapeutic reduction in tremor and with the side effect of stimulation-induced ataxia. The optimum site of stimulation was usually in the posterior subthalamic area, beneath the inferior border of the thalamic nucleus ventralis intermedius. Probabilistic diffusion tractography identified the dentatothalamic tract as the key therapeutic DBS target structure. Supratherapeutic stimulation of this site produced upper limb ataxia, despite continued suppression of tremor. The authors systematically varied stimulation pulse strength and duration to find that stimulation chronaxies of 27 and 52 μs were associated with tremor suppression and the induction of ataxia, respectively. Chronaxie is loosely defined as the minimum duration at which a current twice threshold (minimum current with indefinitely long pulse duration) elicits a response and provides a clue as to the properties of the axons recruited. They reasoned that two different populations of large myelinated nerve fibres were affected: (i) dentatothalamic axons for the therapeutic effect; and (ii) afferent or efferent axons of the red nucleus for the stimulation-induced ataxia. However, the involvement of rubral pathways could not be confirmed with diffusion tractography. This work is an important contribution to a growing literature addressing the mechanisms of DBS and the preferred site of DBS stimulation for essential tremor.

Ventralis intermedius has historically been the preferred stereotactic target for thalamotomy and DBS in the treatment of essential tremor and other tremor disorders (Miocinovic *et al*., 2013), but recent postoperative correlations of electrode location with clinical effect, using MRI, have pointed to the posterior subthalamic area as the optimum site of stimulation. This area includes the cerebellothalamic tract and the zona incerta, and stimulation of these structures has been reported to be superior to ventralis intermedius DBS in many patients (Klein *et al*., 2012; Sandvik *et al*., 2012). However, the optimum site for DBS varies considerably among patients with essential tremor (Klein *et al*., 2012; Sandvik *et al*., 2012). Possible reasons for this variability include limitations of electrode localization with existing surgical atlases and anatomical imaging, variation in human anatomy, variation in tremor pathophysiology because of disease-associated neuroplasticity, and heterogeneity of essential tremor as a clinical entity. Nevertheless, Klein *et al*. (2012) used diffusion tractography to show that effective DBS sites with widely ranging spatial coordinates have the common property of strong connections with

cerebellum and the ventrolateral thalamus-motor cortex loop (Klein *et al*., 2012), and there is considerable evidence that the cerebellothalamocortical motor pathway plays an important role in tremorogenesis, regardless of aetiology (Elble, 2013).

Ventralis intermedius is part of a ventrolateral thalamic nuclear complex that receives afferent input from the contralateral deep cerebellar nuclei (Ilinsky and Kultas-Ilinsky, 2002). Dentatothalamic fibres are by far the largest cerebellar projection to the ventrolateral thalamus, and these fibres project diffusely and densely throughout the complex, making excitatory glutamatergic connections with thalamocortical relay neurons. Axons from the fastigial and interposed nuclei are bundled with those from the dentate nucleus in the cerebellothalamic tract and make similar synaptic connections in the ventrolateral thalamus, but the distribution of fibres from interpositus and fastigium is sparse and patchy (Ilinsky and Kultas-Ilinsky, 2002).

There is evidence that high-frequency stimulation can produce axonal or synaptic failure, thereby producing a 'functional' lesion effect (Zheng *et al*., 2011). Consequently, Groppa *et al*. (2014) propose that DBS in the cerebellothalamic tract reduces tremor by disrupting oscillatory activity in a pathway from the cerebellum to the ventrolateral thalamus. However, there is also evidence that cerebellothalamic DBS could excite the thalamocortical loop, thereby disrupting pathological oscillations in this loop (Miocinovic *et al*., 2013). The ventrolateral thalamus has strong excitatory reciprocal connections with motor cortex, premotor cortex and posterior parietal cortex (Ilinsky and Kultas-Ilinsky, 2002), forming an excitatory loop that could amplify tremorogenic oscillations, regardless of origin. Consequently, precluding the transmission of oscillations from the cerebellum to the ventrolateral thalamus is understandably beneficial regardless of whether the cerebellum is the source of the oscillation or is simply transmitting the oscillation to the ventrolateral thalamus. Stimulation of dentatothalamic fibres is likely to have a far greater effect on the ventrolateral thalamus than stimulation of fastigial or interposed fibres by virtue of the more abundant, diffuse dentate-ventrolateral thalamus projection.

The cerebellothalamic pathway is important in feedforward motor control and motor adaptation, so it is intriguing that DBS in the cerebellothalamic pathway suppresses tremor while making the reaching trajectories in Groppa *et al*. (2014) seem less ataxic. Bastian and Thach (1995) found that strokes in the ventrolateral thalamus are associated with fairly normal reaching trajectories, but cerebellar strokes involving the cerebellar nuclei produce severe impairment of reaching (Bastian and Thach, 1995). Cerebellar nuclear lesions affect connections with contralateral ventrolateral thalamus and the contralateral red nucleus and inferior olive, whereas DBS in the subthalamic cerebellothalamic tract

will not affect rubral and olivary afferents unless the stimulation is sufficiently strong to produce a volume of activation that includes the neighbouring red nucleus. Groppa *et al.* (2014) therefore reason that therapeutic subthalamic stimulation affects dentatothalamic fibres as they enter the ventrolateral thalamus, and supratherapeutic subthalamic stimulation also excites fibres to and from the red nucleus, which is only a few millimetres away from the cerebellothalamic tract. This additional stimulation of fibres to and from the red nucleus (and possibly inferior olive) could cause ataxia (Bastian and Thach, 1995).

However, the studies of Groppa *et al.* (2014) do not exclude the possibility that subthalamic DBS preferentially affects dentatothalamic fibres, with smaller fibres from interpositus being affected when stimulation is increased to supratherapeutic levels. Large and medium-sized neurons of the dentate and interpositus nuclei contribute to the brachium conjunctivum (Matsushita and Iwahori, 1971) and could account for the two chronaxie values of Groppa *et al.* (2014). Chronaxie estimates using extracellular stimulation have been difficult to associate with specific neuronal structures in the brain and must be interpreted with caution (Grill *et al.*, 2005). Furthermore, involvement of red nucleus in these patients could not be confirmed with diffusion tractography. This could be because of limitations of diffusion tractography or to the small size of the rubrospinal pathway (Yang *et al.*, 2011), but it could also mean that the fibres associated with DBS-induced ataxia are from interpositus, bundled with the dentatothalamic fibres. In laboratory primates, muscimol injections into the dentate nucleus produce far less disturbance of reaching trajectories than injections into the nucleus interpositus (Martin *et al.*, 2000). Future studies should include estimates of the volume of tissue activation to determine those structures that may have been affected by therapeutic versus supratherapeutic DBS.

Mild disturbances of cerebellothalamic dysfunction could be missed using the methods of Groppa *et al.* (2014), especially in patients who are severely impaired by tremor. Groppa and colleagues used spatial variability in reaching trajectories of the hand as their quantitative measure of ataxia, but this is admittedly a limited measure. Tremor could not be reliably distinguished from variability caused by impaired coordination of shoulder, elbow and wrist rotations (Bastian and Thach, 1995). Decomposition of movement was not assessed, and the trajectories with therapeutic stimulation in Fig. 2A (Groppa *et al.*, 2014) appear to exhibit some decomposition into vertical and horizontal movements. Other investigators found that the ventrolateral thalamotomy and thalamic DBS impair motor adaptation and feed-forward control of movement (Chen *et al.*, 2006), and DBS does not correct the delay in antagonist muscle activity that causes target overshoot (dysmetria) (Zackowski *et al.*, 2002). Thus, it should be acknowledged that therapeutic thalamic and subthalamic DBS is performed with only relative impunity, and many patients tolerate subtle ataxia in exchange for relief from disabling tremor.

The extent to which the posterior subthalamic area is preferable to ventralis intermedius as a DBS target for essential tremor has not been determined in a properly controlled study. Muscimol injections into nucleus ventralis intermedius suppress tremor (Pahapill *et al.*, 1999), and the thalamocortical loop is ripe with potential pharmacological and DBS targets for essential tremor and

other tremor disorders. The cerebellothalamic afferents, corticothalamic afferents, thalamocortical relay neurons, GABAergic interneurons, and GABAergic projections from the reticular nucleus are all potential targets within the ventrolateral thalamus (Jones, 2009).

In conclusion, the potential benefits of elucidating the role of the cerebellothalamocortical pathway in tremor are considerable, and the work of Groppa *et al.* (2014) is a noteworthy contribution. The cerebellothalamocortical pathway is involved in virtually all forms of tremor (Elble, 2013), and ongoing efforts to improve stereotactic targeting and to deliver more effective stimulation will enhance our ability to treat essential tremor and other pathological tremors, while reducing stimulation-induced side effects, such as ataxia. The elucidation of this pathway in tremorogenesis may also provide clues to the development of effective pharmacotherapy.

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What happens to your hearing if you are born blind?

Our different senses often work together to enhance perception, for instance helping us to understand what was said by the person we are trying to talk to in a noisy bar, or to work out where that other voice came from. Indeed, cross-sensory interactions are so pervasive that many brain regions, including early sensory cortical areas that were previously thought only to process modality-specific information, are now known to receive multisensory inputs (Alais et al., 2010). Another manifestation of the close relationship between the senses is seen in the sometimes profound changes in the way in which early blind or deaf individuals use their remaining senses. In this issue of Brain, Monica Gori and colleagues describe an unexpected example of such cross-modal plasticity by showing that congenitally blind subjects are severely impaired in their ability to perform an auditory spatial task.

Although studies of cross-modal plasticity in blind people have measured the performance of subjects in various auditory or tactile discrimination tasks, a lot of research in this area has focused on whether auditory spatial abilities change after loss of vision. One reason for this is that spatially-aligned visual cues can improve the accuracy of auditory localization (Shelton and Searle, 1980), whereas misaligned visual cues can bias or capture the perceived location of a sound source, as in the ventriloquist illusion (Bertelson and Radeau, 1981). Given the ample evidence for inter-actions between these senses, with vision tending to play the dominant role in resolving spatial conflicts between them and in aligning neural maps of space in the midbrain during development (King, 2009), it might well be expected that early loss of vision would result in impaired spatial hearing.

In fact, several previous studies (Röder et al., 1999; Voss et al., 2004) have reported the opposite result, with blind subjects per-forming as well as, or even better than, sighted controls when tested for their ability to localize sounds in the horizontal plane. Moreover, there is growing evidence that blindness (or deafness) can result in functional changes within the brain that are likely to underlie perceptual improvements in the intact sensory modalities. For example, improved auditory spatial abilities in blind people have been linked to the recruitment of occipital cortical areas deprived of their normal visual inputs (Collignon et al., 2009), whereas studies in animals have shown that sound processing by neurons in auditory cortical areas can be enhanced in the absence of vision (Korte and Rauschecker, 1993; Petrus et al., 2014).

In view of this, the finding by Gori et al. (2014) that an aspect of auditory spatial processing is impaired in congenitally blind people comes as something of a surprise. This is not obviously related to the age at onset or severity of blindness, as improved sound localization accuracy has been reported in both early and late blind subjects (Voss et al., 2004) and even after blindfolding normal-sighted adults for just 90 min (Lewald, 2007). Instead, the fundamental difference between the findings from these studies seems to be related to the nature of the behavioural task that the subjects carried out.

In the earlier studies in which auditory localization performance in blind individuals was found to be as good as or better than normal, subjects were asked to turn toward the perceived location of the sound source from among an array of loudspeakers or to indicate whether the second of two consecutive sounds came from the same location as the first sound or a different one. In contrast, Gori and colleagues employed a more complex spatial bisection task that required their subjects to judge the relative position of the second sound source in a sequence of three sounds presented from different angles in the horizontal plane. They found that their congenitally blind patients either had significantly elevated thresholds relative to the normal-sighted control group or were unable to do the task at all. This in itself is remarkable as the differences reported in previous studies have tended to be more subtle.

The deficits observed by Gori and colleagues were specific to the spatial bisection task—which required a comparison of the perceived difference in location between the first two and last two sounds—as no differences were found between the blind and sighted groups when they switched to more conventional methods in which subjects were asked to point to the perceived source of a single sound or to carry out a minimum audible angle task. Importantly, the blind subjects were also unimpaired in their ability to perform a temporal bisection task—in which they had to