Olea Imagein

Predictive Imaging

Olea MEDICAL

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Edito

Fayçal Djeridane
Founder and President of Olea Medical®

Predicting the future is an eternal quest for human kind. A long time ago, shamans were reading the future in their dreams, using their environment and the present to shape the future. As Prof. Elias Zerhouni said "What will exist tomorrow in the medical field already exists today". The Artificial Intelligence is a good example of that. Already in the 50's, Alan Turing, who can be deemed as one of the fathers of AI, started questioning machine intelligence; but only recently, thanks to the empowerment of the GPU, it became a reality. It is now feasible to predict Alzheimer's disease 6 years in advance!

The beauty of MR imaging is that we are still far from the full expression of the predictive power for all the existing or future sequences. The next major steps in MR scan will be standardization and quantitative imaging. For instance, having reliable and repeatable absolute values is mandatory to diagnose a tumor in an automatic way, predict and follow its response to treatment.

Thirty years ago, when a trauma was arriving in an emergency room, only few images were acquired. Now, around 5000 images are produced. Who can read them all in the context of an emergency? No one. No one? Not really. AI can do it. Dr Peter Chang, head of the AI laboratory of the University of California, Irvine (UCI), has developed an automatic triage of patients in neuro emergencies based on CT scan. The first major AI applications in the medical field will be for CT scan. Indeed, the Hounsfield unit standardizes its values.

For major vendors, healthcare reimbursements are one of the driving forces for the creation of research applications. However, hundreds of new start-ups are taking up the challenges left behind by the big companies which are focused on revenue only. They are leading the development of artificial pancreas, artificial heart, predictive diagnosis, genomic therapy, etc. In all these challenges MR will play an important role.

At Olea Medical®, thanks to our astrophysicists, we provided the Bayesian perfusion, which brings the quantitative perfusion maps to the next level. MR scan is for doctors what telescope is for astronomers. We are overcoming the limits of knowledge to the utmost patients' benefit.

In this issue, we will present some of the most promising MR techniques.
Have a good reading!

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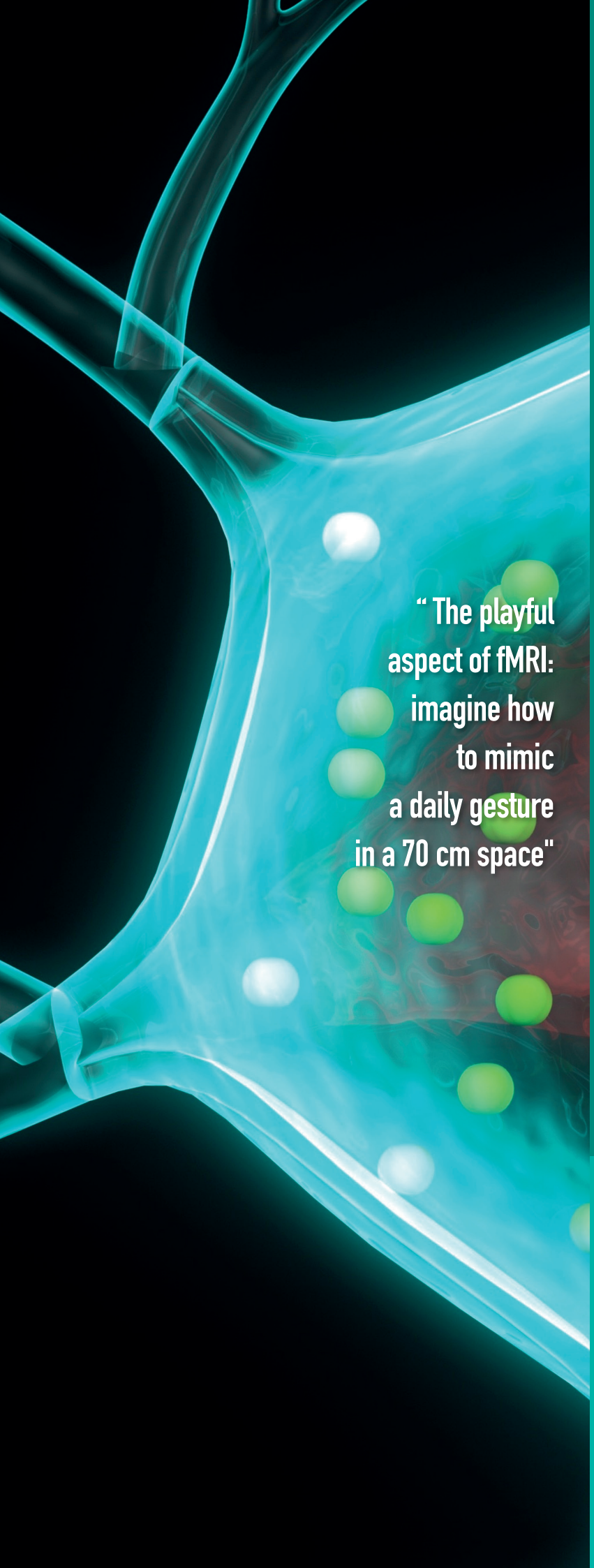
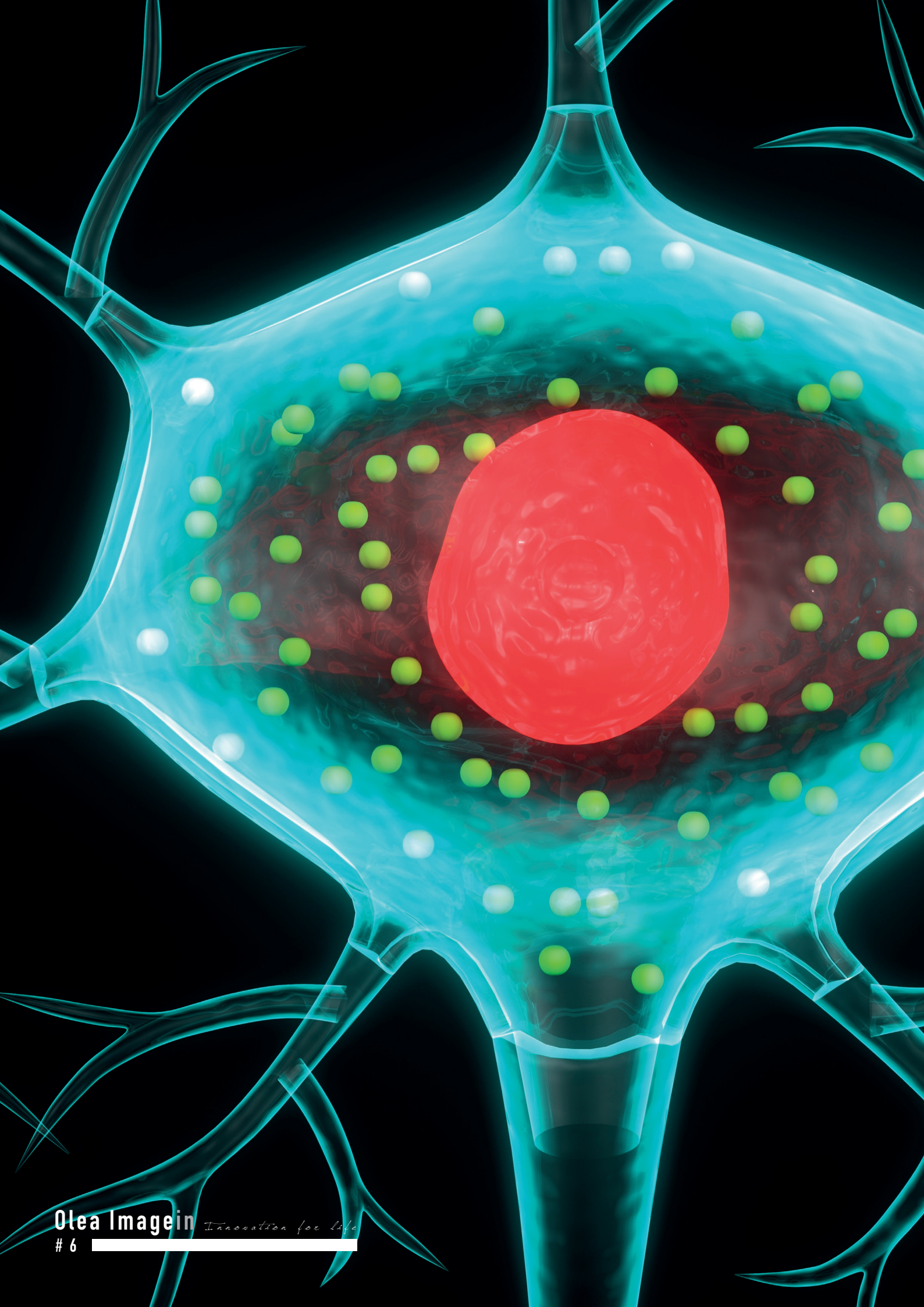
IMPROVED DIAGNOSIS FOR LIFE

Understanding Functional MRI



Charles Mellerio, MD, PhD
Neuroradiologist at Sainte-Anne Hospital, Paris and at Centre cardiologique du Nord, Saint-Denis, France.

Charles Mellerio is a neuroradiologist focused on two main areas: epilepsy and functional imaging. After completing his medical training and radiology residency, he specialized in cerebral imaging and earned his PhD in neurosciences.
His activities as a neuro-radiologist are conducted over two clinical sites: Sainte-Anne hospital (Paris) for academic research, clinical and functional MRI, and Centre Cardiologique du Nord (Saint-Denis) where fMRI and advanced imaging are also performed.



Olea Imagein *Innovation for life*
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Olea Imagein: Could you briefly overview the principles of BOLD fMRI based on task hemodynamic response?

Charles Mellerio: Functional MRI records the cerebral activity through an indirect process. Why indirect? Because, unlike electroencephalography (EEG) or other techniques, the measure is not linked to the electrical activity of the neurons themselves but to their aftereffect, consisting in very local and secondary vaso-reactions. When neurons discharge, they need oxygen, provided by hemoglobin, to proceed. As a consequence, very local increases – accurate to the nearest millimeter – of cerebral blood flow occur, with a massive intake of oxyhemoglobin.

The brilliant point with MRI is that hemoglobin under its oxygenated or deoxygenated form does not have the same signal. It is therefore possible to create brain contrast between activated and "rest" areas.

There are two prerequisite items for fMRI. First, the patient must perform a cognitive task in the scanner. It can be a simple task, such as moving a hand – which of course implies a cognitive control of that movement; or more complex tasks, such as exercises of language, words production, understanding, reading, object recognition or even more high level functions dealing with emotions or memory. Of course, the more complex the functions are, the more difficult they are to highlight in the brain. Simple or primitive functions, i.e. using the primitive motor, visual or auditory cortex, are easier to isolate.

The second prerequisite item is related to the low orders of magnitude of the measured signals. Indeed, fMRI detects a differential between an activated zone and the remaining resting areas of the brain. Unfortunately, cerebral rest does not really exist – except in the deceased subject! Therefore, the only way to detect a weak signal variation – about 5%, is to repeat the task several times and alternate with periods during which the cognitive task is not performed. This sequence is called a paradigm. The most commonly used paradigm in clinical routine is designed according to a block strategy, where for instance motion is alternated with stillness, or passive text listening is alternated with silence, every 15 to 30 seconds during 3 to 4 minutes.

These sequences result in complex cognitive issues. For example, if a story listening task is performed versus silence, a cognitive treatment of language understanding will occur in the brain; but the integration of a noise – i.e. language, will also be treated. Therefore, two different areas are activated: first, the non-language-specific primitive auditory zone, located in the temporal lobe at the Heschl's gyrus level and bilaterally activated no matter what sound is heard – drill, music or language; second, the area we expect to identify and characterize in terms of laterality, named Wernicke's area and dedicated to language understanding.

In other words, the language-specific cognitive information is drowned into other non-language-specific data. Therefore, we have to design pure paradigms able to isolate a particular task, which is both interesting and challenging. In the previous example, we can for instance alternate story versus non-understandable noise listening – what we usually do is reverse the soundtrack to make it unintelligible while still maintaining a similar acoustic processing.

O.I: What about resting state fMRI?

C.M: We did a summary of the principles of task-based fMRI, robust and used in clinical routine, but involving the patient's cooperation. Besides this method, we also have the possibility to conduct resting state fMRI. This technique does not require the patient's contribution, which is a great advantage. The patient only has to try as much as possible to "switch" his brain into rest, for a long time – between 5 and 10 minutes. He/she is told to let his/her mind wander freely, without focusing on a particular idea. The variations of the BOLD signal are then recorded, using the same signal extraction techniques as in task-based fMRI.

What happens is that a brain "at rest" is actually not at all on break. Spatially remote cerebral areas that share functional properties, such as sensory-motor, visual or executive control networks, are spontaneously temporally correlated (i.e. produce a synchronous signal). Thereby, areas with similar signal evolutions over time can be extracted; these areas shape networks. Two main methods of analysis are available for that purpose: the Independent Component Analysis (ICA) which blindly extracts all independent

networks with a statistical approach; and, a region-based technique which starts from defined ROI used to calculate correlations with other voxels of the brain. The issue behind this process is that confounding connections can be wrongly identified, due to head motion, heart rate or cerebrospinal fluid (CSF) variations for example; a preliminary step is therefore necessary to select proper networks.

> "The major fMRI applications described above deal with neurosurgery"

Task-based and taskless fMRI show complementarity. The most used functional imaging technique in clinical routine is the task-based one, because it has been investigated for a very long time and has been validated in clinical studies. In most of the units, resting state is only used in addition to task-based fMRI, in order to provide complementary information especially for patients whose cooperation is difficult to obtain – children or disabled people. Moreover, taskless fMRI is a precious research tool for pools analysis, e.g. epileptic versus healthy people, in order to evaluate the networks modifications when considering pathologic versus normal condition.

O.I: On which criteria do you select the patients for an fMRI exam? What are the applications and the associated chosen paradigms?

C.M: Main indication of fMRI is pre-surgery planning for brain tumors. A patient with a brain tumor located near a functional area is at high risk of post-operative dysfunction if the surgeon damages that critical area, linked to a cognitive function, when removing the tumor. fMRI helps mapping the healthy zone near the tumor that needs to be preserved. From a theoretical point of view, it is a very powerful tool. Unfortunately, especially for high grade tumors that induce local modifications of vaso-reactivity and edema, this can result in false positive and/or false negative responses near the tumor. Therefore, though precious and systematically performed here in Sainte-Anne hospital before any awake surgery, task-based fMRI is not an exam on which the surgeon can rely 100%.

Of course, each patient will not perform all the possible paradigms – there are dozens of them. The choice is established in relation with functional anatomical landmarks, according to the tumor's location. For example, if the lesion is close to the Sylvian fissure either right or left, we will favor language exercises; more precisely, either language production if the tumor is located in the inferior frontal region, or speech comprehension in the temporal region. In case of a lesion close to the central sulcus, the paradigms will be chosen so as to apply to the sensorimotor cortex, with motion exercises and tactile stimulation; if in the occipital area, the visual network will be favored, etc. In summary, according to the tumor's location, a set of paradigms will be selected, as broad as possible while still compatible with the machine's time – less than 30 minutes; beyond that duration, the patient will have trouble achieving the tasks. During that period, slightly longer than a conventional MRI, 3 to 5 paradigms lasting 3-4 minutes each, in addition to anatomical sequences, are achieved.

The second main indication for fMRI relates to patients with an epileptogenic lesion, inducing a chronic and drug-resistant epilepsy. These patients may suffer from epileptic seizures several times a day, sometimes since childhood; they are known to experience a reorganization of the normal functional areas in the vicinity of the epileptogenic site. If the lesion causing epilepsy is for example in the left temporal lobe, generally associated with language, functional regions of language can move in another lobe or even on the right side. Therefore, the contralateral hemisphere can be solicited for a task usually performed in the other side. When the drug-resistance is diagnosed – in about 50% of the cases, meaning that no usual medical therapy can treat the patient, a focal cortical surgery is proposed to remove the epileptogenic lesion. At that stage, knowledge of the normal networks together with their potential re-organizations is essential. fMRI allows to predict and assess the post-operative prognosis regarding language, memory, potential dysfunctions, and therefore to tailor the surgical procedure.

Other indications consist in targeting functional cortical zones with fMRI in order to perform trans-cranial magnetic stimulation or to implant electrodes.

Trans-dural electrodes, positioned near the motor regions, are indeed indicated for treating neuropathic pain – for example pain in a leg following a nervous avulsion, or pain related to the phantom limb syndrome. In the latter, we find bias to identify the former motor functional areas, by asking the patient to imagine the movement of the missing limb.

The major fMRI applications described above deal with neurosurgery, but there are also secondary non-surgery indications in clinical practice – in research, of course, a wider scope of topics is addressed especially in the field of psychiatry.

For a very long time before fMRI, clinicians were basing their assumptions on structural anatomical landmarks, on sulcus positions, since we know that some of them are very stable from one individual to another. However, when a tumor distorts those landmarks, the positions of the functional areas are not reliable anymore, they have to be highlighted by fMRI. Moreover, regarding language, there is a wide inter-individual variability; this is precisely where fMRI is interesting; it is not an imaging technique applied to a group but to an individual, for a personalized medical care.

O.I: Which developments are still expected to improve the mapping of cerebral functional areas?

C.M: The analysis of vaso-reactivity, which is the basis of fMRI, can fail if locally modified by a tumor, due to neoangiogenesis process; this is the main bias. Therefore, improvements could derive from more accuracy regarding vaso-reactivity, for example using a Bayesian method as developed by Olea Medical®. The aim would be to study the hemodynamic

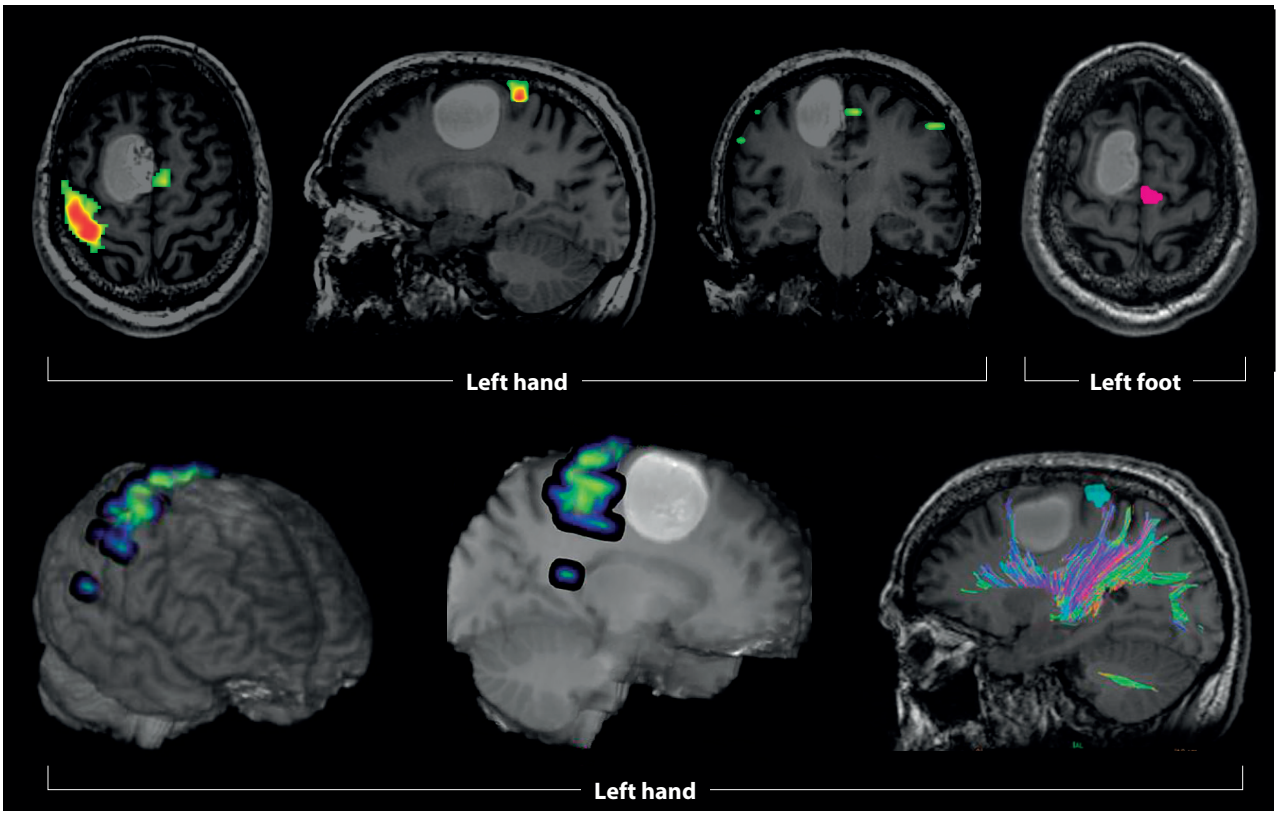


Figure 1: fMRI and DTI in a 45 year-old patient with a right paramedial frontal metastasis using Olea Sphere® software. Anatomical landmarks predict that this brain tumor is close to the Supplementary motor area (SMA). fMRI is thus performed with 2 motor tasks (left foot and left hand) and shows primary motor responses located in the right precentral gyrus, distant to the posterior limits of the tumor. However, SMA responses are only visualized on the left side and can thus be interpreted as a functional reorganization. The pyramidal tract is also visualized with DTI close to the posterior part of the lesion. These informations are precious for the neurosurgeon and are directly transferred to the operating room.

response function (HRF) more individually and more locally, instead of a canonical approach. Therefore, I believe that the main areas for improvement lie in an increased accuracy for HRF estimation, in order to be as close as possible to the neurons' electrical activity.
There is also room for evolution in the design of post-processing tools, currently separated in two groups: either simplistic, nicely displayed but with poor control on the results; either very complex, usually built for and dedicated to research, requiring programming and unable to provide images that are interpretable for a surgeon. The best would be to have a tool at the interface between clinical and research needs. fMRI implies many complex post-processing steps, that need to be controlled and adjusted if needed.

The ideal software would allow such a freedom for clinical checking, while remaining user-friendly, fast for a proper integration in the clinical environment, robust and accurate. Some of the current tools are easy to use, but their level of confidence is low at the first sign of trouble.

Another useful development would be to decrease the duration of the paradigms, the tasks being sometimes exhausting for the patient. In order to reduce the MR time, the radiologist has to make choices, between vision and language for example; this can be frustrating. I do not know yet where the improvements will come from, maybe from the paradigm design or from acquisitions themselves (by acquiring simultaneously multiple slices for example), but I hope to get the possibility in the future to perform more paradigms in less time.

Also, as radiologists we learnt to refrain from imagining motion not allowed in an MRI scanner, such as running; this could be considered as a limitation. However, we can still reproduce many gestures of everyday life - even playing the piano on a plastic board, and many different cognitive tasks. This is the playful aspect of fMRI: imagine how to mimic a daily gesture in a 70 cm space.

O.I: To which other methods can fMRI be combined to capture a larger clinical picture of the patient?

C.M: This is a very interesting and important question. fMRI, if considered independently, has no real value. The technique has first to be included within the patient's anatomy, which requires brain segmentation and visualization tools, with optimal anatomical sequences. Also, fMRI has to be combined and fused with methods able to characterize the lesion, such as diffusion and perfusion, in order to assess its aggressiveness. The problem is that currently, too many tools operate independently of each other; the anatomy, the perfusion and diffusion data, the tensor imaging information are scattered among different computers or even different rooms. The radiologist has no choice but to perform a mental gymnastics to mix all the data. Ideally, we would need powerful and robust synchronization, registration, superimposition of these essential findings for a given patient – without falling in the opposite excess: losing readability because of too many superimposed information.

Of course, not to mention that DTI is part of fMRI. DTI is mandatory when fMRI is performed, they come together and have to be processed by the same tool. This is today fortunately the case, since manufacturers understood the high complementarity between these two indivisible methods.

As a conclusion, I really feel that we are in a transitional phase with fMRI; the early marvelous period, when we were realizing for the first time that we could witness the brain thinking *in vivo*, is now over. This time was followed by a great disappointment related to the lack of 100% reliability. Today, we are at a crossroads, between those who have tremendous expectations and those who would prefer to give up. The coming years will be very open and crucial to make fMRI become either a powerful and essential tool, or a gadget. I clearly belong to the first group.

Principes & Applications of Diffusion Tensor Imaging

"DTI offers two main types of applications: fiber tracking and quantitative imaging"

Damien Galanaud, MD, PhD
Professor of Neuroradiology,
La Pitié Salpetrière, Paris, France.

Damien Galanaud is neuroradiologist at Pitié Salpetrière Hospital. After medicine studies in Paris and a PhD in Marseille directed by Prof. Patrick Cozzone, he is now involved in clinical and research projects related to head trauma, coma and white matter pathology.

His head trauma research is conducted in association with several international centers, including a close collaboration with the Massachussets General Hospital in the United States.

Olea Imagein: Could you shortly summarize the basics of diffusion tensor imaging (DTI) and tractography techniques?

Damien Galanaud: Fundamentally, DTI allows to image the white matter structure using the motion properties of water molecules. This technique is based on the primary diffusion imaging sequence, used in stroke diagnosis. However, diffusion does not by itself inform about the white matter structure, it only identifies cerebral areas where water diffuses easily or not – and hence helps detecting an ischemic stroke in the regions with low apparent diffusion coefficient (ADC). DTI is a refinement of this technique: it does not only evaluate how easily or difficultly water diffusion occurs within the brain, but also in which direction and with which properties. In the cerebral parenchyma, especially within white matter, water molecules are channeled by the axons, the dendrites and the myelin sheaths. Using DTI, we can therefore study both the connections between the cerebral regions and the integrity of the axons and the myelin sheaths. This double ability naturally leads to two main families of applications.

> “…tractography is extensively used for pre-surgery assessment of cerebral tumors”

The first one, fashionable and commonly used in clinical routine, relates to morphological data regarding how the cerebral regions are connected to each other. White matter fiber tracking provides this information, which is interesting in the field of basic research and pre surgical planning of epilepsy and brain tumors. It is usually combined to morphological sequences such as 3DT1 or to functional MRI. The second area of applications deals with the quantification of white matter damage, using other parameters linked to water diffusivity; various mappings can be obtained for different white matter diseases.

In summary, DTI offers two main types of applications: fiber tracking for morphological information and evaluation of white matter damage using DTI-derived biomarkers – fractional anisotropy, mean diffusivity, axial diffusivity, radial diffusivity; these markers are able to quantify the white matter status, they hence belong to the quantitative imaging field.

O.I: What are the main indications for DTI? How relevant is the method for evaluating prognoses?

D.G: From a clinical point of view, open research is conducted to understand the interconnections of brain regions. For that purpose, very accurate sequences are required regarding the measure of diffusion. This accuracy can be reached if the spatial resolution is improved and if the parameters are efficiently computed. To achieve this, the MR sequences need to be more and more complex, for example using Q-ball or NODDI (Neurite Orientation Dispersion and Density Imaging) models. Getting smaller voxels helps better tracking the fibers and therefore to solve our main issue: fiber crossing in the brain, meaning that there is an unknown item in the equation. Advanced sequences can help assessing the detailed wiring of the brain and the multiple directions of the fiber tracts.

As for clinical applications, tractography is extensively used for pre-surgery assessment of cerebral tumors – though it is also sometimes performed during a stroke event, in order to understand if the patient can recover or not. With DTI, the tumor is located with respect to the white matter tracts, providing information regarding the surgeon's margin for tumor excision: is there a risk to cut a track and therefore induce a post-surgery dysfunction for the patient? This is the first application. Some work is also conducted on a medullary level, for myelopathy and multiple sclerosis, but this is a much more unexplored and incidental area of investigation due to the complexity of implementation; indeed DTI resolution is currently insufficient – about 2 mm for isotropic voxels in routine clinical settings, to image the spinal cord; moreover, bone creates large artefacts on the acquisitions.

For quantitative imaging, reaching a high morphological accuracy is not as important as for fiber tracking; the essential factor is rather reproducibility. Diffusion tensor is extremely sensitive to the variations in acquisition parameters and machines. Two MRI scanners with exactly the same magnet, same coil and

same software version can produce slightly different measures; for that reason, we need extremely stable sequences and establish processes for normalizing the values on controls.

Quantitative mapping is used for prognosis in various pathologies, with excellent predictive results in head trauma and cardiac arrest. For both pathologies, the technique can assess whether the patient will wake up and recover, or not. Regarding even mild head trauma, studies have shown that DTI could discriminate between patients with neurologic sequelae, often difficult to evaluate, and patients with good recovery. We can immediately see the potential interest to make an objective assessment of the cerebral injury in head trauma patients, with all the implications this may have in terms of compensation for the injury.

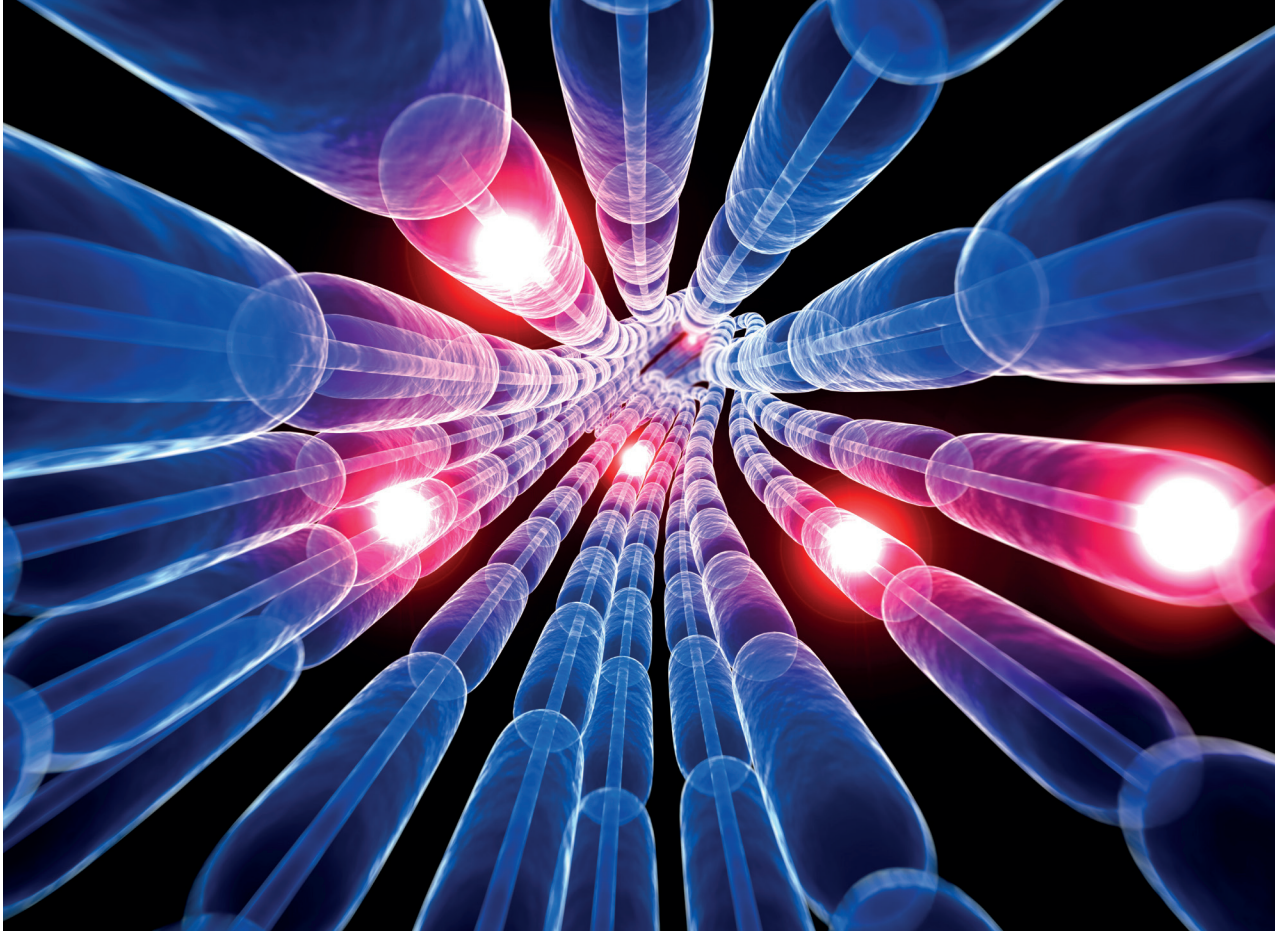
Reaching the aim of reproducibility is possible if we scan normal volunteers as controls on the machines – in that case, it works very well, we have already shown that. Of course, we would prefer not to require these controls by considering several approaches: developing phantoms, as for other sequences, but none really satisfactory are available on the market yet; or using T1 / T2 mapping and myelin imaging to compensate for the variability.

O.I: How predictive and discriminant are the various biomarkers derived from DTI (diffusivity, fractional anisotropy, etc.)?

D.G: Let us proceed from the simplest to the most complicated case. The simplest is cardiac arrest. We used to have numerous and very efficient clinical markers for cardiac arrest prognosis. However, these were developed prior to the introduction of recent therapies. Indeed, unlike what one might think, resuscitating a patient with cardiac arrest is only the first step of the medical care. In a second time, the person is placed in therapeutic hypothermia condition in order to maintain the brain in a resting state for 48 hours – hypothermia has proven to significantly improve the patient's prognosis, even if cardiac arrest remains a terrible pathology with a 90% mortality rate. However, our previous clinical biomarkers are no longer valid with the hypothermia procedure – we noticed that some patients, unfavorably classified by these classical biomarkers, were evolving favorably after hypothermia treatment. These indicators could be replaced by quantitative diffusion tensor analysis. Indeed, our research group and other teams demonstrated that DTI could provide an objective evaluation of the cerebral damage, and could help answering the following question, with more than 95% sensitivity and specificity: will the patient wake up or not? This accurate and reliable evaluation renders the intensive care more secure; if resuscitation is finally stopped, the clinicians definitely know why they made this decision: because the patient had no chance to survive with acceptable neurological sequels.

The second type of pathologies is severe head trauma – when people are in coma. As for cardiac arrest, resuscitation is performed a priori; however, the procedure can last for a very long time, without any clinical or biological tool able to predict the patient's outcome, whether he/she will resume a normal life or will suffer from severe sequelae. Severe sequelae are defined as people integrating rehabilitation or long-stay centers, without ever coming back home. Due to the lack of indicators, clinicians have no choice but to continue the life support in order to give a chance to any salvageable person; but this is made at a high cost, by taking the risk of ending up with a vegetative individual and deeply disturbing entire families as has been publicized by recent famous cases. The high interest of DTI is that it can precisely predict, in 2 out of 3 cases, the patient's outcome. Whereas cardiac arrest algorithm is simple and binary – good or bad prognosis, the head trauma algorithm we developed is more subtle and sophisticated; it generates three groups of people: good outcome with 95% confidence, bad outcome with 95% confidence, impossible to categorize the outcome. In two thirds of the cases, an answer with 95% confidence is provided, implying a possible use in clinical routine. In one third of the cases, however, the tool neither concludes nor decides – which is better than giving a wrong assumption.

The third group relates to subarachnoid hemorrhage. For this type of patients, the tool is less efficient and still in development. When an intracranial hematoma is involved, the pathology is even more complex, and research is currently conducted to improve the prognosis assessment.



This work on the prognosis methods [1] is performed in collaboration with Prof. Louis Puybasset in the neurosurgical intensive care unit of Pitié Salpétrière hospital, the engineer Vincent Perlbarg, and Dr Rajiv Gupta from the Massachussets General Hospital in Boston. The methods have been developed at Public Hospitals of Paris (APHP). To obtain CE-marking and FDA-clearance for the software, a startup named BrainTale has been created.

O.I: In your opinion, what could be the future potential of tractographic reconstructions within white matter?

D.G: First, I wish that we could obtain quantitative models without any necessary control, either by developing phantoms, either by using other cerebral markers to correct the variabilities; research is ongoing on the topic. Second, we might consider in the future to combine DTI mapping with other quantitative information such as T1, T2, myelin imaging; this would provide finer and more accurate tools. Tractography and quantification could even be combined, then they would be able, not only to identify damage in anatomical regions, but also to track the fibers and label the regions where the damage is detected. This would be a combination of functional and quantitative imaging.

With MR scanners that are more and more powerful in terms of magnetic fields and gradients, the spatial and anatomical resolution will improve, for a finer rendering. This will be particularly useful for the mild head trauma, less easy to analyze than the severe one. With a higher spatial resolution, an increased acuteness of quantification and less variability within the machines, tools will become much more reliable.

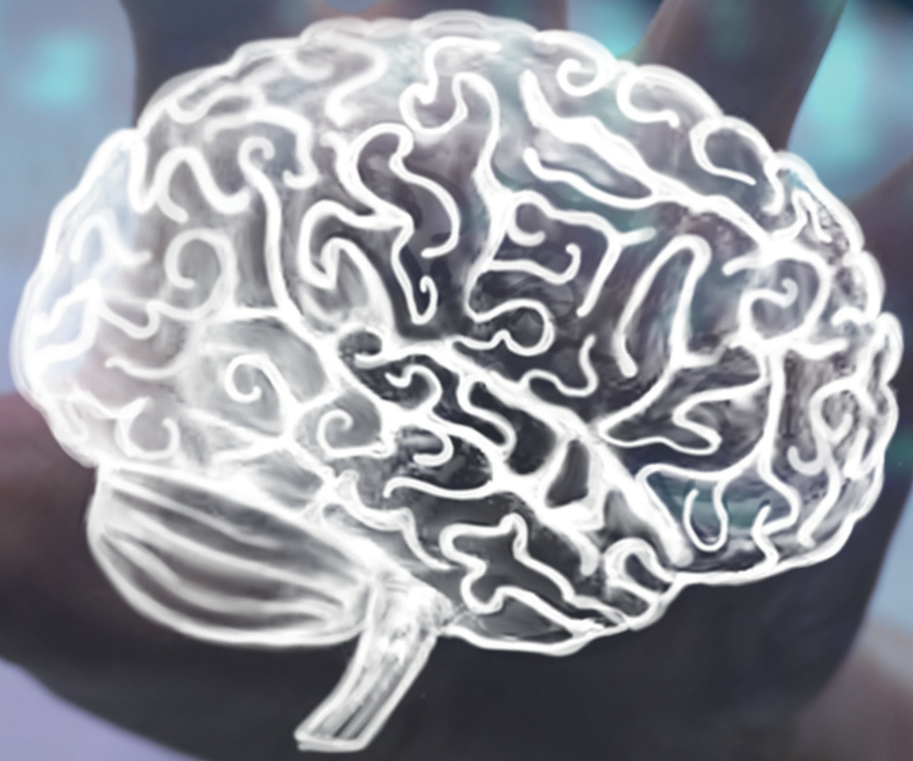
The sequences acquired today are so different from what was achieved 10 years ago; we used to work with 27 mm^3 voxels in 12 directions, versus 8 mm^3 in 64 directions today; the size was reduced by a factor between 3 to 4. I am very confident in all these elements of technological progress. Regarding the directions, I do not think it is currently necessary to increase their numbers in most applications since studies have shown that above 30 directions, the models were stable; so, 64 directions are enough.

As a conclusion, DTI is a unique sequence able to bridge between purely morphological images and quantification / measurement of brain structures.

1. Velly L, Perlbarg V, Boulier T, Adam N, Delphine S, Luyt CE, Battisti V, Torkomian G, Arbelot C, Chabanne R, Jean B, Di Perri C, Laureys S, Citerio G, Vargiolu A, Rohaut B, Bruder N, Girard N, Silva S, Cottenceau V, Tourdias T, Coulon O, Riou B, Naccache L, Gupta R, Benali H, Galanaud D, Puybasset L, for the MRI-COMA Investigators. Use of Brain Diffusion Tensor Imaging for the Prediction of Long-Term Outcome in Patients after Cardiac Arrest: a multicentre, prospective, cohort study. The Lancet Neurology. 2018;17(4):317-326.

Article

Management of Patients with Acute Stroke: Brain is More Imaging than Time in the New Era



Josep Puig, MD, PhD
Kambiz Nael, MD
Marco Essig, MD

Acute ischemic stroke (AIS) is a major cause of mortality and morbidity worldwide [1,2]. About 15 million people suffer from strokes each year; of these, 5 million die and another 5 million end up permanently disabled [2]. Ischemic strokes far outweigh hemorrhagic strokes, accounting more than 80% of all strokes [2]. In 1996, the Food and Drug Administration (FDA) approved the use of intravenous (IV) alteplase for the treatment of AIS within 3 hours of symptom onset. Thus, the National Institutes of Neurological Disorders and Stroke (NINDS) trial showed that patients with AIS treated with intravenous alteplase were 30% more likely to have good functional outcome at 3 months (defined as a modified Rankin Scale score [mRS] of 0 or 1) [3]. Few years later, the European Cooperative Acute Stroke Study III also demonstrated good functional outcome when intravenous alteplase was administered 3 to 4.5 hours after symptom onset (52% vs 45%; OR 1.28; 95% CI, 1.0–1.6) [4]. Recanalization of intracranial thrombus and the subsequent restoration of blood flow is strongly associated with improved clinical outcome in patients with AIS. A meta-analysis encompassing 998 patients showed that recanalization significantly improved 90-day clinical outcome (OR 4.43; 95% CI, 3.32–5.91) and mortality (OR 0.24; 95% CI, 0.7–17.4) [5]. However, the location of the clot is one of the main determinants of stroke outcome; the ability to achieve successful recanalization after intravenous alteplase administration is limited for large-vessel occlusion, in particular proximally located clots [6,7]. Recently, Menon et al. demonstrated that more distal thrombus location and greater thrombus permeability were associated with vessel recanalization after administration of intravenous alteplase; among patients who did not receive alteplase, rates of arterial recanalization were low [7].

Endovascular therapies are often performed in patients who have received IV alteplase but who have persistent large vessel occlusion and high clot burden [8]. These patients are thought to respond poorly to IV alteplase. The ultimate goal of neuroimaging is to help in the triage of patients for revascularization therapy, with the underlying idea to select candidates based on individual vascular and physiologic information rather than on rigid time windows. The effectiveness of these therapeutic options is not entirely time dependent. In this line, growing evidence in expanding the therapeutic window in patients with AIS supports that the use of advanced imaging techniques to distinguish infarct core from penumbra is a critical component of the patient selection process demonstrating the benefit of mechanical thrombectomy far beyond a 6-hour window [9-15]. To tackle this challenge, the role of imaging is changing with a remarkable impact on the diagnostic work-up, treatment decision process and ultimately the treatment itself. With patients now potentially eligible for interventional therapy up to 24 hours after the onset of symptoms, the radiologist should expect to see a marked increase in imaging requests for stroke, with increased emphasis on speed and accuracy. In other words, as imaging has become the pivotal factor in this process, the term "imaging is brain" would have become part of the lexicon of stroke diagnosis.

Two facts explain this evolving scenario. With the recent publication of the DAWN trial (Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) and the DEFUSE-3 trial (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution), the time window to treat has been expanded to 24 hours from onset of symptoms [9,10] on one side, and the 2018 American Heart Association/American Stroke Association (AHA/ASA) guidelines for management of AIS now recommend CT perfusion (CTP), or diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) in the 6–24-hour time period to facilitate decision making for mechanical thrombectomy on the other [16]. The association between endovascular reperfusion and improved functional outcome is not time dependent in patients with clinical or imaging mismatch [17], and that individual patient selection based on imaging can really replace the clock in patients with AIS.

Despite the increasing role of more advanced imaging techniques, the non-contrast CT (NCCT) is the most commonly used imaging modality for patients with suspected AIS, giving its wider availability, fast scanning time, cost-effectiveness and sensitivity to exclude acute hemorrhage [16]. The initial role of NCCT is to exclude contraindications to therapy, such as acute hemorrhage, large infarct or stroke mimics. The signs of acute ischemia include

the hypoattenuation within affected parenchyma, the loss of gray-white matter differentiation due to cytotoxic edema, the 'insular ribbon sign', a sulcal effacement, the 'hyperdense middle cerebral artery' (MCA) sign (thrombus within the M1 segment) and/or the 'dot sign' (thrombus within M2) [18]. The recent guidelines suggest that the presence or absence of a hyperdense MCA sign should not be used as a criterion for therapeutic decision making purposes.

The most widely used method for quantifying the extension of early ischemic changes is the Alberta Stroke Program Early CT Score (ASPECTS). The MCA territory is divided into 10 regions, including the caudate, lentiform nucleus, insula, internal capsule, and six cortical regions; one point is subtracted for each region that demonstrates imaging findings of acute infarct. Therefore, a score of 10 indicates a normal study, and a score of zero indicates that the entire MCA territory is infarcted. The relationship between ASPECTS and functional outcome after reperfusion is controversial. Some studies found a relationship between ASPECTS functional outcome after thrombolysis [19]. However, other publications did not [20,21]. More recently, the findings from the MR CLEAN trial showed that ASPECTS less than 7 did not have a poorer outcome, indicating that the extent of early ischemic changes at NCCT within the first 6 hours of stroke might not be correlated with functional outcome [15]. Although recent guidelines suggest that extension of infarct on NCCT should not be used to decide the intravenous thrombolysis, most clinicians prefer to know this information when making therapeutic decisions, such as mechanical thrombectomy. The other new recommendation is that multimodal CT and MRI, including perfusion imaging, should not delay administration of intravenous alteplase [16].

> "The ultimate goal of neuroimaging is to help in the triage of patients for revascularization therapy"

The main role of CT angiogram (CTA) is to detect an intracranial large vessel occlusion, including the internal carotid artery or M1 segment of the MCA, that would be amenable to mechanical thrombectomy [22]. Patients with a visible occlusion are more likely to benefit from intravenous thrombolysis or mechanical thrombectomy; the latter should not be attempted in absence of an identifiable target on CTA [11,15]. The location of the thrombus influences the recanalization rates after intravenous thrombolysis and endovascular therapy [6,7,23,24]. Recanalization of an occluded distal internal carotid artery only occurs in around 5% of patients after intravenous thrombolysis as opposed to 30% to 90% for the distal M1 or M2 segments of the MCA [13,24]. Large vessel occlusion, longer thrombus, higher clot burden and absence of thrombus permeability are CTA predictors of low recanalization rates after intravenous thrombolysis; these patients are more likely to benefit from additional endovascular intervention [7,11-15,25]. Therefore, the CTA offers the possibility of promoting a more efficient triage of patients that are candidates for revascularization therapies. A noteworthy fact is that the 2018 AHA/ASA guidelines recommend to study the extracranial carotid and vertebral arteries in potential candidates for mechanical thrombectomy, in addition to intracranial vessels, in order to provide useful information on patient eligibility and endovascular procedural planning. The radiologist should also assess the vasculature of the neck for vessel dissections, stenosis and occlusions that may assist in planning endovascular procedures or identify which patients are ineligible for treatment because of vessel tortuosity or inability to access the intracranial vasculature [16].

The exclusion of patients who are likely to have poor outcomes even with prompt revascularization is determinant in demonstrating the benefit of mechanical thrombectomy [9-15]. Because DWI is superior to CTP not only in detecting the core infarct but also in precisely quantifying infarct volume, several studies have shown superior outcomes when MRI is incorporated into the diagnostic imaging work-up of AIS patients [9,10,26,27]. Patients with a small core infarct are most likely to benefit from mechanical thrombectomy [28]. The eligibility for mechanical thrombectomy in the DEFUSE-3 trial

required a core volume of less than 70 ml on DWI; in the DAWN trial, the core ranged from 0 to 50 ml, depending on the National Institute of Health Stroke Score (NIHSS) and patient age [9,10]. DWI excludes patients with large core infarcts and in whom mechanical thrombectomy could result in reperfusion injury, poor functional outcome and even death [14]. Even when the performance of MRI in the hyperacute setting is logistically feasible, the imaging work-up of the AIS patient very often begins with NCCT and CTA. If the patient is still considered as a candidate for mechanical thrombectomy, the patient is sent to MRI for an accurate estimation of core infarct. A fast (6 min) multimodal MRI protocol with good diagnostic quality has been proposed for the evaluation of patients with AIS and, therefore, can result in significant reduction in scan time [29]. According to the recent 2018 AHA/ASA guidelines, MRI would not necessarily be required in selecting patients for mechanical thrombectomy in the 0–6 hour time window [16]. However, in the 6–24 hour time window, both the DAWN and DEFUSE-3 trials used CTP, or DWI and PWI, to select patients for mechanical thrombectomy [9,10]. The recent guidelines now recommend CTP, or DWI and PWI, to be included as part of a standard imaging evaluation for patients within 6–24 hours from onset of symptoms to facilitate decision making for mechanical thrombectomy [16].

> "When risk stratifying patients for mechanical thrombectomy, the absolute size of the core and its relative size to the penumbra are decisive"

Infarct core is defined as irreversibly damage tissue consequently to marked reduction in blood supply. The core is surrounded by the penumbra, a more peripheral region of severely ischemic but potentially salvageable tissue [30]. Penumbral tissue is comprised of stunned cells that have ceased to function properly, secondary to oligemia. If normal blood supply can be reestablished through early reperfusion, penumbral tissue can sometimes return to normal function; this is the tissue that can potentially be saved by prompt reperfusion. When risk stratifying patients for mechanical thrombectomy, the absolute size of the core and its relative size to the penumbra are decisive. With a large infarct core, mechanical thrombectomy could yield without benefit and expose the patient to the risks of therapy. These patients generally will fare poorly with mechanical thrombectomy even with high recanalization rates [31,32]. Conversely, with a small infarct core and a large penumbra (i.e. "mismatch"), the risk-benefit analysis would be more favorable for mechanical thrombectomy. Parameters used to define core and penumbra include mean transit time (MTT), time to maximum (Tmax), cerebral blood volume (CBV) and cerebral blood flow (CBF) [8]. There is no clear consensus on the specific parameters or thresholds that should be used to define infarct core and penumbra [33,34]. Both the DEFUSE-3 and DAWN trials defined infarct core as relative CBF < 30% of normal tissue; DEFUSE-3 defined penumbra as Tmax > 6 s. In DEFUSE-3, CTP criteria for mechanical thrombectomy were infarct core < 70 ml, mismatch volume > 15 ml and mismatch ratio ≥ 1.8 [9]. The definition of mismatch on DAWN was more complex: infarct core volume less than 21, 31 or 51 ml depending on patient's age and NIHSS [10]. DEFUSE-3 used perfusion MRI to randomize patients with a mismatch profile to endovascular treatment or no treatment in the 6- to 16-hour window. Following enrollment of approximately 40% of the predicted sample, an interim analysis showed a high likelihood of benefit in the endovascular group, and the trial was terminated. In DAWN, functional outcomes were better after thrombectomy than with standard care alone in patients with AIS in the 6- to 24-hour window with a mismatch between the severity of the clinical deficit and infarct volume assessed with CTP or DWI. DAWN and DEFUSE-3 trials have been the only randomized clinical trials showing benefit of mechanical thrombectomy more than 6 hours from the onset of the symptoms. Although future randomized clinical trials may demonstrate that additional eligibility criteria can be used to select patients who could benefit from mechanical thrombectomy, at this time, the DAWN or DEFUSE-3 eligibility should be strictly adhered to in clinical practice [16].

Collateral status represents an important factor in the outcome of patients with AIS [8]. Collaterals

have been used to infer tissue salvageability and to predict responses to therapy. Various grading scales have been developed to quantify collateral status using CTA or MRA [35]. Multiphase CTA is a recently developed technique, quick and easy, to assess collateral status [36]. A standard CTA of the head and neck is obtained in the arterial phase. Two additional intracranial scans are obtained in the peak and delayed venous phases. Axial MIP images are obtained for the arterial, venous and delayed phases, and a fast assessment of collateral status of good, intermediate and poor can be made. Good collaterals are correlated with decreased infarct core and penumbra sizes, reduced rate of infarct growth, and improved outcomes [37]. Conversely, poor collaterals result in decline of ASPECTS likely due to rapid transformation of ischemic penumbra into irreversibly infarcted tissue [38]. Collaterals status can be used to select patients for endovascular therapy. Recent trials have shown how patients with good collaterals have better functional outcome after endovascular therapy when compared with intravenous thrombolysis, whereas patients with poor collaterals did not show a differential effect of successful recanalization [39,40]. The ESCAPE trial used multiphase CTA as a mechanical thrombectomy selection tool. Patients with poor collateral status were considered a contraindication to mechanical thrombectomy and patients with intermediate and good collateral status being supportive of proceeding to mechanical thrombectomy [41]. It may be reasonable to incorporate collateral status into clinical decision making in some candidates to determine eligibility for mechanical thrombectomy.

In summary, the recent trials studying the efficacy of mechanical thrombectomy confirm that the association between endovascular reperfusion and desirable outcomes is not time dependent in patients with a perfusion mismatch; thus, individual patient selection, by clinical and imaging criteria, might replace the clock far beyond the 6-hour window. The key question is to accurately identify patients who are likely to benefit from treatment

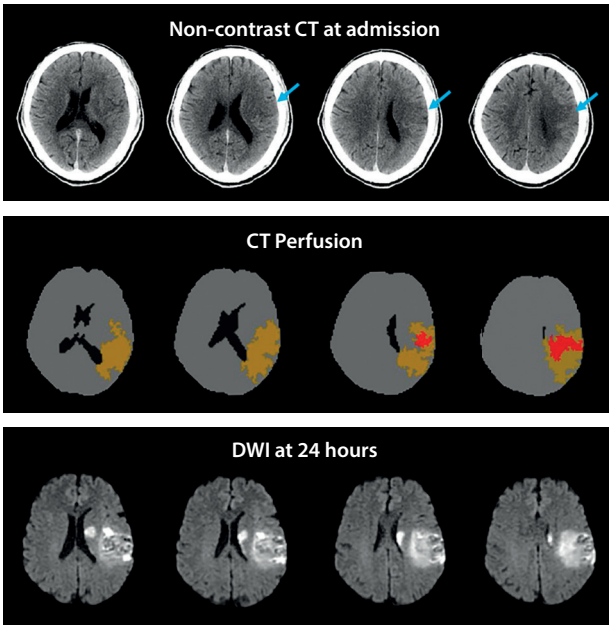


Figure 1: 70-year old man who presented with right hemiparesis and aphasia (NIHSS score, 17). On non-contrast CT, early signs of ischemia is noted (arrows) with a total ASPECT score of 8. CT angiography showed occlusion of the left middle cerebral artery M2 segment (not shown). CT perfusion using rCBF< 30% and Tmax > 6 seconds in Olea Sphere® software shows an estimated ischemic core of 14 ml and critical hypoperfusion (penumbra) of 94 ml shown in red and yellow respectively. Decision was made to proceed with endovascular treatment, TICI2B recanalization was achieved after 3 passes. Follow-up MRI at 24 hours shows the final infarction with some areas of petechial hemorrhages.

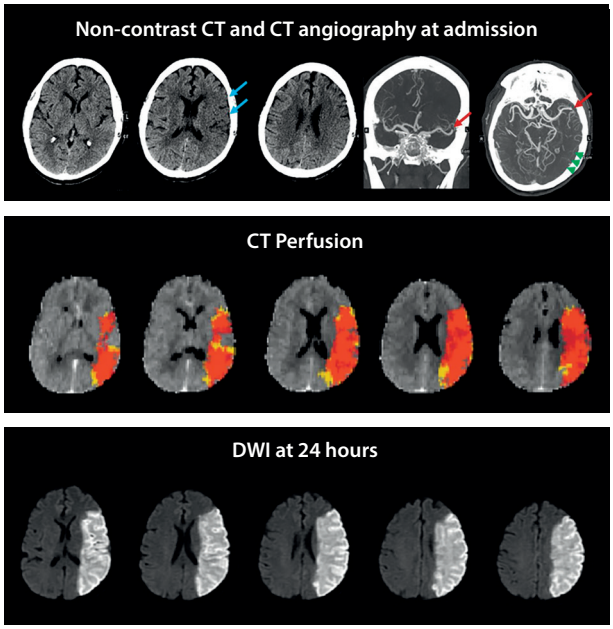


Figure 2: 67-year old male presented with right-sided hemiparesis, gaze deviation, as well as aphasia. Non-contrast head CT shows early and subtle ischemic changes along the left middle cerebral artery territory (blue arrows). CT angiogram shows a left MCA M2 segment occlusion (red arrows). Poor collaterals are seen (arrowheads). CT perfusion using rCBF < 30% shows an estimated ischemic core of 112 ml (in red) and no significant critical hypoperfusion (penumbra) based on Tmax > 6 s (in yellow) in Olea Sphere®. Due to presence of large ischemic core and lack of penumbra, endovascular treatment was not performed. Follow up MRI confirms large established infarction.

and excluding patients who may be unaffected or adversely affected by reperfusion therapies. Selection of patients with AIS for revascularization based on physiologic information may potentially shift the treatment paradigm from a rigid time-based paradigm to a more flexible and individualized, tissue-based approach, which may increase the proportion of patients amenable to treatment. In this scenario, the use of advanced imaging techniques to discriminate infarct core from penumbra is critical. The radiologist must therefore be able to provide accurate and timely information to assist the clinical team for appropriate treatment decisions in patients with AIS.

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Stroke Care

"Collateral circulation is one of the important factors to determine stroke patient's clinical outcome"

Noriko Salamon is Professor of Radiology and Chief of the Section of Neuroradiology at UCLA David Geffen School of Medicine in Los Angeles, CA, USA. She is a world-renowned neuroradiologist and a pioneer in epilepsy neuroimaging. For the last decade, she has specialized in detecting brain abnormalities that cause seizures in patients who, in many cases, have normal MRI reports. She developed the multimodality approach including the process of superimposing PET scans that measure the glucose metabolism of the brain onto an MRI scans to pinpoint the location of a subtle lesion causing the seizures.

Olea Imagein: Your research contributions are valuable in epilepsy but also in stroke imaging, including some works using both arterial spin labeling (ASL) technique and dynamic susceptibility contrast (DSC) perfusion imaging.
Would you like to present your findings?

Noriko Salamon: DSC is a widespread perfusion technique that clinicians and radiologists are familiar with, regarding the imaging findings. ASL has been around for a long time but not used much. This is a perfusion method which does not require contrast agent; it reflects brain perfusion using a process that could be compared to PET studies since both are based on a labeling method. No need for contrast agent injection is one of the practical advantages why people like this approach, which is able to evaluate the cerebral blood flow easily. We found that ASL had equal value to DSC on acute stroke patients [1] and was also useful in Transient Ischemic Attack (TIA) patients [2].

However, neuroradiologists still hesitate to use ASL in their clinical practice because of complicated post-processing. Due to a lack of standardization, not all vendors have the same post-processing, it is therefore very programming - and individual-dependent.
Another issue relates to image resolution; images are very artefactual, and their quality almost looks like the beginnings of SPECT or nuclear medicine, they are therefore very unsatisfactory or sometimes undetermined. As a result, we may be able to detect a large asymmetry, but we cannot analyze subtle findings of stroke. Those are the two major challenges that have to be overcome in order for ASL to be used by regular neuroradiologists. Even though the individual territorial analysis may be a little time-consuming, it has been published in many studies in the research field.

In many clinical centers in the US, how to analyze perfusion imaging is going to be revisited. Is this imaging method validated or not? What interpretation can we retrieve from it? Making decision based on

perfusion only may not be accurate, since over- and under-estimations are still possible due to lack of standardization. If ASL is developed and becomes fast, precise, evenly distributed among the centers with an improved resolution, if we have good understanding of the technical challenges behind the artefacts, then ASL has a very good potential as a functional vascular imaging tool without contrast.

O.I: You also worked on the importance of assessing the collateral circulation in stroke events, particularly to predict response to therapy. Could you please tell us more?

N.S: Collateral circulation is one of the important factors to determine stroke patient's clinical outcome. The Stroke III trial showed that if there is a better collateral grade during re-canalization procedure, there will be a better perfusion, therefore a better outcome. Whatever the treatment we can give, if there are two patients have good and bad collaterals, their outcome will be different even if both diffusion and perfusion imaging results are the same. How much collaterals one person has, as potential resources of reperfusion, is still not well-known. No perfect modality exists yet to visualize the collaterals.

In old days, people were doing angiograms to see how fast vessels were appearing and how much of the collateral vessels were displayed over time; it was therefore technically possible to visualize that. Collaterals are not analyzed with 2D or 3D information; there is a need for time factor as 4D dynamic information, since the tissue status changes over time. With CT angio, by comparing the enhancement in venous and arterial phases, good or poor collaterals can be easily simulated. But I think that information regarding collateral system lies at a much smaller microcellular level. In UCLA, we tend to proceed to visual collateral measures on proximal occlusion patients, based on the delay of perfusion and the contrast enhancement at the arterial phase. But there is room for improvement and development of the technology.

O.I: Your husband, Georges Salamon, was a pioneer in neuroradiology. He is the author of well-known publications such as the "Atlas of Arteries of the Human Brain" in 1974, "Radiologic Anatomy of the Brain" in collaboration with Y.P. Huang in 1978, or "Vascularization and Cerebral Circulation" with G. Lazorthes and A. Gill that same year. What is his major impact in the management of patients with acute ischemic stroke?

N.S: The work done in Georges Salamon's generation is fundamental for the current development of the neuroimaging field. There are more sophisticated techniques and modalities available to the patients and neuroradiologists these days, but we tend to ignore the importance of structural and functional anatomy. The work of Georges Salamon not only just described the anomaly of the structures, but also demonstrated the understanding of the disease process. Same volume of MCA infarction does not demonstrate an exact same outcome for the patients if you do not pay attention to the functional anatomy and which zone is infarcted. This approach was lost and very few people can explain anatomical location, or which functional zone is involved. His work will always be helpful for us to better understand the pathology and outcome of patients. He always reminded me that there was a patient behind each image.

O.I: What are your expectations for improving both stroke detection and prediction of treatment response in the future?

N.S: I think we have to revisit the good clinical examination for the decision making. Nowadays, neurologists or neurosurgeons are heavily dependent upon imaging, which could be dangerous. Imaging may not represent all the reality of what is happening in the brain. Stroke is an ongoing process. Treatment based on imaging made one hour before may not refer to the current status. Diffusion weighted imaging (DWI) can detect early stroke – which was revolutionary progress in this field. But finding a biomarker to predict an outcome and assess tissue fate is still challenging.

The future is to precisely identify the tissue at risk. The question is: what kind of modalities and parameters have to be used for this identification? To be able to understand the imaging and what really means to the patient, we should correlate imaging findings to the clinical symptoms. When we are looking at middle cerebral artery (MCA) occlusion stroke, clinical symptoms are different based on the anatomical location of the infarct. The functional neuro-anatomy component is very important because it is the bridge to understand between the patient and the technology. Same volume of infarction in the primary motor cortex or in the primary language cortex will result in different outcome for the patient. Obtaining the volume is not enough to evaluate the degree of the patient dysfunction and only gross assessment to predict outcome. I think that this is an important issue to be addressed.

Ten years from now, I hope many radiologists use artificial intelligence (AI) wisely and make it part of advanced technology to help us; acute stroke will be red, tissue at risk yellow, volume will be automated, and the outcome will be predicted when the study is done. My contribution is to incorporate the functional neuro-anatomy into this field. I hope that the vendors and scientists will be able to include this aspect in their developments. Also, I believe that AI will help us to improve turnaround time, tedious work, and organize useful information, in order to make decision more precisely and faster. I hope AI will allow future radiologists to spend more time in better understanding the patient care, rather than just juggling all the available data.

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Timothé Boutelier, PhD

Effect of the Rician noise on the detection of ischemic core in DWI

Since its invention in the 80's [1], MR diffusion weighted imaging (DWI) has improved considerably, enabling its use in a broad range of clinical applications. In particular, DWI is recommended for the management of patients in acute ischemic stroke [2,3]. It has been shown in the early 2000's [4-6] that a simple threshold on the apparent diffusion coefficient (ADC) parameter allows to differentiate between tissue with irreversible damages (ischemic core) and tissue that could recover after reperfusion. Combined with perfusion imaging that shows the tissue at risk of infarction, the concept of mismatch ratio appeared [2,3], which is a powerful tool for the physician, used to balance the benefit-risk of performing a thrombectomy.

Recent improvements in parallel imaging and multi band acquisition allowed the development of accelerated DWI sequences for which the acquisition time is considerably reduced (SMS for Siemens, HyperBand for GE, SENSE for Philips, SPEEDER™ for Canon). If not configured carefully, the acceleration can increase the noise level in the image, with a potential dramatic effect on the therapeutic decision. To illustrate this, we generated numerical simulations to show how the Rician [7] structure of the noise in MRI data affects the estimation of ADC, hence the final treatment decision based on this parameter.

Diffusion signal curves were generated at b=0 and b=1000 s/mm^2 using the equation [1]:

$$S(b)=S0e^{-b\,ADC}$$

where ADC = 0.80×10^{-3}mm^2/s is a typical value for the healthy white matter [6], and S0 is arbitrary set to 1. Noise was added assuming a Rice distribution with scale parameter σ. The signal to noise ratio defined as SNR=S0/σ ranges from 0 to 30. For each SNR value, 10^6 in silico voxels were generated with different noise realisation. For each voxel, the ADC was estimated as:

$$ADC_{est}=\frac{\log\left(\frac{S_{b=1000}}{S_{b=0}}\right)}{1000}$$

The 25th, 50th (median) and 75th percentiles of the estimated ADC_est were computed as a function of the SNR, together with the proportion of voxels erroneously labelled as ischemic based on a threshold [8] of ADC < 0.6 $\times 10^{-3}$ mm^2/s (i.e. the false positive rate). The results are displayed in Figure 1, which illustrates the impact of the noise level on the estimation of ADC and on the detection of the ischemic core.

As the noise increases (i.e. the SNR decreases), the dispersion of the estimated ADC increases, which increases the false positive rate. At SNR=10, the false positive rate reaches 20%. This effect is dramatically enhanced below SNR of 10 due to the systematic underestimation of the estimated ADC.

This phenomenon is a direct consequence of the Rician noise distribution that introduces a noise floor [7], which artificially increases the low signal values. The Figure 2 illustrates how the noise floor reduces the slope of the logarithm of the signal, i.e. the ADC.

This simple numerical experiment demonstrates how the noise can impact the detection of the ischemic lesion in DWI, by increasing dramatically the false positive rate and overestimating the volume of the ischemic core. Hence, one needs to carefully use the accelerated sequences and pay attention to the balance trade-off between DWI image quality and acquisition duration in order to guarantee a reliable evaluation of the size of the ischemic core.

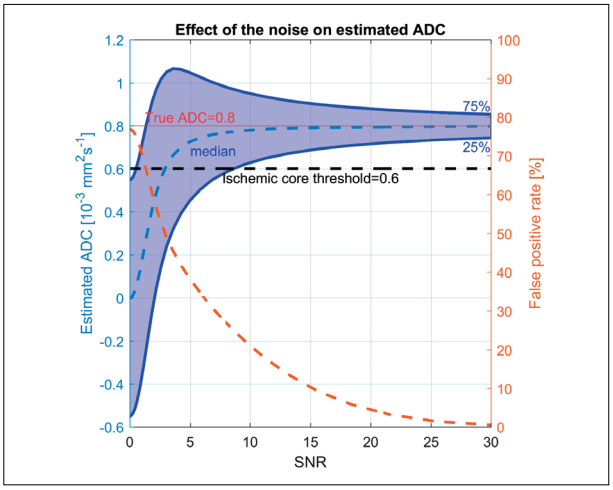

Figure 1: Left axis: median (blue dashed line), 25th and 75th percentiles (blue solid lines) of the estimated ADC as a function of the SNR. The red solid line indicates the expected ADC, and the black dashed line indicates the threshold below which a voxel is labelled as ischemic. Right axis: false positive rate (orange dashed line), i.e. the proportion of voxels with an estimated ADC below the ischemic core threshold.

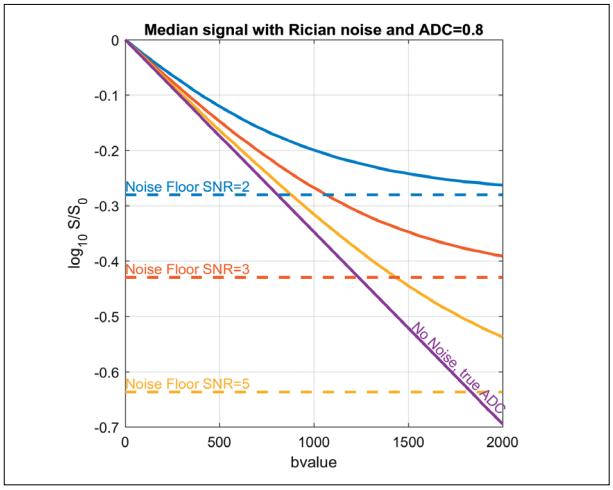

Figure 2: Logarithm of the median of 106 diffusion signal curves generated with ADC=0.8 $x10^{-3}mm^2s^{-1}$, between b=0 and b=2000, for different Rician noise SNR. The dashed lines indicate the noise floor. The purple solid line indicates the theoretical signal expected in the absence of noise.

Timothé Boutelier, PhD
Senior research and innovation engineer at Olea Medical®

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Deep Dive into Computed MRI

Luca Saba, MD
Head and Professor of the Radiology Department at the AOU of Cagliari, Sardinia, Italy

Luca Saba received the MD degree from the University of Cagliari, Italy in 2002. Currently, he works in the University Hospital of Cagliari. His research fields are focused on Multi-Detector-Row Computed Tomography, Magnetic Resonance, Ultrasound, Neuroradiology and Diagnostic in Vascular Sciences.
His work led to more than 250 papers in high impact factor, peer-reviewed journals such as Lancet Neurology, Radiology, American Journal of Neuroradiology, Atherosclerosis, European Radiology, European Journal of Radiology, Acta Radiologica, Cardiovascular and Interventional Radiology, Journal of Computer Assisted Tomography, American Journal of Roentgenology, Neuroradiology, Clinical Radiology, Journal of Cardiovascular Surgery, Cerebrovascular Diseases, Brain Pathology, Medical Physics, Atherosclerosis. He lectured more than 45 times at national and international levels.

Luca Saba won 18 scientific and extracurricular awards during his career. He presented more than 500 lectures, papers and posters in National and International Congress (RSNA, ESGAR, ECR, ISR, AOCR, AINR, JRS, SIRM, AINR). He wrote 21 book-chapters and is Editor of 10 books in the field of Computed Tomography, Magnetic Resonance Imaging, Cardiovascular, Plastic Surgery, Gynecological Imaging and Neurodegenerative imaging.
Luca Saba is member of the Italian Society of Radiology (SIRM), European Society of Radiology (ESR), Radiological Society of North America (RSNA), American Roentgen Ray Society (ARRS), European Society of Neuroradiology (ESNR) and serves as Reviewer for more than 60 scientific Journals.

Olea Imagein: Could you please introduce yourself and your team at the University Hospital of Cagliari?

Luca Saba: My position is Head and Professor of the Radiology Department at the University Hospital of Cagliari, Sardinia, Italy. I like to do research, it is not a work, I enjoy it! It helps me to do this kind of work. My current research areas are Neurovascular, functional MRI, Oncological Imaging and Gynecological Imaging. In particular, in the last years, we have been conducting studies dedicated to ultrasound analysis, but also to machine learning and texture analysis.

My stronger collaborations are with Max Wintermark at Stanford University, California, USA; Lorenzo Mannelli at Memorial Sloan Kettering Cancer Center, New York, USA; Carlo Nicola De Cecco at Emory University, Atlanta, USA; Bruce Wassermann at John Hopkins University, Baltimore, USA; Mark Dewey at Berlin University, Germany; and Aad van der Lugt at Erasmus Center, Rotterdam, The Netherlands.
We are currently running nine trials with them, in all the fields described above.

My team is composed of 20 radiologists – because it is a hospital, 32 residents – because there is a resident school, in addition to technicians, nurses and administrative staff. A couple of them are interested in doing research, like Michele Porcu, MD Research Fellow, for neurology; Giuseppe Corrias, PhD, for body imaging; Alessio Mereu, Research Fellow, for texture analysis and artificial intelligence.

O.I: Could you please explain what Computed MRI is?

L.S: Computed MRI was already described more than 20 years ago, it is an old concept [1]; it is the same as for CT regarding spectral imaging, that was described by Hounsfield in 1974, three years after the first prototype. However, the need in computation stopped the expression of this intuition. Twenty more years were necessary to demonstrate that with only some signals, we were able to calculate all the others [2]. This is the simple concept of Computed MRI.

The equations presented in Figure 1 explain how we can derive, from two standard acquisitions of T1 and T2 mapping sequences providing T1, T2 and PD values, images that are normally acquired from spin echo or inversion recovery, with arbitrary TR, TE and TI.

MP2RAGE is a 3D fast field echo (FFE) sequence acquired with two different inversion time (TI) and flip angle (FA) values for the same position at the same time. The data are acquired at each TI value, so that a T1 map can be generated within the single acquisition. T1-weighted images acquired with this sequence are not affected by non-uniformity of B1 or coil sensitivity.

FSE 2D mEcho is a 2D fast spin echo (FSE) sequence to acquire image data at four different echo time (TE) values for the same position at the same time. The image data are acquired with different TE values as a multi-echo FSE sequence, so that a T2 map can be generated with a single acquisition. The exquisite soft tissue contrast provided by MRI arises principally from differences in the intrinsic relaxation properties. Though the intricate relationships that link tissue microstructure and the longitudinal and transverse relaxation times remain to be firmly established, relaxometry studies potentially offer a more detailed characterization of tissue, compared with conventional qualitative or weighted imaging approaches.

We can see that using these two sequences of T1 and T2 mapping, we can dynamically obtain other sequences, by changing TE, TR or TI (Figure 2). This is the basis, it is simple.

$$\textbf{SE: } S = k * PD * (1 - e^{-TR/T1}) * e^{-TE/T2}$$
$$\textbf{IR: } S = k * PD * (1 - 2 * e^{-TI/T1} + e^{-TR/T1}) * e^{-TE/T2}$$

Figure 1: Signal intensity (S) equations used to produce Computed MRI spin echo (SE) and inversion recovery (IR) images at arbitrary repetition time (TR), echo time (TE) and inversion time (TI) values – k being a proportionality constant which depends on the sensitivity of the signal detection circuitry on the imager; and PD the proton density value [3].

O.I: What are the reasons of your interest in this technique?

L.S: There are two levels of interest in Computed MRI: research and clinical. There are advantages in terms of research, however some options are relevant for both research and clinical applications.

First, Computed MRI is a cutting edge technology for research. It is the far west: everything we describe is new. It is easy to define new hypothesis by using this technique in research, since everything remains to be done. It is important, like writing a new book. Right now, we only know the alphabet, but we are starting to write words, sentences, chapters and so on.

The second point, which is more technical, is that we can explore the intrinsic properties of the tissues. We can obtain pieces of information that do not depend on the sequences or the magnetic field, but are intrinsic properties. In the past, it was not possible to assign a unique number to a specific tissue, it was one of the limiting factors to MRI. When we conduct a study and demonstrate something based on signal intensity, we do not use a number but say that it is brighter, or darker, compared to the muscle for example. These are obvious limitations compared to CT, where we can assess that water is zero and fat is below -80 Hounsfield units. In MRI, there was no quantitative approach. So, we are moving now to the phenotype and quantitative values, this is the concept of the biomarkers. Computed MRI is allowing us to move towards the quantitative era of MRI.

Therefore, we can address the third point, which is standardization of MRI interpretation. If we can assert that this tissue has a value of 800 signal intensity, and we know that 800 is the normal value of the grey matter, we can conclude that there is no epilepsy for example, because the grey matter in that region is normal. This means that standardization in interpretation and creation of a new database in terms of T1 and T2 values of tissues could be reached – it is a new language.

As mentioned, there is also a clinical impact. Indeed, we could theoretically reduce the acquisition time. Since we can create other sequences from only two sequences, we can show that the acquisition time could decrease by acquiring both sequences and comparing the generation time.

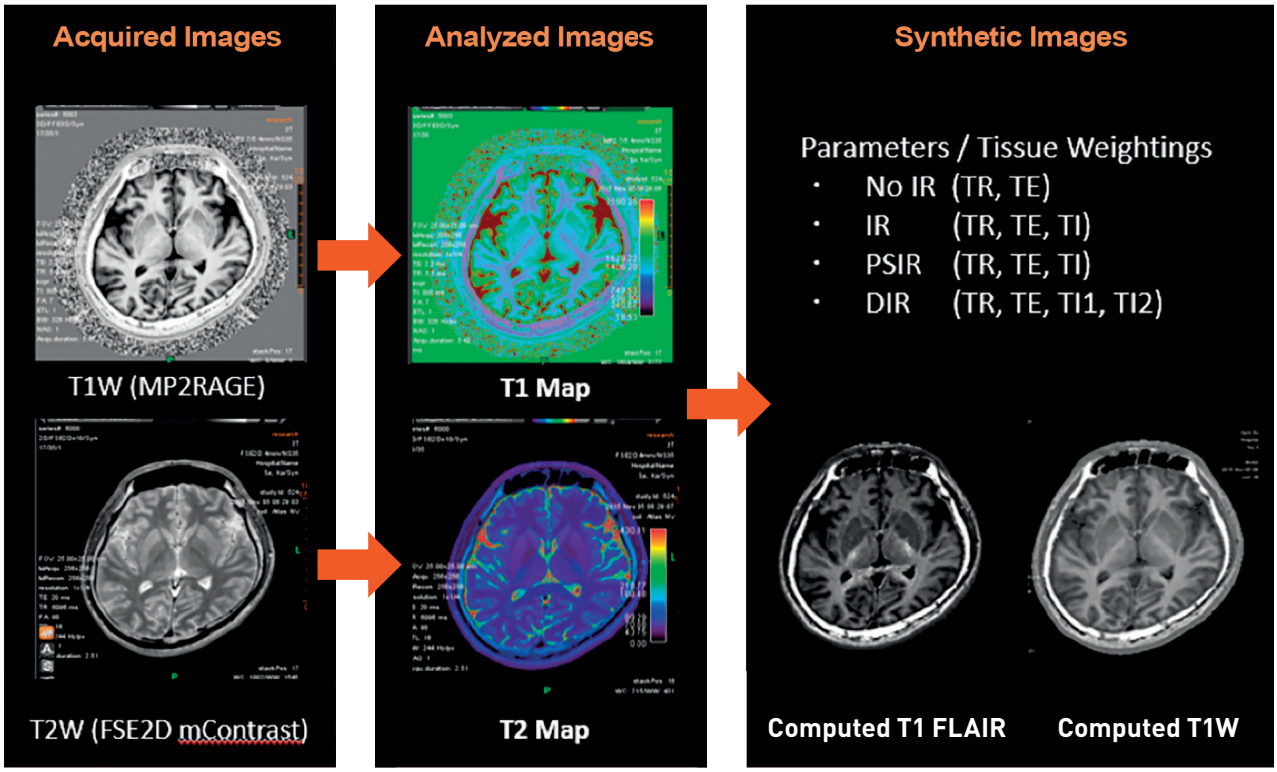

Figure 2: Computed MRI maps generation process using Olea Nova+®: collection, analysis and calculation.

Also, our target in the next studies is to demonstrate that conventional and Computed MRI series qualities are similar; images obtained with Computed MRI could hence potentially replace conventional sequences.

In addition, using Computed MRI post-processing, it is possible to obtain missing sequences – which is not possible with the conventional approach. Indeed, after performing a study with the general protocol, we can read the exam 24 hours later, for example; if, at that time, we realize that one sequence is missing, we can still get it if Computed MRI sequences have been acquired. This is a strong point from a clinical point of view, and we already did it in reality. In one case, a specific sequence was missing because of a particular approach; but, with Computed MRI, we were able to reconstruct it afterwards. It is really useful!

Finally, Computed MRI allows a standardization of workflow. In the future, if this approach is confirmed as robust, we could only have Computed MRI, diffusion and something else, which gives us a very simple approach but with all the information we need. Moreover, this could avoid errors in the acquisition protocol. There is a high personnel turnover and it is necessary to have time to improve skills and understand the technique. If the way is very simplified, we avoid mistakes.

In conclusion, Computed MRI could have a significant impact for both clinical and research practices.

O.I: What is your experience so far with Olea Nova+®?

L.S: We are currently using Olea Nova+® in different organs: brain, rectum, prostate and musculoskeletal (MSK) imaging. For prostate, what is interesting is that we have patients who underwent biopsy or prostatectomy, so that their Gleason score is available. The protocol is very simple; so, when we have time to perform it, we do it in a general clinical setting. For brain, there are cases with some types of pathologies where we always do Computed MRI. Therefore, we have a data bank with control subjects and some groups of patients with pathologies.

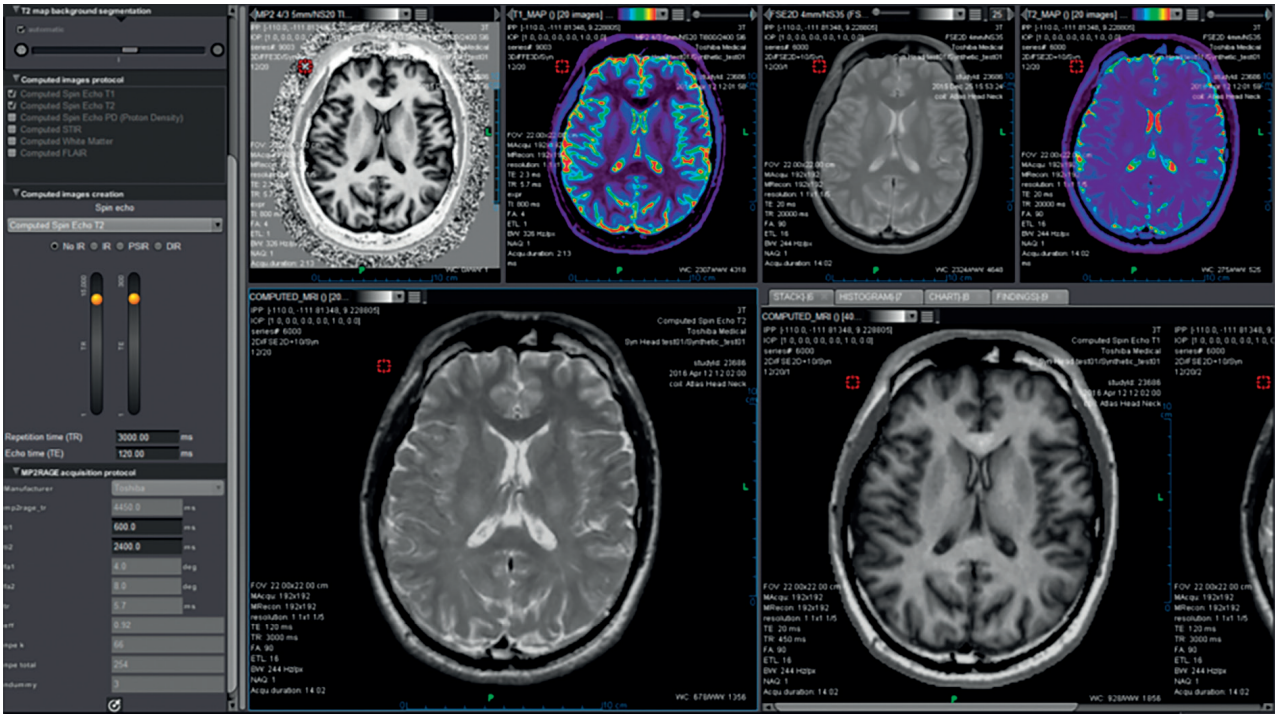

Figure 3: Olea Nova+® application in brain: MP2RAGE with computed T1 map and FSE multi echo with computed T2 map are displayed in the first row; computed spin echo T2 (with TE = 120ms and TR = 3000ms) and computed spin echo T1 (with TE = 20ms and TR = 450ms) in the second row.

That is very important because if we want to create a database of T1 and T2 values in normal brain – this has not been done yet, we need normal brains.
Ongoing studies concern validation among readers and acquisitions on the reproducibility of the sequences obtained from Computed MRI, compared to the conventional sequences in clinical practice of brain MRI. We have presentations to the European Congress of Radiology (ECR) 2019 where we demonstrated the flow charts and the advantage with regard to time, since it removes about six to seven minutes theoretically. That is important, because compared to the 22 minutes conventional protocol, we move to 15 minutes for a high throughput center.

O.I: Will this investment put your hospital in a different position in the European clinical landscape?

L.S: The position in the European clinical landscape is very simple. There are not so many groups which are conducting this type of research compared to the other types of technologies. Only one study explored the reproducibility of Computed MRI in brain in clinical settings with a randomized multicentric trial [4], and there are no other studies in this field.

Our ambition would be to perform this research not only in our center but to share our expertise with other centers and maybe run a multicenter trial. Because there are two problems with new technologies: validation and killer applications. Validation requires not so big numbers compared to killer applications, where it is necessary to demonstrate in big number that by using this approach, a clinical advantage is obtained.

So, if I move alone, it requires 3 or 4 years; if I am with 10 other colleagues who work in the same direction, it requires 6 or 9 months. It depends on the need to push or not this type of technologies – it would be very interesting in my opinion.

O.I: The sequences required for Olea Nova+® provide quantitative information about T1 and T2 relaxation times. Does it bring relevant new information compared to qualitative MRI images?

L.S: Of course, we also studied the contribution of the quantitative analysis. For example, in rectal and prostate cancers, we analyzed the differences in T1 and T2 values between healthy tissues and tumors and found a significant difference in the distribution of these quantitative values between normal and pathological areas (Figures 4 and 5). This is the future, and this is simple.

What could also be interesting is to combine Olea Nova+® with Olea Texture analysis. The massive

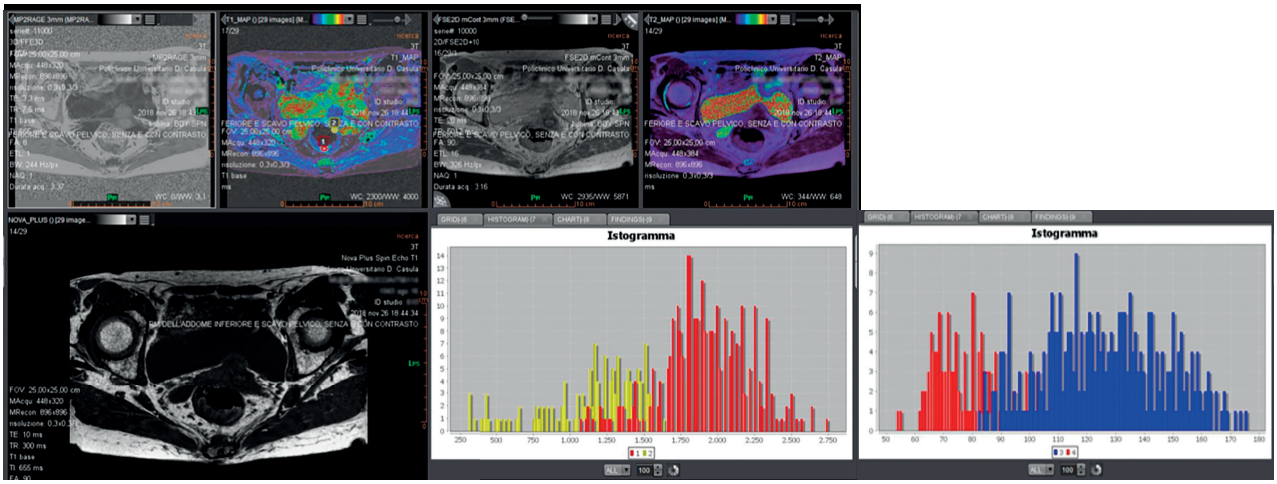

Figure 4: Olea Nova+® application in rectum: MP2RAGE with computed T1 map and FSE multi echo with computed T2 map are displayed in the first row; computed spin echo T1 and histograms in the second row. Two regions of interest have been drawn on T1 map and reported on T2 map, and their histograms were obtained: A/ neoplasm T1 values (red) vs. healthy tissue T2 values (yellow), and B/ neoplasm T2 values (blue) vs. healthy tissue T2 values (red).

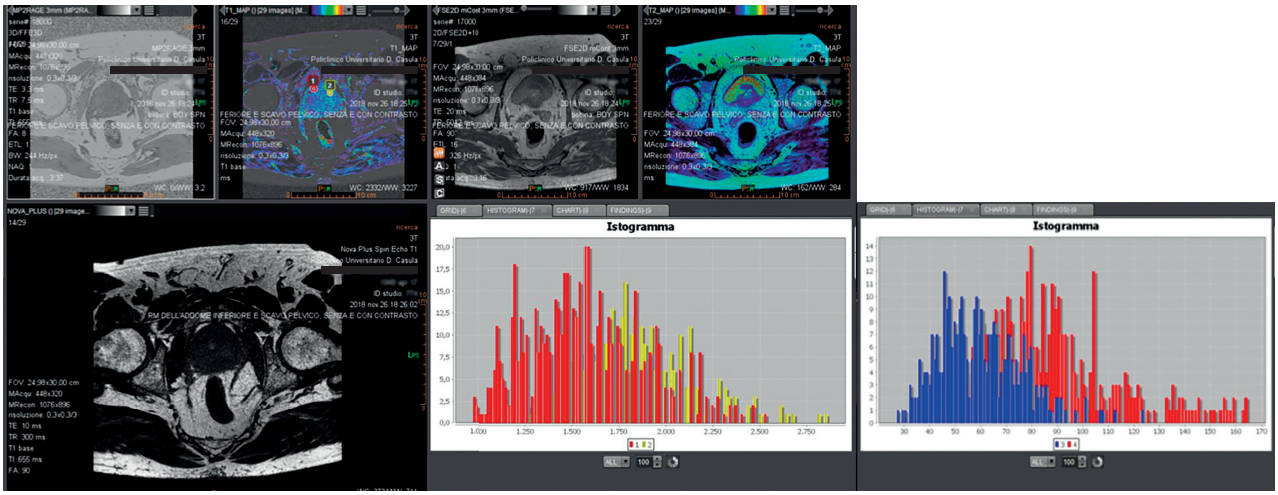

Figure 5: Olea Nova+® application in prostate: MP2RAGE with computed T1 map and FSE multi echo with computed T2 map are displayed in the first row; computed spin echo T1 and histograms in the second row. Two regions of interest have been drawn on T1 map and reported on T2 map and their histograms were obtained: A/ neoplasm T1 values (yellow) vs. healthy tissue T2 values (red), and B/ neoplasm T2 values (red) vs. healthy tissue T2 values (blue).

approach implies that we use all the available features: if we have 120 features, we should use 120 and test to identify which feature has the best performance; so that we could say at the end: the best thing is to perform MRI with the two sequences required for Computed MRI, add the quantitative analysis and use the convolutional matrix inverse feature for example. There are so many opportunities.

O.I: Based on your experience, where do you perceive the best chances for Computed MRI? What other areas could benefit from this technique?

L.S: We applied Olea Nova+® for brain, rectum, prostate and knee. It is meaningful, and it could be useful. I asked my people to test it for gynecology – ovarian or uterine cancer, but the first trials we did were not conclusive because of registration and co-registration problems between the sequences. It was not due to the system but to the fact that ovaries and uterus are moving organs, they are therefore more complicated to image. We obtained very good results on rectum because that part of the body is not moving. In the same way, prostate, brain and knees remain stable. When we get closer to the liver or in the other part of the abdomen, there are movements. Since we must exactly match two sequences with different temporal coordinates, we noticed that the results were not good in moving organs – especially because of T1 mapping acquisitions. However, I think that Computed MRI can have a huge impact in clinical practice, but we need to prove it because no one will accept this message without strong data to support it.

O.I: Computed MRI was the first project jointly led by Canon and Olea Medical® teams. What do you think about collaborative imaging?

L.S: I completely share this view. Joining forces creates more strength. So, if we can create a connection, a cooperation between different experiences, we will do a greater product. I believe that the best thing I have done in the past was to create connections with my colleagues by identifying the people who could collaborate with different points of view. This allows to create bigger things. Not alone. Alone I can do nothing, or not so much. I like this philosophy, it is also mine. I always thought that it is better to win a game with people than to lose alone.

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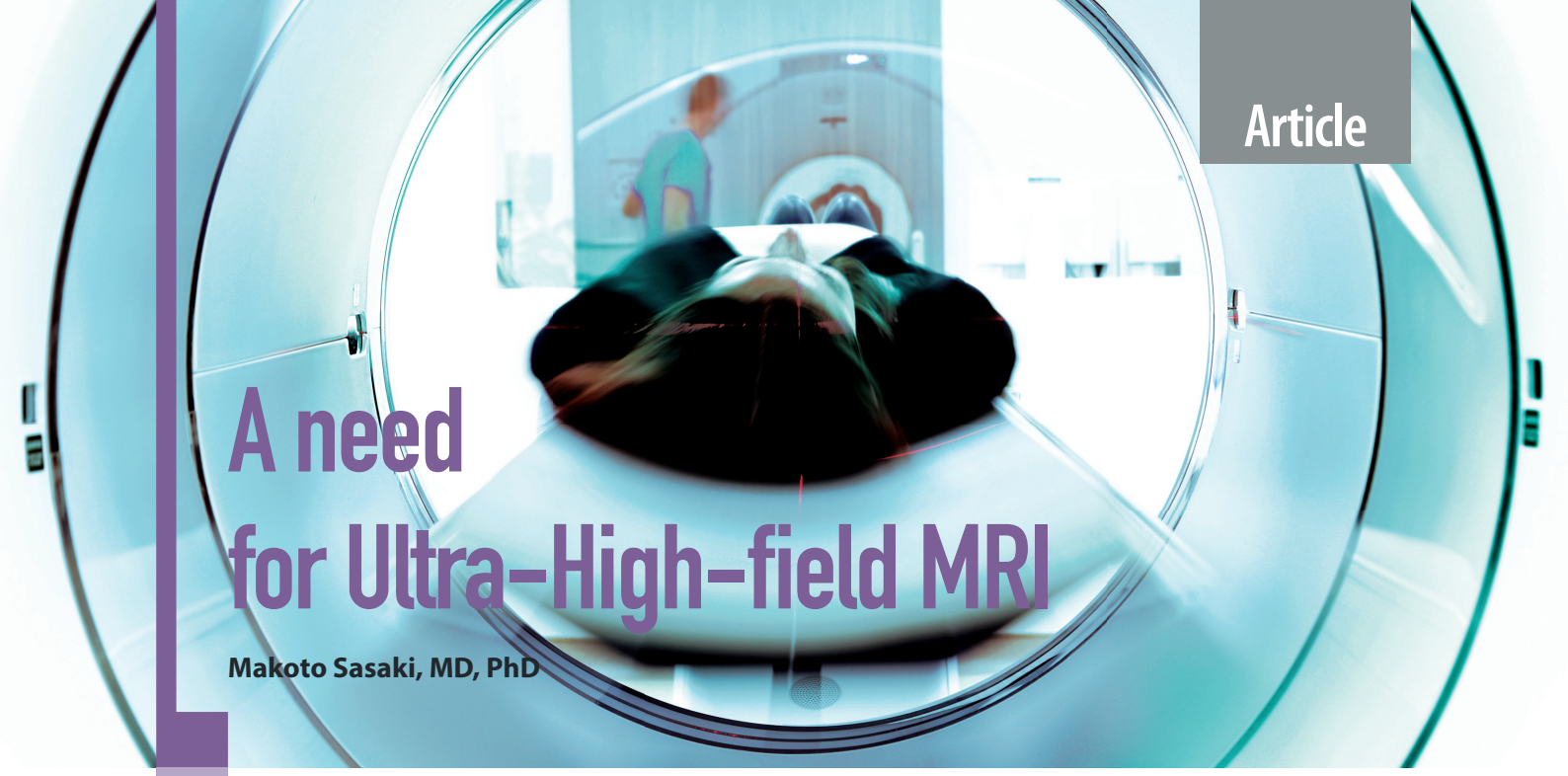

A need for Ultra-High-field MRI

Makoto Sasaki, MD, PhD

The 7 Tesla MRI system has been installed in more than 60 institutions in the world, including 5 institutions in Japan. The 7T MRI system we are using is the second 7T scanner in Japan and the first next-generation system that includes an 8-channel parallel radiofrequency (RF) transmission unit provided by GE Healthcare. We have already performed more than 3,800 examinations for approximately 1,100 patients, with administration of contrast agents in 220 cases.

The 7T MRI includes several characteristics, such as improved signal-to-noise ratio (SNR), increased chemical/phase shift, prolonged T1 relaxation time and enhanced susceptibility effects, which can contribute to improved spatial resolution, tissue characterization and lesion contrast on various images. However, increased susceptibility effects, B1+ heterogeneity and specific absorption rate (SAR) can substantially deteriorate the image quality and feasibilities of several sequences. These characteristics are similar but more extensive than those present in a 3T MRI.

The 7T MRI enables us to obtain high-resolution (HR) structural images with an in-plane resolution of 0.2 mm or an isotropic voxel of less than 0.5 mm, as well as diffusion-weighted images with an isotropic voxel of less than 1.5 mm. The image quality of MR angiography (MRA) is also dramatically improved with the 7T due to the high SNR as well as the prolonged T1 relaxation time. The perforating arteries and medullary arteries are frequently visible on HR-MRA, particularly when using a partial magnetization transfer contrast technique. With this method, we can assess steno-occlusive changes of lenticulostriate arteries and development of leptomeningeal collaterals in acute ischemic stroke, as well as various lesions associated with other cerebrovascular disorders. In addition, the source images of HR-MRA can be used as structural images in which spatial relationships between the minute arteries, lesions, and brain structures are evident, as well as source data for computational fluid dynamics analyses. By using HR vessel-wall imaging techniques, we can also detect mural lesions of intracranial arteries, such as minute atherosclerotic plaques.

Because susceptibility effects become extreme at 7T, we can obtain striking T2*-weighted magnitude/phase images and susceptibility-weighted images (SWIs). On HR-SWIs, deep medullary veins and subependymal veins are readily visualized and nearly identical to those of the specimen. One of the limitations of SWIs at 7T is the presence of substantial artifacts due to erroneous phase modulations such as dipole effects. To overcome this issue, we apply the quantitative susceptibility mapping (QSM) technique. With QSM images, the local susceptibility values of deep nuclei and venous structures are successfully restored.

Furthermore, when we obtain HR-QSM images, we can easily calculate oxygen extraction fraction (OEF) values from susceptibility values of intraparenchymal venous structures by using a simple equation. We have found that there are good correlations between the QSM-OEF and PET-OEF values and that the QSM-OEF could accurately distinguish patients with misery perfusion.

One of the issues associated with the 7T MRI is the substantial signal inhomogeneity due to heterogeneity of the RF-induced local magnetic field (B1+). However, we can overcome this problem by using signal inhomogeneity correction methods or a parallel RF transmission technique. Another major issue with 7T is subjective discomfort, particularly vertigo, during table movement before/after the scan. In our institution, however, substantial vertigo occurred in only 1/10 of the subjects, and all of them found the discomfort acceptable, mainly because of the slow table-feed speed. Another well-known concern is high initial and running costs. Conventional 7T systems with passively shielded magnets of approximately 35 tons need a large magnetically shielded room and periodical refilling of liquid helium; without any medical reimbursement, they can only be used for research. However, a new 7T MRI system has been recently introduced that includes an actively shielded magnet with a zero helium boil-off unit; this system has obtained approval of the FDA and CE. These advances will accelerate the further installation of 7T systems for the purpose of advanced neuroimaging in clinical practice, though body imaging remains challenging.

The 7T MRI has substantial advantages over conventional MRI, in terms of spatial and contrast resolutions. The 7T MRI is expected to have an increased clinical impact in various neurological disorders, particularly cerebrovascular diseases, in the near future. However, additional technological advances tailored to ultra-high-field systems, as well as the accumulation of scientific evidence, are still needed in order to establish its further clinical significance.

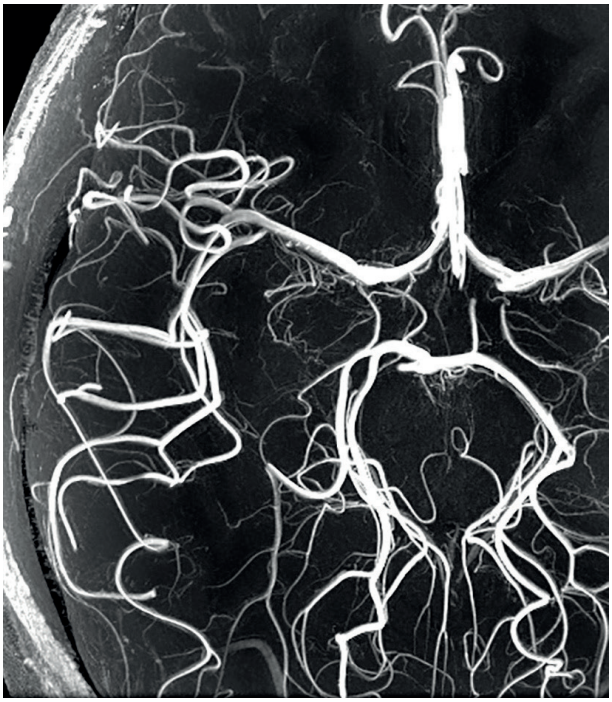

Figure 1: High resolution MRA at 7T

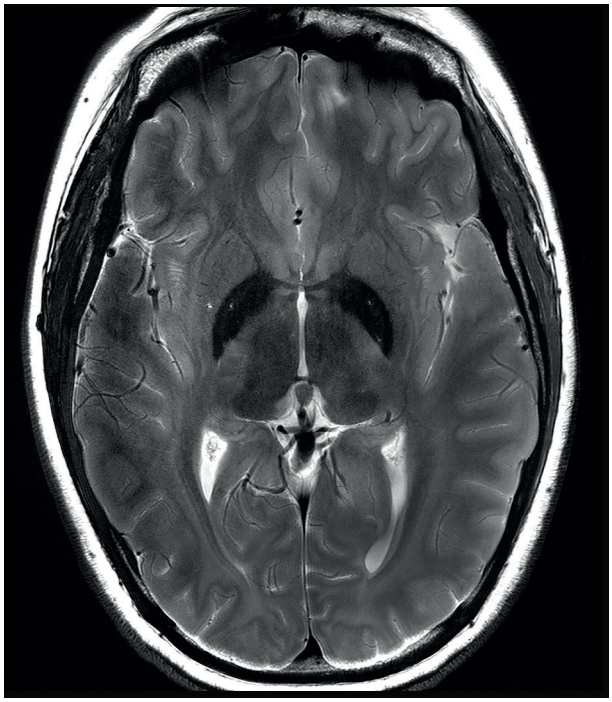

Figure 2: High resolution T2-weighted at 7T

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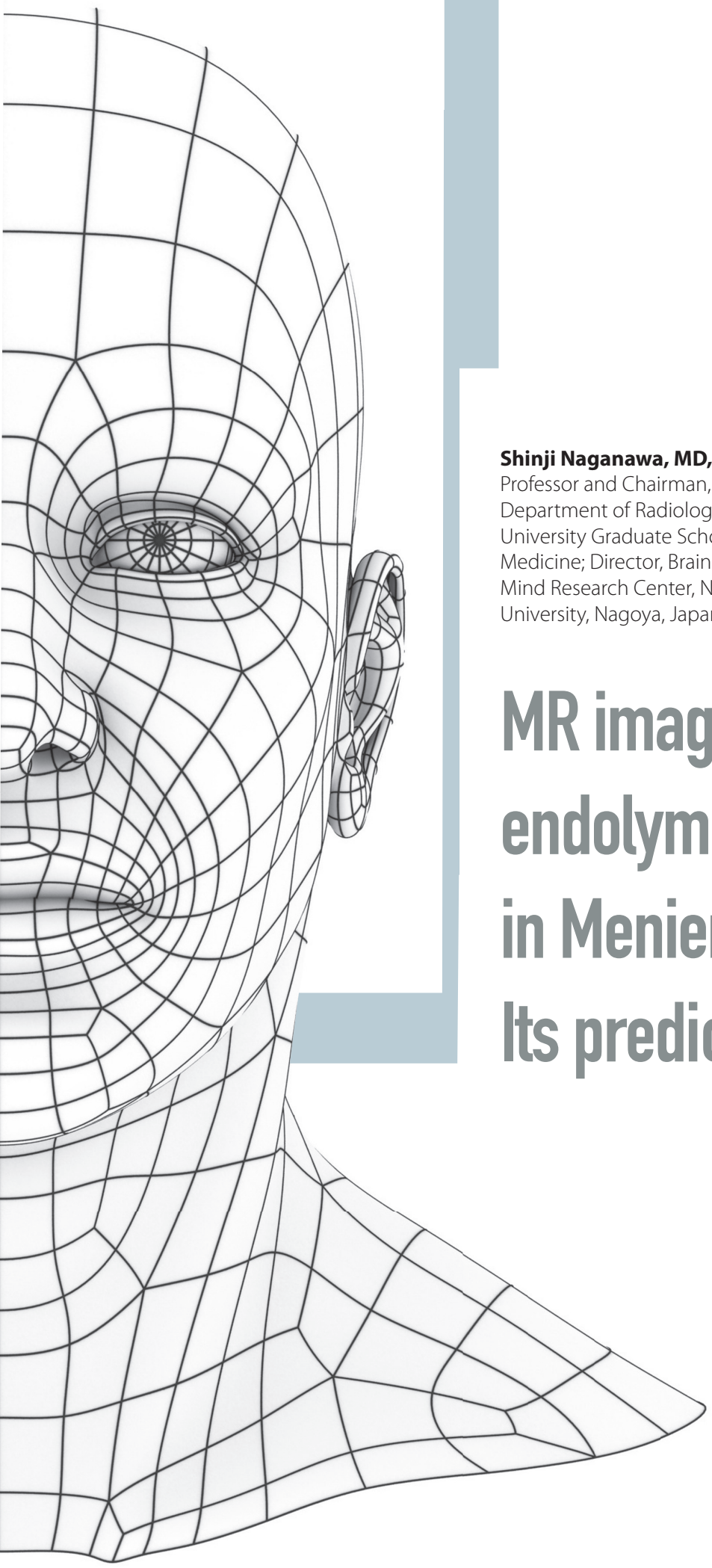
Director of and Professor at the Institute for Biomedical Sciences, Iwate Medical University, Yahaba, Japan

Article



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MR imaging of the endolymphatic hydrops in Meniere's disease: Its predictive value

Abstract

Visualization of endolymphatic hydrops (EH) of the inner ear for the evaluation of Meniere's disease (MD) is now widely performed all over the world using magnetic resonance imaging (MRI). These days, less invasive intravenous administration of gadolinium-based contrast agent (GBCA) and waiting time of 4 hours are usually applied. With the accumulation of clinical experiences, various important knowledge has been obtained. Firstly, mild EH in cochlea, especially in the upper turn, is not rare in healthy subjects. Secondly, EH in contralateral asymptomatic ear of unilateral MD is common. Thirdly, EH in the ears of MD patients is frequently progressive; the degree of this disorder is sometimes parallel to the symptom, especially the cochlear symptom.
Fourthly, not only the degree of EH, but also the degree of enhancement in perilymph seems to be a biomarker of MD. In general, predictive imaging is only possible when a certain image finding precedes the appearance of symptom. Therefore, as EH usually precedes the presence of the symptoms, its MR imaging is one of the most promising candidates for predictive imaging; it not only enables the objective diagnosis of MD, but also has a predictive value.
Furthermore, degree of EH is reported to significantly correlate with the degree of enhancement in the perivascular space of basal ganglia. Perivascular space is the entry of glymphatic system, which was recently proposed as the waste clearance system of the brain. Currently, it is the most important thing to build up a bias-free, automated objective evaluation pipeline to evaluate the degree of EH and enhancement, in order to perform predictive imaging and open the new door of the future neurosciences.

Introduction

Meniere's disease (MD) is an inner ear pathology characterized by repeated vertigo attacks, fluctuating low frequency sensorineural hearing loss, ear fullness and tinnitus. Its pathological hallmark is endolymphatic hydrops (EH) in the inner ear. The diagnosis had been usually made based on clinical symptoms with some assistance from otological functional tests. Recently, the objective diagnosis of EH by magnetic resonance imaging (MRI) became possible and many research results have been reported regarding the imaging methods including HYDROPS imaging by intravenous gadolinium administration, the evaluation methods, the correlation between imaging results and otological functional tests and the correlation between imaging findings and clinical symptoms [1-4].

Clinical significance of endolymphatic hydrops imaging

Firm evidence of the clinical utility of EH imaging has yet to be established. Based on imaging data from more than 200 patients and clinical data from more than 300 patients, MD often showed bilateral EH and comprised a continuum from a monosymptomatic disease to the typical complex symptom stage of the disease [5]; the time delay between hearing loss and vertigo was more than 5 years in 20% of the patients. Thus, it is suggested that EH imaging should be carried out in patients with sensorineural hearing loss, vertigo and tinnitus, to verify the inner ear pathology. This may lead to a better management of the condition, since early detection and intervention might improve the prognosis of patients with MD. For a widespread use of EH imaging, easier, standardized and more reliable evaluation strategies need to be established. If this is made possible, EH imaging might be included in the diagnostic guidelines for MD in the near future [4].

EH has been thought to correlate with the clinical symptoms of MD. Using MRI, it has been reported that EH in MD patients developed longitudinally with deterioration of inner ear function during medical treatment; the natural course of the pathology might be progressive with development of EH at least for a certain period [6].

In one of our studies [7], it was revealed that the cochlear EH was occasionally observed in control ears using MRI, as in normal temporal bone specimens; however, the presence or absence and the degree of vestibular EH were significantly different between ears with MD and control ears. The EH in the vestibule might therefore be a specific predictor of definite MD.

In another study [8], we found that the EH reduced in some cases with MD treated conservatively; this reduction was associated with improvement of the clinical symptoms. Therefore, both EH and symptoms sometimes evolve in parallel, and sometimes do not.

The etiology of MD is multifactorial. A characteristic sign of this pathology is EH, a disorder in which excessive endolymph accumulates in the inner ear and causes damage to the ganglion cells. In most patients, the clinical symptoms appear after considerable accumulation of endolymph has occurred. However, some patients develop symptoms in the early stages of the build-up. The reason for this symptomatologic variability remains unknown, and therefore the relationship between EH and clinical symptoms of MD requires further study [9].

MRI has been optimized to directly visualize EH in the cochlea, vestibule and semicircular canals, and its use is shifting from the research setting to the clinic. The management of MD mainly aims at relieving acute attacks of vertigo and preventing their recurrence. Therapeutic options are based on experiences; they include the control of risk factors and a conservative approach as the first line of treatment. When medical treatment is unable to suppress vertigo attacks, intratympanic gentamicin therapy or endolymphatic sac decompression surgery is usually considered [9].

New classification of Meniere's disease with the use of endolymphatic hydrops imaging

Formally, "certain" MD diagnosis can be done only when the EH is histologically confirmed after the death of the patient. However, an optimization of the classification criteria was proposed based on MRI: after confirmation of EH, MD should now be classified into certain MD, MD, vestibular MD or cochlear MD [9].

EH imaging has taught us that: 1) the cochlear and vestibular compartments can be differently affected; 2) EH is very often present in the asymptomatic contralateral ears. The proportion of contralateral hydropic changes of the inner ear in patients with clinically unilateral MD is surprisingly high, reaching 65% of clinically asymptomatic contralateral ears [10].

In this recent study [10], EH was cochleovestibular in most cases, but vestibular EH was slightly more common than cochlear one. The great advantage of these imaging data over autopsy is the much more detailed clinical description and the perfect temporal association between the EH and the clinical symptoms.

> "The management of MD mainly aims at relieving acute attacks of vertigo and preventing their recurrence"

One study [11] reported that EH was progressive in the long-term course of the disease in a large population of patients, but short-term and middle-term fluctuations of the symptom severity did not involve measurable variations of the EH; furthermore, the symptom severity did not decrease with increased disease duration.

New Insight

A strong negative correlation between the cochlear endolymphatic volume ratio in the inner ear and the contrast enhancement of the perivascular space was recently found [12]. Contrast enhancement of this space might hence be a new biomarker of EH.

The enhancement of the perivascular space in basal ganglia at the GBCA in the blood vessels might have permeated into the cerebrospinal fluid and perivascular spaces.

This might be a first step in the imaging evaluation of the glymphatic system (waste clearance system) of the brain [13], with a possible relationship between EH and glymphatic system.

Technical issue

For a quantitative evaluation of EH, it is crucial to increase the contrast-to-noise ratio (CNR) between endo - and peri-lymph. To do so, a T2-weighted MR cisternographic image was multiplied onto the HYDROPS images [14], as illustrated on Figure 1. The average CNR of the generated images increased to more than 200 times that of HYDROPS images.

Conclusion

Since EH precedes the appearance of the symptoms, their MR detection allows to perform "predictive imaging". Furthermore, EH might correlate with the function of glymphatic system, opening the way to "predictive imaging" for various neurodegenerative disorders such as Alzheimer's disease.

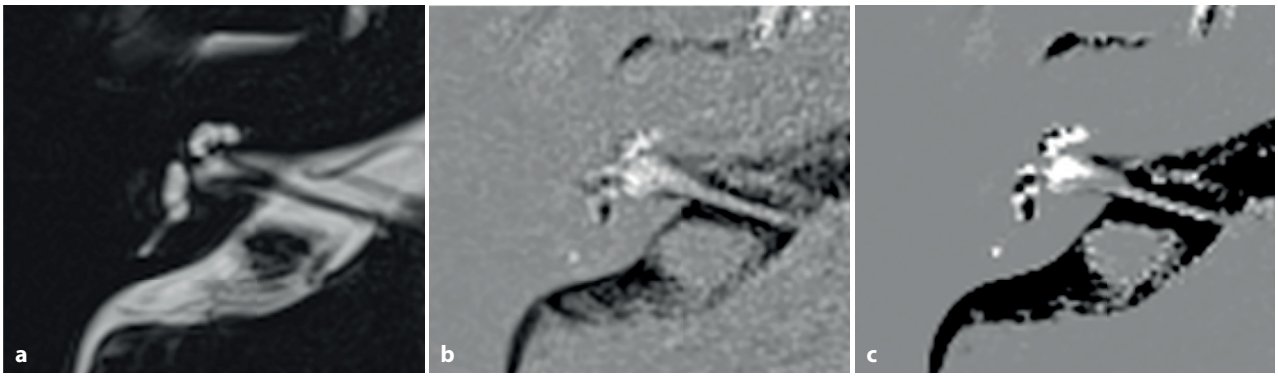

Figure 1: A 63-year-old man with right Meniere's disease. All images are obtained 4 hours after intravenous administration of single dose gadolinium based contrast agent. **a)** MR cisternography shows both peri- and endolymph as bright signal; **b)** HYDROPS image shows perilymph as white and endolymph as black; **c)** HYDROPS-Mi2 (HYDROPS image multiplied by T2-weighted image) allows the suppression of background noise and increase of positive and negative magnitude of peri- and endolymph. This image allows easier segmentation of peri- and endolymphatic space.

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APT Gluco Iopamidol CEST

" Developing new CEST-based tools for more accurate and reliable cancer diagnosis"

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Stefano Casagranda is a trained Biomedical Engineer from the Università degli Studi di Pavia, Italy, with a specialty in Artificial Intelligence applied to Healthcare. After completing his PhD in 2017 in Applied Mathematics to Biological Systems from INRIA (Institut National de Recherche en Informatique et en Automatique) in Sophia Antipolis, France, he joined the Research and Innovation team of Olea Medical®.

Stefano Casagranda is now leading the development of future CEST products at Olea Medical®, where he can leverage his background on Mathematical Modeling, Optimization Problems, Model Fitting, Model Reduction and Process Analysis techniques.

Olea Imagein: Could you please explain the principles of Chemical Exchange Saturation Transfer (CEST) imaging?

Stefano Casagranda: CEST imaging principles are quite simple and involve chemical species which contain in their structure a hydrogen proton that can be exchanged with those of water [1,2] (Figure 1A). By applying a radiofrequency (RF) pulse at their resonance frequencies, the chemical species of interest – such as amide or hydroxyl groups - reach a saturation state (Figure 1B); at this point, their labile excited protons are exchanged with the non-excited protons of the water (Figure 1C). If this process is continually repeated through few seconds of RF irradiation, it leads to a buildup of saturation in water (Figure 1D). In this way, the concentration of the targeted species can be indirectly measured by the decrease of water signal, easily detected by the classic MR imaging sequences (Figure 1E).

O.I: What are the advantages and limitations of this technique?

S.C: Using the process of continuous re-saturation and proton exchange, CEST can enhance the detection of certain metabolites that can be found in human body. In the clinical domain, it could therefore offer an interesting way to detect and characterize tumor tissues.

Indeed, due to a change in the protein content [3,4], tumor cells have a higher concentration of mobile amide protons that can be detected *in vivo* through chemical exchange and water signal attenuation, enabling imaging on clinical MRI scanners [5]. This CEST application is called Amide Proton Transfer (APT) [6] and is an appealing alternative to gadolinium enhancement imaging – especially nowadays where the latter is debatable and a matter for discussion, due to the incomplete metabolization of this contrast agent resulting in potentially harmful effects on the human body [7-10].

Additionally, other methodologies involving the administration of chemical substances that can be detected by CEST MRI arise great interest, like GlucoCEST [11] and Iopamidol-CEST [12] – also known as AcidoCEST [13]. These techniques could provide information regarding the metabolism and extracellular pH of tumor cells.

For all these reasons, CEST-based techniques are very attractive, but they share limitations that need to be overcome.

During the continuous application of RF pulses, other effects take place together with saturation transfer such as direct water saturation (DS) and magnetization transfer (MT) contrast. While CEST contrast is based on chemical exchange between labile protons and water, MT contrast originates from magnetization exchange between water protons and protons in solid/semi-solid environment [14]. For a reliable CEST quantification, these competitive effects need to be neglected.

Based on the supposition that DS and MT contrast effects are symmetrical with respect to the water frequency, the most used metric is called Magnetic Transfer Ratio Asymmetry (MTRasym) [1,2]. This method consists in measuring the water signal reduction at two different saturation frequencies: one is the resonance frequency of the molecule of interest; the other relies on the opposite spectral location, considering the water frequency as the spectral centrum. The difference between the reference and label values is then typically normalized by the signal measurement without RF saturation.

Moreover, because of B0 magnetic field inhomogeneity, caused in part by the patient's tissue properties, the full frequency spectrum could be shifted, leading to an inaccurate calculation of the MTRasym. To overcome this issue, numerous acquisitions at different frequencies around the water's specific frequency are needed (Figure 2A) to obtain voxel-wise the so-called Z-Spectrum, with a proper interpolation (Figure 2B). The Z-Spectrum is then centered so that its minimum corresponds to water frequency, performing a B0 correction for every image voxel (Figure 2C). A correct calculation of MTRasym is then obtained (Figure 2D). Nonetheless, a full-spectral sampling could not be optimal for clinical applications due to the elevated scan time required.

Finally, high magnetic field is preferred, since the chemical shift increases and leads to a larger saturation of the water; the result is a sharper Z-Spectrum. By applying mathematical methods such as multi-Lorentzian fitting, it could be possible to separate the different component effects as amide, amine, nuclear Overhauser enhancement (NOE), DS and MT

contrast peaks [15]. Because MTRasym has several intrinsic weaknesses – for example, many studies have shown that MT contrast was not symmetric with respect to water resonance [5,16], this approach leads to more robust results; however, this mathematical fitting is generally possible on Z-Spectrum acquired at 7T and above (Figure 3).

Considering these limitations and what is feasible in the clinical field, we are implementing different methodologies and alternative metrics that can improve as much as possible the quality of CEST signal on 3T devices.

O.I: What are the reasons of your interest?

S.C: Olea Medical® is one of the partners of the Horizon 2020 GLINT project (GlucoCEST Imaging in Neuroplastic Tumours), aiming at developing new CEST-based tools for more accurate and reliable cancer diagnosis tools [19].

> "CEST can enhance the detection of metabolites found in human body"

The project allowed us to build a strong partnership with leading research institutions and industry from in- and outside the European Union, such as University College London, University of Turin, Max Planck Society, Bracco Imaging, University of Zurich, Tel Aviv University and the European Institute for Biomedical Imaging Research.

One of our tasks in the project is to develop a CEST application able to process and compare the clinical/preclinical data of our partners, based on different CEST methodologies and protocols.

O.I: You implemented 3 different CEST applications based on amide proton transfer (APT), Glucose and Iopamidol. Could you please tell us more?

S.C: The Olea Medical® CEST data processing software is indeed composed of 3 SDK plug-ins.

Our first plug-in aims at processing APT data (Figure 4); currently, amide CEST is the most widespread CEST imaging approach thanks to the absence of contrast agent administration. As mentioned before, the signal originated from proteins and peptides of the tissue increases in tumor regions and can be detected with a certain stability and sensitivity, even at 3T. APT principal application is cancer detection in brain tissue [20] where it has led to impressive results (e.g. discrimination between tumor and edema [2], or between different tumor grades [21] or distinction of tumor recurrence from radiation necrosis after brain tumor therapy [22]); the technique was also applied in breast and prostate cancer tissues [23,24].

Our second plug-in is oriented towards GlucoCEST data processing (Figures 5a, 5b1 and 5b2). This method is based on the measurement of the uptake of the unlabeled glucose through the chemical exchange of labile protons between hydroxyl groups and water [10]. Cancer cells are characterized by an alteration of glucose metabolism, known as Warburg effect [25]; they demand and consume this sugar much faster compared to their healthy counterparts. The common approach in GlucoCEST is to perform an external administration of glucose in the body and to measure its concentration increase, assumed to be higher in cancer tissue; the related metric is called GlucoCEST enhancement (GCE) [5,17].
The goal of this technique is not only to differentiate healthy from cancerous tissue based on their glucose concentration, but also to provide additional information regarding the tumor metabolism and aggressiveness. Furthermore, this methodology could provide a safer alternative to FDG-PET because GlucoCEST uses natural and non-radioactive glucose or even more sophisticated glucose analogue for producing a more intense CEST signal [26]. The improvement of GlucoCEST is the core aspect of GLINT project and Prof. Xavier Golay, pioneer of this method and GLINT scientific coordinator, gave a very interesting overview of the topic in Olea Imagein (Issue Number4 – October 2017).

Finally, our last plug-in treats CEST data acquired after body injection of Iopamidol, a iodinated contrast agent that has a high safety profile and is FDA-approved for clinical CT exams (Figures 5a and 5c). The team of Prof. Silvio Aime and Dario Longo (University of Turin and GLINT partners) studied the potential of this contrast agent for CEST MRI [12].

Iopamidol is characterized by amide groups that resonate at two different frequencies, hence producing two distinct CEST effects; because the exchange rate between amide and water protons is also pH-dependent, a ratiometric method between the two signals enables to measure the pH value of the solution surrounding the Iopamidol [5,27]. While APT is also used to infer pH changes in the tissue [28], the great advantage of Iopamidol-CEST is that, due to the ratio of the two amide CEST signals, the external pH (pHe) can be quantitatively measured, removing the requirement of knowing the local concentration of the CEST agent; this allows to obtain actual quantitative pH maps. pH-metry presents a great interest in tumor studies. Specific tumor cellular mechanisms [29] avoid an excessive intracellular acidity due to Warburg effect, causing an extracellular acidosis that leads to an average pHe of approximately 6.5-7 [30]. The first *in vivo* demonstration of the relationship between tumor acidosis and dysregulated metabolism has been shown by Longo et al. in a murine breast tumor model by using Iopamidol for tumor pH mapping [31]. Owing to the safety of Iopamidol, this approach has been applied at clinical level to assess tumor acidosis in invasive ductal carcinoma or in breast cancer patients [13].

Given the great interest that is emerging for these new innovative techniques and the stunning results of CEST MRI in the clinical field, on our side we are working rigorously to bring a dedicated software capable of processing these data in the most efficient way, leaving the user the freedom to use his/her own acquisition protocol.

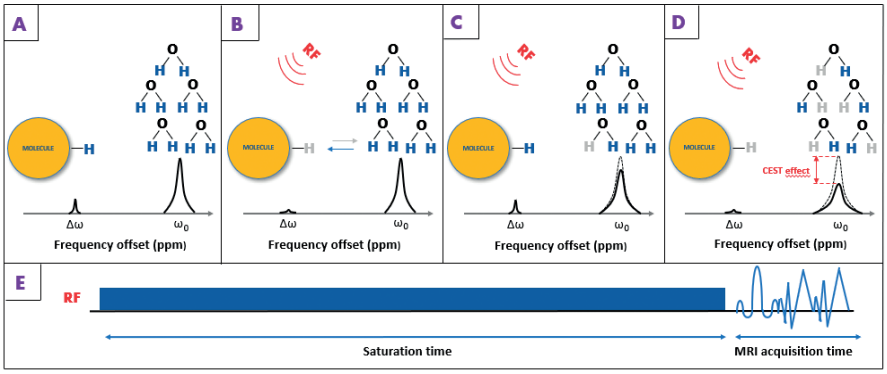

Figure 1: CEST effect and imaging acquisition sequence.
In the below MRI spectrum, the water (at frequency offset ω_0) and the labile proton-containing molecule signals ($\Delta\omega$ ppm away from the water one) are exposed to a magnetic field **(A)**. By applying a RF pulse at its specific resonance frequency, the molecule is selectively saturated **(B)** and its excited protons are exchanged with those of water, whose signal slightly decreases **(C)**. If this cycle is repeated long enough and the exchange rate is relatively large, the water signal decrease becomes visible **(D)**: this is known as CEST effect. In CEST MRI imaging, the saturation protocol is followed by fast acquisition sequences such as single shot echo-planar imaging **(E)**. The saturation time, the power and type of RF pulse depend on the used CEST protocol. Image adapted from Prof. Xavier Golay, ECR 2017.

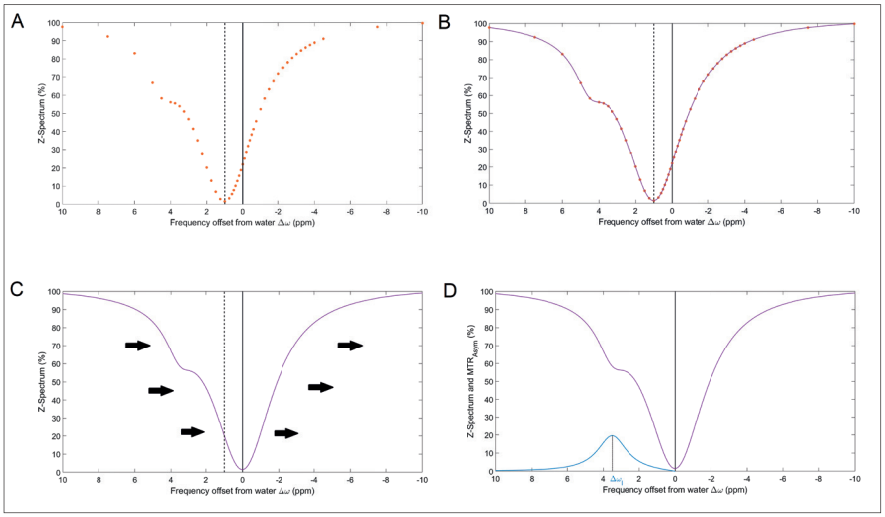

Figure 2: Z-Spectrum, B0 correction and MTRasym.
The Z-Spectrum is a key element for the calculus of CEST signal and due to B0 field inhomogeneities needs to be corrected.
A) Traditionally, a dense sampling is performed around the water offset (dashed line assumed 0 ppm, solid line actual 0 ppm); **B)** an interpolation or spline method is used to calculate Z-Spectrum function passing through the points; **C)** the minimum of the function is then found and shifted at 0 ppm, leading to a correct centering of the full Z-Spectrum; **D)** once the Z-Spectrum is centered, different methodologies can be applied to infer the CEST signal given by the molecule of interest, such as MTRasym, that is the difference between the negative and positive part of the Z-Spectrum. Because, *in vivo* other asymmetric CEST agents and effects are contained in the Spectrum, MTRAsym could not lead to optimal results. $\Delta\omega_i$ is the frequency offset of the molecule of interest (3.5 ppm for the labile protein amide, 1.2 ppm for the hydroxyl groups of glucose, while 4.2 and 5.5 ppm for the amides in Iopamidol [5]). Image adapted from [1].

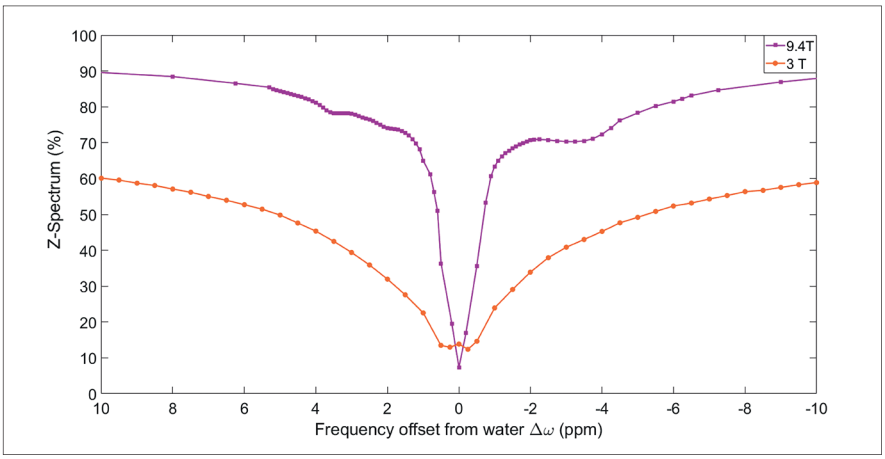

Figure 3: 3T vs 9.4T Z-spectra *in vivo*.
Z-Spectra of a ROI in human brain (grey matter). The orange spectrum was acquired at 3T using a high saturation power protocol (typically used in APT-weighted imaging) while the purple one at 9.4T using a low saturation power protocol. Due to Z-Spectrum shape at high magnetic field, the separation of the different CEST agents and effects – such as amide, amine, guanidinium, NOE, MT and DS – is possible using advanced methods such as multi-Lorentzian fitting. Instead, the traditional protocols at 3T generate Z-Spectra where these effects are broad and can be mixed. While APT-weighted imaging still has great clinical benefits, the extraction and isolation of the CEST agent signal of interest is easier at high static magnetic field strengths. The images were acquired by Anagha Deshmane and Moritz Zaiss of Max Planck Society. Image adapted from [17] and [18].

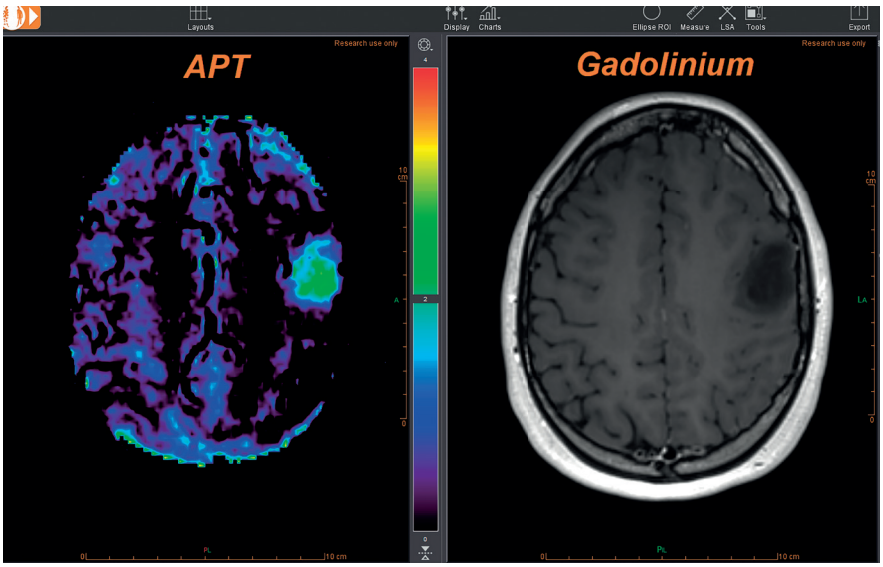

Figure 4: APT vs Gadolinium.
APT-weighted image (left) and gadolinium-enhanced T1-weighted image (right) of a patient with an anaplastic Grade 3 astrocytoma, IDH mutant with ATRX loss, and retained 1p/19q. The images were acquired by Sotirios Bisdas and his Clinical Scientists team (University College London) using a Siemens Magnetom Prisma 3T MRI Scanner and were processed using Olea Sphere® CEST Application. The CEST acquisitions were B0 and B1 corrected. Finally, one of the enhanced metrics proposed in Olea Sphere® CEST Application was applied to generate the APT-weighted image (left). The higher CEST signal intensity is given by the proteins and peptides of the brain astrocytoma on the left temporal lobe (green color). Noteworthy, the conventional MRI findings did suggest a low malignancy tumor but the CEST acts complementary and clearly indicates metabolic activity consistent with higher grade astrocytoma.

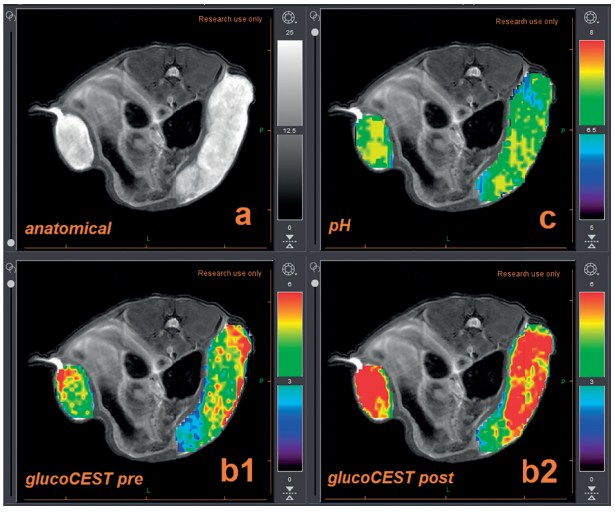

Figure 5: Glucose and Iopamidol CEST effects in tumor tissue.
Anatomical and CEST derived images of a male mouse with human prostate cancer (PC3) cells subcutaneously implanted in both flanks. The mouse underwent glucose intravenous injection (5g/kg) followed by Iopamidol injection (4g/kg) 30 minutes later.
The images were acquired by Silvio Aime and Dario Longo team (University of Turin) using a Bruker 7T MRI scanner and were processed using Olea Sphere® CEST Application.
a) Anatomical T2-weighted image of the mouse; **b)** GlucoCEST maps of the tumor tissue before (1) and after (2) the injection of D-glucose – an enhanced metric of Olea Sphere® CEST Application at the hydroxyl group resonance frequency was applied to generate the two maps (in percentage), and due to tumor glucose uptake, an average signal increase of 3% was detected; **c)** Extracellular pH map of the tumor tissue calculated from CEST acquisitions upon Iopamidol injection – the map shows a moderate tumor acidosis.

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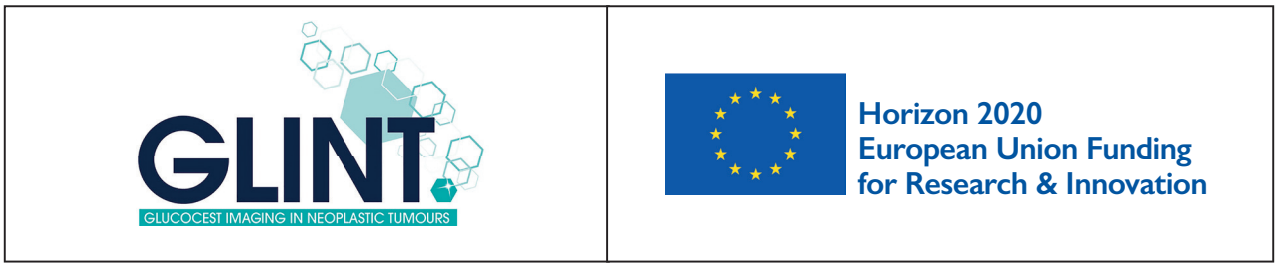

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Interview

CEST Clinical Applications

Sotirios Bisdas, MD, PhD, MSc (Advanced Oncology), FESHNR, EQNR.
Associate Professor of Neuroradiology at the Institute of Neurology, University College London, UK, and Professor of Radiology and Neuroradiology at the Eberhard Karls University, Tübingen, Germany.

Sotirios Bisdas is Consultant Neuroradiologist and MRI Lead in the Department of Neuroradiology at the National Hospital for Neurology in London, UK. He did his training in Radiology and Neuroradiology at the Hannover Medical School, University of Frankfurt, and University of Tübingen. He completed a post-doctoral scholarship in Neuroradiology Research at the Medical University of South Carolina, USA, and holds a MSc degree in "Advanced Oncology" from University of Ulm, Germany. His expertise fields include advanced CT, intra-operative MRI, advanced and functional MRI and molecular MR-PET imaging, and ultra-high-field MRI in brain diseases with particular interest in neuro-oncology.

Sotirios Bisdas has more than 200 scientific presentations and has authored more than 150 peer-reviewed publications (h-index: 38) and 8 book chapters. He is lead section editor and member of the editorial board in several journals in Radiology and Neuroradiology, serves as member of the Executive Committees of the European Society of Head and Neck Radiology and European Society of Medical Imaging and Informatics, and is member of the Head and Neck committee of the European Society of Neuroradiology.

"APT-CEST imaging has become increasingly recognized as a promising imaging tool for brain tumors"

Olea Imagein *Innovation for life*

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Olea Imagein: What is your experience so far with CEST (Chemical Exchange Saturation Transfer)?

Sotirios Bisdas: My research experience with APT (Amide Proton Transfer) - CEST started in 2012, when we included the modality in our comprehensive PET-MRI protocol for brain tumors. The first results were very encouraging, and we thus started using APT-CEST as core part of our multi-parametric MRI protocol in treatment naive gliomas about 4 years later. We gradually moved from a single slice acquisition to a whole brain 3D APT-CEST sequence, which has obvious advantages for capturing the whole tumor's heterogeneity. So far, the results have been very promising and the qualitative assessment of the APT-CEST maps has assisted us in gliomas grading. It is noteworthy that APT-CEST results have occasionally highlighted crucially malignant tumor regions and outperformed other traditional metabolic techniques like amino-acid PET and MR spectroscopy. Currently, we are planning to implement CEST acquisitions in glioma follow-up imaging to cope with the diagnostic uncertainty from treatment-related changes.

O.I: Which clinical applications could be promising for CEST?

S.B: Currently, there are no other MRI methods available to spatially assess proteins and peptides *in vivo*. However, these substances play key role in neurological diseases such as tumors and stroke, and information derived from CEST acquisitions are probably relevant for earlier detection, better spatial definition and improved characterization of diseases. Baseline molecular staging of gliomas, in line with the most recent WHO (World Health Organization) classification, differentiation of treatment-related changes and primary CNS (Central Nervous System) lymphomas from glioblastomas could be 'killer-applications' for CEST. The CEST effect of creatine could be promising as a marker for ischemic brain and skeletal muscle energetics.
Investigating other brain endogenous compounds with exchangeable protons might show favorable results for diagnosis and characterization of neurodegenerative or psychiatric diseases, as well as in treatment monitoring.

O.I: What are your expectations regarding CEST applications?

S.B: APT-CEST imaging has become increasingly recognized as a promising imaging tool for brain tumors, and I expect that it will be streamlined for tumor diagnosis and staging at baseline and in surveillance as well.

Other endogenous CEST contrast agents from amine groups on small metabolites such as glutamate (Glu), creatine (Cr) and hydroxyl groups on myo-inositol (MI) are currently probed, while the association of elevated amine proton CEST signal increases with decreasing pH opens the possibility for the though challenging pH-weighted MRI *in vivo*. Besides endogenous CEST agents, there is also preliminary work in low-molecular-weight, diamagnetic molecules with exchangeable protons as exogenous CEST agents.

> "Eventually, GlucoCEST will offer a true alternative to FDG-PET in brain tumors"

A number of sugars, metabolites, amino acids and other small molecules have been trialed and I expect more intensive research activity in the future. My active involvement as Chief Investigator in the ongoing EU-funded project 'Establishment of GlucoCEST MRI as a Biomarker in Cancer – Translational Study' (Principal Investigator: Prof. Xavier Golay, UCL) attempts to establish the diagnostic value of CEST in capturing exogenous unlabeled glucose uptake *in vivo*, relying on the tumor propensity in anaerobic glycolysis for energy production – a phenomenon that is known as the Warburg effect. Eventually, GlucoCEST will offer a true alternative to FDG-PET in brain tumors and will enhance our understanding for the tumor micro-environment.

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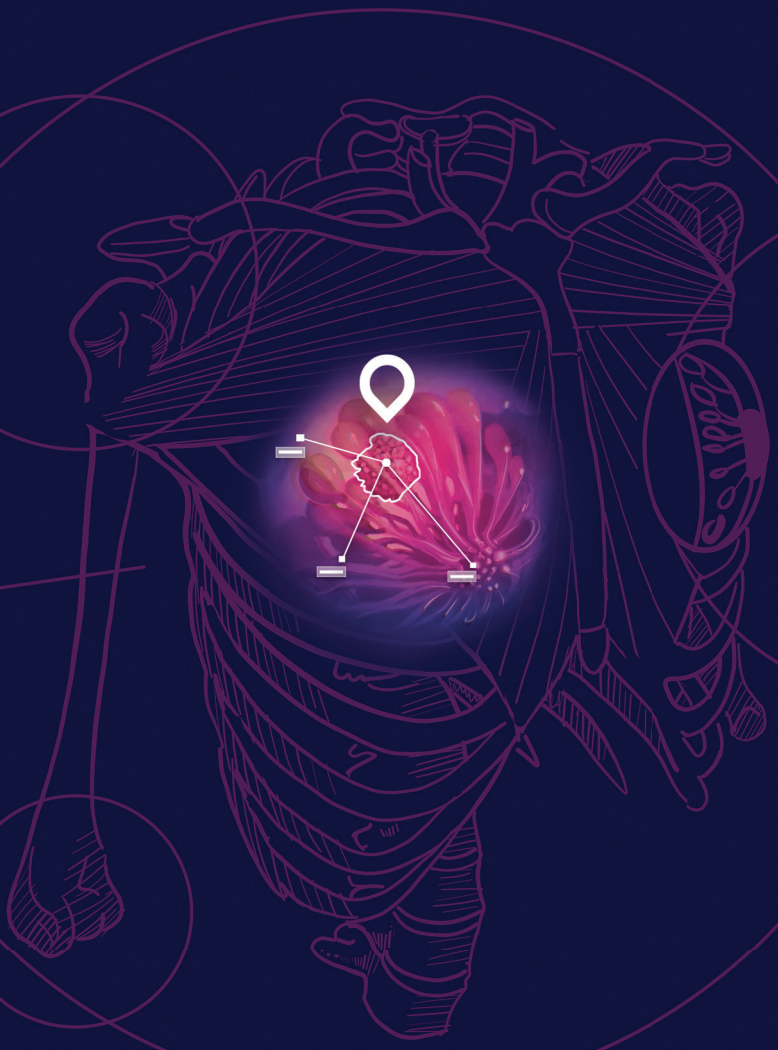

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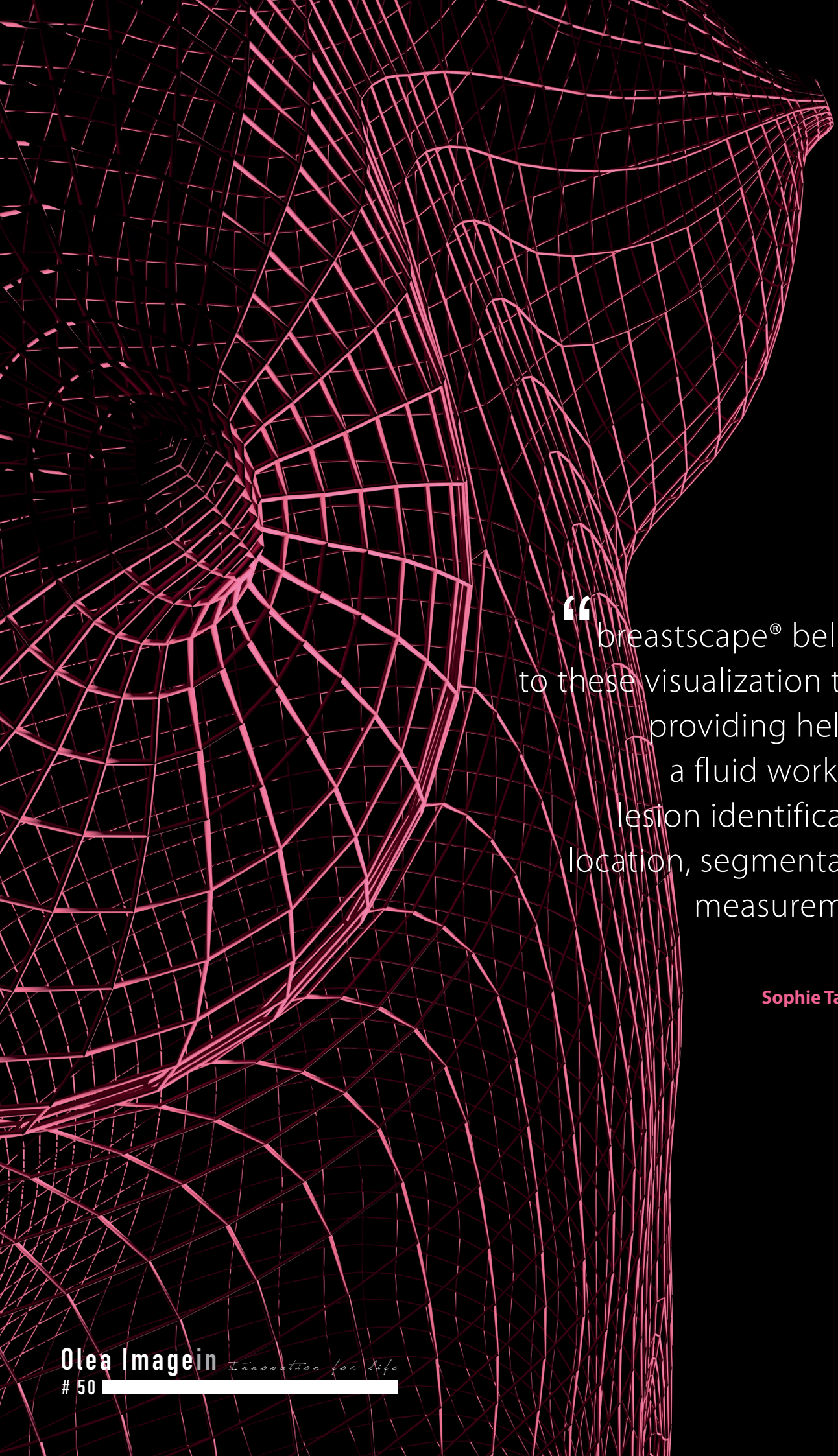
Breast MRI Management

"The main advantage of automated post-processing tools is to save time"

Sophie Taieb, MD
Assistant director of the Medical Imaging Department at Oscar Lambret Center, Lille, France

After achieving medicine internship, Sophie Taieb has been working at the Oscar Lambret cancer center in Lille, France, since 1992. Her areas of interest and specialties focus on woman imaging, i.e. female pelvis and breast, but also on soft tissue sarcomas and bone tumors. Her team has been among the pioneers in the field of uterus and ovary MR imaging, but also in performing breast MRI from 1996. The early indications were dedicated to women with gene mutations, but they were gradually extended as knowledge progressed. The major part of the activity, though, remains the screening of women with mutations, with about 800 to 1000 breast MRI per year.



"breastscape® belongs to these visualization tools, providing help for a fluid workflow: lesion identification, location, segmentation, measurements"

Sophie Taieb, MD

Olea Imagein: What is the role of MRI in breast cancer management?

Sophie Taieb: Breast MRI is performed for several indications. First, for the screening of women at high risk, basically higher than 25% of having a breast cancer in their entire life. Second, for diagnosis purpose in women with metastatic lymphadenopathy and normal breast conventional imaging – mammography and echography. The third indication is related to patients already diagnosed with breast cancer: either for women with specific types of lobular histology, in order to detect potential multi-focality due to dissemination; either for women under 40, since surgery needs to result in safe margins in order to decrease the risk of recurrence; either for women with gene mutations because other cancers can sometimes be detected or for planning a prophylactic mastectomy of the contralateral healthy breast. The fourth indication is the follow-up of neo-adjuvant chemotherapies to assess the treatment efficacy. Finally, a more limited part of breast MRI is performed for workup of treated breast cancer, since treated and irradiated breasts are sometimes more difficult to analyze with mammography and echography; MRI is also a good exam for reconstructed breasts with prosthesis.

O.I: Which biomarkers can predict clinical outcome or a response to treatment?

S.T: Currently, the major biomarker when available is the cancer antigen (CA) 15-3. If the CA 15-3 level is high before treatment, the prognosis will be poorer. However, the follow-up of neo-adjuvant chemotherapy will be interesting to estimate. It has been shown that MRI was more accurate than mammography and echography to evaluate the benefit of therapy, with classic volume criteria. Also, several teams and studies showed that the analysis of the tumor perfusion could be meaningful, that diffusion could highlight a decrease in cell density associated with a decrease in signal, and that spectroscopy could be interesting as well. However, spectroscopy provides follow-up for tumors larger than 1cm; in case of efficient treatments able to decrease the tumor's size, this follow-up in time with MR spectrometry is not possible.

Intuitively, all these biomarkers can be well understood; however, what is missing is thresholding. We do not have the cutoff values in diffusion or perfusion to assert, for instance, that response to treatment is positive despite only small variations of tumor volume. Those criteria do not exist yet, I am not sure we will know them one day.

O.I: How do you benefit from the introduction of automated post-processing tools in your clinical practice?

S.T: The main advantage of automated post-processing tools is to save time. If we can display on the screen all the series that we need for the general overview, and then focus on a finer vision at a glance without searching for the sequences, it really saves time. A second feature able to reduce our time-consuming tasks is the possibility to click on a breast lesion and get its location in space, in the three planes, the distances to the nipple, to the skin, to the thorax. Also, an automatic and accurate one-click segmentation of the tumor, without further manipulation to adjust the shape, is a substantial added value to the interpretation process. breastscape® belongs to these visualization tools, providing help for a fluid workflow: lesion identification, location, segmentation, measurements.

Today, artificial intelligence interface is expected to be developed and set up by the MRI manufacturers between the acquisition and visualization consoles of the radiologists; this would allow faster exams, with less contrast agent, etc. AI could also be used to identify specific biomarkers; this is not really post-processing anymore but a work in progress. Of course, this does not save time yet, on the contrary, validation and learning are long and laborious processes, so that this side of AI still needs a lot of improvements to be used in clinical routine. The aim is to get the parametric maps faster, with sorted information to identify the most relevant ones among the huge quantity of data.

O.I: What about automated post-processing tools for biopsy?

S.T: Breast biopsy is fundamental. Breast MRI produces a high rate of false positive exams. Once a lesion is identified as suspicious on MRI, an echography is performed, but about 12% of the MRI breast cancers are not detected by echography. Therefore, we absolutely have to do a biopsy. In our institution, we have been using biopsy tools since 2004, i.e. 14 years of experience. We tested several systems and finally selected the solution thought to be the most efficient. First, in the MRI room, a marker clip is positioned within the lesion; after this procedure, the patient leaves the room and the technical gesture of biopsy is performed. This protocol allows to limit the occupation time of the MRI room to 10-12 minutes, since biopsy and compression are achieved outside. The patients are seen again 8 days later: MR imaging – sometimes followed by mammography, is conducted to locate the clip, check whether the biopsy was properly performed, and assess the size of a potential hematoma; it is also the time for the medical consultation and discussion with the patients regarding the biopsy results. All those steps last approximately 30 minutes. This organization, set up since 2010, provides flexibility and allows to perform non-programmed biopsies, if needed – it requires two tables and two breast coils for both biopsy and diagnosis.

O.I: Do you think the evaluation of texture parameters could have an added value in breast cancer management?

S.T: Texture is a big question and a great hope. Many studies showed that, according to MRI contrast enhancement, a diagnosis of molecular subtype could be approached. If we could manage to make customized texture analysis depending on molecular sub-types, it would be very interesting. Texture analysis could also be used to evaluate neo-adjuvant chemotherapy, and we are waiting for you, Olea Medical®. As radiologists, we expect from our partners to start and conduct Radiomics studies on breast cancer, but not only. In an anticancer center, we follow a large population before and after chemotherapy, before and after radiotherapy, we follow the tumors and their evolutions. Today, we use criteria such as size, CT density or PET scan findings. It is likely that we need other tools, since none of those has proven its perfect efficiency. Therefore, we are ready to collect all the data related to breast cancers treated with chemotherapy, and work with computer scientists and engineers in order to combine the mathematics and computer tools with the medical knowledge. The association of both pieces of intelligence can make us move forward.

O.I: How do you imagine the future of breast MRI, especially with artificial intelligence (AI) arrival?

S.T: As mentioned before, AI can intervene at two levels: at the time of image acquisition, for faster and more accurate exams; at the time of interpretation, for helping in structuring a smooth workflow for the radiologist. But we can see a little bit further and imagine that the exams could be sorted by AI into a certain numbers of sets, "most probably normal" or "most probably pathologic". If AI is able to do that, the radiologist will again save time: if 10% of the exams are considered as normal and 10% are considered as pathologic with a 100% level of confidence, the radiologist will gain time on these 20% of exams that do not need to be analyzed like the others.

Currently, a 90% confidence, even if superior to the human performance, is not enough because the 10% confidence missing implies that we still need to interpret those exams. However, important questions about AI remain unanswered: if I make a mistake, I can explain and talk to the patient; but if AI makes a mistake, who will explain? No answer at the moment. Therefore we are waiting.

Interview

Denis Le Bihan, MD, PhD
Founding Director of NeuroSpin, CEA Saclay-Center, Gif-sur-Yvette, France.

Elastography

"Diffusion, a powerful concept deeply rooted in nature"

Olea Imagein: In your book "Looking inside the Brain (Le Cerveau de Cristal)", you have recently talked about the "song" and the "dance" of water molecules for MRI. Could you please explain to our readers how these songs and dances are related to Diffusion MRI virtual Elastography?

Denis Le Bihan: Of course, the song and the dance of water molecules are just analogies. With standard MRI, magnetized water molecules produce radiowaves, whose frequencies reflect their location in the body; hence, altogether we can say that they produce a beautiful sound. The dance refers to their random microscopic movement due to Brownian motion, the basis of Diffusion MRI which I pioneered more than 30 years ago. Both song and dance are transformed into images which mirror the movement of water molecules within the tissue microstructure.

Diffusion MRI Virtual Elastography exploits the dance of the water molecules, deeply affected by the tissue content – cells of different shapes or sizes, fibers, etc. Mechanical elasticity also depends on the tissue content: there are hard or soft tissues, according to their nature. Physicians have known this very well, as they have always used manual palpation to examine their patients – looking for any local hardness in the breast or the prostate for instance, as tumors are harder than normal tissues. This "palpation" can be done in a more rigorous and quantitative way by actually measuring tissue elasticity using ultrasounds or MR elastography (MRE). My intuition was that one could also use Diffusion MRI to "palpate" tissues through the dance of the water molecules.

The idea looks simple but came to my mind only three years ago. Together with my Japanese colleagues from the University of Yamanashi, I started to study patients with liver diseases. Liver fibrosis is very frequent in Asia due to the high rate of viral hepatitis. Standard MRE is used to assess and stage the liver stiffness, which increases during fibrosis; high degree of fibrosis may lead to cirrhosis and then cancer. We found that there was a very strong and linear relationship between MRE and Diffusion MRI measurements, to such an extent that we could accurately derive liver elasticity (units are kPa with MRE) from Diffusion MRI. Currently, this relationship is only empirical, as there is no physical model yet to link tissue microscopic properties (to which Diffusion MRI is sensitive) to their elasticity (measured with MRE).

O.I.: Could you please explain the relationships between tissue elasticity and diseases?

D.L.B: This relationship has been known for many years by physicians doing palpation on their patients: tumors are harder than surrounding tissues. Self-palpation of their breast sometimes leads women to discover a tumor, unfortunately most often at an advanced stage since the tumor needs to be big enough to be felt. Liver palpation is not that easy as the liver is usually located under the ribs, unless it becomes very large due to advanced fibrosis or other disease. Five stages from F0 (normal) to F4 (severe, which might lead to cirrhosis) can be distinguished. As mentioned above, there is a direct relationship between the degree of fibrosis and the tissue stiffness; this is the reason why MR standard elastography is used in the liver, with the expectation that it may replace invasive biopsy, which is not always accurate and has its own complications (hemorrhage, infection).

O.I.: What are the advantages of Diffusion MRI virtual Elastography compared with conventional elastography? How about its limitations?

D.L.B: The first problem with standard MR elastography is that we have to use a device to produce mechanical waves, located as close as possible to the organ to investigate, for example on the chest wall for the liver. This device produces vibrations in direction of the organ. The system is somewhat costly, and it takes time to install it – time is precious in a clinical setting. With Diffusion MRI virtual elastography, let us call it Diffusion MRE, there is no need for any equipment at all – besides the MRI scanner, of course. It is much easier for the patients and the staff, faster and much less expensive than standard MRE.

Second, the MRE device cannot be placed anywhere. If it is fine for liver or breast, it might be cumbersome for deep organs, for instance prostate. With Diffusion MRI, and so with Diffusion MRE, one can virtually investigate any organ.

Third, standard MRE relies on the phase of the MRI signals, which are shifted when tissue undergoes movement induced by the propagating mechanical waves generated by the device. To be efficient, those waves and the acquisition must be well synchronized,

which means that most often only single slices can be acquired – this is an important limitation if we consider that fibrosis may not be at all homogeneous throughout the liver. Furthermore, estimation of tissue elasticity from phase images is not straightforward and only small parts of the field of view are often reliable enough. With Diffusion MRE, which is a signal amplitude-based multislice modality, the whole liver can be investigated at once.

The fourth problem is that the spatial resolution of standard MRE is limited, set by the wavelength of the mechanical waves. Short waves needed to obtain high resolutions require high frequencies and do not propagate very well in the tissues.

Diffusion MRE has limitations too, but they are different. First, Diffusion MRE is generally sensitive to motion artifacts. In the liver, especially, motion can be important due to breathing and heart beating; some parts of the liver located on the left side are more often prone to such artefacts. Of course, this is also true for standard MRE; however, breathholding, respiratory and cardiac gating may help.

The second limitation of Diffusion MRE is that, in order to get elasticity information, a somewhat high degree of sensitization of the images to diffusion has to be used (high b-value); at this level, the MRI signal becomes very low. If the signal within background noise is too low, the images are not usable. One efficient way to increase the signal level is to acquire multiple image sets for each b-value, which represent the degree of diffusion sensitization – only 2 are necessary for Diffusion MRE. However, this repetition is at the expense of scanning time. Overall, image quality depends on the performance of the MRI scanner (especially its gradient hardware, but also field strength and radiofrequency coils) and its level of tuning. Cooperation with vendor technicians may greatly help for sites where MRI signals are border line. This issue is not specific to Diffusion MRE, but affects Diffusion MRI at large. Given that Diffusion MRI is now a well-established modality installed on most MRI scanners worldwide, we may think that technical progress is beyond the corner to boost image quality. Indeed, some manufacturers have already made available very performing gradient systems for Diffusion MRI.

One third important limitation is that the relationship between diffusion parameters and elasticity remains only empirical at this stage. Hence, some calibration is necessary from standard MRE to obtain quantitative results, i.e. elasticity in kPa. This is what we have done in the liver. Calibration should be done once for all, as it should not depend on the MRI scanner. However, this calibration step will have to be performed before extending the application of Diffusion MRE to other organs, a work which is in progress.

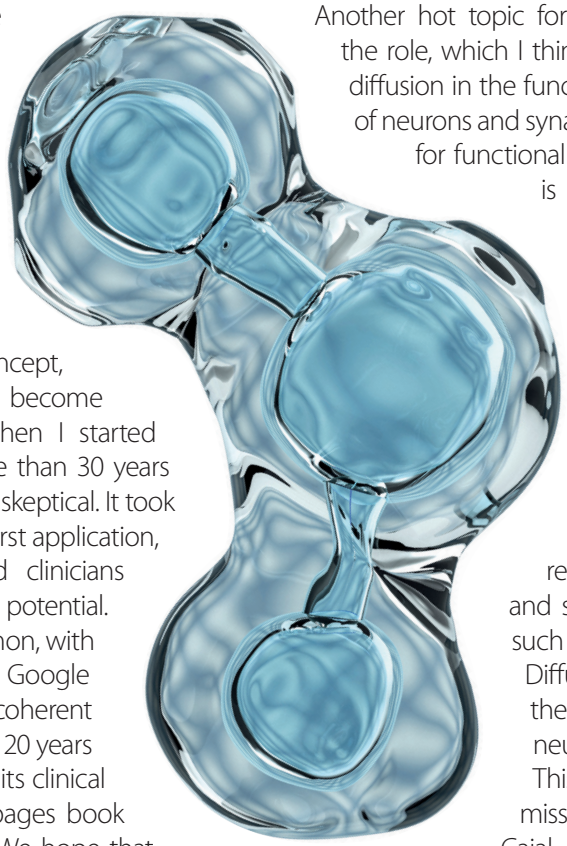
O.I.: How do you think that MR Elastography will develop in the future? For which applications, in which anatomical structures?

D.L.B: Standard MRE is mainly used in the liver, this is the reason why we chose this organ first to establish the Diffusion MRE method. Elastography, whether real or virtual, looks very promising to non-invasively assess liver fibrosis, instead of using biopsy. Kidney fibrosis, which is a concern for kidney transplants, could probably also benefit from the technique. However, elastography has good potential in other organs too, especially in the field of oncology to detect or characterize tumors, such as in breast or prostate. One advantage of Diffusion MRE is that there is no need for dedicated hardware, so that it should be tried easily. The only issue would be that calibration would be required at some point - not necessarily versus standard MRE but, for instance, versus ultrasounds. The problem with ultrasounds is that results depend on the pressure applied on the organs; this method is therefore operator-dependent whereas MRE is more neutral. Spleen is also an organ to look for, as high degree of fibrosis in the liver might result in portal hypertension, a complication making tissue harder which can be seen on the spleen. In the brain, things are a little bit more complicated because of the anisotropy for diffusion, implying that elasticity should be anisotropic as well. Doing elastography in the brain should be extremely interesting, even if it is a bit challenging. Furthermore, deep organs like pancreas or female pelvis for instance, where standard MRE is not used today, are also candidates for Diffusion MRE.

O.I.: What about the validation today?

D.L.B: We have run a preliminary validation study in a small cohort of patients with liver diseases. The initial study was conducted in Japan at the University of Yamanashi with Professor Motosugi and Doctor Ishikawa. The concept is now under validation with a much larger population with very promising results, especially in

terms of clinical potential (fibrosis staging). We need to investigate patients with a wider range of liver diseases to confirm that the method works well and to identify possible issues. For instance, some patients may have other features like steatosis or hemochromatosis which are known as pitfalls for standard MRE. In principle, Diffusion MRE should be immune to those problems, but this has to be checked.



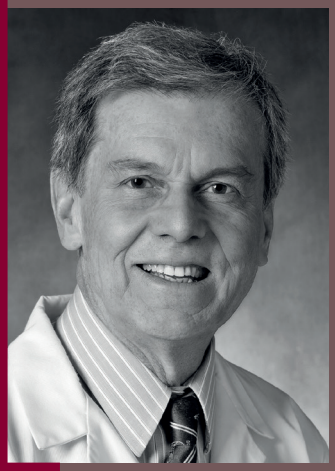
As it is a completely new concept, it might take time for it to become an accepted clinical tool. When I started introducing Diffusion MRI more than 30 years ago, the community was rather skeptical. It took more than 10 years before the first application, brain acute stroke, convinced clinicians and MRI manufacturers of its potential. Diffusion MRI is now very common, with more than 1 million of entries in Google Scholar! For IntraVoxel Incoherent Motion (IVIM), it took more than 20 years before the community realized its clinical potential, as shown in a 500 pages book which has just been released. We hope that things will be much faster for Diffusion MRE, as both Diffusion MRI and standard MRE are already well-established modalities, although the combination of both is not straightforward.

With Olea Medical®, we will do our best to help everybody interested in implementing and testing the method. Our colleagues should not be afraid, it is not so difficult, but they need the right MRI protocol and the right software.

O.I.: ADC, IVIM, Kurtosis, now Elastography, all derive from the same phenomenon: Water Diffusion. Is there an end to this list? Do you imagine that Diffusion can still help creating new medical modalities?

D.L.B: No, there is no end, of course. Diffusion is not a method. It is a powerful concept, deeply rooted in Nature – all elements of the Universe are subject to Brownian motion and diffusion, even the stock market can be modeled with diffusion! MRI is just a means to see it and measure it. I have been working on diffusion for so many years, still the idea to use it to estimate elastography came only very recently to my mind. Another hot topic for me would be to understand the role, which I think is crucial, of water and water diffusion in the functioning of the brain at the level of neurons and synapses. Diffusion MRI can be used for functional MRI instead of BOLD. Diffusion is directly linked to neuronal activity while BOLD relates to the changes in blood flow accompanying neuronal activity. When neuron networks get activated, many synapses are involved since each neuron has almost 10 000 connections with other neurons. It seems that this activity is closely related to the dynamically swelling and shrinking of neuronal elements, such as dendritic spines, to which Diffusion MRI is sensitive. What is the importance of this change in neuronal shape for brain function? This point has been completely missed by neuroscientists despite Cajal, when he discovered neurons in 1895, clearly stated that "the swelling of the dendrites could correspond to activation state while the retraction of the synapses and the dendrites could correspond to rest condition". He even called neurons the "butterflies of the soul which could explain somedays the secret of our mental life". Diffusion MRI is now here to verify this visionary statement. After the dance of the water molecules, let us now look at the dance of the neurons!

> "Deep organs like pancreas or female pelvis are also candidate for Diffusion MRE"



Joao Lima, MD
Director of Cardiovascular Imaging at the Johns Hopkins Hospital and Professor of medicine, radiology and epidemiology at the Johns Hopkins School of Medicine, Baltimore, MD, USA.

MR Cardiac Imaging

"MRI is the most sensitive method for measuring perfusion in the heart"

Joao Lima is a professor of medicine and radiology at the Johns Hopkins School of Medicine. His pioneering work in cardiac imaging using advanced MRI, CT and echocardiography has led to noninvasive techniques for predicting cardiovascular disease and calculating its extent, as well as measuring the effectiveness of modern cardiac treatments. He holds numerous patents on devices and methods for cardiac imaging and image-guided therapies.

Joao Lima graduated from medical school at the University of Bahia, Brazil. He completed his cardiology fellowship at Johns Hopkins Hospital and spent two years on the faculty of the University of Pennsylvania before returning to Johns Hopkins as a Faculty member in 1992. A long-time investigator with the Multi-Ethnic Study of Atherosclerosis (MESA), Joao Lima is credited with more than 175 articles out of that study and nearly 575 publications over his career. He was associate editor of the Journal of the American College of Cardiology for 8 years and serves on the editorial board of Circulation Cardiovascular Imaging while reviewing for other journals including the New England Journal of Medicine, Circulation and Annals of Internal Medicine. Joao Lima has been invited to present his research throughout the Americas, Europe and Asia.

Olea Imagein: Could you please introduce yourself?

Joao Lima: I am a professor of medicine and radiology at Johns-Hopkins University. I was trained as a cardiologist with interest in cardiovascular imaging. I bridge the departments of medicine and radiology, since I am professor in these two fields. My areas of concentration are MRI and CT, although I have also done research using ultrasound. I run research primarily in populations, the most established ones being the multi-ethnic study on atherosclerosis, called the MESA study. It was the first large study using MRI in populations.

O.I: What is the role of MRI in cardiac imaging?

J.L: MRI is marvelous as a phenotypic tool, able to very well depict disease before a patient develops symptoms. MRI has an important role in screening, which is what we demonstrated in the MESA study. But most of all, MRI has a very powerful diagnostic role, particularly for the patient who is hospitalized with heart disease. There are two areas where MRI shines. First, for the diseases of the heart muscle itself, called the myocardium: that is the best tool to show what kind of diseases affects the heart – for example; heart failure or syncope disorders associated with malignant arrhythmias; in other words, a prodrome to sudden death. So, for those individuals with cardiomyopathies, MRI is excellent.

Second, MRI is very important in showing ischemia during stress; we usually give adenosine to produce maximal vasodilation for that purpose. For patients with coronary-artery disease, MRI is very helpful even before any damage has occurred to the heart. I mentioned the hospitalized patient, because MRI has not been exploited as much as it should for the patient who is not: generally, MRI is restricted to "in-patients", mainly because of access to the technology, although I hope that changes in the future.

O.I: How do you identify patients who are at risk to develop heart attack?

J.L: Generally, there are several ways MRI can be used for that purpose. The most common is to do a stress test for patients with suspected coronary-artery disease, which is the main application of MRI. In other words, we give the patient adenosine or regadenoson or dipyridamole, and next we image the heart as we inject a gadolinium-based contrast. If there is a blockage, that part of the myocardium is going to be all dark – so there is a perfusion defect. This task has been shown to be highly sensitive and specific. Most importantly, it predicts prognosis. So, if you have a perfusion defect by MRI, you are at high risk of a heart attack. In fact, MRI is the most sensitive method for measuring perfusion in the heart, the most sensitive compared to PET. PET has been the traditional gold standard, but it is even harder than MRI in terms of access. To summarize, the main application of MRI to assess myocardial infarction risk is to assess perfusion with very high sensitivity and specificity.

We can also measure plaques with MRI. Plaques tell us if someone has arteriosclerosis; we have measured atherosclerotic plaques in the carotids and the aorta, but we can also perform coronary imaging and see the plaques directly in the heart. Coronary imaging is the preferred method for very young people like kids, people to whom we don't want to give radiation associated with CT or invasive angiography. Right now, CT angiography is generally the method of choice if the patient is older than 35 for men and 45 for women. However, MRI is being developed quite quickly to compete with CT in that area. We are part of that development with Canon, and that is very exciting.

O.I: How do you discriminate the different prognosis of heart attack, from simple risk to certain death?

J.L: The magnitude of the defect is what differentiates the prognosis. If the defect is small when we are doing a stress test, the risk is generally small, because it means that one single artery is involved – the heart has 3 arteries, 3 main branches. If the defect is large, it generally means that the artery is occluded very proximally, that is at the very beginning of the artery, or that more than one artery are involved.

Therefore, the amount of myocardium at risk defines less certain risk from much greater risk for complications in the future: the probability increases a lot for a future heart attack or cardiac death if the defect is very large.

O.I: Do you consider MRI cardiac exam as predictive imaging?

J.L: Yes. And even in populations. It is the most specific method to measure, for example, the volume of the heart, to assess how the heart functions via ejection fraction, and to depict the anatomy. We have demonstrated it in large populations such as in MESA study, and now, in Great Britain they are performing the UK Biobank study, including 100 000 people using MRI. The next step will be to have MRI available to the clinician in the office or in the practice group, as an "out-patient". It will be so easy to get an MRI that the clinician can order an MRI and easily perform it.

O.I: Which new technology seems most promising or interesting for you?

J.L: Intellectually, MRI is a very exciting and challenging field. The possibilities are almost limitless, we can have so many new technologies by playing with the MR parameters. The ones that we are working primarily with Canon are related to coronary imaging with deep learning reconstruction. We can teach machines to do very complex jobs; if we teach them how to reconstruct an MR image after the signal is acquired, we can get rid of a lot of artefacts, and we think that is what is going to make coronary imaging clinical. Our goal is to make it clinical for all individuals and for those who are younger than 40, to be the method of choice, because there is no radiation involved.

The second technique that I think is very exciting is to shorten the echo time – the technique is called ultra-short TE, and we develop it at this time, to image fibrosis in the heart. Every type of damage in the heart leads to the formation of a fibrotic scar. If we were able to apply ultra-short TE to detect scar in the heart, we would not need contrast agents either, which would decrease the risk of MRI to almost zero. That would be ideal. As we discussed earlier, the main application of MRI for the heart right now is in the diseases of the myocardium, the heart muscle, the cardiomyopathies. But for those applications, we need to administer contrast. If we develop ultra-short TE to the point we do not have to use contrast, it would be just wonderful.

The third technique is 4D flow. 4D flow is the process of tagging the blood as it flows through the vessels, and seeing exactly where blood flow is going and at which speed – we actually quantify how much blood is going where. This has been a quantum leap, for example in pediatric applications. Kids can have congenital holes in the heart, they may be born with those – the original name for that condition in the US was the blue babe syndrome.

Surgery for congenital heart disease began at Johns Hopkins more than 6 decades ago and ushered the development of cardiac surgery in general. For congenital disease applications, 4D flow is wonderful because we can see exactly where the blood is going. Invasively, through cardiac catheterization, we have to deduce from measuring oxygen at different places in the heart; with 4D flow we can actually see it, which makes life much easier. 4D flow is a very exciting technology.

> "MRI is marvelous as a phenotypic tool, able to very well depict disease before a patient develops symptoms"

Finally, the technique I have been attracted to almost my entire career is the use of a higher magnetic resonance field to image the heart. MRI of the heart deals with images of the hydrogen atoms, in water or in fat. That is what an MR image is. But if we were using a higher field magnet, we could have images let's say from sodium, even potassium maybe. That creates a new world of opportunities because the cells in our body are very good at regulating sodium and potassium, they keep sodium out and potassium in. By playing with these ions, we could really develop a whole new series of cutting-edge applications in MRI.

These are the techniques that are basically the most exciting for the cardiovascular imager, for the people who work with the heart and the vessels. Of course, for neuro or MSK, there are other methods, the list is long and different.

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MAY 11-16

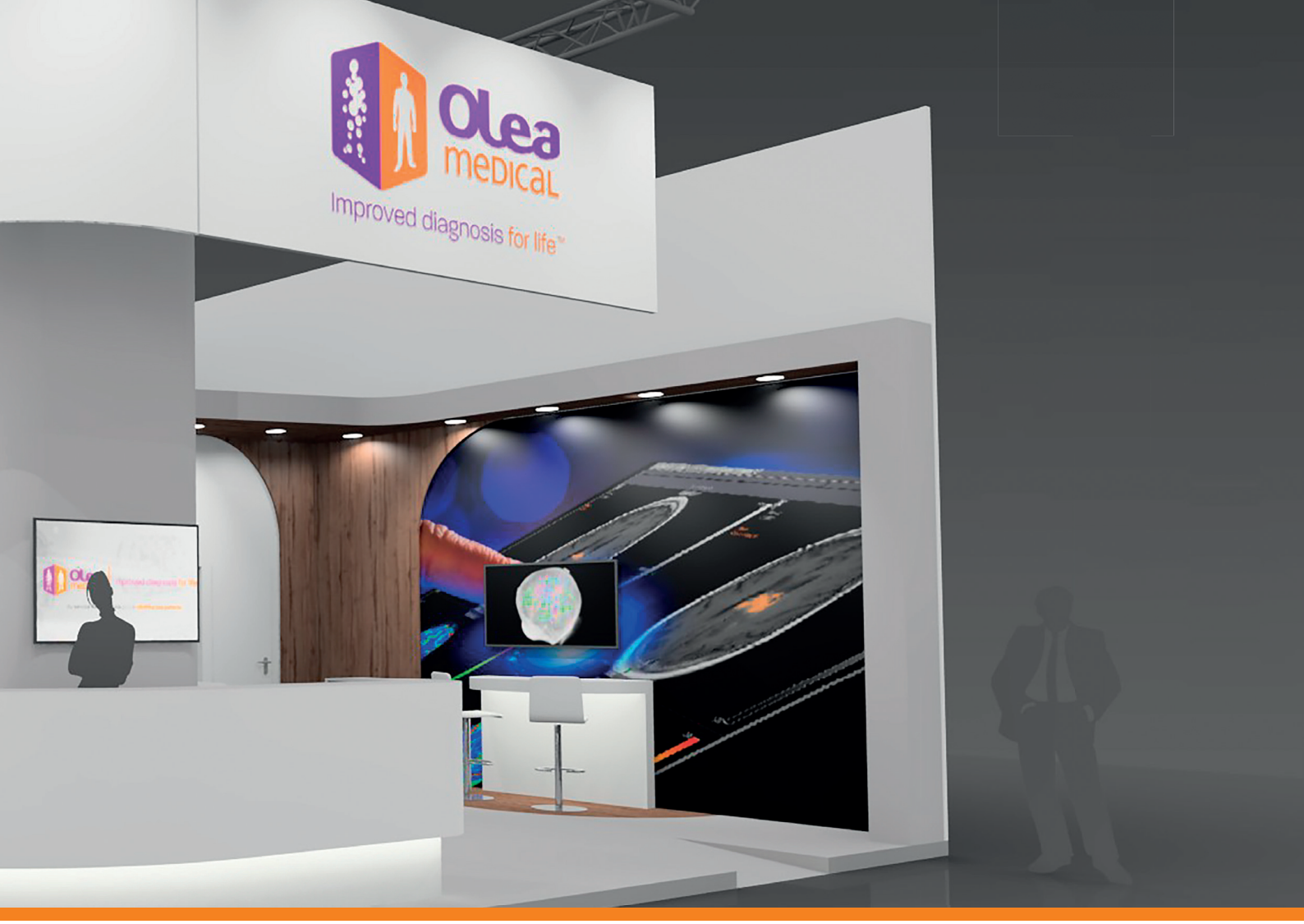
International Society for Magnetic Resonance in Medicine (ISMRM)
27th Annual Meeting & Exhibition - Montreal, **Canada**

MAY 18-23

American Society of Neuroradiology (ASNR) - 57th Annual Meeting - Boston, **USA**

MAY 22-24

European Stroke Organisation Conference (ESOC) - Milan, **Italy**



JUNE 13-15

Société d'Imagerie de la Femme (SIFEM) - Lille, **France**

SEPTEMBER

European Society of Neuroradiology (ESNR) - 42nd ESNR Annual Meeting - Oslo, **Norway**

OCTOBER 9-12

NeuroRAD - Frankfurt, **Germany**

OCTOBER 11-14

Journées Francophones de Radiologie (JFR) - Paris, **France**

DECEMBER 1-6

Radiological Society of North America (RSNA) - Chicago, **USA**

Word scramble

I	B	V	I	R	M	D	E	T	U	P	M	O	C	R
W	C	V	Q	U	C	Q	L	R	S	I	A	W	A	O
J	E	F	Z	R	A	J	H	P	D	R	Z	P	D	F
T	L	Ç	R	Q	Y	E	O	V	O	M	H	H	R	V
W	A	F	S	N	A	R	T	Y	B	L	X	N	D	F
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I	T	W	T	Y	A	X	X	Y	Y	N	I	I	J	Z
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M	R	B	G	Z	K	I	I	E	T	T	S	A	Q	B
L	A	C	E	S	T	A	K	D	F	C	Y	M	Y	U
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D	H	N	D	B	R	D	I	F	F	U	S	I	O	N
A	Y	O	E	T	K	X	O	D	A	F	Z	Q	Z	T
F	I	R	S	A	C	R	F	S	O	V	U	R	F	F

- FUNCTIONALMRI
- DIFFUSION
- DTI
- RICIAN
- NOISE
- COMPUTEDMRI
- CEST
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"Those who do not learn from the future are destined to make mistakes in it."

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