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REVIEW

Functional brain mapping: overview of techniques and their application to neurosurgery

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Abstract
Functional brain mapping (FBM) is an integral part of contemporary neurosurgery. It is crucial for safe and optimal resection of brain lesions like gliomas. The eloquent regions of the cortex like motor, somatosensory, Wernicke's, and Broca are usually mapped, either preoperatively or intraoperatively. Since its birth in the nineteenth century, FBM has witnessed immense modernization, radical refinements, and the introduction of novel techniques, most of which are non-invasive. Direct electrical stimulation of the cortex, despite its high invasiveness, remains the technique of choice. Non-invasive techniques like fMRI and magnetoencephalography allow us the convenience of multiple mappings with minimal discomfort to the patients. They are quick, easy to do, and allow thorough study. Different modalities are now being combined to yield better delineations like fMRI and diffusion tensor imaging. This article reviews the physical principles, applications, merits, shortcomings, and latest developments of nine FBM techniques. Other than neurosurgical operations, these techniques have also been applied to studies of stroke, Alzheimer's, and cognition. There are strong indications that the future of brain mapping shall see the non-invasive techniques playing a more dominant role as they become more sensitive and accurate due to advances in physics, refined algorithms, and subsequent validation against invasive techniques.

Keywords Brain mapping · Glioma · Eloquent · Spatial · Seizure

Introduction

A great challenge that confronts neurosurgeons during resections is to excise brain lesions to the greatest extent possible without injuring the surrounding "eloquent" cortical areas, that are areas whose injury can lead to cognitive or motor deficits, like the primary motor area, somatosensory area, Wernicke's area, or Broca's area. The resection becomes a risky quest when the lesion is bordering or infiltrating into an eloquent area. Best prognosis is achieved by carrying out maximal resection of the offending lesion. In fact, there is a plethora of strong evidence that a higher extent of resection in gliomas (including GBM) is associated with improved overall survival [5, 9, 51, 79]. Hence, it becomes imperative for the neurosurgeon to precisely differentiate between eloquent areas and the lesion to effect gross total resection. Although anatomical landmarks of the brain can be used to identify many eloquent regions, they cannot be relied upon in a diseased brain. Mass effect and plasticity changes the boundaries of eloquent regions in patients with brain tumors and even healthy brains show a great variability in the location of eloquent cortices. Functional brain mapping (FBM) has emerged as a crucial tool enabling neurosurgeons to address these challenges. *The Society for Brain Mapping and Therapeutics* defines functional brain mapping as the study of the anatomy and function of the brain and spinal cord through the use of imaging, immunohistochemistry, molecular and optogenetics, stem cell and cellular biology, engineering, neurophysiology, and nanotechnology. FBM is done by a mélange of techniques, most of which are neuroradiological techniques. These techniques differ in their principles, efficacy, cost, and reliability.

Previous reviews have offered broad discussion of the history of FBM, including development of techniques like EEG and direct electrical stimulation (DES) [63]. FBM techniques can be stratified by many criteria, including electromagnetic versus non-electromagnetic techniques, activation versus inhibition studies, and invasive versus non-invasive methods.

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This article shall review nine different techniques from these various groups and their roles in modern neurosurgery.

Direct electrical stimulation

Originating in the nineteenth century, DES of the cortex is the oldest brain mapping technique [27]. DES can be done in intraoperative and extraoperative setups. Extraoperative DES is usually done in epilepsy patients after intraoperative implantation of electrodes while the patient is on a monitoring unit in a hospital, with the goal being localization of epileptogenic foci and mapping of the eloquent cortex [33]. Two types of electrodes are used for DES: monopolar and bipolar. The bipolar setup comprises a pair of electrodes (cathode and anode), which stimulate the cortex between them on passage of electricity. The bipolar stimulation is carried out passing by a train of pulses at low frequency of 50–60 Hz for 2–4 s [65]. The bipolar technique suffers from two grave disadvantages: intraoperative seizures and obstruction of microneurosurgery due to muscle movement [74]. Monopolar stimulation is done by passing a train of pulses at high frequency (250–500 Hz) for duration of 0.5 ms. It is more objective, quicker, carries significantly lower risk of seizures, and is preferred for motor mapping [65]. Szelenyi et al. have thoroughly reviewed the methodological aspects of intraoperative DES [82] in great technical details (Fig. 1).

For intraoperative language mapping, the patient remains awake and undergoes a neuropsychological evaluation that involves verbal and non-verbal tasks [71]. Awake craniotomy is done via one of the following anesthetic techniques: "asleep-awake-asleep," "awake throughout," and "asleep-awake," [72] and a detailed discussion can be found here [52]. Once awakened, the patient is asked to perform tasks like naming, reading, counting, and small calculations. For motor mapping done alongside awake language mapping or in an awake patient to achieve greater sensitivity, the movements elicited by cortical stimulation are recorded with an electromyogram. Pure motor mapping without language mapping can also be done under general anesthesia, in which case motor responses can be visualized or recorded with an electromyogram. For subcortical mapping, the white matter tracts are followed progressively from the eloquent sites on the cortex already mapped into the depths [18]. The resection is continued until eloquent white matter tracts are encountered, and then, the surgeon proceeds on the boundaries of the functional regions. Intraoperative seizures during mapping can be resolved by irrigating the cortex with ice-cold Ringer's or saline [71], and, in a patient under general anesthesia, a rapidly metabolizing anesthetic with antiepileptic properties like propofol can also be administered.

DES enjoys excellent spatial (5 mm) [56] and unparalleled temporal resolution (instantaneous) (Table 1). It is therefore the benchmark against which all the other non-invasive techniques are compared for their efficacy. Many large-scale studies have underlined the prowess of this technique [74, 78]. Indeed, today, DES is widely regarded as the "gold standard" for brain mapping [50] but its status as the gold standard remains under some degree of scrutiny [8]. Most of the criticism is focused on its deeply invasive nature. It requires a large area of the cortex to be exposed well beyond the surgical target so that surrounding eloquent cortex can be identified and preserved. Sanai et al. used a "negative mapping" strategy that allowed for minimal cortical exposure [71]. DES is very stressful for the patients and they may also get agitated by misconstruing careless utterances of the OR staff. DES combined with DTI has shown promising results at mapping of white matter tracts [4].

Intracarotid amobarbital or Wada test

The intracarotid amobarbital (amytal) test (IAT) is an invasive method often described as the gold standard test for determination of language dominance. For the test, a bolus of a short-acting anesthetic agent (usually amobarbital) is injected into the internal carotid artery to achieve transient inactivation of a hemisphere. Upon injection, an anesthesia lasting about 4 to 8 min is induced in the cerebral hemisphere whose ICA was injected. Once the contralateral hemiplegia sets in, the patient is subjected to a battery of neuropsychological tests that helps determine the language-dominant hemisphere. The Wada test is also used for predicting the postoperative memory status in patients of refractory medial temporal lobe epilepsy (MTLE).

The Wada test suffers from the drawbacks associated with an invasive procedure. Loddenkemper et al. reported complications in 10.9% of the cases of which the major complications were encephalopathy (7.2%) and seizures (1.2%) [47]. The hemiplegia and aphasia can be distressing to the patients. The test cannot be repeated at short intervals due to its invasive nature and long half-life of amobarbital. Efforts are being made to look for a viable alternative to amytal. Loddenkemper et al. compared amobarbital and methohexital, and found no difference in the determination of language and memory lateralization [46]. Since methohexital has a shorter half-life, repeated injections can be performed. But it is an epileptogenic barbiturate and induces briefer sedation than amytal.

Positron emission tomography

For PET imaging, a molecular probe (tracer) is injected into the subject. The tracer has a positron-emitting radioisotope (^{11}C, ^{13}N, ^{15}O, or ^{18}F). The positron emitted by the radioisotope collides with an electron and gets annihilated in an event that produces two gamma ray photons of 0.511 MeV each, which travel in opposite directions. It is these photons that

Fig. 1 Direct electrical stimulation (DES). DES is being performed by an OCS2 Ojemann cortical stimulator (Integra Lifesciences) on the frontal lobe of the cortex of a patient undergoing glioma resection in the OR

are detected by the scintillation detectors of a PET scanner to produce the image of the desired body region.

Brain activity can be gauged by measuring cerebral perfusion or cerebral glucose metabolism. Two compounds, 2-^{18}F-fluoro-2-deoxy-D-glucose (FDG) and $H_2{}^{15}O$, are prominently used as tracers. Since ^{18}FDG is an analog of glucose, it is transported into the cells and gets phosphorylated by hexokinase to ^{18}FDG-6-phosphate that keeps accumulating inside the cell [22]. Thus, the rate of uptake of ^{18}FDG gives us a fairly good idea of cerebral glucose metabolism. The FDG is administered intravenously, followed by a waiting period of at least 45 min before image acquisition [13]. The *European Association of Nuclear Medicine* recommends an interval of 60 min between FDG infusion and image acquisition [6]. The patient performs a task and the subsequent rise in FDG uptake is contrasted against FDG uptake under control conditions to map out areas of activity. To measure cerebral perfusion, $H_2{}^{15}O$ is used. Cerebral perfusion is first measured at rest (control) and then during task performance by the patient [36].

Because radiotracers bind to specific biomolecules, PET enjoys very high sensitivity [88]. This extreme sensitivity also leads to poor signal-to-noise ratio in FDG PET, and the difference between gliomas and surrounding normal brain tissue is not that appreciable [60]. To counter this limitation, ^{18}F-labeled amino acid tracers like ^{18}F-fluoroethyl-L-tyrosine (^{18}F-FET) and 3,4-dihydroxy-6-^{18}F-fluoro-L-phenylalanine (^{18}F-FDOPA) were developed. Dunet et al. have shown that 18F-FET is superior to ^{18}F-FDG at delineating the gliomas [19]. The spatial resolution of PET compares poorly with fMRI (4 against 1 mm, respectively), and it suffers from poor temporal resolution owing to the time taken for metabolic changes to take place [88]. Being an invasive technique, it cannot be repeated at short intervals and the use of radioactive tracers limits its use in certain age groups like children. FDG-PET imaging is an important tool for identification of epileptogenic foci, especially in patients with normal or discordant MRIs [90].

Table 1 Summary of different functional brain mapping techniques

Functional brain mapping techniques				
	Technique	Spatial resolution	Temporal resolution	Principle
Invasive	DES	5 mm [56]	Instantaneous	Electrical stimulation of cortex
	Wada	Hemisphere	Not applicable	Transient cerebral inactivation
	ECoG	< 10 mm [35]	< 1 ms [35]	Electrical recordings
Non-invasive	PET	~4 mm [88]	45 s [88]	Hemodynamic
	fMRI	1 mm [88]	~3 s [88]	Blood oxygen level-dependent signal
	MEG	2–3 mm [85]	1 ms [70]	Magnetic signals
	DTI	2.0–2.5 mm [92]	Not applicable	Water diffusion
	TMS	5–10 mm [76]	> 70 ms [7]	Magnetic stimulation
	EEG	7–10 mm [85]	2 ms [25]	Electrical recordings
	fNIRS	1 cm [10]	100 ms [10]	Absorption spectrum

Shown are the characteristics of different invasive and non-invasive brain mapping techniques

ms milliseconds

EEG and ECoG

EEG involves recording the electrical potentials of the brain with a grid of electrodes placed on the scalp. EEG produces different waveforms whose characteristics depend on the state of arousal and disease status of the brain. EEG is a quick, simple, cheap, and widely available technique. Since the electrodes are on the scalp, the electrical signals suffer attenuation due to scalp, skull, and dura.

Electrocorticography or ECoG involves detecting the electrical discharges of the cortex with electrodes placed directly on the cortex. Unlike DES, ECoG does not induce seizures though it can be used for electrical stimulation as well. ECoG is primarily used for the delineation of epileptogenic zones in patients with medically intractable epilepsy [91]. Interictal fast ripples (250–500 Hz) detected by ECoG serve as important indicators for epileptogenicity. A study showed that resection of FR cortical areas as identified by ECoG led to better postop seizure freedom [89]. Besides mapping epileptogenic foci, ECoG also has DES-like application in speech and motor mapping prior to epilepsy surgery which can help define the safe resection zones of epileptic foci in children, who are technically challenging to map intraoperatively [30]. ECoG is an invasive technique and its use prolongs the surgery. Both the techniques have excellent temporal resolution but the spatial resolution of ECoG is much better than EEG as it does not face the problem of attenuation and distortion of the signals due to intervening connective tissue of the scalp and skull (Table 1).

Functional magnetic resonance imaging

fMRI measures brain activity by recording concomitant changes in cerebral perfusion (neurovascular coupling). fMRI uses blood oxygenation level-dependent (BOLD) signals [55] to highlight areas of active neuronal activity. The BOLD signal arises out of the different magnetic properties of HbO (diamagnetic) and HbR (paramagnetic) [59]. The paramagnetic HbR increases the inhomogeneity in the magnetic field resulting in shortened T2 and diminished BOLD signal. But the BOLD signal increases during brain activation rather than decreasing because whenever the neuronal activity—hence the local oxygen consumption—increases the neurovascular coupling causes marked increase in the cerebral blood flow (CBF). The increase in CBF is disproportionate and quickly overwhelms the active regions with HbO [24]. This overcompensation leads to increase in the BOLD signal and the activated regions "light up" [48]. Other than blood oxygenation, BOLD signal also depends on cerebral blood volume and cerebral blood flow. The spatial resolution of fMRI is 1 mm and temporal resolution is 3 s [88].

fMRI scores over other "gold standard" technique; in that, it is non-invasive, safer, quicker, less distressing, and repeatable. It is safer for use in children. Since fMRI is derived from T2*-weighted imaging, it is quite susceptible to distortions and artifacts. Cardiac pumping and breathing movements introduce motion artifacts. Patient's head movements are the most frequent cause of poor fMRI images [43]. The BOLD signal gets distorted in the vicinity of some types of tumors. Proliferation of neovasculature leads to neurovascular uncoupling that may give false-negative results. fMRI poorly images regions of tissue-air interfaces like nasal and sinus airspaces in the orbitofontal cortex [15].

fMRI is now routinely used for language lateralization in patients of epilepsy surgery [68]. Many studies have shown high levels of concordance between fMRI and Wada test [66, 39]. This has led many authors to recommend fMRI as a replacement of Wada test [57]. Szaflarski et al. have published a guideline for the use of fMRI in the preoperative assessment of epilepsy patients [81]. Another major application of fMRI is the preoperative mapping of eloquent cortex [86]. For the mapping of language cortex, tasks like verb generation, picture naming, and grammatical judgment are used [83]. For motor mapping, a finger-tapping task is used, and if the patient has mild to severe hand paresis, then hand clenching is sufficient [80]. fMRI has been validated against DES with high levels of concordance [49].

Anisotropic diffusion tensor imaging

Diffusion tensor imaging (DTI) is the only technique that creates in vivo images of white matter tracts. MRI is first used to record the diffusion of water molecules in the neural tissue. Water diffusion is same in all directions in gray matter and CSF, hence *isotropic*, while in the white matter, unimpeded diffusion takes place parallel to the axonal tracts but not in the direction perpendicular to them [61], hence *anisotropic*. The diffusion tensor is the simplest tool that allows us to quantify this anisotropic diffusion. The diffusion tensor is a 3D ellipsoid figure whose longest axis is in the direction of maximum diffusion. This 3D ellipsoid can be physically defined by six properties: the length of the longest, middle, and shortest axes (called eigenvalues, $\lambda 1$, $\lambda 2$, and $\lambda 3$) and their orientations (called eigenvectors v1, v2, and v3). Once a diffusion tensor gets defined, it can be used to create an image of the fiber tracts with the eigenvectors v1 acting as its direction. Anisotropy was earlier attributed to myelin, as it is unique to the white matter, but it was found that it is the axonal membrane that is primarily responsible for this anisotropy [3].

DTI is primarily used to visualize, on MRI subcortical networks and tracts, for which it has a spatial resolution of 2.0–2.5 mm [92] (Table 1). Examples of tracts that can be visualized by DTI include the corticospinal tracts, optic radiations, and language pathways. DTI of the corticospinal tracts is valuable in preoperative planning as well as postoperative followup as it helps in determining the preoperative involvement of the corticospinal tracts which helps in predicting and gauging the postoperative motor deficits [44]. DTI of the optic radiations offers a non-invasive and highly accurate modality to track the fibers in Meyer's loop. The tracking of the optic radiations in Meyer's loop by DTI has been shown to have great concordance with anatomical dissections [75]. DTI has also been valuable in the visualization of white matter tracts integral to the processing of language, such as (1) the arcuate fasciculus and superior longitudinal fasciculus, which run longitudinally within each cerebral hemisphere and connect frontal cortex with postrolandic areas, the temporal and inferior parietal lobes, respectively, and (2) the inferior longitudinal fasciculus (ILF) and inferior frontal-occipital fasciculus (IFOF), which are long intrahemispheric association fibers that extend along the length of the temporal lobe. Negwer et al. used DTI to assess surgery related aphasia and correlated it with injury to these subcortical tracts [53]. A study comparing diffusion tensor imaging with DES of cortex for language mapping found a high correspondence between the language tracts outlined by either methods [45]. These tracts are just examples of the tracts that DTI can visualize, as Nowinski et al. imaged 40 major tracts of white matter using DTI [54]. Aside from the role of DTI in visualizing these tracts, DTI also plays other roles of value for neurosurgeons. DTI is able to accurately differentiate abscesses from necrotic glioblastomas and cystic metastases, which is difficult to do with routine MR imaging [84]. Choudhri et al. have used DTI on pediatric patients of intramedullary spinal cord neoplasms [11] to achieve gross total resection.

The major drawback of DTI is that the images it constructs are not based on direct visualization of white matter tracts but on the measurement of diffusion of water molecules. Lesions like brain tumors can influence the diffusion properties, thus significantly changing the apparent anatomy of fiber tracts. Furthermore, DTI cannot account for the brain shift that may occur intraoperatively as initial tumor resection and resolution of edema causes sinking of the cortex relative to the preoperative MRI. This can be overcome by using intraoperative DTI [12, 87], intraoperative ultrasonography [20], intraoperative MRI [40], or augmented reality [31]. In addition, depending on the algorithm, deterministic or probabilistic [14], DTI results can vary. Feigl et al. tested different DTI fiber-tracking programs and found that the anatomical information differed significantly [23]. DTI also suffers from lack of standardization. A well-rounded discussion on the drawbacks of DTI can be found here [17].

The combination of fMRI with DTI has been investigated as a potentially more accurate guide because it maps eloquent cortex as well as the associated white matter tracts. The activated areas imaged by fMRI serve as seed regions for white matter tractography by the DTI [41, 73]. This allows for a more accurate and holistic mapping.

Magnetoencephalography

Magnetoencephalography (MEG) measures magnetic signals produced by the cortical neurons to map brain function. The ionic currents, especially postsynaptic currents of pyramidal neurons, induce a magnetic field that can be detected extracranially by biomagnetometers. These extracranial magnetic fields are extremely weak and are measured in femtoteslas (10^{-15}). The cortical activity produces a magnetic field in the range of 10 to 100 fT. This field is 10^9 times weaker than earth's magnetic field (25–65 μT). To enable biomagnetometers to detect such feeble magnetic fields, they are coupled with the most sensitive magnetic field detectors presently available, superconducting quantum interference devices (SQUIDs). SQUIDs use superconductors maintained in liquid helium to detect the extremely weak magnetic fields [34]. As superconductors have practically a resistance of 0 Ohm, magnetic fields even on the scale of femtoteslas induce an electric current within them. Since the amplitude of the induced current is directly proportional to the peak magnetic strength, the current's magnitude gives us the magnetic field's strength. The neuromagnetic fields are recorded by placing the patient's head under a helmet-shaped array of numerous (> 100) SQUID devices. The SQUID does not come in physical contact with the scalp.

The primary neurosurgical application of MEG is preoperative localization of epileptogenic foci. Many authors reported excellent utility of MEG in epilepsy patients [21, 32, 85]. Papanicolaou et al. and Doss et al. found a concordance of 87 and 86%, respectively, between results of hemispheric dominance obtained from Wada test and MEG [58, 16].

Though EEG closely matches its temporal resolution (< 1 ms) [70], MEG enjoys better spatial resolution (2–3 mm) [85] (Table 1). Unlike the electrical signal that gets attenuated by scalp, skull, dura, and other intervening tissues between the probe and cortex, the magnetic signal is unaffected by these factors. Since MEG device does not come in physical contact with the patient's scalp, it is mostly immune to artifacts arising out of muscle or eye movement. MEG has a better signal-to-noise ratio but is also highly susceptible to stray magnetic fields in the environment like the earth's magnetic field. A detailed review of MEG can be found here [2].

Transcranial magnetic stimulation

TMS is fundamentally the inverse of MEG. The TMS setup consists of an electromagnetic coil through which a current of high magnitude is passed in brief pulses. This generates a fluctuating magnetic field that induces an electric current near the coil. When the coil is placed close to the skull, the electric current evokes motor responses that can be detected by EMG. Depending on the area of interest, the coil can be moved over the skull to induce an electric current at a desired spot in the cortex. Figure-of-eight coils are usually used for a better focusing [69].

TMS coupled with neuronavigational devices is called navigational TMS (nTMS). Motor cortex mapping by nTMS has been shown to be nearly as good as DES and superior to fMRI and MEG [42]. Sollmann et al. found that language mapping by nTMS matched that of DES and was more accurate than fMRI [77]. In fact, it has been shown that accurate anatomical localization and safe resection can be performed with rTMS and DTI in patients who do not qualify for awake neurosurgery [37]. Frey et al. have shown that motor cortex mapping by nTMS considerably improves treatment outcome [26].

A unique advantage of TMS is that it is the only non-invasive technique capable of inducing transient lesions in the cortex. rTMS is used to produce speech arrest to map out language processing areas [77]. Rogic et al. have developed a protocol for inducing transient lesions in Broca's area by rTMS [67]. A major disadvantage of TMS other than poor spatial resolution is that repetitive TMS is known to cause seizures, and on rare occasions, syncope [69].

Functional near-infrared spectroscopy

Functional near-infrared spectroscopy (fNIRS) is a non-invasive method of brain mapping that uses light in the NIR range to measure brain activity. Jobsis first showed in 1977 that light in NIR range could be used to non-invasively detect the level of cerebral oxygen saturation. Most tissues in the human body show high transparency to light in the NIR range (650–900 nm). But there are some chromophores in the tissues that absorb light within NIR range, like hemoglobin, cytochrome oxidase, and bilirubin. The absorption spectrum of hemoglobin and cytochrome oxidase in their oxygenated state is quite different from their deoxygenated state. Just like fMRI exploits the differences in the magnetic properties of oxyhemoglobin (HbO) and deoxyhemoglobin (HbR), fNIRS exploits the differences in the optical properties of HbO and HbR. Due to neurovascular coupling, an area of enhanced neuronal activation shows increased HbO, depleted HbR, and increased total hemoglobin (HbT). By measuring the relative concentrations of HbO, HbR, and HbT, activated brain regions can be highlighted. When NIR light is incident on the scalp, it follows a banana-shaped profile from its entry to exit at scalp and can be detected using photodetectors.

fNIRS is being used for presurgical evaluation of language functions [28], but it has not yet seen widespread applications in neurosurgery. High safety, low cost, portability, immunity to motion artifacts, and better temporal resolution than fMRI are some of its advantages. Its temporal resolution is 100 ms but suffers from poor spatial resolution (1 cm) [10] into the cortex [28]. A major disadvantage is lack of standardizations and validation against other established techniques. fNIRS has been suggested as an alternative to Wada test [29].

Conclusion

The role of functional brain mapping has become increasingly crucial to neurosurgical oncology in light of numerous studies correlating extent of resection with patient survival for gliomas [5, 9] (Table 1). Though the invasive techniques are still the gold standard, many non-invasive techniques have been improved to augment them and, in selected cases, offer an alternative. Combining techniques may combine their advantages and reduce the impact of any associated limitations in fidelity. Some examples of combinations to have shown promising results are fMRI used with DTI, fMRI with nTMS [38], MRI guided by combined EEG-MEG [1], and PET combined with MEG [64]. Functional brain mapping techniques can also be integrated with standard surgical tools. For example, Raabe et al. have described a novel technique where they integrated the mapping probe at the tip of a new suction device. The logic behind this was that the suction device will be in contact with the tissue where the resection is performed, thus performing dynamic mapping as well [62]. Validation and integration of new and different techniques is bound to improve our ability to map more accurately, thereby providing the desired outcome of maximal safe surgical resection.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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