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IMAGING (L MECHTLER, SECTION EDITOR)

Imaging of MELAS

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Abstract Mitochondrial diseases are multisystem disorders that frequently involve the central nervous system. The clinical presentation of these disorders may be challenging to differentiate from cerebrovascular disorders. Various imaging techniques are now available that provide a wide range of imaging modalities during initial clinical evaluation and throughout the disease course. Recent technological advancements have introduced advanced neuroimaging modalities that provide detailed information of metabolic disorders at the tissue level. Imaging findings, though diverse, usually have characteristic features that support differentiating these disorders from vascular syndromes. This article provides an overview of various neuroimaging modalities available along with the advent of new imaging techniques being utilized in these disorders.

Keywords MELAS · Mitochondrial myopathy · MRI · Stroke-like episodes

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Introduction

Mitochondrial myopathy, encephalopathy with lactic acidosis, and stroke-like episodes (MELAS) is a maternally inherited, mitochondrial metabolic disorder, usually affecting people under 40 years of age in a diffuse multisystemic fashion [1]. The strong dependence of the central nervous system on oxidative metabolism predisposes to injury from mitochondrial disorders [2]. The defect in the respiratory chain and oxidative phosphorylation remains the principal mechanism that leads to stroke-like episodes (SLEs), migraine headaches, and seizures [3]. MELAS is usually characterized by (a) SLEs before the age of 40 years, (b) encephalopathy characterized by seizures and dementia, and (c) lactic acidosis, ragged-red fibers, or both. SLEs are the most distinguished manifestations of this disorder, while there has been recent emphasis regarding the genetic heterogeneity and phenotypic variation [4].

Imaging plays a pivotal role in diagnostic evaluation of metabolic disorders and helps physicians to differentiate pertinent imaging abnormalities from other etiologies. Neuroimaging supplements the clinical examination to evaluate the location of various lesions, especially ischemic, based on the arterial territory involved [5]. Neuroimaging in MELAS has been studied with fervent interest related to the various characteristics and location of stroke-like lesions (SLLs). SLLs occur in majority of MELAS patients and tend to correlate with focal neurological symptoms, particularly SLEs [6]. Yoshida et al. showed improvement in clinical symptoms and imaging of few MELAS patients within few weeks, reflecting different pathophysiology of these lesions when compared with cerebral ischemia [7••]. Gradual onset and less intense symptoms usually differentiate MELAS from other ischemic etiologies [8••].

Lesions in MELAS are usually located in the temporal, parietal, or occipital lobes. These lesions do not follow any vascular territories when compared to the distribution of ischemic lesions [9–12]. SLLs in MELAS demonstrate T2 hyperintensity with a predilection for the parietal and occipital cortices. Subcortical deep brain structures including basal ganglia and brainstem are often affected. We compiled an extensive review of the imaging modalities used in MELAS patients to date and discuss the expanding experience with the neuroimaging features of MELAS.

Clinical Aspects of MELAS

MELAS usually present with stroke-like episodes that could confound the diagnosis with cerebral ischemia. It is frequently associated with migraine headaches, seizures, hearing loss, growth retardation, and neuropsychiatric dysfunction that tend to steer the diagnosis away from ischemia [13]. Incidence and recurrence rates could potentially differentiate metabolic disorders from cerebral ischemic events. High recurrence rate in ischemic stroke is well established that warrants antithrombotic therapy [14], while in comparison, similar data is scarce in the literature regarding metabolic disorders. Few authors studied the pattern of SLLs in association with seizure episodes and stressed over the use of antiepileptic drugs for effective seizure control to prevent the development and recurrence of SLLs in MELAS [15]. Headaches are frequently migrainous in nature and could either develop without SLLs or present as an initial symptom with SLEs. Pain could be associated with visual field defects and hallucinations and usually are located in retro-orbital and temporal regions [16]. Migraine headaches have been found to be well associated with stroke-related hereditary disorders including MELAS, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and hereditary hemorrhagic telangiectasia [17]. Consideration of these clinical aspects during initial evaluation supports clinicians to differentiate stroke-like symptoms from ischemic pathology.

Imaging Techniques Used in MELAS

Various imaging techniques have been developed to discern the characteristics and location of lesions involved in mitochondrial disorders. Conventional imaging techniques have been the key imaging techniques for decades, while several other imaging approaches have recently emerged that provide new dimensions in the evaluation of such metabolic lesions (Fig. 1).

Conventional Imaging Techniques

Conventional imaging techniques have been used in MELAS for several decades. These techniques include computed tomography (CT), magnetic resonance imaging (MRI), and cerebral angiography. CT and MR imaging techniques demonstrate various spectrums of lesions and morphologies seen in mitochondrial disorders, while cerebral angiography tends to assess the vessel patency and differentiate it from cerebral ischemic lesions.

Computed Tomography

CT has been used for decades as an initial imaging modality due to its widespread availability during acute SLEs and seizures in MELAS patients [18]. Bilateral basal ganglia and thalamic calcifications on CT are common findings [19, 20]. CT in MELAS reveals cortical areas of hypodensity usually located in one or both occipital poles and not confined to single vascular territory, differentiating these lesions from cerebral ischemia [21]. MRI remains the main imaging technique to evaluate metabolic disorders due to superior spatial resolution and characterization across numerous imaging sequences [22]. Imaging findings are usually diverse, constituting focal T2 hyperintense lesions with a predilection for the cerebral cortex rather than underlying white matter. Typical lesions in MELAS are not limited to arterial territories, and serial imaging has shown these lesions to migrate over time [18]. SLLs are cortical in location commonly affecting occipital and parietal lobes, although deep grey matter such as the thalamus can also be affected [23]. Few studies have also described bilateral symmetric abnormalities in the deep grey matter and brainstem [24], diffuse white matter abnormalities with cerebral and cerebellar atrophy [25]. The increased signal intensity on T2-weighted sequence continues to evolve over time with subsequent development of gliosis and atrophy.

Magnetic Resonance Imaging

(A) Diffusion-Weighted Imaging

Diffusion-weighted imaging (DWI) sequence has been used for decades to diagnose ischemic pathology. This technique has also proven its worth to diagnose other non-ischemic lesions, including mitochondrial disorders that could mimic cerebral ischemia [26]. DWI shows high signal during acute phase with changes occurring within minutes of cerebral insult. There have been multiple reports regarding ADC signal pertaining to the presence of vasogenic or cytotoxic edema in MELAS patients [27]. Yoneda et al. stated that the signal on ADC maps is either similar or less reduced when compared to DWI, supporting vasogenic edema as the likely pathophysiology in SLLs of MELAS [28]. However, other authors challenged these findings as they reported decreased ADC signal consistent with cytotoxic edema, especially in the acute phase of SLEs [27, 29, 30]. Recent studies have shown that the development of

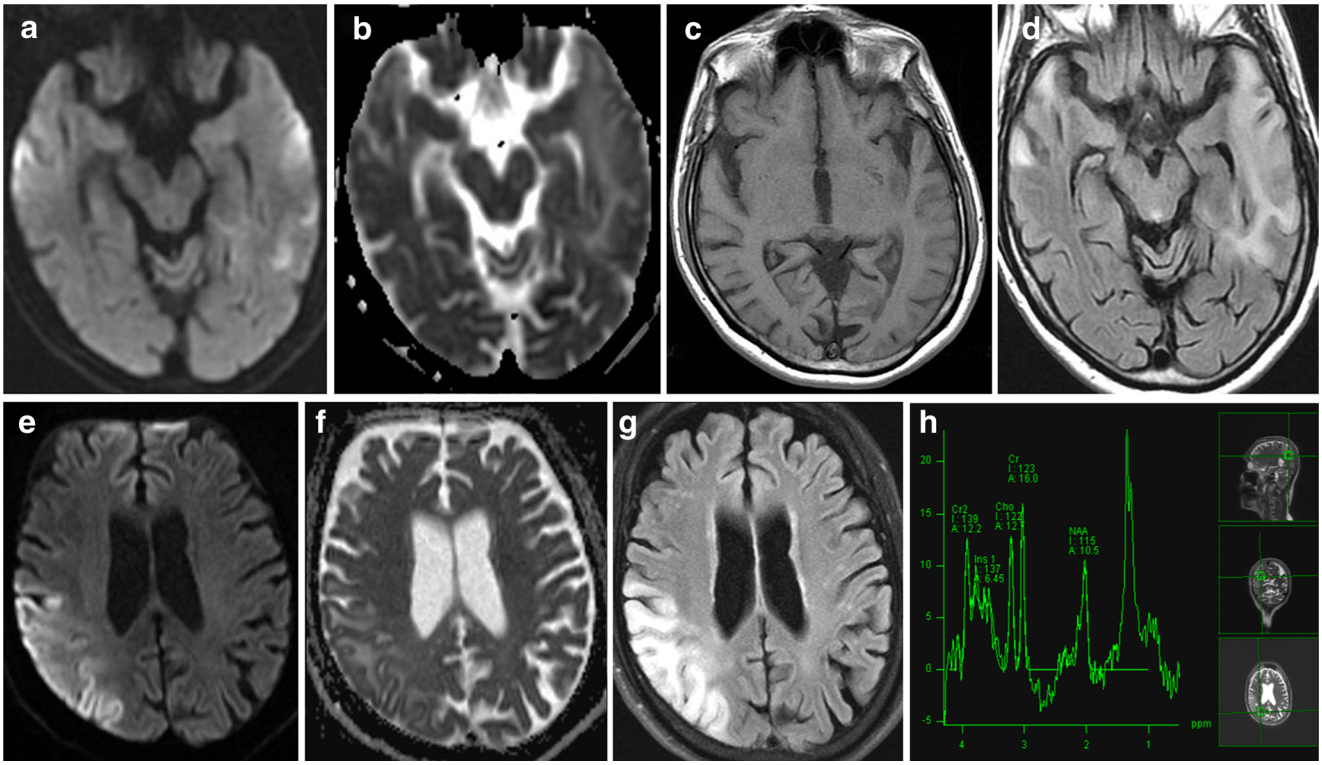

Fig. 1 Fifty-two-year-old male presented with progressive cognitive decline and paraphasic errors. Initial MRI of the brain shows that **a** diffusion-weighted imaging (DWI) sequence shows hyperintensities in gyriform pattern in the insular and bitemporal cortices. **b** Apparent diffusion coefficient (ADC) sequence shows iso/hyperintensities corresponding to DWI lesions. **c** T1-weighted image shows pronounced cortical atrophy in temporal and occipital cortices. **d** Fluid attenuated inversion recovery (FLAIR) sequence showing bitemporal hyperintensities, likely vasogenic edema. His initial symptoms improved, but patient presented 3 months later with involuntary movement of his left arm. Repeat MRI brain showed new migrating lesions along with old lesions from prior scan. **e** DWI shows gyriform diffusion hyperintensity in right parietal lobe. **f** ADC sequence showing iso/hyperintense corresponding to DWI lesion. **g** FLAIR sequence with hyperintensity in right parietal region. **h** MR spectroscopy shows decreased NAA/Cr ratio and a large lactate peak suggestive of MELAS

cytotoxic edema as represented by decreased ADC is likely due to initial neuronal energy insufficiency [31]. Subsequent development of extracellular edema in surrounding region leads to increased ADC signal. This temporal overlap of initial cytotoxic edema in acute phase and vasogenic edema in subacute to chronic phase of lesions is likely a plausible explanation [32]. The consensus in the literature still remains unclear and warrants clarification in future studies.

(B) Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is a non-invasive method to assess chemical information from the brain tissue in various metabolic disorders. It especially provides information of various, in vivo, brain metabolites. MRS detects a wide array of metabolites including *N*-acetyl aspartate (NAA), creatine, choline, myoinositol, glutamate, glucose, taurine, scyllo-inositol, and lactate. Proton magnetic resonance spectroscopic imaging (H-MRSI) is a newer technique that has been widely used in the diagnosis of metabolic disorders and to determine the disease severity [18].

Decrease in NAA on MRS with increase in lactate peak has been shown to be useful in diagnosing patients with MELAS [33–35], though these changes are not specific and could also be found in other metabolic disorders [9]. Lactate peaks on MRS usually reflect anaerobic metabolism, though it has been reported to occur even in normal-appearing brain [36, 37]. Lactate peaks tend to vary based on different stages of disease process including acute, subacute, or chronic phase. Detection of lactate signals also rely over type of mitochondrial disease, concentration of lactate, or location of involved cerebral tissue. Interestingly, lactate signals could only be detected in normal CSF in approximately one third of patients [38].

MRS has been used to ascertain the disease course of MELAS and assess disease progression. Lactate peaks on H-MRSI have also been associated with increased disease severity and reduced survival. Elevated lactate in affected region of brain tends to gradually resolve as these lesions evolve further into cerebral atrophy [39, 40]. Recent studies have been promising using H-MRS to identify

biomarkers and progression to full spectrum of MELAS disease in patients with the m.3243A>G mutation [41].

(C) Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is a fairly new imaging technique that has been used for research purposes to investigate the integrity of white matter. DTI tends to detect damage of white matter tracts that could be potentially missed on conventional MR imaging techniques. Virtanen et al. studied structural changes in white matter tracts using DTI in MELAS patients with m.3243A>G mutation [42]. They observed diffuse microstructural damage of white matter tracts with loss of directional organization and reduced brain volumes.

Cerebral Angiography

Cerebral angiography demonstrates the patency of vessels and has been effective in various ischemic pathologies. Evaluation of vessel patency has been seldom used in metabolic disorders to differentiate SLEs in MELAS from ischemic stroke due to large vessel occlusions. CT angiography in MELAS often shows patent vessels in affected areas and rarely is associated with vasodilation. Few case reports described occlusions in large cerebral vessels, while all of these studies were performed weeks after SLEs [43, 44]. Yeh et al. found patent vessels during acute stage of SLEs in MELAS patient [8••]. A few other studies confirmed these findings of dilated cortical vessels with early venous filling, likely due to vasodilation [45]. These findings corroborate with hyperemic changes in SLLs during hyperacute and acute stages.

Cerebral Perfusion Imaging Techniques

There have been numerous imaging techniques to assess brain function that provide insight into clinical practice of using and assessing cerebral perfusion imaging. Some of these techniques have been used to study cerebral blood flow (CBF) and tissue metabolism in various metabolic disorders such as MELAS.

Positron Emission Tomography

Positron emission tomography (PET) imaging is commonly used to assess CBF and tissue metabolism in diseased states like malignancy, metabolic disorders, or infectious etiologies. The technique involves measuring the concentration of tracer uptake that is comparable to tissue metabolic activity. Various exogenous contrast agents have been used as radiotracers, while fluorodeoxyglucose (FDG) remains as the most commonly used tracer. PET imaging helps to assess glucose utilization, regional cerebral blood flow, and redox energy states. It has been used as one of the imaging modalities in MELAS patients to elucidate the pathogenesis of acute SLLs. Molnar et al. used FDG-PET and showed impaired cerebral glucose uptake in temporal and parietal lobes of MELAS patients [46]. PET scans have been used to study cerebral oxygen and glucose metabolism along with cerebral blood flow in MELAS. Few studies have shown initial increase in blood flow and glucose metabolism as a response to oxidative stress [47], while subsequent subacute phase comprised of reduced blood flow and glucose metabolism even with oxidative stress. This is usually followed by a chronic phase of decreased blood flow and glucose use without any evidence of oxidative stress likely due to neuronal death [23].

Single-Photon Emission Computed Tomography

Single-photon emission computed tomography (SPECT) is a nuclear medicine imaging technique that involves delivery of gamma-emitting radioisotopes. These radioisotopes are usually attached to specific ligands resulting in radioligand that are delivered via bloodstream to various tissues. Emissions from the radionuclide bound to cerebral tissue of interest are finally captured using a gamma camera. SPECT imaging is used to assess perfusion status during various phases in MELAS, especially around onset of SLEs or SLLs on imaging. The acute phase of SLEs is characterized by hyperperfusion that is gradually followed by a chronic stage of hypoperfusion within several months [48, 49]. This is in agreement with Ito et al. who showed hyperperfusion during hyperacute stage of SLLs [11]. In contrast, few authors discovered decrease in cerebral blood flow as a prominent feature in hyperacute stage of SLEs [50, 51]. Nishioka et al. further described perfusion changes in SLLs as hypoperfusion in hyperacute stage, hyperperfusion in acute stage followed by hypoperfusion in chronic stage of these lesions [48]. This hypoperfusion was likely related to decreased regional CBF or due to affected brain tissue in MELAS. They further described that altered hemodynamics ordinarily persists through acute and interictal phases of SLEs, while tends to worsen with disease progression. Yeh et al. stated that SLLs in MELAS fail to uptake tracer with hyperperfused background, while regions around SLLs did show increased uptake as compared to rest of the brain [8••].

Arterial Spin Labeling

Arterial spin labeling (ASL) is a non-invasive MRI-based technique that has provided new dimensions in evaluation of cerebral perfusion. It involves magnetic labeling of the spins of water molecules present in endogenous blood and extracts a final perfusion image following multitude of automated image processing. There have been various reports supporting both hypoperfusion and hyperperfusion to be evident in affected areas of MELAS patient [52]. Regional cerebral perfusion changes have been studied with great interest recently using ASL perfusion techniques. MRI sequences designed to study

motion of blood flow are widely available in clinical practice. These sequences have been used in MELAS patients to show increased CBF in newly developed lesions [31, 53]. Ikawa et al. found perfusion changes in dormant SLLs using ASL perfusion MRI [54]. They also noted regional hyperperfusion lasting for more than 3 months before evidence of any clinical onset of SLEs in MELAS patients.

Cerebral perfusion has been studied with a keen interest in MELAS patients, especially during ischemic events. Dynamic susceptibility contrast-enhanced MRI (DSC-MRI) has been used to evaluate cerebral blood volume and blood flow. Conventional imaging techniques such as DSC-MRI usually fail to detect increased perfusion in the preclinical period, while gradually transforming into acute SLLs on MRI. Early use of ASL perfusion imaging in MELAS patients might be able to predict emergence of SLEs.

Novel Imaging Techniques

Conventional imaging including CT and MR sequences provides structural data of lesions in MELAS, while more advanced imaging techniques have emerged that render detailed functional and metabolic information, in addition [55, 56]. These new imaging techniques including oxygen extraction fraction, transcranial doppler and magnetoencephalography have given an additional perspective to these metabolic disorders.

Oxygen Extraction Fraction

Oxygen extraction fraction (OEF) provides an insight into oxygen extraction from the blood and tissue metabolism. It has been found to be an effective hemodynamic measure during episodes of cerebral ischemia [57•]. Oxygen metabolism especially in the affected cerebral region of MELAS patient tends to be severely reduced. Reduced oxygen extraction rates have been found with preserved cerebral blood flow during acute episodes of MELAS, especially in posterior cortex [58]. MR OEF imaging has been used in MELAS showing significant reduction in oxygen extraction in SLLs along with unaffected brain regions. Yu et al. found quantitative changes in OEF during different phases of SLEs in MELAS patients [59]. Severe reduction of OEF in SLLs during acute and subacute phases usually indicates impaired mitochondrial function in affected brain tissue [57•]. The severity of OEF reduction has been shown to vary during acute SLEs of MELAS for unclear reason.

Trancranial Doppler

Trancranial Doppler (TCD) is a non-invasive method to assess flow velocities in the major arteries of circle of willis [60]. It has been used in various clinical scenarios including presence of vasospasm in subarachnoid hemorrhage, detection of spontaneous microemboli, and assessment of cerebrovascular reserve in steno-occlusive lesions. Kudoka et al. studied the cerebrovascular reserve using TCD in patients with metabolic disorders. They showed impaired cerebrovascular CO_2 reactivity of patient with MELAS, while TCD was found to be an effective method to evaluate hemodynamics in such patients [61].

Magnetoencephalography

Magnetoencephalography (MEG) has been used to study intracellular electric current flow in the brain tissue that provides data at neuronal level. It involves functional brain mapping of primary somatosensory cortex using somatosensory evoked potentials (SSEPs) and has been widely accepted for source localization in clinical practice [62]. Rossini et al. investigated MELAS patients for early and late responses of SSEP after monohemispheric lesions and speculated that the later response tends to be preserved due to synaptic relays as compared to earlier responses [63]. Various authors have found independent sources that affect early and late responses in MEG, and late responses are likely effective in detecting early signs of neurological recovery [64].

Characteristic Imaging Findings in MELAS

Brain imaging changes have been described largely with the context of SLEs in the literature. These changes typically involve SLLs, deep grey matter (DGM) changes, white matter (WM) changes, and chronic changes involving cerebral atrophy.

(A) Stroke-Like Lesions

Stroke-like lesions refer to diffuse infarct-like areas usually located in cerebral cortex that characteristically does not follow usual pattern of vascular distribution [11]. Various studies based on imaging have mainly focused over these lesions in MELAS patients till date [65••]. These lesions could be present in any cerebral location but tend to have a predilection for parietal, temporal, and occipital lobes [19]. Of much interest, ADC signal changes in SLLs continue to be the topic of interest and remain disputed in the literature [27].

(B) Deep Grey Matter Changes

Deep grey matter (DGM) changes have been studied for decades with conventional imaging studies in MELAS patients. These changes are mainly subcortical involving caudate nuclei, globus pallidus, putamen, pulvinar of thalamus, and dentate nucleus of cerebellum. Tschampa et al. reported that majority of m.3243A>G mutation carriers with DGM changes did not experience SLEs or corresponding SLLs. Interestingly, half of their patients

who reported SLEs were found to have similar but less conspicuous DGM changes [65••]. Microcalcifications in vessel walls along with sidero-calcific deposits have been shown to occur along with DGM changes in the putamen and globus pallidus [66]. Susceptibility-weighted imaging along with gradient-echo T2-weighted imaging has been utilized in MELAS patients to demonstrate mineral (calcium or iron) deposition in basal ganglia [67].

(C) White Matter Changes

Changes in the white matter tracts have not been described in great detail in the literature. These changes are usually more prevalent in MELAS patients with SLEs as compared to individuals with m.3243A>G mutation lacking SLEs.

(D) Brain Atrophy

There have been many articles in the literature pertaining to pathology of SLLs in MELAS patients. Betts et al. showed that chronic SLLs usually comprise of extensive neuronal loss, microvacuole formation, and gliosis [68]. SLLs have been shown to progress and chronically evolve into atrophic regions on serial brain imaging. Tschampa et al. reviewed imaging of MELAS patients with m.3243A>G mutation and showed the presence of brain atrophy in majority of their study population [65••]. They found the atrophy especially in cerebellum that is well published in the previous literature [42].

Differential Diagnosis

Patients with MELAS can present with varied clinical and radiological manifestations that could pose diagnostic challenges. Various clinical manifestations in these patients include seizures, headaches, visual loss, neuropsychiatric dysfunction, gastrointestinal (GI), and cardiac rhythm abnormalities. According to previous literature, MELAS patients presenting with similar symptoms have been misdiagnosed as epilepsy, cerebral infarction, encephalitis, myasthenia gravis, GI, or cardiac diseases [18]. Similarly, discrete neuroimaging findings could pose difficulties, especially in hyperacute and acute phases. However, certain radiological mimickers in MELAS patients that need to be ruled out include herpes encephalitis, Creutzfeld-Jacob disease, gliomatosis cerebri [69], and lymphoma. Emergence of various neuroimaging modalities has been a boon for physicians in differentiating such lesions with certainty.

Conclusions

MELAS is a rare and complex neurodegenerative disorder with characteristic SLEs and SLLs rendering the evaluation and diagnosis a bit arduous at times. Clinical and radiological findings may pose a challenge to initially differentiate from cerebral ischemia. Neuroimaging supplements the clinical history and further delineates stroke-like lesions from ischemic stroke. Typical SLLs in MELAS are not confined to single vascular territories, have a tendency to migrate over time, involve cortical locations with sparing of deep white matter, and evolve gradually into atrophic regions over time. MRI along with its various sequences especially perfusion and spectroscopy is the most preferred imaging modality in MELAS that supplement clinical diagnosis and tend to narrow the myriad of differentials. Novel imaging techniques have emerged that provide supplementary details of involved cerebral tissue, and hence the prognosis in these patients. Future research studies are expected to involve multimodal imaging aspects focusing over prognosis in these patients in greater detail.

Compliance with Ethical Standards

Conflict of Interest Konark Malhotra declares no conflict of interest.
David S. Liebeskind declares NIH-NINDS grant support and being a consultant for Imaging Core Lab for Stryker and Medtronic.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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