Acute Stroke: What the Physicist Can Add

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Physicists, together with other healthcare professionals, play critical roles in the development, validation and translation of new imaging techniques in acute stroke. The term 'physicist' in this context is most appropriately defined to include a broad range of highly qualified individuals with advanced training, typically holding a doctoral degree, in biomedical engineering, biophysics, chemistry, computer science, mathematics, physics, statistics, or another area. These individuals bring a comprehensive array of scientific and technical expertise to bear on important clinical problems in stroke. Physicists represent a critical 'leg' of the 'three-legged' team advancing MR imaging in acute stroke. As already described in this session, the other 'legs' consist of neurologists (or other clinicians) and neuroradiologists.

Acute stroke is a relatively new application of neuroimaging. The precipitating need was the establishment, in 1995, of thrombolysis within 3 h of onset as the first approved stroke therapy.[1] Neuroimaging was required to verify absence of hemorrhage before treatment. Early trials relied on computed tomography (CT) to restrict thrombolytic treatment to non-hemorrhagic patients. Neuroimaging assessment has remained a critical requirement prior to acute stroke therapy and provides information for stroke management. The time from onset to thrombolysis has been extended in some situations to 4.5 h after onset,[2] however, the need for neuroimaging to exclude hemorrhage and to assist with patient management remains.

MR imaging can also be used to guide treatment decisions.[3] Like CT, it can be used to screen for hemorrhage,[4] but in addition MR imaging has the potential to provide a rich assortment of additional imaging-derived information on the acute stroke patient.[5,6] In Calgary, we were early proponents of 1) using high-field (3 T) MR imaging to triage acute ischemic stroke [7-13] and 2) a team-based, multi-disciplinary, approach to acute stroke imaging consisting of physicists, neuroradiologists, and stroke neurologists, as well as research and clinical trainees. We have worked effectively in a highly collaborative environment that encourages individual researchers to move outside of their respective areas of traditional expertise. Germane to this presentation is the concept of *physicist 2.0* – an individual that is familiar with *discovery science*, but who, to work more effectively with neuroradiology and neurology, also appreciates *idea translation*, *clinical science* and, possibly, *health outcome* (Figure 1). (In parallel broaden roles are seen for *neuroradiologist 2.0* and *neurologist 2.0*.)

Acute stroke represents a challenging target for MR imaging. "Time is brain" – there is urgency to properly diagnose those suffering from acute stroke. Protocols have been proposed to reduce scan time from ~15 min in 1999 [14] to ~6 min in 2015.[15] Decreasing imaging time is important because it is estimated that during stroke 1.9 million neurons die for every minute without blood flow being restored.[16] (For reference the typical adult human brain has about 22 billion neurons in the neocortex.) The need to image quickly is universally acknowledged, though in practice using a *too* abbreviated protocol may prevent a comprehensive evaluation. It remains unclear if fast MR protocols are indeed clinically efficacious; nonetheless, acute stroke MR imaging remains acquisition-time limited challenge. The physicist has an essential role is driving the development and evaluation of new technologies and providing additional scientific guidance to ensure their translation and clinical adoption. Here, we will review examples of previous contributions and muse on future roles.

Key Contributions to Acute Stroke Imaging - Physicist

Rowely [17] described the key goals of acute stroke imaging as assessing: 1) *parenchyma*, 2) *pipes*, 3) *perfusion*, and 4) *penumbra*. The so-called four '*P*s' have helped organize development of techniques around these critical clinical needs. Specifically, in the case of *parenchyma*, the use of T2*-weighted techniques can identify hemor-

rhage,[18] and diffusion-weighted imaging (DWI) can identify regions of restricted water diffusion.[19] Conventional (unenhanced) and contrast-enhanced MR angiography (MRA) can image arteries (>0.5 mm in diameter) to identify thrombotic or embolic occlusion in the *pipes*,[20] as well as vessel supplying blood to the brain.[21,22] Blood flow in the brain tissue (*perfusion)* can be assessed with temporally resolved techniques that follow a bolus of MR contrast agent.[23,24] Finally, information about *parenchyma*, *pipes* and *perfusion* can be combined to assess the *penumbral* region of brain tissue that is at risk of further damage.[25,26,3,27,28] Historically, the primary value add of the physicist is to interpret these concepts and realize/improve MR imaging techniques for their assessment in humans.

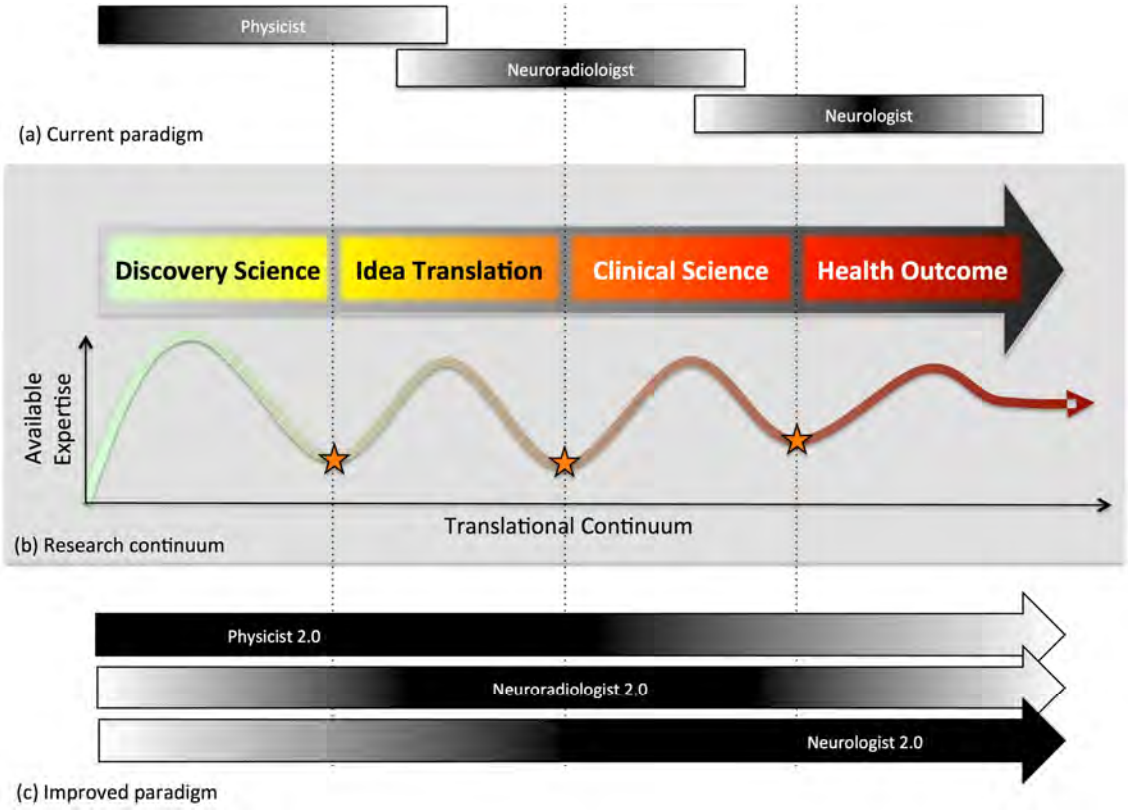

Figure 1: ***Translational continuum underlying development of new imaging techniques*** *– starting with a* discovery*, that is then* translated *through animal and human studies, becoming a* clinical science *approach under assessment and, eventually, evaluated for* health outcome *on patient care (b). Considerable effort is required to move through this continuum. At interfaces between expertise areas, there exist 'valleys' in the available expertise (stars). Historically, these valleys map to 'gaps' in expertise between physicists, neuroradiologists and neurologist (a). An improved team-based approach intentionally extends the breadth of individual expertise to ensure multi-disciplinary knowledge is available at each interface (c). For the 'physicist 2.0', this requires familiarity not only with discovery science, but also aspects of idea translation, clinical science and, potentially, patient outcome. Similar broadening of expertise is required for* neuroradiologist *2.0 and neurologist 2.0.*

1. Parenchyma

The health of brain tissue can be assessed using a number of MR imaging techniques: DWI can detect very early changes resulting from cytotoxic edema,[19] while fluid-attenuated inversion recovery (FLAIR) and T2-weighted fast spin echo (T2-w FSE) imaging are sensitive to the subsequent vasogenic edema (Figure 2 and Figure 3).[29,30,12] The MR signal in DWI is sensitive to changes in the diffusion rate of water molecules in tissue. Apparent diffusion coefficient (ADC) maps can be calculated from DWI data.

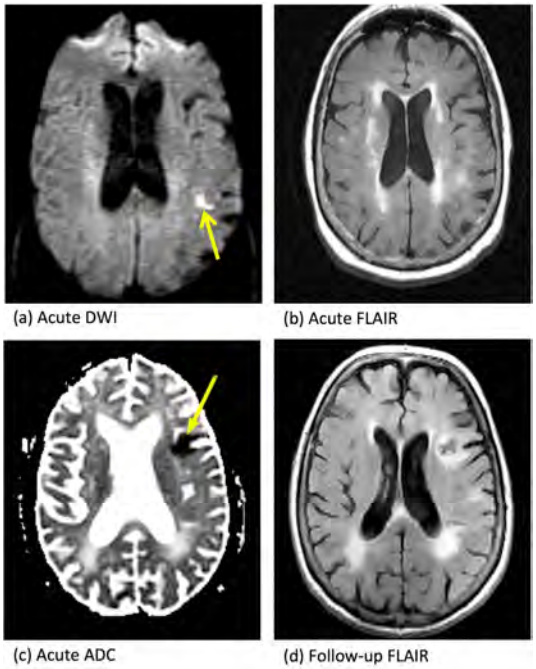

Figure 2: ***Acute and follow-up (30 day) DWI, ADC and FLAIR imaging*** *in two patients (a-b and c-d). Ischemic changes (yellow arrows) are seen on acute images. FLAIR imaging shows only late changes.*

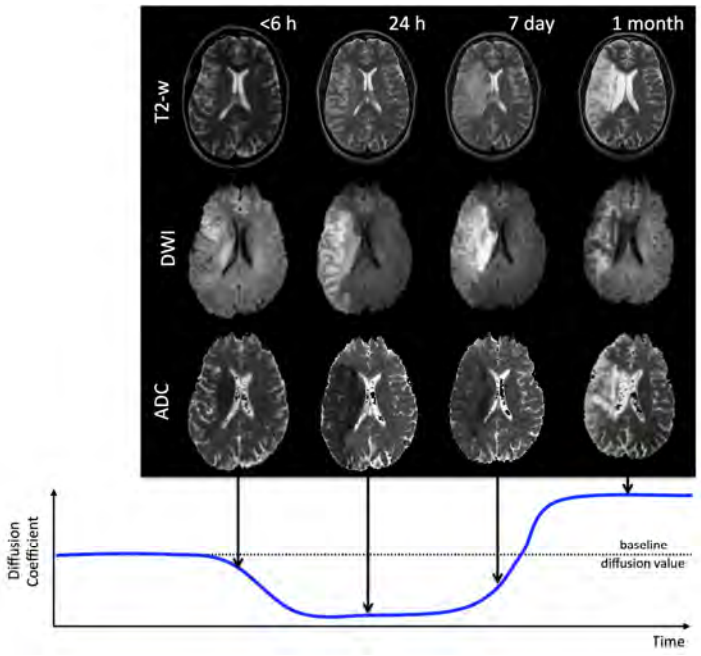

Figure 3: ***Time course of T2-w, DWI and ADC signal changes*** *over 1 month post stroke onset. DWI and ADC changes occur early, with T2-w changes occurring latter. The diffusion values in the ischemic lesion initially decrease due to cytotoxic edema, and then increase with vasogenic edema.*

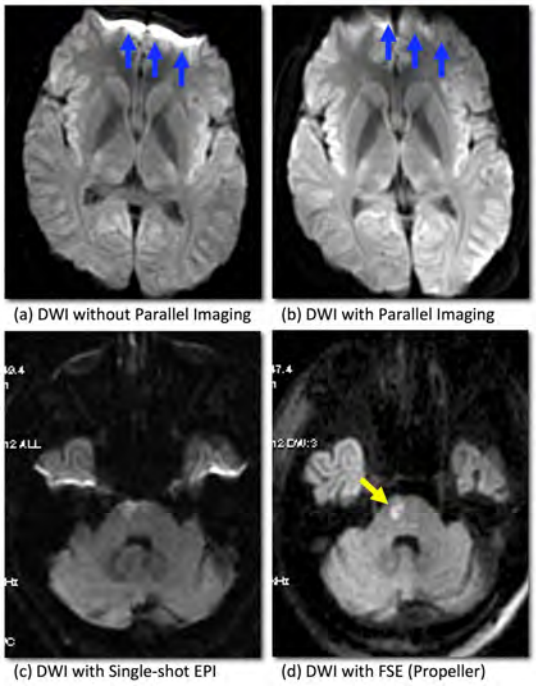

Figure 4: ***Impact of advanced MR imaging techniques****: (a,b) parallel imaging and (c,d) non-EPI based acquisition strategies on DWI image quality.*

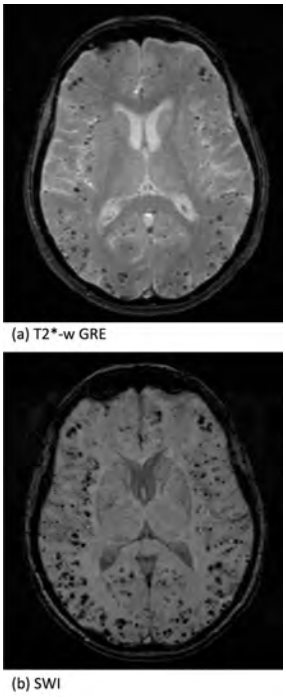

Figure 5: ***(a) T2*-w GRE imaging and (b) SWI of micro-bleeds*** *(regions of hemorrhage). Signal difference is due to change in susceptibility due to blood iron.*

DWI typically uses echo-planar imaging (EPI) to quickly acquired data and to decrease sensitivity to patient motion.[12] EPI, however, introduces significant artifacts into the resulting images, particularly near regions of susceptibility change (*e.g.*, sinuses, base of brain, Figure 4). Parallel imaging and the use of non-EPI acquisitions strategies (*e.g.*, Propeller [31]) can improve image quality.

Detection of hemorrhage is critical prior to committing to thrombolysis for acute stroke.[5] A variety of approaches are available that are sensitive to the change in magnetic susceptibility due to the iron in hemorrhagic blood. T2*-w gradient-recalled (T2*-w GRE) [18] and susceptibility-weighted imaging (SWI) [32] are two approaches for visualizing hemorrhage and micro-bleeds (Figure 5).

2. Pipes

MRA can be used to assess both the intra- and extra-cranial vessels. In the brain, MRA is used to look for occluded vessels (Figure 6) and evidence of vascular disease. 3D Time-of-flight (TOF) imaging is able to produce high-resolution images of the circle of Willis and distal vessels. Imaging after the injection of an MR contrast agent (*i.e.*, a gadolinium chelate) has been shown to help identify thrombus and collateral filling. Extracranially, both TOF and contrast-enhanced MRA (CE MRA) are used to typically investigate the carotid, basilar and vertebral arteries (Figure 7). More sophisticated techniques are also in use and development for characterizing carotid artery disease.[22]

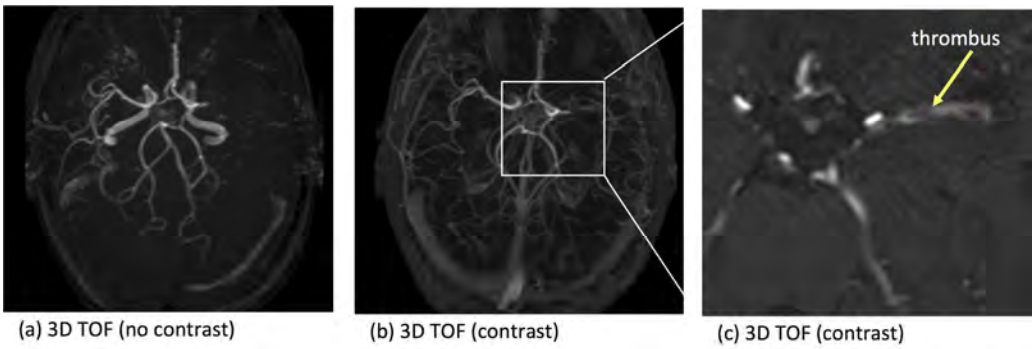

Figure 6: ***3D TOF projection images (a) before and (b) after injection of a MR contrast agent****. (c) A thrombus (yellow arrow) is visualized after contrast injection in the middle cerebral artery of this patient.*

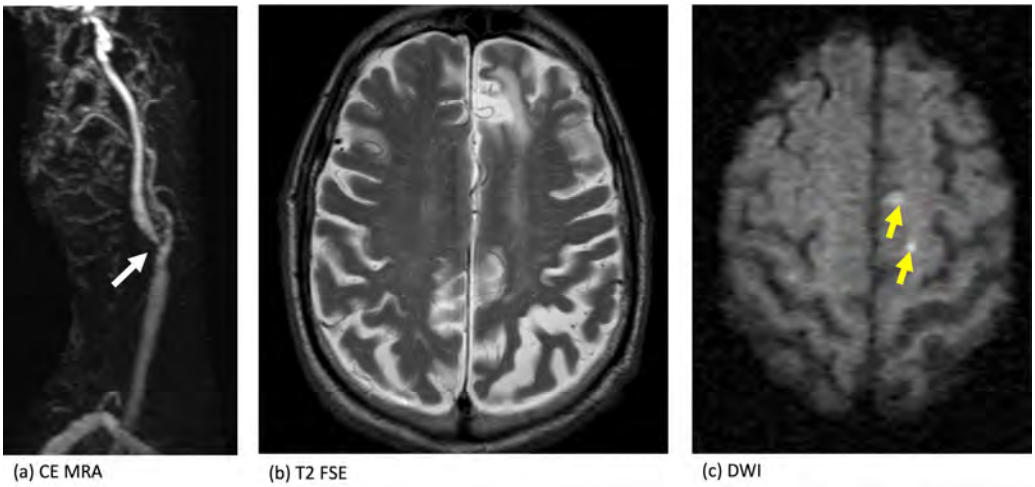

Figure 7: ***CE MRA of a carotid artery with disease*** *(white arrow) at the bifurcation (a) showing evidence of acute infarction on (c) DWI (yellow arrows) but not on (b) T2 FSE imaging.*

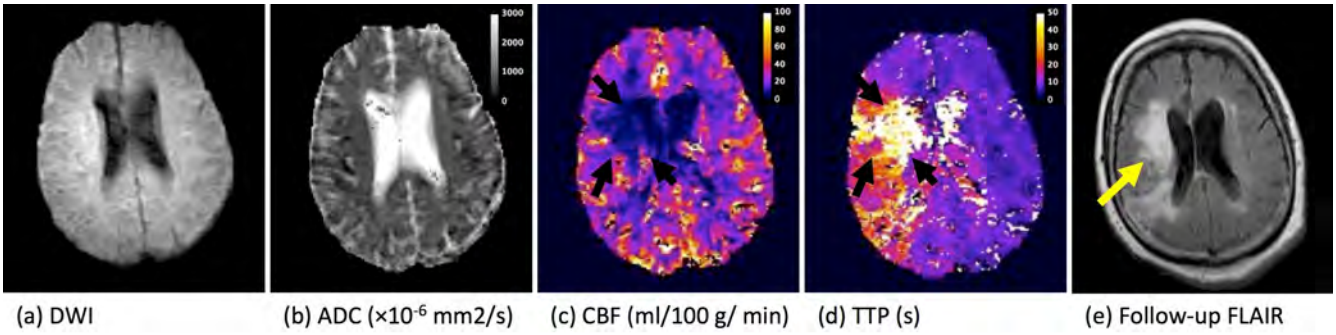

Figure 8: ***Early ischemic changes (black arrows) are seen on (c) CBF and (d) rTTP perfusion maps*** *that approximate the final lesion (yellow arrow) on (e) follow-up FLAIR imaging. Changes were not visualized on (a) DWI or (b) ADC maps.*

3. Perfusion

MR can assess the perfusion (*i.e.*, blood delivery to brain tissue) by using endogenous or exogenous alterations to the MR signal from blood. Arterial spin labeling (ASL) [33] use endogenous approaches by labeling the blood in the neck before it flows into the brain.[34] It is less commonly used in acute ischemic stroke because the label is not persistent, making perfusion assessment challenging in older subjects, or in the presence of proximal arterial occlusion and/or collateral flow. Exogenous approaches follow the passage of a bolus of MR contrast agent, typically with an EPI sequence that is sensitive to T2* changes (a technique known as dynamic susceptibility contrast (DSC) imaging).[35]

DSC perfusion imaging can make both relative and quantitative maps of perfusion parameters, including: 1) cerebral blood flow (CBF, in ml/100 g brain tissue/min), 2) cerebral blood volume (CBV, in ml/100 g), 3) mean transit time (MTT, in s) and 4) time-to-peak (TTP, in s). Relative CBV, MTT and TTP (rCBV, rMTT, and rTTP) can be calculated from the signal *versus* time curves. Quantitative perfusion estimates (Figure 8) require conversion from signal to concentration and then deconvolution of the arterial input function (AIF) to obtain the contrast agent residue function. Because of partial volume effects in the AIF and other non-linear effects, it is generally necessary to rescale the results (by cross-calibration, *i.e.*, setting normal white matter CBF to 22 ml/100 g/min).[36]

4. Penumbra

A key element of any therapeutic decision in acute stroke is the identification of penumbral tissue – which is defined as tissue that is at risk of subsequent infarction.[37,25] No one MR imaging technique identifies penumbral tissue. Typically penumbra is defined based on multiple techniques and operationally generally consists of tissue that has compromised perfusion but is not infarcted. This notion is described as the diffusion-perfusion mismatch.[25] Information from MRA (such as an intracranial occlusion or suggestion of collateral blood flow) and T2*-w imaging (presence of hemorrhage) can confirm or potentially modify identification of tissue at risk and, thus, serve as a basis for treating appropriate patients. Other, more quantitative, approaches [38,24] have attempted to look at thresholds in ADC maps and combinations of perfusion based thresholds.

Future Roles – *Physicist 2.0*

Physicist 2.0 will have an expanded role in MR development in acute stroke and related cerebrovascular conditions. Not only will they focus on the core area of *discovery science* (Figure 1), but as part of appropriately assembled research teams, *physicist 2.0* will also influence *idea translation* and *clinical science*, as well as having a lesser role in *health outcome* assessment.

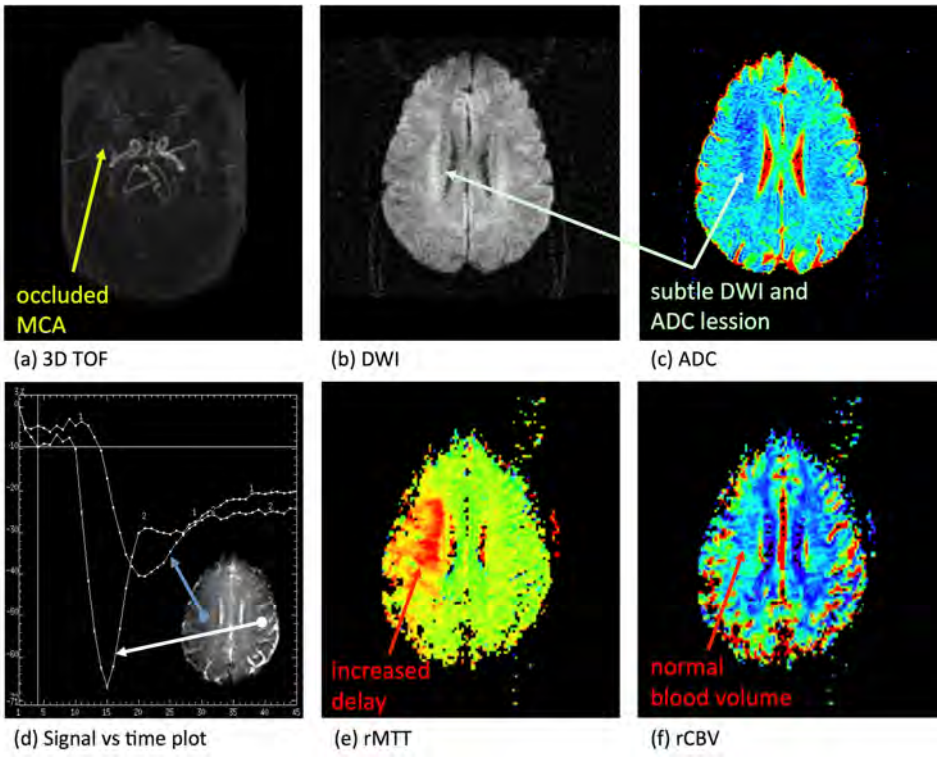

Figure 9: ***Penumbral imaging 2.2 h after stroke onset****: (a) 3D TOF imaging shows an occluded right middle cerebral artery, (b,c) DWI an ADC show subtle deep changes, (d-f) perfusion imaging shows difference in measured MR signal vs time during contrast agent passage, increased rMTT and normal rCBV. The penumbra region (tissue with perfusion change but no or subtle diffusion change) suggests brain tissue is salvageable.*

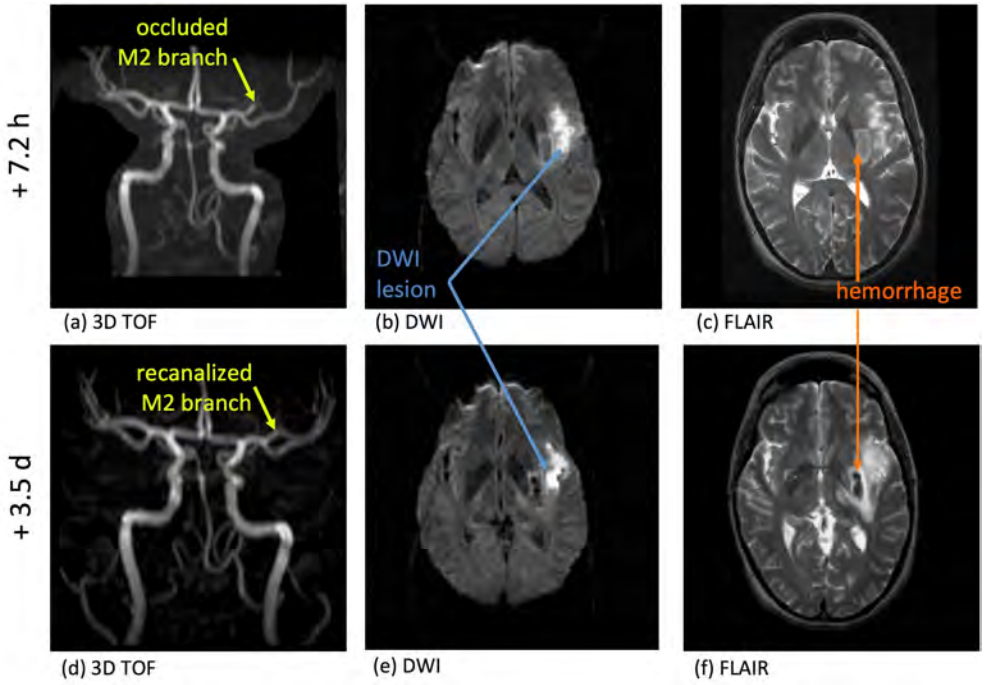

Figure 10: ***Penumbral imaging at 7.2 h post stroke onset*** *with (a) 3D TOF showing a right middle cerebral artery M2-branch occlusion, (b) diffusion changes and (c) a previous stroke with hemorrhage. At 3.5 days post onset, (c) the vessel recanalized but some evolution of infarct was seen on (e) DWI and (f) FLAIR imaging.*

Ongoing work quantifying T1, T2 and other changes seen in animal models of acute stroke (*cf.,* [39,40]), requires further study for *parenchymal* characterization. Investigation of quantitative susceptibility mapping approaches may allow for better understanding of hemorrhage [41] and micro-bleeds.[42] Work on development of high resolution, large coverage time-resolved CE MRA techniques show significant promise for assessment of the *pipes* in the neck and brain as well as estimation of key *perfusion* parameters.[43] Improved MR imaging methods for characterizing cardiac and vascular disease will potentially allow for better assessment of stroke risk and recurrence.[44] Imaging, particularly at 7 T, has shown that small perforating arteries can be imaged, possibly, allowing for improved assessment of collateral flow pathways.[45] Development of dynamic contrast-enhanced (DCE) T1-weighted perfusion imaging approaches [46] suitable for use with near intact blood brain barriers will allow for absolute perfusion measurement (in a fashion similar to CT perfusion) without a need for cross-calibration. DCE techniques may also allow for estimation of permeability using advanced kinetic modeling.[47] Novel cerebrovascular reactivity techniques may also allow for critical functional assessment of minor stroke.[48] The definition of *penumbra* (*i.e.*, diffusion-perfusion mismatch), while useful clinically, remains inexact. Opportunities, thus, exist to develop more comprehensive predictive models [49] that incorporate not only DWI and perfusion maps, but also MRA and T2* imaging, plus the described and other emerging MR imaging concepts.

To most achieve the full impact of these discoveries, efficient paradigms for translation and for clinical evaluation need to be developed. This will require *physicist 2.0* to be active members of multi-disciplinary research consortia and networks, and to participate fully in the development of acquisition and reporting standards. Finally, current and future imaging techniques need to account for the emergence of tele-stroke and related methods for distributed stroke care, as well as new interventional methods of stroke therapy.[50,51]

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