Prospects of Photo- and Thermoacoustic Imaging in Neurosurgery

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The evolution of neurosurgery has been, and continues to be, closely associated with innovations in technology. Modern neurosurgery is wed to imaging technology and the future promises even more dependence on anatomic and, perhaps more importantly, functional imaging. The photoacoustic phenomenon was described nearly 140 yr ago; however, biomedical applications for this technology have only recently received significant attention. Light-based photoacoustic and microwave-based thermoacoustic technologies represent novel biomedical imaging modalities with broad application potential within and beyond neurosurgery. These technologies offer excellent imaging resolution while generally considered safer, more portable, versatile, and convenient than current imaging technologies. In this review, we summarize the current state of knowledge regarding photoacoustic and thermoacoustic imaging and their potential impact on the field of neurosurgery.

KEY WORDS: Photoacoustics, Thermoacoustics, Theranostics, Functional imaging, Molecular imaging, Neurosurgical imaging

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Current imaging modalities have greatly enhanced the specificity and accuracy of neurosurgical diagnosis and treatment thus reducing morbidity and mortality.[1] However, there still exist limitations that prevent optimization of care. While magnetic resonance imaging (MRI) and x-ray computed tomography (XRCT) provide ever evolving volumes of information, they are costly to purchase, install, and maintain.[2,3] In addition, they are generally centralized, requiring transport of patients to the scanner vs being able to conveniently perform imaging in standard operating theatres, at the bedside, or in the clinic. Safety concerns also exist with the use of ionizing radiation and toxic exogenous contrast agents.[4] An ideal imaging modality would be inexpensive, portable, real time, high resolution with appropriate penetration depth and not require the use of ionizing radiation or toxic contrast agents. Although there is not yet a single brain imaging modality that meets all those criteria, recent advances have brightened the horizon. The photoacoustic phenomenon, first described by Alexander G. Bell in 1880, refers to the generation of acoustic waves from an object absorbing pulsed or intensity-modulated optical waves.[5,6] Light-based photoacoustic and microwave-based thermoacoustic hybrid imaging technologies combine high ultrasonic resolution with strong optical and radiofrequency contrast, respectively.[5,7,8] Photoacoustic technology has been demonstrated to provide real-time images via an ultrasound-detection system in a portable device. In this review, the current state of knowledge about photo- and thermoacoustic imaging is summarized focusing on technological advances, safety, limitations, and potential future applications in neurosurgery.

ABBREVIATIONS: AR, acoustic resolution; **cKRGDf,** cyclo(Lys-Arg-Gly-Asp-Phe); **HAuNS,** hollow gold nanosphere; **Hb,** hemoglobin; **fPAM,** functional PAM; **IVPA,** intravascular photoacoustic imaging; **MRI,** magnetic resonance imaging; **OCT,** optical coherence tomography; **OR,** optical resolution; **PACT,** photoacoustic computed tomography; **PAM,** photoacoustic microscopy; **PAT,** photoacoustic tomography; **PET,** positron emission tomography; **TAT,** thermoacoustic tomography; **XRCT,** x-ray computed tomography; **US,** ultrasound

TABLE 1. Comparison of Imaging Methods Used in Neurosurgery and Current Photo-/Thermoacoustic Imaging[8-12]

Modality	Imaging contrast	Penetration depth (mm)	Resolution (μm)	Ionizing radiation	High magnetic field	Potentially toxic intravascular contrast	Cost	Portability
US	US scattering	≤240	40-1000	No	No	No	Low	Yes
XRCT	X-ray absorption	Full body	200-300	Yes	No	Yes (iodine)	High	No
MRI[a]	Nuclear magnetic resonance	Full body	500-1500	No	Yes	Yes (gadolinium)	High	No
PET	Positron annihilation	Full body	4000-10 000	Yes	No	Yes (radioactive tracer)	High	No
PAT	Light absorption	≤70	0.2-800	No	No	No	Low	Yes
TAT	Microwave absorption	≤150	170-2200	No	No	No	Low	Yes

MRI , magnetic resonance imaging; PAT, photoacoustic tomography; PET, positron emission tomography; TAT, thermoacoustic tomography; US, ultrasound; XRCT, X-ray computed tomography.
[a]1.5T MRI.

CURRENT BRAIN IMAGING MODALITIES

Current imaging modalities (Table 1) provide insight into brain pathology, but neither XRCT, positron emission tomography (PET), MRI, nor ultrasound (US) alone has proven to be sufficient in providing rapid, low-cost, non-invasive, high-resolution, real-time brain imaging. XRCT, PET, and MRI are bulky, expensive, and involve either ionizing radiation, potentially toxic intravascular contrast or strong magnetic fields with long acquisition times.[8-12] These factors limit usage in patients with common pathologies such as renal failure or patients with metal foreign bodies or implanted devices. Moreover, these modalities currently are incapable of distinguishing microvasculature without a significant reduction in temporal resolution and exposure to ionizing radiation.[13] US is advantageous in that its scattering is 2 to 3 orders of magnitude weaker than optical scattering in biological tissues[14,15] which translates into high spatial resolution.[11] It can also be integrated into low-cost, fast, real-time, and portable systems.[16] Unfortunately, transcranial applications of US are limited by the attenuation and distortion of round-trip ultrasonic waves.[8] Even if the skull is absent, US currently is not effective when attempting to visualize the microvasculature or blood oxygenation because of its acoustic-impedance contrast.[17] Given that the basis of US imaging is the contrast from the acoustic mismatch between various types of tissues, its ability to discriminate different soft tissue structures that have close acoustic characteristics is limited.[18] Light-based ballistic (minimally scattered) imaging modalities such as confocal microscopy, 2-photon microscopy, and optical coherence tomography (OCT) have been introduced in the field of 3D imaging. These technologies provide excellent spatial resolution at the expense of penetration depth which does not exceed the optical diffusion limit (approximately 1 mm in the skin).[8,15,19] The other category of light-based imaging modalities is diffusive (multiscattered) imaging which includes diffuse optical tomography. This modality uses multiple scattered photons to surpass the ballistic imaging depth limitation, but offers poor spatial resolution.[19] OCT and US are also limited by speckling artifact.[8,20]

PRINCIPLES AND MODALITIES OF LIGHT-BASED PHOTOACOUSTIC AND MICROWAVE-BASED THERMOACOUSTIC IMAGING

Photo- and thermoacoustic imaging rely on ultrasound wave generation in the tissue in response to light or radiofrequency waves, respectively. These are highly scalable hybrid technologies combining the spatial resolution of US-based imaging with the contrast of light/microwave-based modalities for wide imaging applications from organelles to organs (Figure 1) (Table 2). Advantageously, given that endogenous chromophores like melanin and hemoglobin (Hb) have different light absorption spectra, they can be distinguished using different irradiation wavelengths.[18,21]

Photoacoustic Tomography

Photoacoustic tomography (PAT) involves detectable photoacoustic wave induction in the target tissue by a pulsed or intensity-modulated continuous-wave laser beam (Figure 1).[5] Unique photoacoustic signatures can be detected from in Vivo chromophores (Figure 2).[5,22] Two current implementations of PAT are photoacoustic microscopy (PAM) and photoacoustic computed tomography (PACT) (Figure 1).[5,12] These 2 implementations primarily differ based on their optical illumination and acoustic detection approaches.

PAM renders an image based on point by point detection and raster scanning.[23] Optical resolution (OR)-PAM primarily focuses on capillary-level imaging and offers high spatial resolution at the expense of depth, staying within the optical diffusion limit (Figure 1).[24-27] As OR-PAM technology is rapidly advancing, several high-speed systems including

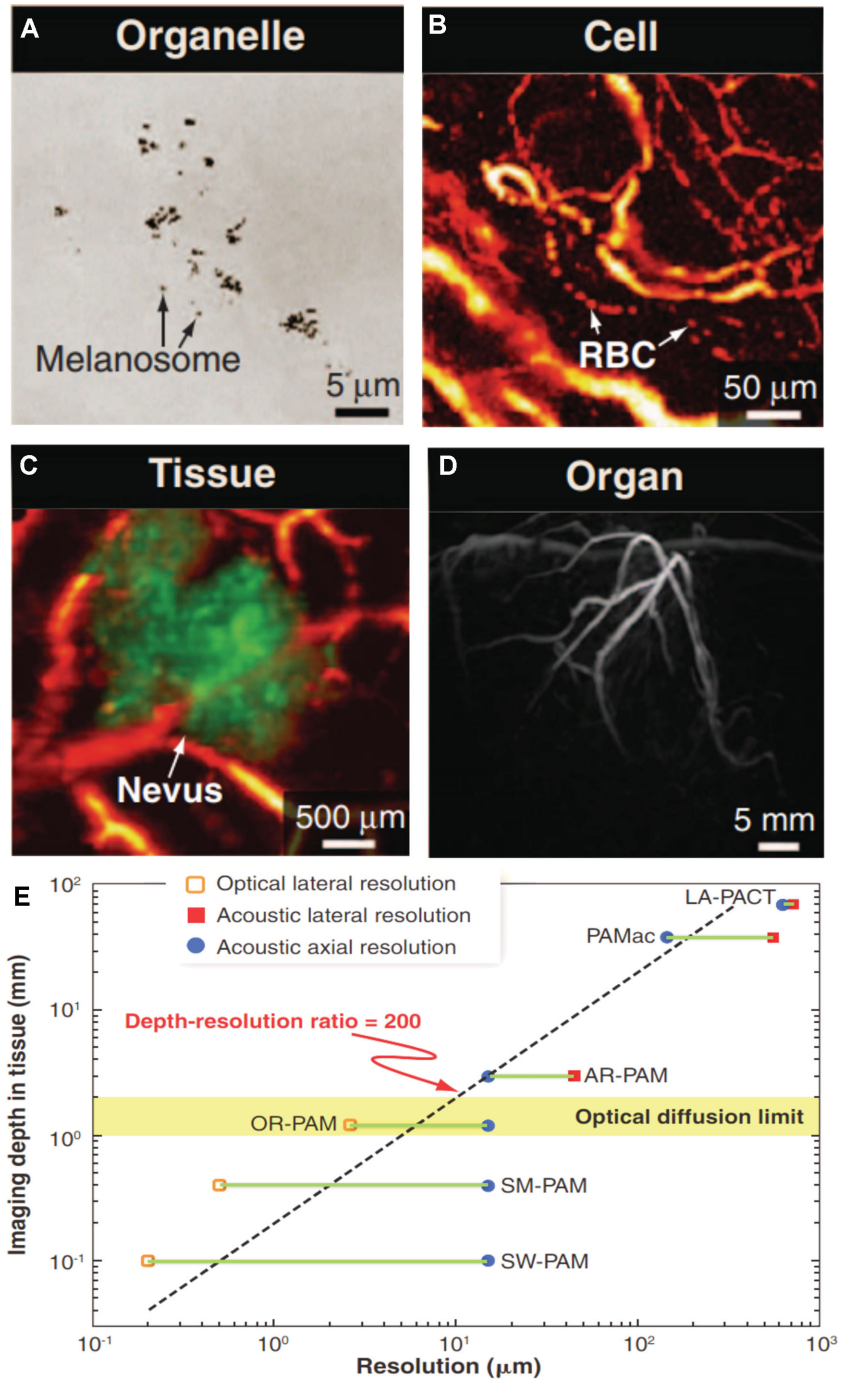

FIGURE 1. *Multiscale photoacoustic tomography (PAT) of organelles, cells, tissues, and organs in Vivo.* **A**, *Subwavelength (SW) photoacoustic microscopy (PAM) of melanosomes in the ear of a black mouse.* **B**, *Optical resolution PAM (OR-PAM) of individual red blood cells (RBCs) traveling along a capillary in a mouse ear.* **C**, *Acoustic resolution PAM (AR-PAM) of a nevus on a human forearm.* **D**, *Photoacoustic computed tomography (PACT) of a human breast.* **E**, *Imaging depth vs spatial resolution in PAT. LA, linear-array; PAMac, photoacoustic macroscope (resolution at the resolving ability of human eye); SM, submicron. From Wang LV, Hu S. Photoacoustic tomography: in vivo imaging from organelles to organs. Science. 2012;335(6075):1458-1462.*[12] *Reprinted with permission from AAAS.*

TABLE 2. Comparison of Major Photoacoustic and Thermoacoustic Imaging Modalities

Modality		Principle	Penetration depth (mm)	Lateral resolution (μm)	Benefits	Current limitations	Current applications	Likelihood of clinical translation	Potential applications in clinical neurosurgery
Photoacoustic imaging									
PAM	OR-PAM[27,47,52]	Nearly diffraction-limited optical focusing	$\leq$1.2	0.2-5	Very high resolution (can resolve single red blood cells)	Very limited penetration depth due to high ultrasonic scattering	Small experimental animal model in Vivo transcranial (after removal of scalp), skin microvascular, and wound healing imaging	Moderate	Intraoperative probes for cortical microvasculature imaging, intraoperative tumor margin imaging with histology-like resolution, functional cortical imaging based on capillary blood sO_2 (eg, detection of interictal epileptic foci, ischemia detection)
	AR-PAM[5,12]	Acoustic focusing	1-3	15-50	Maintains relatively high resolution with increasing imaging depth due to low acoustic scattering	Increasing imaging depth requires high energy/low repetition rate lasers resulting in slow scanning rate	Small experimental animal model in Vivo functional transcranial imaging, experimental in Vivo human skin lesion, and microvasculature imaging	High (currently clinical trial stage in US)	
PACT	UA-PACT[5,12,32,54]	Uses full-field optical illumination. Photoacoustic waves detected by piezoelectric UA (linear or curved/circular) or OD system (FPI) and an inverse algorithm is used to reconstruct a high-resolution image	3-70	70-800	Markedly increased penetration depth, high contrast	Relatively low resolution which decreases with decreasing element size. Higher resolution can be achieved with higher frequency, but it reduces SNR. Currently cannot penetrate beyond hard depth limit (50 mm)	Small experimental animal whole-body in Vivo imaging and transcranial brain imaging including functional imaging. Human in Vivo experimental carotid and jugular vein imaging and clinical imaging studies of human breast, skin cancer	High (currently clinical trial stage in US)	Portable superficial transcranial brain imaging (including intraoperative applications), carotid artery imaging for endarterectomy evaluation
	OD-PACT[5,78]		5.5	50-100	Small detector element size, optically transparent detector array with FPI - high acoustic performance (high resolution)	Resolution degrades rapidly beyond 1 mm depth due to high ultrasonic scattering	Experimental small animal model in Vivo internal organ and blood vessel imaging	Moderate	Intraoperative probes for cortical microvasculature imaging, functional cortical imaging based on capillary blood sO_2 (eg detection of interictal epileptic foci, ischemia detection)

TABLE 2. Continued

Modality	Principle	Penetration depth (mm)	Lateral resolution (μm)	Benefits	Current limitations	Current applications	Likelihood of clinical translation	Potential applications in clinical neurosurgery
Doppler PAT[33,55,56]	Utilizes Doppler shift of the photoacoustic wave when its source is in motion relative to detector. Can be based on either PAM or PACT	~1	5-10	Free of speckle artifacts, offers very high resolution, high contrast flow direction and speed measurements at significant depths. Can be combined with spectroscopy to measure O_2 metabolic rate	Currently most advanced and promising are OR-PAM-based methods with high resolution at the cost of penetration depth. Improvements in measurement accuracy risk excessive reduction of penetration depth	Small experimental animal model in Vivo blood flow imaging	Low	Intraoperative blood flow measurement probes for exposed vessels, cortical microvasculature, vascular malformations, grafts (relevant for bypass surgery), local cortical ischemia/tumor detection (O_2 metabolic rate)
PAE[72-74,76]	Pulsed laser delivered through optical fiber in an endoscopic probe. US detection and illumination can be automatically rotated to obtain cross-sectional image	3	30-450	Allows for highly sensitive internal organ and intravascular imaging utilizing endogenous contrast of different tissues and molecules with markedly greater penetration depth than EUS	Higher repetition rate and faster wavelength switching as well as miniaturization of the probe necessary for further clinical use optimization	Experimental animal model in Vivo GI, GU, intravascular imaging. Soft tissue phantom imaging through ex Vivo human skull and vertebra specimens. Experimental ex Vivo human blood vessel imaging	High (currently clinical trial stage in US)	Real-time intraoperative neuroendoscopy guidance to delineate tumor boundaries, identify location of carotid arteries etc. Real-time guidance of spine surgery (eg, pedicle screw placement)
Thermoacoustic imaging								
TAT[38-40,86]	Utilizes microwave frequency irradiation to induce photoacoustic wave emission through thermal expansion	≤150	170-2200	Allows for much deeper tissue penetration and less distortion from bone than any of current photoacoustic modalities	Relatively low resolution results in greater need for exogenous contrast	Experimental transcranial in Vivo primate brain imaging. Imaging through intact human skull ex Vivo with tissue mimicking phantoms. In Vivo animal and human joint and liver imaging	High (currently clinical trial stage in US)	Transcranial deep brain structural imaging

AR-PAM, acoustic resolution photoacoustic microscopy; EUS, endoscopic ultrasound; FPI, Fabry-Perot interferometer; GI, gastrointestinal; GU, genitourinary; OD-PACT, optical detection photoacoustic computed tomography; OR-PAM, optical resolution photoacoustic microscopy; PACT, photoacoustic computed tomography; PAE, photoacoustic endoscopy; PAM, photoacoustic microscopy; PAT, photoacoustic tomography; SNR, signal-to-noise ratio; TAT, thermoacoustic tomography; UA-PACT, ultrasound array photoacoustic computed tomography.

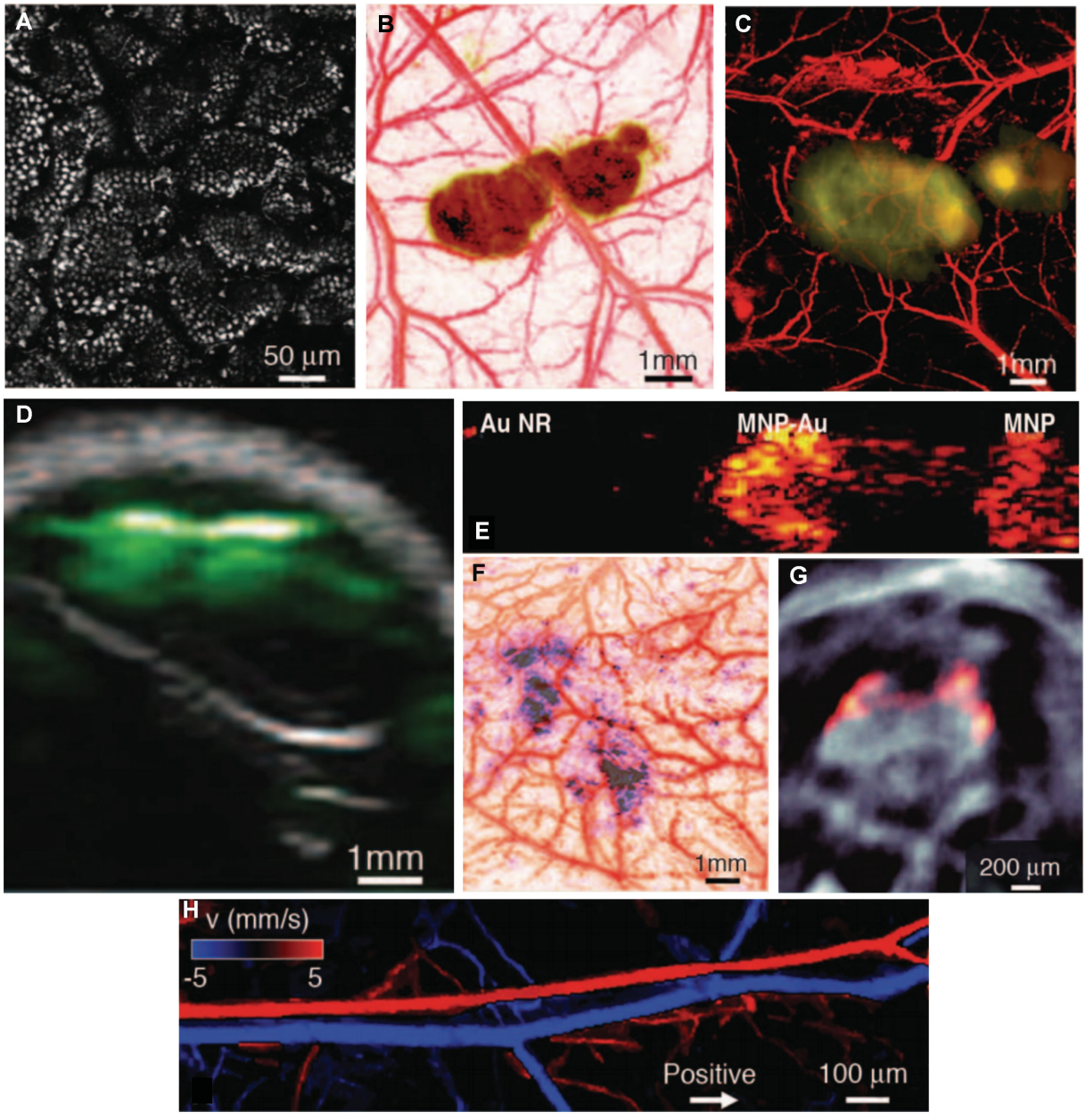

FIGURE 2. *Multi-contrast photoacoustic tomography (PAT) of tissue anatomy, function, molecular biomarkers, and gene expression.* **A**, *Optical resolution photoacoustic microscopy (OR-PAM) of epithelial cell nuclei in the intestinal villi of a mouse ex Vivo by excitation of DNA and RNA.* **B**, *Acoustic resolution PAM (AR-PAM) of a subcutaneously inoculated B16-melanoma and the surrounding vasculature on the back of a living mouse.* **C**, *AR-PAM of a subcutaneously inoculated B16-melanoma labeled with targeted gold nanocages on the back of a living mouse.* **D**, *Dual-contrast ultrasound (gray) and photoacoustic (green) imaging of a single-walled carbon nanotube targeted tumor in a living mouse.* **E**, *Magnetomotive PAT of a polyvinyl alcohol phantom with three 2-mm-diameter inclusions.* **F**, *The left inclusion contains gold nanorods with absorption comparable to the 3 nm magnetic-gold hybrid nanoparticles placed in the center inclusion, and the right inclusion contains 3 nm magnetic nanoparticles. AR-PAM of a lacZ-marked 9 L gliosarcoma and the surrounding vasculature under the scalp of a living rat.* **G**, *PACT of the brain of a 6-mo-old mCherry-expressing transgenic zebrafish.* **H**, *OR-PAM of blood flow velocity and direction in the ear of a living mouse. MNP, magnetic nanoparticles, NR, nanorods. From Wang LV, Hu S. Photoacoustic tomography: in vivo imaging from organelles to organs. Science. 2012;335(6075):1458-1462.*[12] *Reprinted with permission from AAAS.*

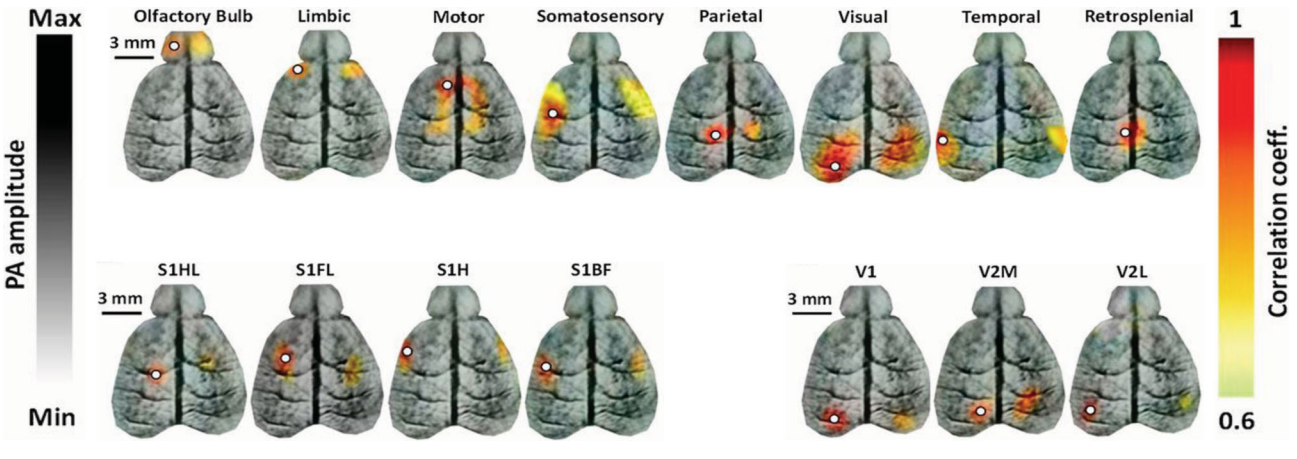

FIGURE 3. *Functional connectivity maps in a live mouse brain acquired noninvasively by functional connectivity photoacoustic tomography (PAT). Functional connectivity maps were created using a seed-based algorithm. Correlation maps of the 8 main functional regions (upper row), the 4 subregions of the somatosensory cortex (lower row left), and the 3 subregions of the visual cortex (lower row right) superimposed onto a cortical vascular functional connectivity PAT images are demonstrated. White circles - seed regions. S1HL, primary somatosensory cortex-hindlimb region; S1FL, primary somatosensory-forelimb region; S1H, primary somatosensory-head region; S1BF, primary somatosensory-barrel field. V1, primary visual cortex; V2M, secondary visual cortex-medial region; V2L, secondary visual cortex-lateral region. Reprinted from Nasiriavanaki M, Xia J, Wan H, Bauer AQ, Culver JP, Wang LV. High-resolution photoacoustic tomography of resting-state functional connectivity in the mouse brain. Proc Natl Acad Sci USA. 2014;111(1):21-26.*[85]

galvanometer-based and hexagon-mirror OR-PAM have been developed.[28-30] In one of the latest OR-PAM iterations published by Lan et al. in 2018, imaging of a 12 × 15 mm^2 area of tissue took only 12 s.

Acoustic resolution (AR)-PAM offers lower resolution, but deeper tissue penetration than OR-PAM utilizing much lower acoustic scattering (Figure 1).[12] Given these characteristics, a hybrid imaging approach combining OR- and AR-PAM has been proposed that can switch between different lateral resolutions at the expense of penetration depth.[31] Nevertheless, further advancements to increase imaging depth will likely require the use of high-energy lasers at low repetition rates which could result in scanning rates that are too slow for many clinical applications.[12] For this reason, PACT systems utilizing single-element transducers or multi-element transducer arrays in circular or linear shapes have been developed. PACT creates images by merging information from all transducers and retrieving absorption distribution using an inverse algorithm.[32] PACT offers high-contrast imaging depth up to several centimeters with sub-millimeter lateral resolution and accelerated acquisition rates.[12,23,32,33]

Doppler PAT has been demonstrated using both PAM and PACT technologies.[34] This system is being developed to image blood flow in Vivo with high spatial and velocity resolution. Currently, Doppler OCT is limited by penetrance of only one optical transport mean free path (soft depth limit). Acoustic flowmetry has too much background scatter, meaning it cannot accurately measure slow flow rates.[8] Laser Doppler flowmetry suffers multiple light scattering, which limits sensing depth as well as flow direction information. The photoacoustic Doppler effect discovered by Fang et al in 2007[35] utilizes the Doppler shift of the photoacoustic wave when its source is in motion relative to the detector.[8] Photoacoustic Doppler flowmetry introduced by Wang in 2008[8] allows for the measurement of both speed and direction of particle flow at the depth of a few millimeters inside an optically scattering medium, offering a spatial resolution of tens of micrometers without limitations of speckling artifacts.[8]

Functional PAT

Functional PAT allows imaging of dynamic biologic processes based on endogenous chromophore concentration. By measuring arrival time of the acoustic waves and performing a 2-dimensional scan, a volumetric image can be produced based on the optical energy absorption of endogenous chromophores. Dynamic detection of total Hb concentration and oxygen saturation can provide valuable information about tissue metabolism.[33] PAT is the only current imaging modality that can measure vessel diameter, total Hb concentration, oxygen saturation, blood flow velocity, and tissue volume needed to calculate the metabolic rate of oxygen consumption combining different endogenous contrasts.[12] Functional imaging can be achieved with both PAM and PACT (Figures 3 and 4). Acquisition speed of functional PAM (fPAM) can be increased utilizing higher repetition-rate laser systems with multiple wavelength laser sources, shortened wavelength switching time, and sufficient pulse energy.[28,31,36] Recently, a high-speed fPAM system has been constructed. The short wavelength switching time allows for real-time oxygen saturation imaging of circulating red blood cells.[36]

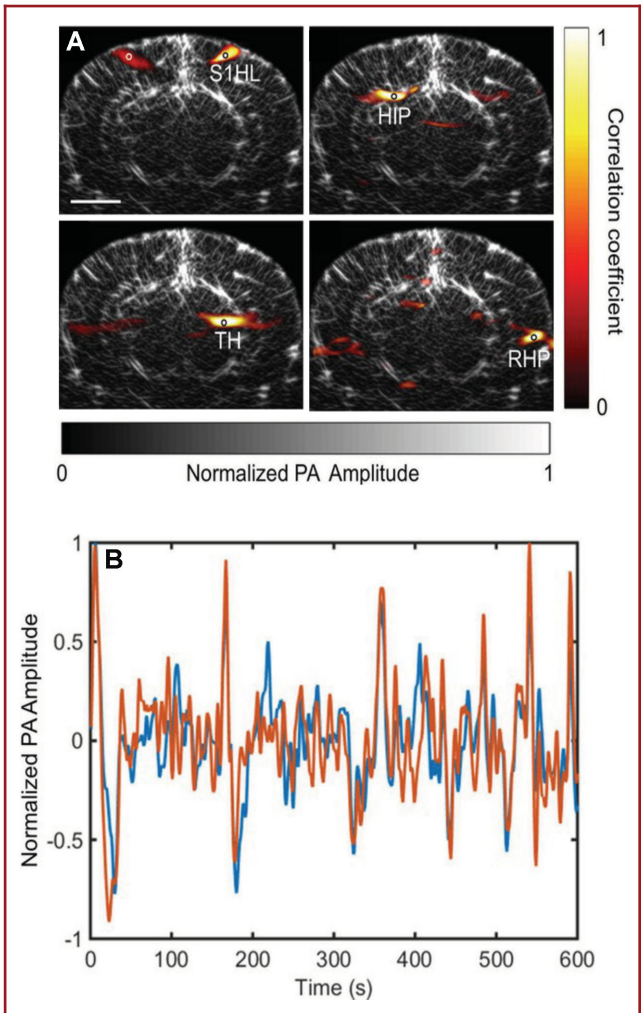

FIGURE 4. *Functional connectivity in a mouse brain acquired by a linear-array photoacoustic tomography (PACT) system.* **A**, *Correlation maps calculated at 4 representative functional regions (black circles) are overlaid onto the anatomic image that was synthesized from multiple limited-view images (Bregma−1.0 mm).* **B**, *Time series of the filtered PA signals of a pair of correlated regions as marked in* **A**. *The red and blue curves are corresponding to the points marked in white and black circles, respectively. Amplitudes are normalized to the maximum. The scale bar is 2 mm. S1HL, somatosensory 1, hindlimb region; HIP, hippocampal region; TH, thalamus; RHP, retrohippocampal region. From Zhang P, Li L, Lin L, et al. High-resolution deep functional imaging of the whole mouse brain by photoacoustic computed tomography in vivo. J Biophotonics. 2018;11(1).*[32] *Reprinted with permission from © 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim*

Functional PACT has been recently utilized for mouse brain imaging, detecting glucose metabolism based on the uptake of a contrast agent.[37] Unlike PET, the recently developed glucose-analog fluorescent exogenous contrast, 2-deoxy-2-[N-(7-nitrobenz-2- oxa-1,3-diazol-4-yl)amino]-D-glucopyranose, used in PACT, is not radioactive. PACT can potentially be faster than functional MRI and not limited to those patients who can tolerate strong magnetic fields. PACT sets itself apart in its sub-millimeter resolution and its depth penetration beyond the optical diffusion limit, all at a lower cost than either of its competitors.[8]

Thermoacoustic Tomography

Thermoacoustic tomography (TAT), which uses microwave irradiation to induce acoustic waves in the tissue, does not suffer as much from tissue scattering as from diffraction due to a longer wavelength (Figure 5).[8,38,39] Advantageously, at sufficiently low frequency, radiofrequency penetration depth reaches beyond 10 cm.[8] Moreover, as TAT and PACT share the same ultrasonic detection system, they have good compatibility. A downside of TAT is that, given that the difference in dielectric properties of different brain structures is relatively low, the contrast is also low and translates into greater need for exogenous agents.[8] Nevertheless, the potential portability, high sensitivity, imaging depths, and 1-way ultrasound transmission make TAT an attractive modality for deep transcranial imaging. In 2006, Xu and Wang reported the first application of TAT in 2-dimensional primate transcranial brain imaging.[40] The acoustic signals could penetrate the skull (1-2 mm simulates human infant skull thickness) with minimal distortion and relatively clear imaging of the brain at a depth of 3 cm. Image quality and resolution was expected to be further improved by implementing a 3-dimensional TAT and reducing skull artifacts with aberrant correction techniques. In 2008, Jin and Wang[41] proposed a numerical model taking into account the ultrasound reflection and refraction caused by heterogeneities in the human skull. Further improvements in transcranial TAT quality and accuracy have been investigated utilizing different imaging algorithms.[38] The initial step into investigating TAT utility in transcranial human brain pathology imaging was taken only recently by Huang et al,[42] who reported the use of a tissue-mimicking phantom enclosed with a human skull. In this brain tissue phantom, higher salt concentration agar mixtures were focally implanted mimicking intracranial hemorrhage. Their system was able to clearly show the localization, shape, and size of the implanted foci transcranially based on their higher conductivity. Given the potential of TAT to provide deep transcranial imaging, it has the potential to complement or compete with XRCT and MRI by providing detailed diagnostic imaging of intracranial pathology.

POTENTIAL CLINICAL APPLICATIONS OF PHOTOACOUSTIC IMAGING IN NEUROSURGERY

Vascular Pathology Detection and Blood Flow Measurements

Currently available XRCT or MR angiograms can produce false negative results and can be difficult to interpret in complex vascular cases.[43,44] To characterize certain vascular lesions, a catheter angiogram is still required and has inherent risks due to

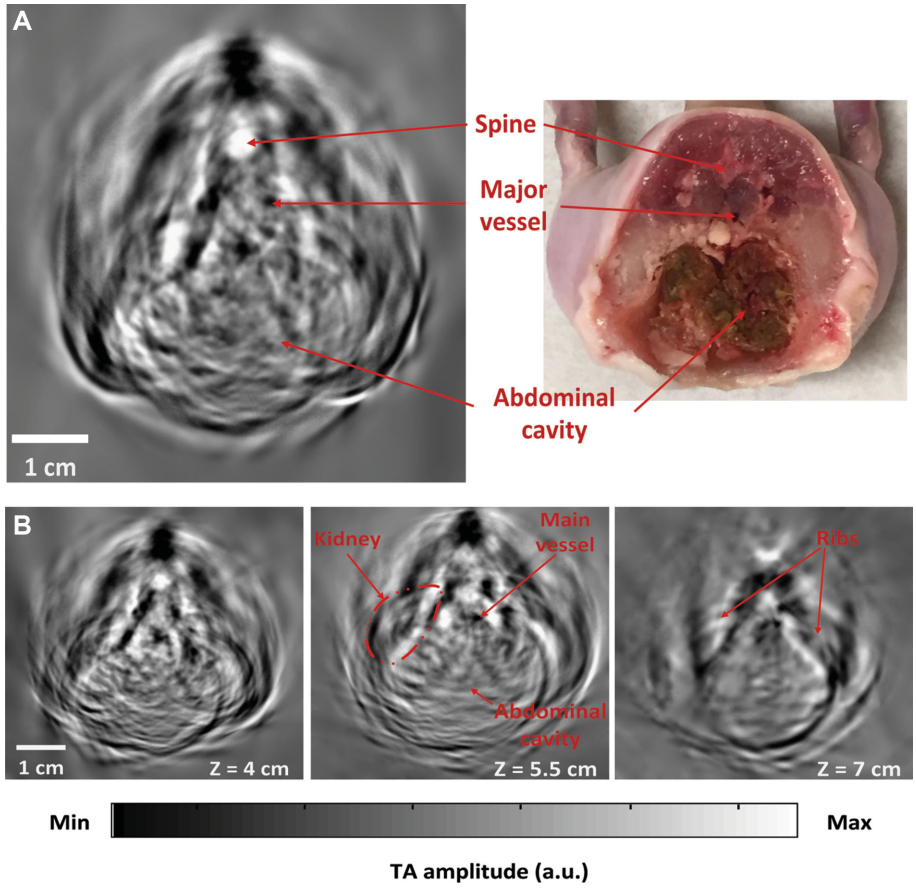

FIGURE 5. *Cross-sectional in Vivo imaging of the rat's trunk using thermoacoustic tomography (TAT).* **A**, *A TAT image of the rat and the corresponding photograph.* **B**, *TAT images of the rat's trunk at different cross sections. From Yan A, Lin L, Liu C, Shi J, Na S, Wang LV. Microwave-induced thermoacoustic tomography through an adult human skull. Med Phys. 2019.*[86] *Reprinted with permission from © 2019 American Association of Physicists in Medicine.*

its invasive nature, ionizing radiation exposure and iodine-based contrast agent. In some cases, repeat imaging is necessary which exposes patients to increasing doses of radiation and procedural risk.[43] Preoperative mapping of intracranial vascular malformations and aneurysm angio-architecture is important for clinical decision-making and assists with open surgical, endovascular, or radiosurgical planning and targeting.[45] A portable, safe, high-resolution, low-cost imaging system could provide neurosurgeons with crucial diagnostic information and image guidance while exposing patients to less risk.

Transcranial photoacoustic imaging differentiating healthy and pathologic vessel morphology in phantoms and in an in Vivo small animal model without exogenous contrast agent use has been reported.[46,47] In 2018, Sun et al[48] reported the first use of high-resolution, label-free photoacoustic in Vivo imaging for vascular malformation sclerotherapy guidance in a rabbit model. The photoacoustic imaging system generated detailed vascular images and detected locations of sclerosing agent activity and intravascular thrombi. Recently, a high-speed, high-resolution, transcranial photoacoustic imaging in a mouse model of cortical hemorrhage and stroke was reported (Figure 6).[49] These and numerous other reports suggest that PAT has broad and growing applications in vascular imaging, many of which could be applicable to neurosurgery.[5,17,50-53] High-resolution peripheral blood vessel photoacoustic imaging is rapidly advancing[50,54] and could be tested for intraoperative use in vascular neurosurgery in the near future. As the ability to compensate for skull attenuation advances,[41] the potential applications for these technologies will come into sharper focus.

Current blood flow imaging modalities based on the Doppler principle are limited either in their penetration depth or resolution.[55] Current MRI and XRCT-based perfusion imaging techniques are expensive, time consuming, involve strong magnetic fields or ionizing radiation, and are not well adapted for intraoperative use.[56] Various photoacoustic methods utilizing Doppler shift, density tracking, particle transit time, and

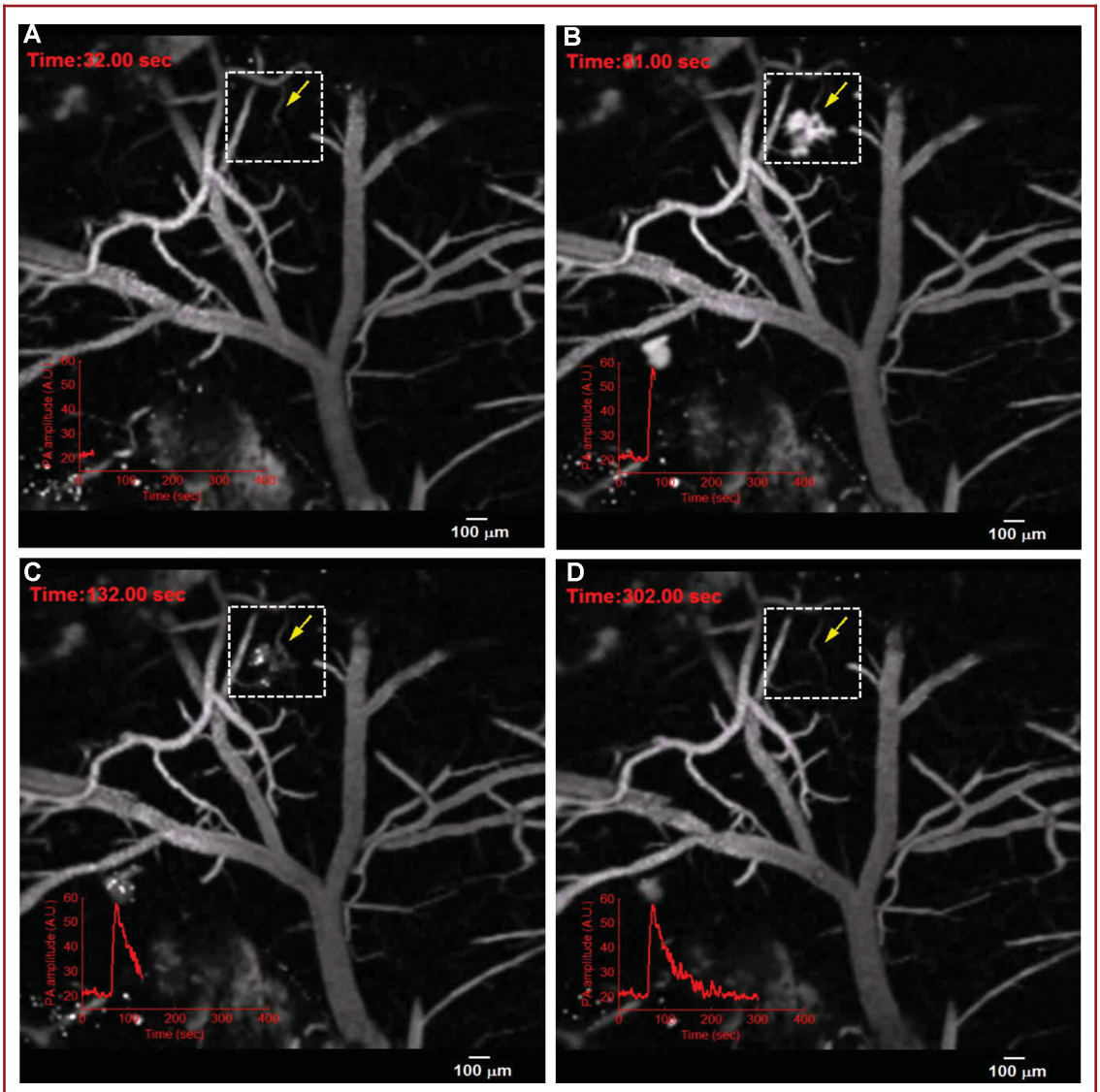

FIGURE 6. *Spontaneous mouse brain microhemorrhage dynamics using high-speed optical resolution photoacoustic microscopy (OR-PAM). Dynamic imaging showing bleeding at* **A***, 32 s,* **B***, 81 s (peak of photoacoustic intensity amplitude),* **C***, 132 s, and* **D***, 302 s. Imaging demonstrates that the hemorrhage stops within 8 s and the extravasated red blood cells are then cleared within 80 s. From Lin L, Yao J, Zhang R, et al. High-speed photoacoustic microscopy of mouse cortical microhemodynamics. J Biophotonics. 2017;10(6-7):792-798.[49] Reproduced with permission.*

amplitude encoding have been used to image blood flow.[56] To date, there have been multiple reports of photoacoustic blood flow measurement systems where transducers are placed in direct contact with the tissue using a coupling medium.[34,49,55,56] In 2018, the first noncontact photoacoustic blood flow imaging system based on photoacoustic Doppler bandwidth broadening techniques was reported.[55] Although limited in its penetrance, this technique represents the first step towards noncontact photoacoustic blood flow imaging. Recently, a rapid volumetric PAT system was used to visualize peripheral vascular vasomotor responses to thermal stimuli in humans.[51] This system provided an imaging depth of up to 14 mm allowing for 3-dimensional visualization of the dorsalis pedis artery as well as small digital vessels. This technique could have applications in carotid artery stenosis/occlusion as well as in cerebral revascularization.

Tumor Diagnostics

Monitoring angiogenesis in Vitro and in Vivo can improve the understanding of tumor growth and metastasis and provide greater insight into anti-vascular chemotherapeutic effect.[57]

Tumors can be differentiated from normal brain tissue by increased microvascular densities, greater vascular complexity and tortuosity, abnormal branching patterns, and expression of specific molecular markers. The oxygenation status of tumor tissue reflects metabolic rate and can provide valuable information about tumor growth and resistance to treatment.[8,58]

Li et al[58] implanted one million human U87 glioblastoma cells stereotactically into immunocompromised nude mice at a depth of approximately 3 mm from the scalp surface. Spectroscopic PAT was then used to image the tumor with a molecular imaging probe, an indocyanine green derivative, IRDye800-c conjugated with cyclic peptide cyclo(Lys-Arg-Gly-Asp-Phe) (cKRGDf) referred to as IRDye800-c(KRGDf).[58] The novel spectroscopic PAT combines molecular and functional imaging modalities and is able to record the unique optical absorption signature of an object by changing the laser wavelength. KRGDf has an increased affinity for integrin $\alpha_v\beta_3$, which is known to be overexpressed in glioblastoma. This exogenous contrast agent was able to provide an in Vivo functional image of the Hb oxygen saturation distribution, which could then be mapped to individual blood vessels using oxy- and deoxyHb as endogenous contrast agents. The glioblastoma containing tissue region showed drastic deoxygenation—a characteristic of tumor hypermetabolism. Using this contrast agent, glioblastoma detection can be done with greater specificity and sensitivity. In 2009, Zhang et al[59] used 2 human tumor models with different pathophysiology grown in nude mice to demonstrate differences in vascular architecture and density with high-resolution 3D PAT. This imaging system was able to differentiate microvascular features of the 2 tumor models offering an imaging depth up to 5 cm with spatial resolution less than 100 μm.

Epilepsy Imaging

Currently, epilepsy protocol MRI is used as an initial screening tool to evaluate for structural lesions given its relatively high resolution. Nuclear imaging modalities such as PET and single photon emission computed tomography are used adjunctively with MRI to visualize regional blood flow changes related to epileptic pathology.[60] Nevertheless, there are still significant limitations such as insufficient resolution for cases with subtle abnormalities, high magnetic fields or ionizing radiation, prolonged imaging time, high cost, and lack of portability.[61] Photoacoustic imaging has the potential to identify epileptic foci with high spatiotemporal resolution and low risk thus complementing or possibly replacing some current imaging modalities.[61,62]

As discussed, photoacoustic imaging allows mapping of Hb oxygen saturation in individual blood vessels. Local deoxygenation follows after increased blood flow and oxygenation during a hypermetabolic state in response to intensive neuronal firing in seizure foci.[61] Neurovascular coupling refers to the association between neural activity and changes in cerebral hemodynamics and utilizes parameters such as total Hb concentration, Hb oxygen saturation, and blood flow to map brain activity.[63] In 2008, Zhang et al[61] demonstrated, for the first time, that PAT can be used to precisely localize seizure foci in a bicuculline rat model in Vivo with the same sensitivity as epidural cortical electroencephalography. Subsequently, the first use of label-free OR-PAM to monitor neurovascular coupling after direct electrical somatosensory cortical stimulation was demonstrated in a mouse model.[63] In this model, simultaneous detection and analysis of individual cortical microvessel responses to electric stimulation was shown. In 2013, Tsytsarev et al[64] reported the simultaneous use of OCT and PAM to perform mapping of in Vivo-induced epileptic activity in a mouse model through a craniotomy (Figure 7). This novel approach recorded modulation of the optical refractive index along with hemodynamic changes in cortical areas during seizures with high spatiotemporal resolution. This imaging approach could potentially be utilized to determine the margins of epileptic foci intraoperatively. Parallel to this study, Xiang et al[62] reported the use of noninvasive, real-time PAT imaging to visualize seizure foci and networks in a rat model of focal epilepsy through intact skin and skull. They used an upgraded version of the previous PAT system with higher temporal and spatial resolution. Moreover, they were able to demonstrate primary seizure focus causal influence on the surrounding regions illustrating the epileptic propagation network. Vasomotor changes in microvasculature closely correlated with the interictal discharges seen in simultaneous electroencephalographic recordings reflecting a sudden increase in metabolism.

Atherosclerotic Vascular Change Diagnostics

Atherosclerosis is a major contributor to carotid disease and ischemic stroke. Carotid artery stenosis or occlusion can lead to critical blood flow reduction requiring endovascular intervention, surgical endarterectomy, or revascularization.[65] The composition of the atherosclerotic plaque determines its predisposition to rupture and subsequent distal thromboembolic events.[66,67]

In 2012, the first in Vivo imaging of carotid arteries using real-time, hand-held, multi-spectral PAT was demonstrated in healthy volunteers providing insights into its potential clinical relevance.[54] The system showed improved image quality at clinically relevant depths. As there currently is no in Vivo imaging modality that can effectively quantify plaque lipid composition, spectral photoacoustic imaging holds the potential for high-resolution vessel wall characterization due to its ability to differentiate biological compounds, including lipids, collagen, and Hb based on their optical absorption coefficients.[68] Moreover, it is important to differentiate the normal lipids present within the arterial wall from the pathological accumulations in atherosclerotic plaques.[66,68] To address this, Jansen et al[68] combined 2 wavelength intravascular photoacoustic imaging (IVPA) with intravascular US to image phantom and human coronary arteries ex Vivo. Their system generated images that closely reflected

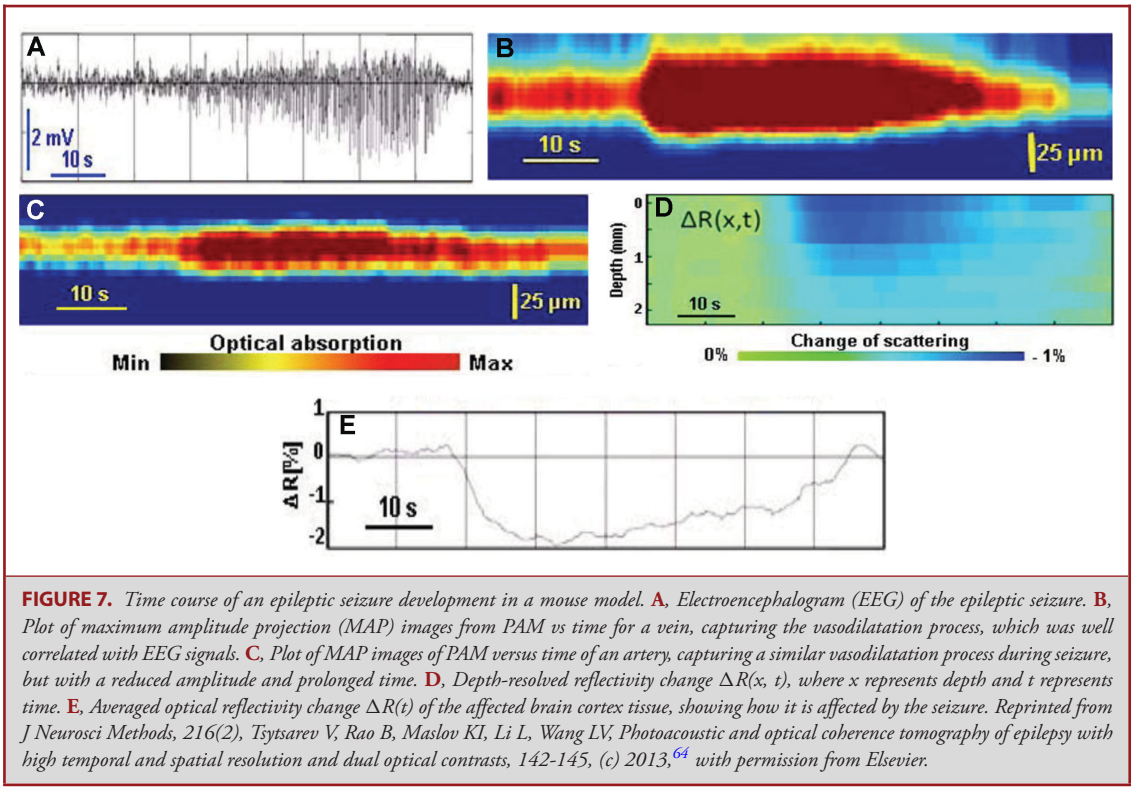

FIGURE 7. *Time course of an epileptic seizure development in a mouse model.* **A**, *Electroencephalogram (EEG) of the epileptic seizure.* **B**, *Plot of maximum amplitude projection (MAP) images from PAM vs time for a vein, capturing the vasodilatation process, which was well correlated with EEG signals.* **C**, *Plot of MAP images of PAM versus time of an artery, capturing a similar vasodilatation process during seizure, but with a reduced amplitude and prolonged time.* **D**, *Depth-resolved reflectivity change $\Delta R(x, t)$, where x represents depth and t represents time.* **E**, *Averaged optical reflectivity change $\Delta R(t)$ of the affected brain cortex tissue, showing how it is affected by the seizure. Reprinted from J Neurosci Methods, 216(2), Tsytsarev V, Rao B, Maslov KI, Li L, Wang LV, Photoacoustic and optical coherence tomography of epilepsy with high temporal and spatial resolution and dual optical contrasts, 142-145, (c) 2013,*[64] *with permission from Elsevier.*

histological findings and was able to spectrally differentiate peri-adventitial and plaque lipid compounds. Recently, a co-registration of IVPA and intravascular US to specifically detect and differentiate lipids in a vessel-mimicking phantom demonstrated further improvements.[69] Portable, hand-held configurations of these technologies have the potential to contribute to the carotid stenosis/occlusion diagnostics and endarterectomy procedures in the future (Table 2).

PHOTO- AND THERMOACOUSTIC IMAGING LIMITATIONS AND FUTURE APPLICATIONS

While many of the photo- and thermoacoustic imaging modalities are currently undergoing clinical trials, there are limitations which need to be overcome to facilitate their applications in neurosurgery (Table 2). Although PAT and TAT involve 1-way ultrasound propagation and are most promising for transcranial imaging, they still suffer significant phase distortion of the ultrasonic waves from the skull. Given that skull distortion can be quantified using measurements from XRCT or MRI,[41] it is possible that numerical compensation could be programmed into the future photo- and thermoacoustic systems. Given that the radiofrequency used in TAT provides deeper tissue penetration than the light used in PAT, it is being extensively studied for deep transcranial imaging applications.[38,40-42] Ongoing studies of portable configurations of photo- and thermoacoustic imaging systems could permit cost-effective and convenient real-time clinical applications such as transcranial or transvertebral imaging and guided neuroendoscopy (Table 2).[18,70-76] Ongoing improvements in image acquisition technique have the potential to increase resolution, imaging depth, and speed thus facilitating point-of-care applications.[47,70,77,78]

Theranostics, a novel nanomedicine field focused on noninvasive diagnostic imaging modality integration with targeted therapeutic approaches, holds exciting new possibilities for photoacoustic imaging in neurosurgery.[79,80] Theranostic exogenous contrast agents can be used not only for imaging enhancement, but also as vehicles for pharmaceutical or photothermal therapy and image-guided surgery as well as therapeutic response indicators.[79] Nanoparticles, conjugated with drugs, antibodies, proteins, or nucleic acids create nanosystems that can target specific types of tissues or focal pathology.[79,81] Intravenous, integrin targeted hollow gold nanospheres (HAuNS) can provide optical contrast for implanted tumor imaging using PAT and facilitate focused photothermal ablation upon switching to increased laser power.[82] A PAT system with HAuNS enhancement has already been shown to provide clear visualization of the cerebral vasculature in an in Vivo mouse model, imaging microvessels as small as approximately 100 μm without acute toxicity.[83] Targeted nanospheres loaded with the anti-angiogenic agent sunitinib in combination with an embolization agent have recently been proposed for the treatment of arteriovenous malformations.[84]

CONCLUSION

Photoacoustic imaging technology is capable of providing better spatiotemporal resolution while eliminating exposure to ionizing radiation or strong magnetic fields. The introduction of this new platform technology to clinical neurosurgery promises parallel advancements in contrast agents and theranostics. The contributions of photo- and thermoacoustics to clinical medicine are inevitable and will be disruptive to the current standard of care. As we have before, neurosurgery is again poised to shepherd a new technology into clinical medicine.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

The work is an interesting review of the current state of photoacoustic and thermoacoustic imaging. Neurosurgery has changed dramatically with the development of computer tomography and magnetic resonance imaging, allowing us to diagnose and localize lesions with greater precision compared to the times when only angiograms and pneumoencephalograms were available. However, these imaging modalities are not without drawbacks, including size and cost of the equipment. The authors make an interesting case that photoacoustic and thermoacoustic imaging will complement our diagnostic armamentarium by bridging the gaps left by existing modalities. The review does an excellent job at explaining the pros and cons of each emerging technology and to detail the current level of development and in-vivo testing. We draw the reader's attention to Figure 1, as it provides a summary of the trade-offs of each of these emerging technologies and respective limitations in depth of tissue penetration or resolution. It is recognized that these are emerging technologies and not ready for clinical use. That said, there is a significant opportunity for neurosurgeons to participate in the translational effort of bringing these modalities to the bedside in a way that will be of practical use and benefit to our patients. Some of these technologies can be more portable than current scanners and be deployed to operating rooms or emergency departments with less constraints. To this end, the authors summarize the translational limitations and opportunities such as cost, portability, likelihood of human translation and possible applications in Tables 1 and 2. These can serve as guides to those interested in becoming partners in development and implementation.

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