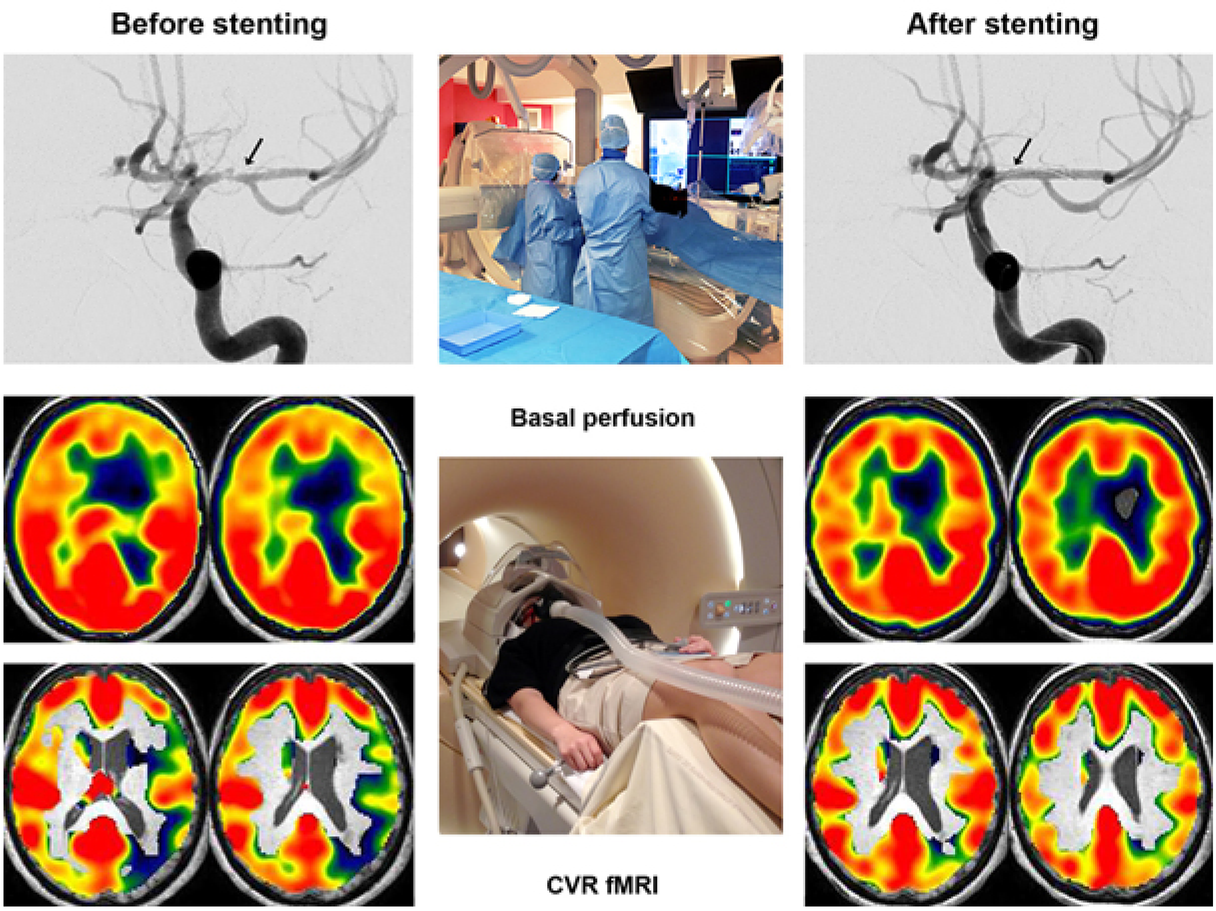
International Day of Radiology 2014
Interview on brain imaging
France / Prof. Alexandre Krainik

Brain imaging is the theme of this year's International Day of Radiology and the ESR met with Prof. Alexandre Krainik, professor of radiology at Joseph Fourier University (Grenoble Alps University) and chairman of the department of neuroradiology and MRI at Grenoble University Hospital, to talk about the importance of imaging in neuroradiology and how brain imaging has developed in France.

European Society of Radiology: Imaging is known for its ability to detect and diagnose diseases. What kind of brain diseases can imaging help to detect and diagnose?
Alexandre Krainik: Imaging is useful to detect and diagnose most brain diseases, such as vascular disorders like stroke and intracranial haemorrhage; infectious diseases like herpes, tuberculosis, and AIDS-related infections; inflammatory diseases like multiple sclerosis and auto-immune diseases; primary brain tumours; metastasis; toxic, acquired and inherited metabolic diseases; epilepsy; neurodegeneration; and of course trauma.
Indeed, brain imaging is indicated for most central neurological symptoms, such as palsy, headaches, confusion, coma, seizures, abnormal movements, and cognitive disorders. Recent advances in magnetic resonance imaging (MRI) can demonstrate additional structural, metabolic, and functional abnormalities in various conditions, including psychiatric diseases. All these breakthroughs were made possible thanks to close collaboration between radiologists, physicians, anatomists, neuroscientists, physicists, and engineers.

ESR: How useful is imaging in brain disease management? Does it improve the understanding of disease or improve patient prognosis?
AK: Imaging covers all aspects of the medical management of brain diseases. Brain imaging provides reliable data to assess and rule out most diagnoses, identify aetiology and risk factors, define the pre-therapeutic status, discuss the best treatment, and to monitor post-therapeutic changes. In addition to diagnosis, interventional neuroradiology offers great therapeutic solutions in many cerebrovascular diseases. Within this field, French neuroradiologists have been innovative and successful pioneers, such as Profs René Djindjian, Luc Picard, and Pierre Lajaunias, who made major steps in the diagnosis and treatment of vascular diseases and malformations of the brain and the spine, using intravascular catheterisation. Interventional neuroradiology is a technical, clinically driven subspecialty with appropriate patient selection based on advanced brain imaging.
Here is an illustrative case of the potential of neuroradiology to help us better understand and potentially improve patient prognosis (Attye *et al*. Hum Brain Mapp. 2014;35:1320-4). A 63-year-old woman was referred for a stroke that revealed a severe stenosis of the left middle cerebral artery (arrow on the arteriography of the upper left image). Despite aggressive medical treatment, this patient experienced additional transient ischaemic attacks and stroke. This suggested that recurrent plaque emboli occurred or that the cerebrovascular reserve was exhausted. To test the cerebrovascular reserve and the ability of the autoregulation to dilate arteries downstream the stenosis in order to maintain cerebral perfusion, we measured the basal perfusion using arterial spin labelling (ASL) and the functional changes of perfusion during a hypercapnic inhalation using blood oxygenation level dependent functional MRI (BOLD fMRI) (lower middle image). The pre-therapeutic examination showed a preserved basal perfusion out of the deep stroke sequella (middle left image). BOLD fMRI showed a clear decrease in the cerebrovascular reserve into the territory of the left middle cerebral artery (cold colours in the lower left image), suggesting an exhaustion of the autoregulation when additional vasodilation is necessary. This examination supported the decision to perform arteriography and intravascular stenting of the stenosis in our department (middle upper

image and arrow on the right left image). The five-month post-operative examination showed a preserved basal perfusion (middle right image) and a normalisation of the cerebrovascular reserve (lower right image). After two years, this woman is still symptom free.



This example illustrates how the medical knowledge of radiologists in collaboration with neurologists and neurosurgeons can bridge the gap between the results of large cohort studies and individual clinical cases. Indeed, we added the cerebrovascular reserve imaging in order to better understand the symptoms and to choose the best treatment. This example also illustrates how modern neuroradiology, based on the most advanced diagnosis methods, combined with interventional neuroradiology offers therapeutic solutions.

ESR: What kind of technology and techniques do radiologists use to image the brain? Are there any specific techniques for particular diseases?

AK: Most brain imaging relies on computed tomography (CT) and MRI. While arteriography can help to look for a subtle vascular abnormality when angio CT and angio MR are negative, arteriography is now indicated when endovascular treatment has already been decided or remains to be discussed.

Technological advances in brain imaging now provide critical information far beyond gross morphology in clinical routine and all vendors have made huge efforts to provide easy-to-use software to be handled into the clinical workflow.

High-resolution MRI allows millimetre-sized structures and abnormalities to be visualised, which is useful for diagnosis and pre-surgical mapping. Diffusion MRI is also able to depict parenchymal ischaemia very quickly after the onset of symptoms. In stroke and cerebrovascular diseases, vascular and perfusion imaging is now performed daily using CT or MRI. Functional imaging of cerebral perfusion is promising in vascular diseases, neurodegeneration, neuro-oncology, etc. MR spectroscopy shows metabolic disorders in acquired or inherited metabolic diseases. Susceptibility weighted MRI is able to show very small haemorrhages after trauma or in cases of microvascular

diseases. BOLD fMRI remains useful for mapping eloquent areas before surgical resection of brain tumours or epileptic cortex. Diffusion tensor imaging allows white matter tractography to show the main neuronal fibre bundles. In fact, most brain diseases may harbour abnormalities when using all these techniques, especially brain tumours. Other techniques such as resting state fMRI have been proposed to characterise cognitive and psychiatric disorders, but their individual performance is still poor and their impact on the management of care is still questionable. The technical knowledge of radiologists in data acquisition and post-processing is crucial to validating and guaranteeing the reliability of the information provided by all these fascinating but complex techniques.
Doppler ultrasound sonography (US) is a useful technique for extracranial vascular imaging. Experienced operators can also perform intracranial screening. When necessary, angio CT and angio MR can be used to complete US examinations.
Plain x-rays are not used anymore for diagnostic imaging of brain diseases. However, very specific indications may remain, such as those for perioperative deep brain stimulation (DBS) guidance. However, perioperative MRI allows DBS guidance.
In France, single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are still handled by nuclear doctors. They undergo a dedicated and specific four-year training programme. It is difficult for a French radiologist to be involved in nuclear medicine practice. I regret that the gap between radiology and nuclear medicine remains so hard to bridge. Thus, both techniques might be considered rather more competitive than complementary. This situation may hamper imaging schemes in daily practice. Beyond economic considerations, this may also partially explain our delay in installing combined imaging technique such as PET/MRI.

ESR: What is the difference between a radiologist and a radiographer? Who else is involved in performing brain imaging exams?
AK: In clinical practice, radiologists and radiographers are the ones who conduct brain imaging. The radiologist is responsible for the entire imaging examination, from its prescription to the delivery. The radiologist has to justify the chosen imaging modality, define the data acquisition procedure, interpret images according to the medical history and the status of the patient, and provide clear and reliable documents that answer to the questions raised by physicians. All invasive procedures, such as arteriography and interventional radiology, are only performed by radiologists.
The role of the radiographer has grown with the increasing complexity of our techniques. The radiographer has to ensure the patient’s safety prior to and during the examination; to conduct and adapt the imaging procedure according to the patient’s condition and the examination findings; to post-process images; to produce and send images on plain films or, as is used now, a picture archiving and communicating system (PACS). Most of these procedures are defined according to standardised protocols. When necessary, changes in the protocols are requested or validated by the radiologist.

ESR: How many patients undergo brain imaging exams in your country each year?
AK: We do not have this information. But let me try to estimate it. We have about 600 MR scanners that perform at least 5,000 MR exams a year, 50% of these exams are neuro, adding up to approx. 1,500,000 brain MR exams a year. We have about 1,200 CT scans that perform about 10,000 CT exams a year, 25% of these exams are neuro, which means approx. 3,000,000 brain CT exams a year. This means that we perform about two neuro CT exams for every one neuro MRI exam. Taken together, this would represent about 4.5 million brain imaging exams a year, for 60 million French citizens. These numbers are fairly accurate according to Prof. Jean-Pierre Pruvo, general secretary of the French Society of Radiology. Anyway, this is an important activity and I did not include the number of cerebral arteriographies and interventional procedures. This would account for at least 10,000 additional procedures a year in France. We ought to have a clearer picture this autumn, during an assembly of the French Society of Neuroradiology dedicated to interventional neuroradiology.

ESR: Access to modern imaging equipment is important for brain imaging. Are hospitals in your country equipped to provide the necessary exams?

AK: The quantity of modern imaging equipment remains low in France. For instance, we have about 10 MR scanners per million inhabitants. We also have significant differences across regions, ranging from about 6 MR scanners per million inhabitants in Burgundy and Corsica, up to 15 MR scanners per million inhabitants in Paris and Nord-Pas de Calais. Despite important efforts during the last decade that led to tripling of this rate, it remains about half the mean European rate (source: http://www.sfrnet.org/). However, imaging equipment quality is excellent in most French hospitals. Moreover, our outstanding social health policy allows all patients to receive care. The population is very proud of and concerned about its healthcare policy despite its economic burden and recurrent deficit. Here, we see that further developing our technical capability may lead to an increase in the overall cost of healthcare if our financial model remains unchanged. This critical issue, which covers all medical fields, has been in debate for years now.

Besides access to modern imaging, numerous technical advances have been made available in the last decade. One of the greatest challenges for the French Society of Neuroradiology and the French Society of Radiology was to provide dedicated training in advanced neuroradiology. Thus, we give numerous lectures during the annual meetings of these societies. The French Society of Neuroradiology also organises workshops focused on methods such as perfusion, spectroscopy, diffusion, fMRI, and vascular imaging. These workshops are conducted in close collaboration with methodologists, especially physicists and engineers. Thus, we provide clues and tips to better understand the values and limits of these new techniques. Now, major companies are greatly involved in these workshops. Indeed, vendors are eager to show their products to radiologists. And radiologists are always keen to master new techniques and enhance their clinical practice.

ESR: In many countries there are waiting lists for MRI exams. How long can patients typically expect to wait for an exam in your country?

AK: In 2013, the mean waiting time for an MRI examination was 30 days, while it was 36 days in 2004. There are also important differences across regions. At the regional level, there is a significant negative correlation between the number of MR scanners and the waiting time for an examination (source: http://www.sfrnet.org). Having more MR scanners decreases this delay. Besides the inconvenience for patients, clinicians and radiologists, an excessive waiting time for MR exams leads to increased use of CT scanners. We observe that the information given by CT to characterise a lesion or demonstrate the absence of lesion is usually not sufficient to satisfy the demand for MR exams. Thus, waiting lists for MRI have obvious adverse effects. They raise the activity of brain CT examinations and the radiation exposure to the population. In hospitals it is worse as they increase the average length of stay. Both effects have important related costs.

However, during the last decade, the number of MR scanners tripled, by up to 200%, while the mean waiting time decreased by only 20%. This suggests additional cofactors that counterbalance the increase of MR installation. We all know the excellent diagnostic performance of MRI in brain imaging. Radiologists, clinicians, and even the general public prefer to have a brain MRI than other techniques, for various reasons, including reliability, cost, perception, etc. In my opinion, this phenomenon is also due to the growing role of imaging in patient management. Previously, imaging was mainly used to depict the presence and the characteristics of lesions. Now, imaging is also frequently used to demonstrate the absence of lesions. This approach is clearly driven by an increasing societal reluctance to face uncertainty and risks. This is obvious for both patients and physicians. Sometimes, I have the feeling that our work is shifting from providing evidence for medical care to producing evidence for a court, just in case of a lawsuit. This is particularly true in cases of trauma where imaging now accompanies medical certificates. This issue is hard to address because the cost of managing uncertainty and risks is infinite. As I mentioned above, our healthcare model is challenged by both increasing demands and economic realities. As medical doctors, we have to consider the medical condition of the patient first; and this is the case in daily practice. In fact, the mean waiting time for an MRI examination does not reflect precisely the quality of healthcare in terms of imaging purposes.

In institutions that have a stroke or a trauma centre, local organisation allows brain imaging to be performed immediately. When MRI is used to monitor chronic diseases such as multiple sclerosis, tumours, vascular malformations, an MRI schedule is planned according to the chosen treatment. And when necessary, an MRI examination can be easily performed in an emergency in most hospitals. When MRI is used to investigate neurodegenerative diseases, MRI may be conducted within several weeks according to the patient's care schedule. Thus, the role of radiologists is crucial to organising the clinical workflow, and to give priority access when necessary. For years, we have been promoting closer interaction between hospitals and private offices to organise more efficient patient management. However, the lack of clear roadmaps for patient care, specific duties for each medical structure, and rational funding of these radiological activities regarding the duties and expertise of the actors, and effective large-scale medical imaging networks limit the rise of this approach. Anyway, close collaboration with clinicians is absolutely necessary to avoiding misunderstanding and inappropriate communication with the patients.

ESR: As the global population gets older, the risk of developing neurocognitive and neurodegenerative disorders increases. How can imaging help tackle this issue?

AK: Imaging allows us to use objective biomarkers at a millimetre-scale so that we can better diagnose neurocognitive and neurodegenerative disorders. Moreover, imaging allows us to identify, among patients with similar symptoms or diseases, subgroups of subjects based on morphological and functional criteria. In addition to more accurate clinical examination, neurocognitive tests, biology, and pathology, imaging allows us to reconsider nosological frameworks. For instance, in Alzheimer's disease (AD) it is amazing how different brains may appear across patients, e.g. the severity of parietal atrophy and microangiopathy, despite similar hippocampal atrophy. Advanced multimodal imaging analyses show that among these patients, several patterns could be identified. Thus, pathophysiological differences are likely among patients with probable AD. However, it is unclear whether these differences illustrate different diseases, pre- or co-existing conditions.

Technical advances such as those provided by ultra-high MR fields (7 Tesla) are also fascinating. Preliminary studies showed morphological abnormalities of the substancia nigra in idiopathic Parkinson's disease. We can imagine that in AD high spatial resolution of the hippocampus could also provide a brand new semiology at the cortical layer level.

Imaging also provides evidence for pathophysiological disorders that are not properly considered yet. For instance, functional disturbances of the brain microvascularisation have been shown in small samples of AD. These impairments of the vascular function should be further investigated. They could ground potential therapeutic targets and would help to better select patients for medical trials.

To better advocate our results obtained using advanced techniques, radiologists have to be as demanding with functional imaging as they are with structural imaging. This remains challenging because morphological abnormalities can be confirmed by pathological studies. Indeed, it is much harder to validate functional abnormalities detected by MRI on living tissues at the same spatial resolution with alternative techniques. It could rely on invasive investigations and close collaboration with preclinical researchers.

In fact, all these advances could be considered in clinical practice, once these additional data have a significant impact on the therapeutic care.

ESR: Some imaging techniques, like x-ray and CT, use ionising radiation. What risk does this radiation pose to the patient and what kind of safety measures are in place to protect the patient?

AK: France is very sensitive to the ALARA principle (as low as reasonably achievable) for radiation exposure, especially in paediatric care. The lack of MR scanners is obviously responsible for excessive use of CT scanners, which is much more accessible and easier to perform. Again, we face the economic dilemma.

In France, several safety measures have to be respected in x-ray imaging to protect the patient against excessive ionising radiation.

1. Radiologists and radiographers must attend a specific training every 10 years.

2. All departments of radiology should be monitored by a radiation safety officer and a technician.
3. Diagnostic radiation exposure levels have to be measured for standard examinations and sent to the National Agency for Radioprotection and Nuclear Safety.
4. Quality check of x-rays devices has to be performed regularly (1–3 months for conventional radiography and CT; 1–12 months for angiography).
5. Radiological reports must detail the dose area product (DAP) for x-rays and arteriography, and the dose length product (DLP) and the volume CT dose index ($CTDI_{vol}$) for CT.
6. In cases of radiation overexposure, a clinical survey is recommended and an inquiry is conducted.

ESR: What kind of role can imaging play in preventing and predicting brain diseases?
AK: Besides brain imaging in symptomatic patients, the availability and diagnostic performance of brain imaging have been emphasised to seek asymptomatic abnormalities in case of related-risks to family or personal history. In clinical practice, this prevention policy ought to be very well defined. In my opinion and despite our natural curiosity, the collected information can only lead to validated changes in patient management. The radiologist has to guarantee the medical justification of the radiological procedures, based on the clinical presentation and the impact of their findings. This condition preserves the medical role of the radiologist, the reliability and the positive predictive values of our techniques, limits inappropriate care, and manages the economy of radiology.

ESR: In general, patients don't see the radiologist. A patient will discuss the image with the neurologist, neurosurgeon or oncologist. When they ask a question, they're often told: "I'm not a radiologist". Why don't radiologists discuss the image with the patient first?
AK: In France, we still promote clinical radiology. Most patients are seen by radiologists. However, I know that it is becoming harder to reach this goal. Demands are increasing. Image acquisition is faster and the duration of brain imaging is shorter. We also tend to add a series to obtain additional information. Advanced techniques require rigorous quality control and post-processing. Important investments in expensive devices urge radiologists to maintain economic viability. And I haven't even mentioned teleradiology yet. Taken together, all these elements indicate that radiologists investigate more patients and analyse more images. Thus, radiologists tend to reduce their time with the patient. This is particularly true in university hospitals, where junior radiologists also need to take sufficient time to interpret their findings. However, seeing patients remains, in most cases, medically relevant, and always essential. I agree that this time has a cost. Because radiologists are medical doctors, we have to keep practicing medicine with accuracy to avoid medical mistakes and with empathy for our patients.
In the last decade, PACS were installed widely. We all have been fascinated by the power of these tools, especially to review previous examinations. As high-speed networks were installed between hospitals, teleradiology appeared to be a 'modern solution' for 'modern medicine.' First, it allows us to have a second look and deal with the lack of specialists in smaller units and secondly, it allows us to fully interpret examinations in order to avoid hiring a radiologist in remote areas and maximise investments. Are there any thresholds? Who would state the thresholds? Administrations, investors? I agree that 'PACS radiology' is helpful for expertise, to better cover broad territories, and to maintain continuity of care. However, after several years of practice, I do better understand the reluctance of my mentors. Now, I feel that we are admitting to miss the deep and necessary knowledge of the medical conditions of each patient. And of course to see each patient; I think radiologists have to maintain close contact with all patients.

ESR: How expensive are radiological examinations to the health service and is there a risk that some of these examinations could be blocked by health technology assessment agencies deeming them to be not cost-effective (especially in relation to screening)? If so, how can patients help to ensure that these examinations are made available?

AK: It is hard to evaluate the annual cost of brain imaging in France precisely, because radiological costs in hospitals are not properly individualised. However, and to have an idea, I can take the numbers of brain examinations estimated above. In France, an MRI examination costs about €260, so 1,500,000 exams amounts to about €390 million. A CT examination costs about €130, which for 3,000,000 exams amounts to €390 million. In total this adds up to about €780 million. This is a huge amount of money. We have seen the growth in the demand for imaging, and the increasing complexity of the techniques. In the French economic context, keeping medical radiology is economically challenging. In such a situation, I think that all individuals, patients, clinicians, and first of all radiologists, have to assume the responsibility of facing uncertainty and risks, and better consider cost-effectiveness studies. Radiologists have to lead the evolution of their practice.

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He has published 31 review articles and book chapters and has organised several MRI and neuroradiology courses and workshops. He is a member of the board of the French Society of Neuroradiology.