Insights into the mechanisms of deep brain stimulation

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Abstract | Despite long-term and widespread use of deep brain stimulation (DBS) in a variety of neurological conditions, the underlying mechanisms of action have been elusive. Growing evidence suggests that DBS acts through multimodal mechanisms that are not limited to inhibition and excitation of basal ganglia circuits. DBS also seems to act over variable time spans — for example, the effects on tremor are immediate, whereas the effects on dystonia emerge over several weeks — suggesting that large networks are targeted. Studies reviewing the use of DBS in pain and obsessive–compulsive disorder have demonstrated direct involvement of axonal fibres rather than grey matter. In this Review, we draw on clinical and experimental data to examine the various hypotheses that have been put forward to explain the effects of DBS. In agreement with several other experts, we suggest that the term 'deep brain stimulation' warrants modification. A potentially more accurate term is 'deep brain neuromodulation', as the mode of action spans an array of therapeutic effects over a variable period of time, and is not just limited to 'stimulation' of the basal ganglia brain centres. Terms such as 'electrical neuro-network modulation' may be useful for applications in which deep brain structures are not the primary target.

Deep brain stimulation (DBS) is a well-established functional neurosurgical technique that is used to treat a variety of neurological disorders[1]. In 1987, Alim Louis Benabid and colleagues demonstrated that in patients with Parkinson disease (PD), DBS not only mimicked the beneficial effects of ablative surgery, but also offered adjustability and reversibility if adverse effects of stimulation were evident[2]. Since then, the technique has opened up new frontiers in the surgical treatment of hyperkinetic disorders, pain, epilepsy, and some neuropsychiatric conditions.

Despite the widespread use of DBS, the mechanisms underpinning its therapeutic efficacy remain unclear. Initial views on these mechanisms were based on the classic 'rate model', in which the motor symptoms of PD are attributed to altered neuronal firing rates in the basal ganglia. The predictions of this model, combined with the observation that the clinical effects of DBS mimicked those of lesioning techniques, lent support to the idea that overactive basal ganglia were inhibited by DBS to relieve these motor symptoms. Alternative hypotheses have subsequently been proposed, causing researchers to revise their understanding of the physiology of the basal ganglia–thalamus–cortex organization. A better understanding of the mechanisms underlying DBS will permit fine-tuning of surgical methods to maximize benefits and reduce adverse effects.

In this Review, we explore the mechanisms that are proposed to underlie DBS, drawing on insights from clinical and investigational models, and assessing the various hypotheses that have been put forward to explain the effects of this intervention. We conclude by suggesting a change in terminology to better reflect the myriad effects of DBS, which go beyond stimulation of the basal ganglia.

Lessons from Parkinson disease

PD is a neurodegenerative disease in which dopaminergic neurons of the substantia nigra pars compacta (SNc) are lost. The ensuing loss of dopamine disrupts the function of striatal circuits and leads to imbalance of the so-called direct and indirect pathways through the basal ganglia. Consequently, activity of the basal ganglia output targets, such as the globus pallidus internus (GPi) and the substantia nigra pars reticulata (SNr), also becomes altered, leading to movement disorders and the classic 'parkinsonian triad' — akinesia, rigidity, and tremor — as well as to posture and gait deficits, and cognitive and emotional disorders[3–5]. As DBS was first used in PD, much of our current understanding of this technique stems from PD-related studies.

Local field potential (LFP) and spiking activity studies in parkinsonian animals and patients have identified characteristic pathological neuronal firing patterns, such

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Key points

- Deep brain stimulation (DBS) is a well-established functional neurosurgical technique that is used to treat a variety of neurological disorders, but the mechanisms underpinning its therapeutic efficacy remain unclear
- As DBS was first used in Parkinson disease (PD), much of our current understanding of this technique stems from PD-related studies; however, insights have also been gained from other conditions, including dystonia, intractable pain and psychiatric disorders
- The time course and patterns of symptom improvement vary considerably among conditions that are treatable by DBS
- Initial views on the mechanisms of DBS were based on the classic 'rate model', in which the motor symptoms of PD were attributed to altered neuronal firing rates in the basal ganglia
- Recent observations indicate that DBS acts through multifactorial mechanisms, including immediate neuromodulatory effects, synaptic plasticity, and long-term neuronal reorganization
- In light of this complexity, a change in the terminology from deep brain 'stimulation' to deep brain 'neuromodulation' is proposed

as 'bursting' and abnormal beta-oscillatory (13–35 Hz) activity. Firing rates are shown to increase in the GPi and the subthalamic nucleus (STN)[6,7], but to decrease in the globus pallidus externus (GPe)[7]. Beta oscillations are especially prominent in the GPi, GPe, STN and SNr[8]; in addition, discharge from these nuclei, which are normally independent, becomes hypersynchronized in PD[5]. Increased incidence and frequency of the bursting phenomenon has been shown to correlate strongly with severity of symptoms in PD[9], and these pathological patterns have replaced the traditional belief that neuronal firing rates alone are affected in PD.

The implications of these findings in PD are profound. Understanding of neuronal firing rates and patterns in the STN in PD, and recognition of the pivotal role of this nucleus in basal ganglia physiology and pathophysiology, have led to its emergence as the surgical target of choice in PD[10,11]. DBS might achieve its therapeutic effect by disrupting the abnormal synchronization of the basal ganglia functional circuits, allowing normalization and restoration of 'functionality' rather than actually repairing the pathological basal ganglia system[12].

It is still unclear exactly how DBS exerts its therapeutic effects; however, advances in DBS mechanisms and PD pathophysiology form an interdependent relationship whereby each advance in our understanding forces researchers to re-evaluate the current models. One such example is the utilization of beta-band activity as a biomarker to devise closed-loop DBS systems that deliver more physiological and efficient therapy[13].

Lessons from other conditions

The expansion of indications for DBS has provided us with vital insights into the underlying mechanisms. The time course and patterns of symptom improvement vary immensely among conditions that are treatable by DBS (FIG. 1): tremor and rigidity typically respond within minutes, whereas bradykinesia can take hours and dystonia or mood changes in depression can take months to resolve[14]. Given these diverse time frames, suggestions have been made that DBS therapy should be tailored to target specific sets of symptoms emanating from different brain nuclei, regardless of the underlying disorder. These observations may reflect the fact that DBS acts via a multitude of therapeutic mechanisms, and not solely via inhibition or excitation of locally stimulated axons. It seems plausible, therefore, to consider this therapy as a multimodal neuromodulation technique, rather than simply stimulation of local axons.

In patients with dystonia, DBS is believed to modify cortical plasticity, which might explain the gradual improvement observed in these patients[14]. The underlying dysfunction in dystonia seems to stem from abnormal modulation of cortical motor pathways by the basal ganglia; underactivity of inhibitory cortical, brainstem and spinal connections[15]; and excessive plasticity of the cortex[16]. Tisch *et al.* have shown that DBS of the GPi contributes to normalization of the cortical plasticity, resulting in a gradual reduction in symptoms over months as neural reorganization takes shape[16,17].

For over half a century, DBS has been used to treat intractable pain. The periaqueductal grey (PAG) and the periventricular grey (PVG) matter are just two of the targets used for low-frequency DBS in this context. DBS of the PAG is thought to enhance endogenous opioid release and to exert ascending modulation of the ventral posterior nucleus of the thalamus[18], whereas DBS of the PVG is thought to modulate autonomic function[19] by engaging passive coping mechanisms alongside increased vagal output[20,21]. Pereira *et al.* confirmed these responses in 2013 by recording local field potentials and infusing the opioid blocker naloxone along with saline during stimulation of the PAG and PVG[20]. These observations indicate a much broader therapeutic set of mechanisms of DBS, perhaps rendering the term 'stimulation' inadequate.

DBS has also been used with some early promise in psychiatric conditions. One example is refractory obsessive–compulsive disorder (OCD), in which decreased rates of anxiety, obsessive thinking and ritualistic behaviours were reported following high-frequency stimulation (HFS)[22–25]. In contrast to DBS for the treatment of movement disorders or pain, the mechanisms of DBS for psychiatric conditions are thought to manifest through modification of the white matter tracts rather than the grey matter, targeting specific tracts such as the ventrocaudal parts of the anterior limbs of the internal capsule in the case of OCD[26]. Consequently, the mechanism of action of DBS in the treatment of psychiatric conditions might resemble an internal electroconvulsive therapy, activating multiple white matter tracts, rather than the typical DBS, which targets a specific grey matter nucleus[27]. This mechanistic difference could explain why higher DBS voltages are needed to treat psychiatric conditions than to treat movement disorders.

It has also been suggested that current spread during DBS of the ventrocaudal anterior limbs of the internal capsule to the shell of the nucleus accumbens (NAc), situated directly below, is at least partly responsible for the beneficial effects in psychiatric disorders[28]. The NAc occupies a central position between the amygdaloid complex, the basal ganglia, the mediodorsal thalamic complex, and the prefrontal cortex circuitry, and dopaminergic

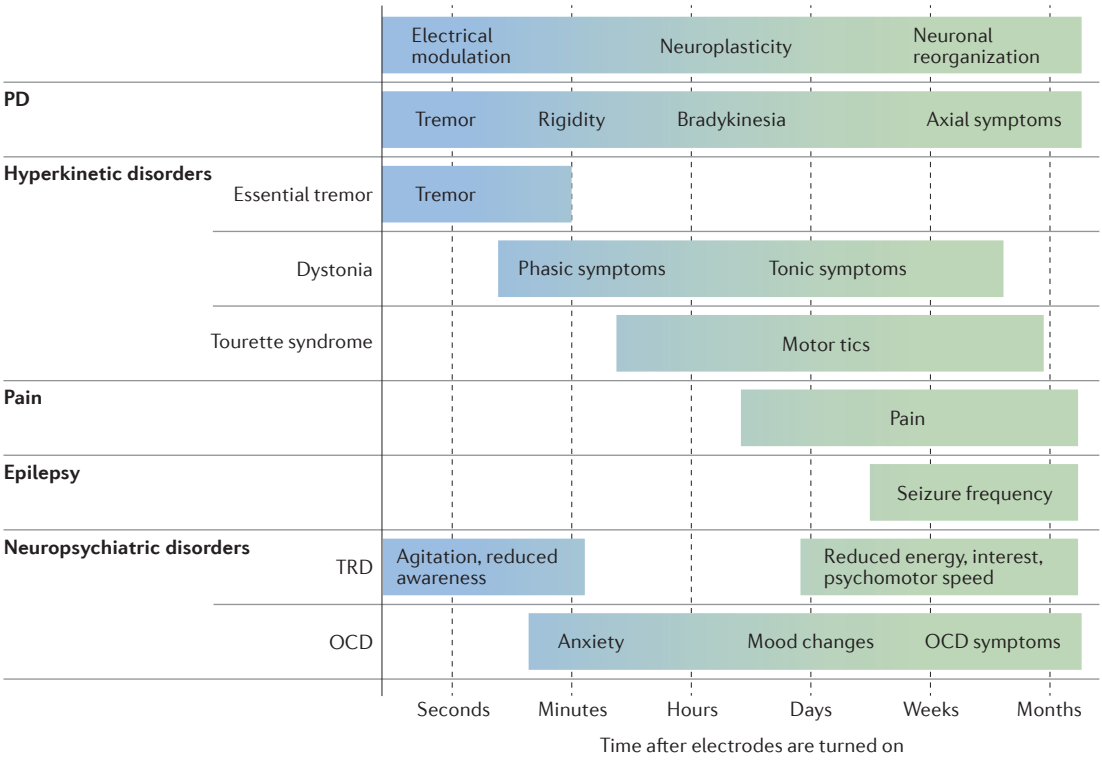

Figure 1 | **Timing of the effects of deep brain stimulation.** Logarithmic scale showing patterns of symptom improvement following the switching on of deep brain stimulation electrodes in patients to treat a range of disorders. OCD, obsessive–compulsive disorder; TRD, treatment-resistant depression. Adapted from Herrington *et al.* (2016)[73].

dysfunction of this circuitry has been implicated in OCD[29]. Thus, the NAc also works as an effective DBS target for the treatment of OCD. However, neuroimaging studies indicate that the therapeutic effect of NAc DBS involves an increase in striatal dopamine release[29], further widening the range of therapeutic mechanisms of DBS.

Investigational models

Several methods, including extracellular recordings, field potential recordings and functional imaging studies, have been used to investigate the cellular effects of DBS.

Extracellular recordings permit analysis of single or multiple action potentials from electrodes positioned in the extracellular space. The frequency and amplitude of action potentials and synaptic currents surrounding the electrode are recorded[30].

LFPs, which can be measured using electrocorticograms or EEG, or from DBS electrodes themselves, are used to compare the spectral content of the recorded signals in different behavioural states, including healthy and diseased states[30]. Functional imaging studies involving functional MRI (fMRI)[31], single-photon emission CT[32] and PET[32] have also been used to assess brain activity and metabolism. A real-time bioluminescence imaging technique that permits study of inflammation, axogenesis and neurogenesis alongside brain stimulation in mice was recently developed[33]. Although this technique has yet to be used to probe deeper brain structures, it has the potential to enable further real-time *in vivo* analysis in the future.

Techniques to investigate DBS in PD have been trialled across a spectrum of pathological models, including mouse, primate, *ex vivo* and *in vitro* models, as well as in human patients. Human studies are limited largely by ethical issues, such as the difficulty of obtaining sufficient control data from healthy individuals. By contrast, ample healthy control data are available for animal studies. However, electrophysiological studies in animals often rely on models that utilize neurotoxins to produce dopaminergic cell loss, which only partially recapitulate the pathophysiology of PD[30]. Other challenges include the production of brain stimulation apparatus that fit small animals while still resembling human devices. Furthermore, neuronal behaviour in small animals might not be directly translatable to human models[11,34]; for example, in DBS studies on oscillation frequencies, the beta band in human neuronal oscillations was found to lie at a different frequency from that reported in several animal studies[35,36]. Despite these limitations, investigational models have permitted the expansion of our understanding of PD and the role of DBS, as outlined in the sections that follow.

DBS mechanisms: current hypotheses

Classic rate model

The initial hypothesis regarding the mechanisms of DBS, termed the 'inhibition hypothesis', postulated that overactive basal ganglia neurons in the STN and/or GPi were blocked by DBS, concordant with the classic rate model. This model hypothesized that dopamine depletion in the

parkinsonian state culminated in increased firing rates from the STN and GPi and resulted in decreased thalamic firing and akinesia. The idea was in keeping with observations that the clinical effect of DBS resembled that of anatomical lesioning and physiological inactivation (for example, by a GABA agonist)[37]. Studies purporting to support this model, however, were hampered by limitations in their design, such as the failure to account for stimulus artefacts[38–40]. When new computer algorithms were used to eliminate these artefacts, acute DBS was shown — contrary to the inhibition hypothesis — to produce an increase in STN somatic activity, which was followed by a sharp decrease in activity immediately following cessation of stimulation[41].

Ideas continue to develop, and a number of controversial hypotheses have been put forward. These hypotheses attempt to address whether neurons are stimulated or inhibited, which parts of the neuron are modulated, whether afferent or efferent axons are stimulated, whether DBS has local or more systemic effects, whether neurons or glial cells are affected, and whether the efficacy is sustained over acute or chronic timescales. We explore some of these hypotheses below.

Local versus systemic effects

Early studies relied on the assumption that activity predominantly local to the implanted electrode was directly relevant to the therapeutic efficacy of DBS[41]. However, further investigations of the downstream effects of DBS have confirmed a more systemic mechanism involving excitation of axons both afferent and efferent to the site of stimulation[42–44]. In both rodent and human studies, an increase in neurotransmitter release in the downstream structures was noted[45–48].

Functional imaging studies conducted in both animals and humans undergoing DBS provide additional evidence that HFS excites axons both locally and systemically, leading to increased neurotransmitter and second messenger release from the axons[39,45,49,50]. However, owing to the substantial noise component on fMRI, these results must be interpreted with caution[51].

Beyond the rate model

Evidence from human and primate models of PD indicated a reduction in discharge rates from the GPe and the ventrolateral nucleus of the thalamus, and increased firing in the STN and GPi. However, various observations have contradicted these rate models, in particular, when explaining the pathophysiology of dystonia or dyskinesia. In 1999, Jerrold Vitek and colleagues reported both decreased firing rates and — more importantly — irregular firing patterns in the GPe and GPi in patients with dystonia, leading to an alternative model of basal ganglia function[52].

Jamming theory. The concept of jamming was first described by Benabid and co-workers[53]. The authors postulated that stimulation of efferent axons via DBS imposes a time-locked high-frequency regular pattern of discharge on the axons. The short intervals between DBS pulses might prevent the neurons from returning to their spontaneous baseline activity, including the pathological patterns observed in patients with PD. According to this hypothesis, DBS does not reduce neural firing, but instead induces modulation of pathological network activity, causing network-wide changes.

Bursting. GPi activity is known to become irregular in PD, and HFS might work by normalizing these pathological bursting oscillatory patterns. In a computational simulation experiment, Rubin and Terman showed that regulation of GPi firing following STN DBS permitted a normal thalamic response[54]. High-frequency DBS of approximately 130 pulses per second is thought to resonate with the average physiological oscillation frequencies of the basal ganglia–thalamus–cortex system, thereby accounting for the therapeutic effects of high-frequency DBS and simultaneously offering an explanation for the adverse effects of low-frequency DBS[41,55,56].

Disrupting pathological oscillation. The oscillations that are normally detected in functioning neural networks are thought to facilitate dynamic communication and plasticity between spatially disparate populations of neurons. Pathological beta-band oscillatory activity in the sensorimotor loops between the cortex, basal ganglia, thalamus and cerebellum is thought to contribute to the motor symptoms of PD, as normal beta oscillations probably contribute to the maintenance of 'status quo' (stop) behaviour. Thus, excessive beta oscillations might cause akinesia or bradykinesia, and DBS could disrupt and suppress the beta-band oscillations to reduce levels of bradykinesia and rigidity[57–64]. This phenomenon was directly demonstrated in a proof-of-concept study by Little *et al.* in eight patients with PD[13]. In these individuals, symptoms improved by 50% when STN stimulation was delivered in response to beta-oscillatory activity, as opposed to traditional continuous or random stimulation. However, given that natural beta fluctuations are associated with movement, it remains to be seen whether closed-loop strategies will provide similar results in ambulatory individuals[65].

Cellular perspective

At the cellular level, DBS directly activates astrocytes as well as neurons, causing release of various gliotransmitters, such as glutamate, D-serine and ATP[66]. Once stimulated, astrocytes contribute to the modulation of neuronal firing[67]. Astrocytes also have direct effects on cerebral blood flow, causing either an increase or a decrease in neuronal activity by mediating neurovascular coupling[68]; this finding was confirmed in PET studies[69].

An increase in adenosine levels has been shown to occur following HFS of the ventrolateral thalamus, as ATP from astrocytes is broken down into adenosine in the extracellular space. In one study, Bekar *et al.* observed decreased tremor levels after identifying increased adenosine levels around the electrode in a mouse cortex[70]. Therefore, adenosine might contribute to the efficacy of HFS by promoting neuronal inhibition. Furthermore the 'microlesion' effect often observed after

DBS, whereby an improvement in symptoms is observed following placement of the electrodes before HFS is commenced, is also thought to be astrocyte-mediated[68]. This microlesion effect, combined with the modulation of cerebral blood flow, might explain some of the systemic mechanisms of DBS[68].

Neuroprotection. Neuroprotection of nigral dopamine-secreting neurons is the ultimate goal of PD therapy. Evidence is accumulating that DBS confers protection on dopaminergic cells, adding a further twist to the mechanism of action of DBS. A primate study showed that up to 24% of dopaminergic neurons were preserved following STN DBS[71], and a rodent study demonstrated a 30% increase in levels of glial cell line-derived neurotrophic factor — a protein with neuroprotective properties — in response to GPi DBS[72]. Thus, DBS might offer neuroprotection to dopaminergic cells that would normally degenerate as part of the disease process, offering hope that DBS is not only a therapeutic tool but also slows down the progression of the pathology[73]. Clearly, human studies will be crucial to verify this potential.

Electrotaxis. Electrotaxis describes the migration of progenitor cells towards the DBS electric current — and, thus, the pathological brain — by means of the electric field, perhaps providing neural protection and restoration[74]. The mechanisms underlying electrotaxis might be explained by the effects of DBS on transcription factors and gene expression: increased cerebral blood flow and neurogenesis could result in enhanced neuroplasticity at the molecular level[75]. Enhanced neural proliferation following DBS has been noted in human post-mortem studies[76]. Furthermore, HFS might reduce the adverse effects of microglial activation, thereby also enhancing neuroplasticity[77]. Although it is possible that this effect on neuroplasticity adds to the overall effects of DBS, it is unlikely to be the main contributor, as DBS has been shown to provide immediate amelioration of motor symptoms in PD[78]. Studies in this field are limited to cortical stimulation rather than subcortical DBS, so further work must be done to investigate this phenomenon in the deeper brain structures.

Beyond basal ganglia to cortex

Recent investigations have shown that acute DBS exerts a marked influence on the cortex by reducing excessive coupling between beta oscillations and broadband activity[14]. Therefore, although the site of DBS current delivery is at the basal ganglia, its mechanism of neuromodulatory action seems to be at least partly mediated (antidromically or orthodromically) remotely at the cortex. This phenomenon is particularly relevant for dystonia, in which a change in cortical plasticity is thought to be fundamental to the therapeutic effect of DBS[16].

Terminology: time for a change?

Medicine is an evolving field. As new knowledge emerges, we often find ourselves revising past hypotheses and inventing new terminology to better reflect our current view of reality. Thus, phrases such as 'pulseless electrical activity' in cardiology and 'chronic obstructive pulmonary disease' in respiratory medicine have come to replace the terms 'electromechanical dissociation' and 'chronic obstructive airway disease', respectively. Similarly, in light of the growing understanding of the mechanisms underlying DBS, we propose a change in traditional nomenclature to 'deep brain neuromodulation' (abbreviated to DBN), as the mode of action spans an array of therapeutic effects over a variable period of time, and is not limited to 'stimulation' of the basal ganglia brain centres.

The idea that the term 'deep brain stimulation' requires a rethink is not new: many groups have indicated that the time for a nomenclature change has arrived. Criticism stems from the notion that the current term is too general, and in some instances misleading. 'Stimulation' targets now span a wide range of structures to include not only deep brain nuclei but also white fibre bundles joining the cortical, subcortical and deep brain networks. In addition, a wealth of literature investigating the many possible mechanisms of action of DBS — some inhibitory and some excitatory — has emerged.

The first investigators to suggest a change in nomenclature were Michael Okun and Genko Oyama, who proposed the term 'electrical neuro-network modulation' (ENM)[79]. Although this term has merit in better describing the mechanism of action of DBS, it is rather general and can, for example, be applied to other functional interventions such as vagal nerve or spinal cord stimulation, which similarly have both local and remote 'network' corticothalamic effects. In our view, the term 'deep brain neuromodulation' clearly defines the specific physical location of the hardware within the brain, differentiating the procedure from other functional neurosurgical procedures, while retaining the more reflective and all-encompassing term 'neuromodulation', which acknowledges that the mechanisms of action go beyond stimulation.

Conclusions

Since the first application of DBS by Alim Louis Benabid, several authorities, including Andres Lozano, Cameron McIntyre, Jerrold Vitek, Michael Okun and Genko Oyama, have strived to unravel its underlying mechanisms. Ultimately, the difficulty of exploring the mechanisms of action of DBS reflects challenges in understanding brain physiology and pathophysiology. Experiments and hypotheses are based on the assumption that current physiological models are accurate, and if the results fail to confirm these models, our concepts of brain physiology, pathophysiology and DBS mechanisms of action must be re-evaluated. Precisely how DBS exerts its effects is still unknown, although experimental techniques have vastly expanded our knowledge, permitting the adoption of new techniques that will ultimately modify and improve delivery of the therapy.

Future work should take a systems-based approach, connecting upregulation of transcription factors with the molecular findings of neurogenesis, astrocytic action, increased cerebral blood flow and electrotaxis. Another potential avenue to explore is the combination of DBS

with other therapies; for example, preliminary studies are investigating the combined effects of gene therapy and DBS[80].

Contemporary research confirms that DBS acts not just via local excitatory and inhibitory mechanisms, but through a plethora of local and remote factors. This complexity is reflected in the characteristic variance in the response of different symptoms to DBS over time (FIG. 1). These observations support the theory that the mechanisms of DBS are multifactorial and include immediate neuromodulatory effects, synaptic plasticity, and long-term neuronal reorganization. In light of this shifting view, we propose a change in the terminology from deep brain 'stimulation' to deep brain 'neuromodulation' to more accurately reflect the contemporary evidence.

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P.R., H.B. and I.U. researched data for the article. K.A. and P.R. discussed the content. K.A, P.R. and I.U. wrote the article. K. A., H.B. and I.U. reviewed and edited the manuscript before submission.

Competing interests statement
The authors declare no competing interests.