SCIENTIFIC COMMENTARY

DBS for refractory epilepsy: is closed-loop stimulation of the medial septum the way forward?

This scientific commentary refers primarily to 'Closed-loop stimulation of the medial septum terminates epileptic seizures' by Takeuchi *et al.* (doi:10.1093/brain/XXXXX), with additional reference to 'Medial septal GABAergic neurons reduce seizure duration upon optogenetic closed-loop stimulation by Hristova *et al*. (*in press* in *Brain*).

Epilepsy affects ~1% of the population worldwide, and 30% of patients develop uncontrolled drug-resistant epilepsy despite optimal medication. This refractory form of the disease is associated with high comorbidity rates and increased mortality, and represents an enormous burden to society (~$10 billion per year, Yoon *et al.*, 2009). In the vast majority of cases, it is characterised by recurrent seizures which arise in a single brain region (the epileptic focus) and can then spread and generalise to the entire brain. The most common form originates in the temporal lobe and accounts for ~70% of patients undergoing epilepsy surgery (Blumcke *et al.*, 2017). Indeed, the only effective solution for people with refractory epilepsy is the resection of the epileptic focus, and even this is only possible in a minority of cases. Rates of drug resistance have not changed in three decades, despite the introduction of more than 15 new anti-seizure drugs (Chen *et al.*, 2018), and it is therefore imperative that more effective treatments are identified. To this end, a number of alternative approaches are being developed, including the ketogenic diet, gene therapy and deep brain stimulation (DBS). In this issue of *Brain*, Takeuchi and co-workers explore whether DBS of the medial septum can stop seizures in a rodent model of temporal lobe epilepsy (TLE) (Takeuchi *et al*., 2021).

DBS is an important part of the therapeutic arsenal for treating movement disorders and psychiatric conditions. Evidence suggests that electrical stimulation can also disrupt seizure activity and could therefore provide a reversible, adjustable alternative to surgical resection. In line with this, focal stimulation of the hippocampus and anterior nucleus of the thalamus (ANT) has been shown to significantly reduce seizure frequency in patients suffering from TLE (Li and Cook, 2018), and 'responsive' DBS, triggered by specific features of the EEG, has been approved by the FDA. However, stimulation of other structures such as the cerebellum and subthalamic nuclei has yielded inconclusive results, and DBS may also cause unwanted effects on mood and memory, depending on the exact location of stimulation (Li and Cook, 2018). Further investigation is thus warranted in order to better understand the efficacy of DBS for the treatment of epilepsy, and to optimise the location of stimulation, as well as the specific protocols used, while minimising potential harmful side effects.

Against this backdrop, Takeuchi *et al.* hypothesised that electrical stimulation of the medial septum would disrupt seizure generalisation in an animal model of TLE. Indeed, the medial septum has been proposed as a potential DBS target for the treatment of drug-resistant TLE (Fisher, 2015) and presents a number of advantages when compared to the hippocampus or the ANT. First, it is highly interconnected with the hippocampal formation, and this interaction is key to controlling hippocampal rhythmic activity, and theta oscillations in particular (Buzsáki, 2002; Müller and Remy, 2018). Second, it projects strongly to the entorhinal cortex, which is a gateway between the hippocampus and neocortex, and is frequently involved in seizure generalisation. Finally, it is located at the midline, eliminating the need for bilateral electrode insertion and therefore reducing the burden of complex surgery on the patient. Overall, then, in contrast to focal hippocampal or ANT stimulation, intervention in the medial septum promises a far greater influence on the temporal lobe while also being potentially simpler and safer to implement.

Using a kindling animal model of TLE—consisting of intermittent stimulation of the hippocampal commissure for 10 days, after which generalised seizures can be reliably induced—Takeuchi *et al.* investigate whether and how medial septum stimulation can be used to stop seizures. To this end, they evoke generalised seizures, with or without simultaneous electrical stimulation of the medial septum, and record seizure activity from an impressive number of sites (up to 30) to precisely follow seizure propagation within both hippocampi, as well as in the entorhinal, somatosensory, and motor cortices. Behavioural seizures are also quantified via video-monitoring. They employ a responsive medial septum stimulation protocol, where stimulation occurs on demand in response to seizure activity, and distinguish between two stimulation paradigms: an open-loop configuration, where a fixed electrical pattern is used, and a closed-loop configuration, where the stimulation closely follows the temporal pattern of seizure activity, and the timing of stimulation relative to the oscillation phase can be varied (see Fig. 1B). Using this approach, they find that closed-loop stimulation reduces hippocampal seizures, as well as their propagation to cortical areas and the behavioural manifestations associated with this generalisation. In contrast, the open-loop protocol either appears to have no effect, or in fact promotes the generalisation of seizures that are otherwise sub-threshold. This is essential information for future therapeutic development as it demonstrates that the precise stimulation pattern used, relative to seizure activity, can determine whether the final outcome of DBS is beneficial or detrimental to the patient.

While closed-loop stimulation of the medial septum does appear to have a clear anti-epileptic effect overall, the authors find this to be surprisingly binary: the stimulation protocol either reduces seizures significantly, or has no detectable effect, on a trial-by-trial basis. This variation does not appear to be related to the phase of the oscillation at which the stimulation is applied, but instead to the precise coupling of the stimulation to the seizure oscillations. In other words, the faster and more accurately the oscillations are detected, the more precise the stimulation can be and therefore the better the

outcome. Determining the exact relationship between coupling efficiency and seizure reduction merits further investigation, and will certainly require novel and more advanced seizure detection methods.

Under what conditions does open-loop electrical stimulation facilitate seizures? Previous work in a different TLE model found that non-responsive open-loop stimulation of the medial septum, where a fixed stimulation pattern is delivered regardless of seizure activity, had anti-seizure effects (Izadi *et al.*, 2019). Here, Takeuchi and colleagues introduce fixed pre-conditioning stimuli before evoking generalised seizures partially mimicking a non-responsive open-loop protocol and find, in stark contrast to Izadi *et al* (2019), that this promotes seizures, decreasing their induction threshold (Fig. 1C). The difference in TLE models (kindling versus pilocarpine) and stimulation protocols (20 Hz for Takeuchi *et al.* versus 8 Hz for Izadi *et al.*) could easily explain these opposing findings, but they serve as further evidence that open-loop paradigms (responsive or not), while simpler to implement, have the dangerous potential to exacerbate seizures (Fig. 1C). Closed-loop DBS of the medial septum, on the other hand, appears relatively safe, producing at worse no effect and at best a strong anti-epileptic action.

The mechanism(s) underlying these effects are complex. The medial septum connects not only to the hippocampal formation and entorhinal cortex, but also to the amygdala, ventral tegmental area and hypothalamus, and importantly it houses at least three different classes of projection neurons (Fig. 1A, Müller and Remy, 2018). Using selective optogenetic methods, Takeuchi *et al.* set out to probe the individual roles of these medial septum neuronal subclasses in seizure modulation. They begin by expressing channelrhodopsin under the pan-neuronal synapsin promoter, and activate medial septum neurons by means of an optic fibre implanted above the structure. By combining this methodology with their closed-loop experiment, they confirm that indiscriminate activation of medial septum neurons reduces seizure duration and prevents their generalisation. They then seek to reveal which of the neuronal subtypes—GABAergic, glutamatergic or cholinergic (Fig. 1A)—is responsible for this anti-seizure effect by using transgenic rats expressing Cre recombinase in the different cell types (GAD-Cre, CaMKII-Cre or ChAT-Cre) together with viral injections to achieve Cre-dependent channelrhodopsin expression in the medial septum. In this way, they find that closed-loop stimulation of GABAergic cells is effective in terminating generalised seizures, but that activation of either glutamatergic or cholinergic neurons has no effect on epileptic activity. This latter finding is somewhat surprising given the known involvement of glutamatergic and cholinergic cell types in hippocampal rhythmogenesis (Müller and Remy, 2018). Interestingly, however, when activated during the pre-ictal phase, cholinergic neurons exert an anti-epileptic effect, augmenting seizure threshold, while activation of GABAergic neurons becomes pro-epileptic (Fig. 1C). The conflicting results of electrical stimulation during the pre-ictal phase described above could therefore perhaps be explained by the preferential recruitment of specific cell types by the different stimulation protocols used by Takeuchi *et al.* and Izadi *et al.* (2019).

The hippocampal kindling model employed in this study is a powerful experimental paradigm in which to study evoked seizures in TLE, but it does not fully reproduce the disease's aetiology. Indeed, it will be important to confirm the effect of medial septum DBS in a chronic TLE model with spontaneous seizures. Along these lines, a complementary study by Hristova and colleagues, also *in press* in *Brain*, explores whether optogenetic stimulation of medial septum GABAergic neurons can affect spontaneous seizures in a chronic model of epilepsy. Hristova *et al.* use intrahippocampal kainate injections to induce status epilepticus, after which animals develop spontaneous electrographic hippocampal seizures that occasionally generalise. Importantly, hippocampal sclerosis, a characteristic feature of TLE, is also present in this model. Given the strong interconnection between the hippocampus and medial septum (Müller and Remy, 2018), it is conceivable that similar structural alterations may occur in the medial septum (Fisher, 2015), thereby jeopardising the efficacy of DBS, or optogenetic stimulation, in this area. Hristova *et al.* address this important question, looking at medial septum GABAergic cells specifically, and reveal that neither their number nor their connections to the hippocampus are altered in this model of TLE, despite apparent hippocampal sclerosis. In line with this, rhythmic optogenetic stimulation of these neurons successfully entrains hippocampal oscillations throughout the hippocampus, including in the sclerotic region. Finally, using a complex combination of wireless electrographic transmitters and optical stimulation with online seizure detection, they show that activation of medial septum GABAergic cells during spontaneous seizures has an anti-epileptic effect, reducing seizure duration. Together, these experiments strongly support the findings of Takeuchi *et al.* and further strengthen the case for the medial septum as a target in the treatment of TLE.

The question of optimal stimulation protocols remains open, however. Indeed, Hristova *et al.* find that responsive open-loop stimulation of GABAergic medial septum neurons is effective in their model, whereas Takeuchi *et al.* report no effect of this protocol in theirs. As previously mentioned, this could be due to the use of different stimulation frequencies (10 Hz for Hristova *et al.* and 20 Hz for Takeuchi *et al.*), and requires further investigation. Finally, Hristova *et al.* were unfortunately unable to record sufficient generalised seizures due to experimental constraints and could therefore only detect a clear effect of their intervention on electrographic hippocampal seizures. Whether stimulation of the medial septum, by optogenetics or DBS, can prevent generalisation of spontaneous seizures in a chronic TLE model therefore still remains to be determined.

Taken together, the innovative work by both Takeuchi *et al.* and Hristova *et al.* shows that stimulation of the medial septum is a strong therapeutic candidate for alleviating seizures in TLE. Furthermore, while uncertainty still remains with regards to optimal stimulation strategies, closed-loop DBS is likely to be both the most effective and the safest approach. Finally, understanding whether long-term medial septum DBS (weeks to months) is beneficial, not only for seizure control but also for reducing comorbidities associated with TLE such as memory and learning disabilities, will be essential for

clinical translation. Thus, while more work is clearly needed, these important studies shine a light on the medial septum and pave the way for future exciting experimental and clinical investigations.

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Competing interests

The authors report no competing interests.

Figure legend

Figure 1 DBS of the medial septum for the treatment of refractory epilepsy. (**A**) Schema of the medial septum and its projections to the hippocampus. Takeuchi *et al.* insert a stimulating electrode in the medial septum to influence hippocampal activity. CPu: caudate putamen; EC: external capsule; LV: lateral ventricle (**B**) Schema of the different configurations of responsive DBS. Takeuchi *et al.* use both open- and closed-loop stimulation to test whether medial septum activation can terminate seizures. (**C**) Summary of findings from Takeuchi *et al.* and Hristova *et al*.

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