Review Article

Imaging the aged brain: pertinence and methods

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Abstract: The global population is ageing at an accelerating speed. The ability to perform working memory tasks together with rapid processing becomes increasingly difficult with increases in age. With increasing national average life spans and a rise in the prevalence of age-related disease, it is pertinent to discuss the unique perspectives that can be gained from imaging the aged brain. Differences in structure, function, blood flow, and neurovascular coupling are present in both healthy aged brains and in diseased brains and have not yet been explored to their full depth in contemporary imaging studies. Imaging methods ranging from optical imaging to magnetic resonance imaging (MRI) to newer technologies such as photoacoustic tomography each offer unique advantages and challenges in imaging the aged brain. This paper will summarize first the importance and challenges of imaging the aged brain and then offer analysis of potential imaging modalities and their representative applications. The potential breakthroughs in brain imaging are also envisioned.

Keywords: Brain imaging; aging; neuroscience; neurovascular coupling; magnetic resonance imaging (MRI); optical imaging; positron emission tomography

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Biological aged brain

Aging has become the next global public health challenge (1). For the first time in history, the number of people aged 65 years and older in the world outnumbers children aged younger than 5 years (2-4). A total of 10–20% of people aged 60–80 years are estimated to have one of three neurological diseases, including stroke (5,6), Alzheimer's disease (7), and Parkinson's disease (8,9). The notion that the aged brain differs from the young brain is not a new one. Intuition alone emphasizes notable differences in maturation, processing speed, and baseline function between the preadolescent and the elderly brain. In order to advise on healthy ageing, it is critical to first understand the fundamental biological differences between the young and old brain. The anatomical aged brain is marked by distinct changes in brain volume, general cognition, vasculature, and neurovascular coupling (10) (*Figure 1*). For the purposes of this concise review paper, the young brain is considered to be a preadolescent brain before neural pruning; the elderly brain is considered to be in the middle stages of degradation around the US senior citizen average age of 62. Further, imaging discussed in this paper considers both healthy and degenerative disease affected aging.

The volume and size of the brain is one of the most obvious targets of age. Over time, the aged brain loses 5% of its volume with each decade past the age of 40, with this rate of mass loss often escalating after the age of 70 (10-18). Additionally, there is specific volume loss in white matter tracts and myelin degeneration (19-26). Loss of white matter tracts behaves in a "last-in-first-out" manner beginning in posterior, frontal, and parietal sections of the brain and first degrading tracts that typically form towards the end of puberty (19). Of the subdivisions of the brain, the prefrontal cortex and striatum seem to be most affected by this age-induced deterioration while the occipital lobe remains the least affected (10,27). The hippocampus also suffers degradation, and this can be linked to a vast number

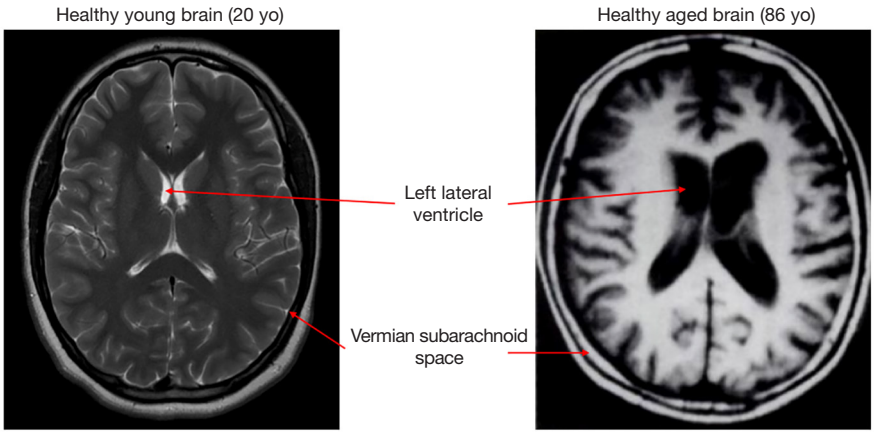

Figure 1 Horizontal slice magnetic resonance imaging scans of a healthy 20-year-old brain (left) and a healthy 86-year-old brain (right). Side by side comparison to show the anatomical changes to brain structure in only the presence of aging. Notable differences occur in the widening of the third ventricle, the left lateral ventricle, the vermian subarachnoid space, and left circular sulcus. Widening can be noted by the greater presence of dark space on the scans.

of age-related memory disorders (10,28-31). Substantial loss in brain volume over time heavily impacts imaging and statistical significance when a healthy aged brain is compared to a structurally different, healthy adolescent brain.

The aged brain also presents differences in cognition. Incorrectly attributed to decreased volume, cognitive decline is better explained by changes in dendritic shape and connection (32-36). Deterioration of dendritic spine length or shape heavily impacts the functionality of neural networks and can be linked to age related impairments in processing and integrating information (32,36). Even discounting aged related disease, the aged brain has stark differences in cognition and processing that impact elderly citizens in society. The biggest changes in cognition occur in reasoning, episodic and semantic memory tasks, and integration speed (37-42). Most notably, younger brains perform better in tasks that require problem-solving or adaptable application of skills, whereas older brains perform better at tasks that require accessing stored information or applying an often practiced skill (37).

Change in vasculature and blood pressure in the brain is the third most notable effect of age (43-50). Blood vessels become more fragile with time and use and become vulnerable to white matter lesions, clots, and tears (51). Atrophy and grey matter loss can additionally result in higher blood pressure (10,52-55). Changes in blood vessel size and durability are associated with increased risk of dementia, Alzheimer's disease, and stroke (10). These changes should be paid special attention in imaging because they are present even in the normal ageing process and can be indicators of predisposition for age related degenerative diseases.

Finally, even in healthy ageing, the brain has reduced increases in blood flow at moments of key firing and in response to various stimulations. This phenomenon, named neurovascular coupling or functional hyperemia, is the brain's method of supplying sufficient amounts of oxygen and vital nutrients via blood flow during elevated brain activity and activation (56). The study of the relationship between blood micro-vessels and astrocytes is paramount in the analysis of healthy ageing. Healthy ageing also impacts both elements of this mechanism. It has been suggested that dysfunction in both the astrocyte end of calcium signaling and the blood vessel mechanism through cellular oxidative stress or IGF-1 deficiency could affect the efficiency of neurovascular coupling in the brain (56). This mechanism has particular importance in brain imaging because functional magnetic resonance imaging (fMRI) fundamentally relies on measuring this speed of reactance. The blood oxygenation level dependent (BOLD) signal in fMRI is heavily related to the magnitude of oxygenation in the brain and, in aged brains, the decreased neurovascular coupling can be used as an indicator of age-related

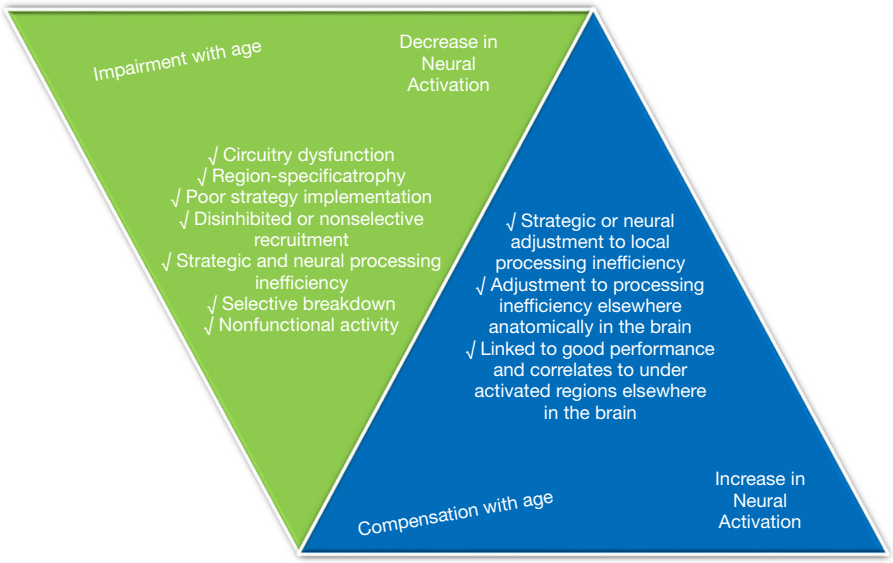

Figure 2 Extrapolated points of difference between younger brains and older brains during functional neuroimaging study completed by Reuter-Lorenz and Lustig (62). Regions of impairment indicate loss of function with age and areas of compensation (usually paired with regions of impairment) are areas of higher activation in older brains trying to operate at a functional level in the task.

neurodegenerative diseases (57). Indeed, neurovascular coupling has already been considered in a large number of aged brain imaging and research (58-61).

Challenges of imaging the aged brain

As discussed above, the rate, type, and general presentation of ageing presents drastically differently in each person, in health or in disease. This makes standardizing imaging and designing experiments that are widely applicable a very challenging task (*Figure 2*). For example, MRI is arguably one of the most powerful forms of imaging in anatomical and functionality studies that relies heavily on BOLD signals (63-69). However, changes in blood vasculature and neuronal structure of the brain can be misinterpreted in MRI as activity or lack thereof in functionality studies (70,71). The standard hemodynamic response function (HRF) is fit to data for younger brains and applying this standard to a different vasculature system can result in a less accurate fit and misleading result (70). This issue also manifests itself in structural standards to identify aging-induced anomaly. Spatial normalization is applied in imaging to account for small differences in structure between individuals. However, the standard will continue to bend a participant's images to match the HRF which can lead to overestimation errors in structural analysis (70). In fact, all statistical analysis using young brain data must fundamentally warp the data of older brains because of the identified structural and functional differences. This presents the big challenge of lacking a proper standard against which to compare healthy aged brains.

Beyond the functional challenges, there are also many participant and involvement based challenges when imaging elderly volunteers. Health becomes a larger factor in activity of elderly adults, so running self-selecting studies could result in bias due to which adults feel healthy enough to participate (37,72-74). Participants with decreased mobility or limited independence will by nature of their living circumstances be underrepresented in such studies. Since the participant pool is limited by health and mobility among other factors, the problem of getting a statistically relevant sample size then arises (73).

Similarly, longitudinally assessing healthy ageing through imaging tools becomes increasingly difficult when studying elderly adults. Longitudinal studies are the most helpful tool in quantifying change over time, but they require multiple visits or attempts at a task with a healthy participant, and this is not always the easiest parameter to achieve (37,75-82). Participants are always at risk of developing a cognitive or physical impairment during the course of a study even if they began the trial neurologically and physically fit. Such consistency is hard to achieve due to the changing nature

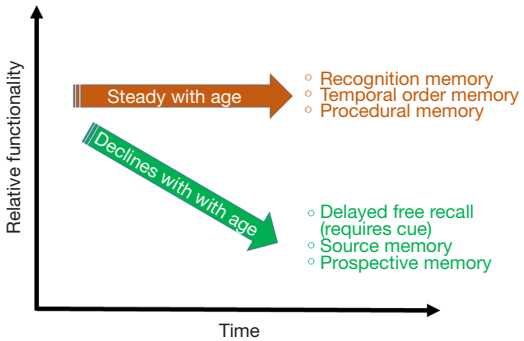

Figure 3 Graphical representation of memory functions that either stay stable or decline with age.

of physical health and the long symptomatic manifestation time of cognitive disorders.

Impact (meeting the need)

Increasingly, our society is becoming more and more flushed with elderly citizens. With better health care and longer lifespans, the number of Americans over the age of 65 is projected to reach 88.5 million in the year 2050 (37). Healthy ageing is taking center stage as society must learn how to cater to this new generation of older adults who are experiencing cognitive decline despite being free of degenerative disorders. These changes to their cognition, for example memories as shown in *Figure 3*, however small, are impacting the daily lives of an increasing number of people and efforts must be made to further understand healthy ageing in order to cater to the day to day lives of the elderly.

Imaging the aged brain would not only give us better standards against which to create the benchmark of healthy cognitive ageing, but it would also reveal more about the connectivity and functional methods of the brain. If certain functions are discovered to be lost over time due to degeneration, more could be illuminated about the functionality of both older and younger brains. Especially on the technological brink of imaging, more information on the structure, function, and working principles of the brain can only help in establishing both the standard of and deviations from healthy brain function.

Technologies for imaging aged brains

The human brain is the most complex, powerful and mysterious organ of the human body (83,84). Although scientists have been avidly discovering the secrets of the brain, the knowledge accumulated so far still falls far short of a comprehensive understanding. Thanks to modern biomedical imaging technologies, our understanding of the brain has advanced over the last few decades at an accelerated speed (85,86). Looking back, the history of neuroscience is also a history of applying new imaging technologies to look at the brain in a more informative way. However, imaging the human brain is also the most challenging application for many imaging technologies because the brain functions as a highly-coordinated system with functional connections at various spatial scales ranging from the single cell level (e.g., within a cortical circuit) to the tissue level (e.g., between cortex and hippocampus) (*Figure 4*). Large efforts are currently supported by the NIH BRAIN Initiative to image brain functions at different scales and to understand the relevance of its dynamics during development, aging, and in disease (87,88). Human brain mapping has become one of the most exciting contemporary research areas with major breakthroughs expected in the following decades. So far, many imaging technologies have been applied for imaging aged brains in preclinical studies and clinical practice (89-95). These technologies can be grouped into three major categories based on their spatial resolutions and corresponding maximum imaging depths: microscopic imaging, mesoscopic imaging, and macroscopic imaging. Here, we will briefly introduce the representative imaging technologies in each group, together with their strengths and limitations in brain imaging.

Microscopic brain imaging

At the microscopic level (<10 μm), optical imaging has been the dominating player, providing cellular and subcellular images of brain structures and functions, especially at the neuronal level (96-102). Taking advantage of the short wavelengths of photons, optical imaging, including confocal and multiphoton microscopy (103-107), can achieve a spatial resolution on the level of ~1 μm, which is sufficient to resolve single neurons and even dendrites, the basic communication units of the brain. Moreover, optical imaging can provide rich image contrast by using a large library of exogenous optical labels such as fluorescent dyes, quantum dots, and genetically encoded fluorescent proteins. These optical labelling tools have been widely applied to small animal brain imaging providing direct or indirect measurements of the brain's morphological and functional status, including neuronal connection, hemodynamics,

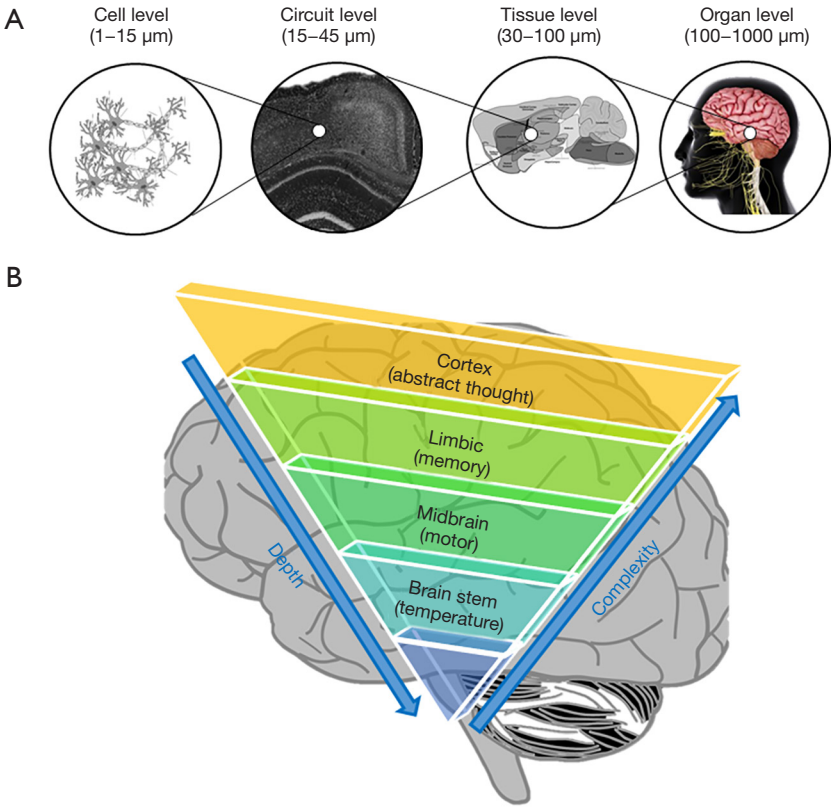

Figure 4 Illustration of the brain hierarchy, showing (A) the functional units at different scales and (B) the connections at different brain regions.

action potential firing, and signal transmission (*Figure 5A*). One important example is non-invasive real-time optical reading of the brain's neuronal activities based on calcium or voltage-sensitive indicators (112-117). The advantage of optical imaging over electrode recording is the high throughput that supports simultaneous interrogation of thousands of neurons, allowing the study of neural circuits and networks. However, the drawback of optical imaging is also clear: the penetration depth is limited to the superficial brain tissue, typically less than 1 mm into the brain tissue, mainly because of the strong optical scattering of the tissue. Multi-photon microscopy takes advantage of the longer excitation wavelengths and has achieved a penetration depth of 1.5 mm (118-121). Nevertheless, optical imaging is mainly used for small animal brain imaging, such as on fruit flies, zebra fish, and mice. Invasive methods have also been developed to circumvent the imaging depth by inserting miniaturized optics into the brain tissue (122,123), which, however, may induce undesired damage to the brain functions.

Mesoscopic imaging

On the mesoscopic scale (10 μm–1 mm), several imaging modalities have been used for brain imaging, including X-ray, CT, MRI, and ultrasound imaging. Mesoscopic imaging can provide structural and functional information on the neural circuit level, and more importantly, deep penetration into the brain. In particular, X-ray CT and MRI are routinely used for human brain imaging in clinical practice (124,125), allowing simultaneous mapping of the whole brain including structures such as the gray and white matter volumes as well as tissue density (*Figure 5B,C*). More advanced technologies such as contrast-enhanced X-ray CT and MRI have been used in imaging brain vasculature in neurological diseases such as stroke, AD, and brain tumor (126,127). The advent of *in vivo* diffusion tensor imaging (DTI) allows direct measurement of the bulk tissue microstructure ordering by virtue of mapping water proton motions within the tissue microenvironment (128). DTI has been playing an important role in studying the aged brain, especially in studies on neurodegenerative processes that

cause changes at the microstructural level through the rate of myelination or demyelination, degradation of microtubules, or loss of axonal structure (129). Ultrasound imaging is not typically used for the brain, with the skull as a physical barrier to the acoustic waves (130,131). However, using low frequency ultrasound around 2 MHz, transcranial Doppler ultrasound imaging is able to measure the cerebral blood flow through the skull's acoustic windows, including temporal, orbital, suboccipital, and submandibular windows (132). Transcranial Doppler ultrasound has been applied to study blood flow velocity, arterial pulsatility, and resistance with aging. The results have collectively shown that cerebrovascular hemodynamics may carry important implications in vascular diseases associated with advanced age, increased risk of cerebrovascular disease, cognitive decline, and dementia.

Macroscopic imaging

At the macroscopic level (1 mm to 1 cm), fMRI (133-135), PET (136-139), and diffuse optical tomography (DOT) (140-143) are the major imaging techniques being used to study brain function and metabolism. Based on different contrast mechanisms, all these imaging techniques can provide the macroscopic functional status of the brain in the resting state and under stress. fMRI is sensitive to the blood oxygenation dependent signals, which are closely correlated with neuronal activities through neurovascular coupling. As a totally noninvasive imaging modality, fMRI has been the most popular tool in studying the cognitive decline in both diseased and aged brains and has shown that healthy aging reduces the cerebral hemodynamic responses to visual challenges (144). It has also shown that the brain's resting state activities are significantly different in normal aging, mild cognitive impairment, and Alzheimer's disease (145). PET relies on the accumulation of radiolabeled tracers to map the brain's metabolism status and other important pathophysiological indicators. Despite the low resolution and the ionizing radiation, PET has been a powerful tool in studying the brain's normal aging process and neurodegenerative diseases, with its high sensitivity and specificity. For example, PET has been increasingly used in studying the rate of accumulation of pathological tau in normal aging and Alzheimer's disease and has shown different tau deposition rates over the whole brain in the early Alzheimer's disease onsets (111,138) (*Figure 5D*). DOT has been a relatively new player in functional brain imaging, compared with fMRI and PET. DOT shares the same contrast principle as fMRI, and optically detects the neuronal activities through the brain's hemodynamic responses. Increased blood volume and oxygenation are two important physiological parameters measured in DOT. DOT typically can provide brain functions only in the neocortical layer, limited by the penetration depth of near-infrared photons through the intact scalp and skull. However, compared with fMRI and PET, DOT is more portable, much faster, and can provide real-time monitoring of brain function. Moreover, DOT is a much less expensive technology. DOT has recently gained more popularity in mapping distributed brain functions and networks (146), such as in patients with Parkinson's disease and implanted deep brain stimulators that preclude fMRI.

Conclusions and prospects

As the brain ages in health and in disease, there are numerous structural, functional, molecular, and cognitive changes at a wide range of scales from cellular to whole organ levels. These changes are intrinsically interconnected through the extremely complex signal pathways and neural networks in the brain. Alterations of the aging brain can result from multifactorial processes and be reflected by many functional and molecular biomarkers. However, the knowledge accumulated so far still falls short of a comprehensive understanding. The knowledge gap about the functional disruption and remodeling of the aging brain is largely due to a lack of imaging technologies that can provide longitudinal imaging with the required spatial-temporal resolutions and imaging depth (147). Due to relatively low spatial-temporal resolution, MRI and PET are not suited for microscopic studies (148,149). Optical imaging methods lack the penetration depth for accessing the brain regions beyond the cortex, and thus cannot study the spatial heterogeneity of brain damage and restoration (150). Ultrasound imaging still lacks the sensitivity to most brain functions outside of blood flow. Histological examination of brain slices cannot provide functional information. Therefore, to better understand aging brains, we still need an imaging technology that can provide high spatial-temporal resolution, deep penetration, and functional information.

New imaging technologies that harness novel contrast mechanisms may provide new opportunities in studying aged brains. One example is photoacoustic tomography that physically combines light and ultrasound to probe the tissue's

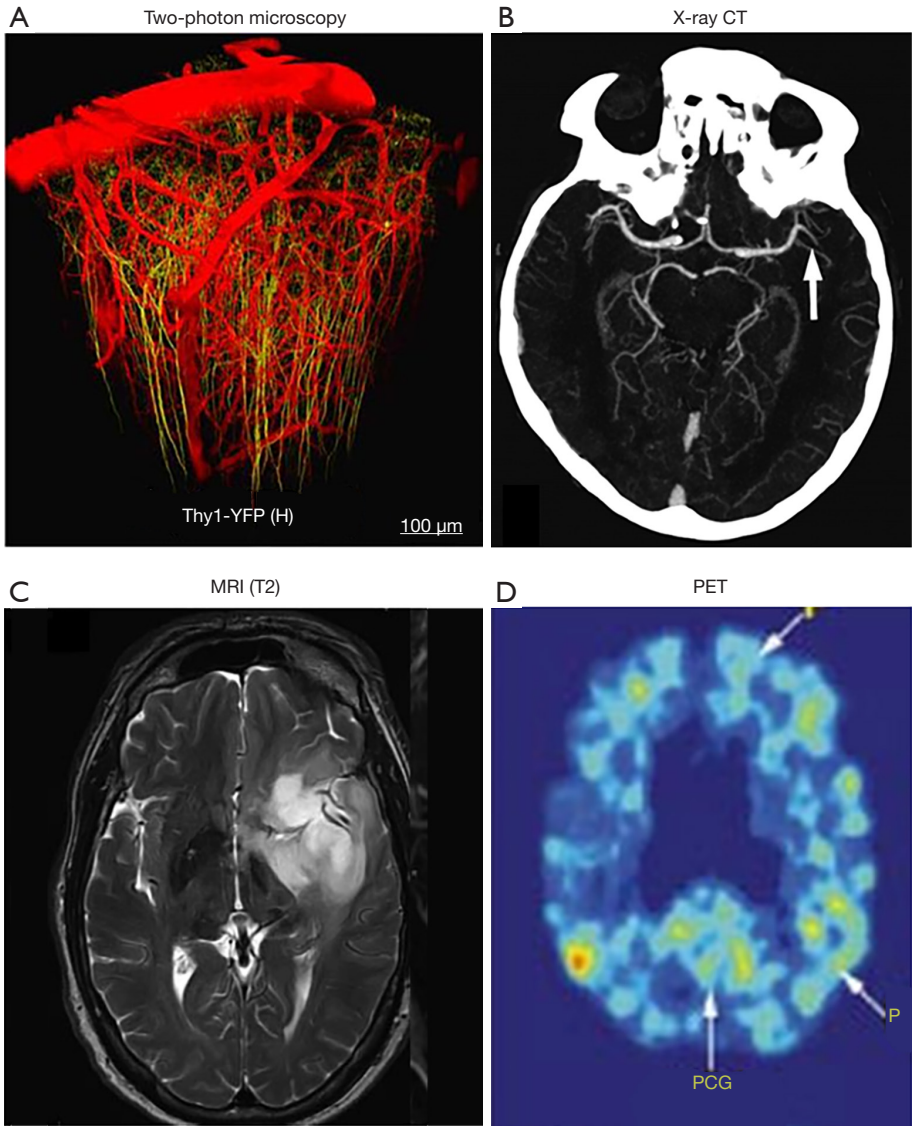

Figure 5 Representative brain imaging technologies. (A) Two-photon microscopy of dendrites of pyramidal neurons (shown in yellow) and blood vessels (shown in red) in somatosensory cortex of the Thy1-mitoCFP and Thy1-YFP mice. Adapted with permissions from (108). (B) Timing-invariant CT angiography image in a patient with a left-sided middle cerebral artery occlusion in the M2 segment. Adapted with permissions from (109). (C) Brain MRI: axial T2-weighted image of the brain demonstrates a hyperintense infiltrating mass of the left posterior frontal and temporal lobe with mass effect. Normal flow void is also noted through the left MCA branches. Adapted with permissions from (110). (D) PET scan in the parietal region in one subject with mild cognitive impairment who was reclassified on follow-up as having Alzheimer's disease. Red and yellow areas correspond to high amyloid senile plaque values. Adapted with permissions from (111).

functional and molecular information with balanced spatial resolution, penetration depth, and imaging speed (151-158). Although the skull still acts as a significant barrier for the ultrasound waves, photoacoustic tomography shows great promise in human brain imaging, with advances in light delivery, ultrasound detection, and image reconstruction.

Another promising technology is magnetic resonance fingerprinting that permits the non-invasive quantification of multiple important properties of the brain simultaneously with improved sensitivity, specificity, and speed when compared to conventional MRI (159,160). More importantly, when combined with appropriate pattern recognition and

data mining methods, magnetic resonance fingerprinting can potentially reduce the cost of the MRI by using lower magnetic field and shorter scanning times (161-163).

Further, to understand the aged brain, one also needs to understand how one region of the brain influences another. The ability to image these changes at different scales will help not only to understand normal brain functional architectures but also how complex diseases disrupt normal brain functions (164,165). For example, we could better understand how normal aging changes the connection between the hippocampus and cerebral cortex to translate the transient cortical neuronal activities (microscopic connection) to long-term memory (macroscopic connection). We may also better understand how Alzheimer's disease progresses from memory loss in the hippocampus to impaired judgment and reasoning in the cortex. However, there exist substantial barriers in scale and contrast mechanism among the traditional brain imaging modalities, which can study the aged brain only at the microscopic scale (e.g., two-photon microscopy) or the macroscopic scale (e.g., fMRI) with dramatically different signal origins. Correlation between different imaging tools is truly an engineering challenge due to their dramatically different imaging scales and contrast mechanisms. To study the complex brain systems, we need imaging technologies that can simultaneously image the aged brain at both microscopic and macroscopic scales. In other words, to better understand the brain, *in vivo* brain imaging at different scales needs to be joined to best extract the information. On one hand, imaging systems that can operate at multiple scales have been reported (166), such as ultrasound and optical imaging with multiple detection frequencies or wavelengths, or incorporate multiple modalities, such as the integrated PET and X-ray CT (167). On the other hand, with the fast advances in machine learning technologies (168-170), data fusion among different brain imaging modalities becomes more practical, not only to match the anatomical structures at various scales, but also to correlate the functions at different hierarchy levels.

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Footnote

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