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第 33 回本田賞授与式 記念講演（2012 年 11 月 19 日）

「ヒトの脳内水分子を活用したエコテクノロジー」

仏ニューロスピン超高磁場 MRI 研究所長

デニ・ルビアン博士

Ecotechnology of the Water Molecule in the Human Brain

Commemorative lecture at the 33rd Honda Prize
Award Ceremony on the 19th November 2012

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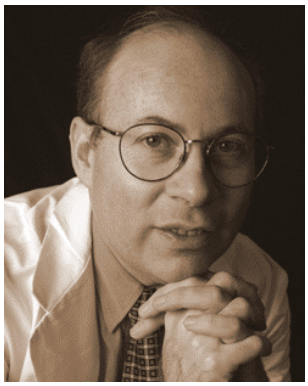

■生まれ

1957年７月30日　仏ナンテール（フランス国籍）

■学　歴

医学（パリ大学）

1987年	仏放射線学委員認定
1984年	パリ大学医学博士
1981年～87年	脳神経外科・核医学科・放射線科研修医

物理学（パリ大学）

1987年	エコール･ポリテクニーク物理科学博士
1985年	核･素粒子物理学 DEA
1984年	基礎物理学 MA
1983年	基礎物理学 BS

人類生物学（パリ大学）

1979年	神経生理学･中枢神経系高等学位
1978年	生物数学･データ処理学・統計学 AEA
1977年	コンピュータ科学高等科卒

■職　歴

2007年～現在	仏ﾆｭｰﾛｽﾋﾟﾝ(NeuroSpin)超高磁場 MRI 研究所長
2005年～06年、08年～現在	京都大学医学研究科附属脳機能総合研究ｾﾝﾀｰ脳機能画像領域客員教授
2000年～現在	仏連邦脳機能画像研究所(ﾊﾟﾘ)所長
1999年～06年	CEA ﾌﾚﾃﾞﾘｯｸ･ｼﾞｮﾘｵ勤労病院(仏ｵﾙｾｰ) 解剖学･機能的神経画像研究所長
1997年～98年	同研究所副所長兼研究部門長
1994年～96年	同研究所研究方法論部門チーフ
1991年～96年	ｼﾞｮｰｼﾞﾀｳﾝ大学病院(米ﾜｼﾝﾄﾝ D.C.) 放射線科臨床准教授
1989年～91年	同病院放射線科臨床助教授
1990年～94年	米国立衛生研究所(米ﾒﾘｰﾗﾝﾄﾞ州ﾍﾞｾｽﾀﾞ) 放射線診断研究部門チーフ
1987年～90年	同研究所臨床ｾﾝﾀｰ放射線診断科 客員准教授

■Born

July 30, 1957 in Nanterre, France (French citizenship)

■Education and Training

Medicine (University of Paris):

1987	French Board Certification in Radiology.
1984	MD, Doctor in Medicine with Distinction, University of Paris.
1981-87	Residency in Neurosurgery, Nuclear Medicine and Radiology.

Physics (University of Paris):

1987	PhD in Physical Sciences, with High Distinction, Ecole Polytechnique.
1985	Extensive Studies Degree (DEA) in Nuclear and Elementary Particles Physics, with Distinction.
1984	Maitrise ("MA") in Fundamental Physics, with High Distinction.
1983	Licence ("BS") in Fundamental Physics, with High Distinction.

Human Biology (University of Paris):

1979	Higher Studies Degree in Neurophysiology and Central Nervous System Functional Exploration.
1978	Extensive Studies Degree (AEA) in Biomathematics, Data Processing and Statistics, with major in Mathematical Models in Medicine.
1977	Higher Studies Degree in Computer Sciences.

■Employment History

NeuroSpin, CEA-Saclay, France 2007-present: Director

Kyoto University, Japan: 2005-06, 08-present: Invited Professor, Graduate School of Medicine, Human Brain Research Center.

Federative Research Institute on Functional Neuroimaging, Paris, France: 2000-present: Director

Service Hospitalier Frédéric Joliot, CEA, Orsay, France 1999-2006 : Director, Laboratory of Anatomical and Functional Neuroimaging 1997-98: Vice-Head and Research Director 1994-96: Chief, Research and Methodology Section.

Georgetown University Hospital, Washington, DC, USA, 1991-96: Clinical Associate Professor of Radiology, Dept. of Radiology, 1989-91: Clinical Assistant Professor of Radiology, Dept. of Radiology.

National Institutes of Health, Bethesda, MD, USA 1990-94: Chief, Diagnostic Radiology Research Section (with Tenure) 1987-90: Visiting Associate, Diagnostic Radiology Department, Clinical Center.

■略　歴

ルビアン博士は、人間の脳機能の研究に用いられる新画像法開発に多大な貢献をしたことで国際的に高く評価されている。博士は、超高磁場磁気共鳴設備を持つ新研究所 NeuroSpin の創設者兼所長として、マウスから人までの脳を理解するために、超高磁場磁気共鳴画像(MRI)を用いて科学的、臨床的に応用・研究を進めている。また、MRI、画像、神経科学、放射線医学の分野で250超を寄稿(共著を含む)。仏科学アカデミー会員で、磁気共鳴医学国際協会の金賞(2001年)、全米科学アカデミー及び仏科学アカデミーの Lounsbery 賞(2003年)、仏学士院ルイ　D 賞(2003年・S. Dehaene 博士と共同)等を受賞。仏 National Order of Merit 騎士の称号も受けている。

■出版物

『Imagerie par Resonance Magnetique (Bases Physiques) 』Masson, Paris(1984年)

『Magnetic Resonance Imaging of Diffusion and Perfusion (Applications to Functional Imaging) 』Lippincott-Raven Press, N.Y.(1995年)

『Water, the forgotten biological molecule (福山秀直共著 2011年) 』 Pan Stanford Publishing, Singapore

『Le cerveau de cristal, ce que la neuroimagerie nous révèle 』(in press, Odile Jacob)

■Biographical Sketch

Denis Le Bihan has achieved international recognition for his outstanding contributions to the development of new imaging methods allowing, in particular studying human brain function. His work has combined extremely innovative methods, developed for Magnetic Resonance Imaging (MRI) with the application of these methods to questions of the utmost scientific and clinical importance. He is a full member of the French Academy of Sciences and currently the Founding Director of NeuroSpin, a new Institute aimed at developing and using ultra high field Magnetic Resonance to understand the brain, from mouse to man. He has authored or co-authored over 250 articles, book chapters and review articles in the fields of MRI, imaging, neuroscience and radiology. For his contributions, he was awarded in 2001 the Gold Medal of the International Society for Magnetic Resonance in Medicine. He is also the 2002 recipient of the Lounsbery Award from the National Academy of Sciences (USA) and French Academy of Sciences and a 2003 corecipient (with S. Dehaene) of the prestigious Louis D. Award of the Institut de France. He is Knight of the French National Order of Merit.

■Publications

Imagerie par Resonance Magnetique: Bases Physiques. Masson, Paris, 1984. *Magnetic Resonance Imaging of Diffusion and Perfusion: Applications to Functional Imaging.* Lippincott-Raven Press, NY, 1995. *Water, the forgotten biological molecule* (with H. Fukuyama), 2011, Pan Stanford Publishing, Singapore, *Le cerveau de cristal, ce que la neuroimagerie nous révèle* (in press, Odile Jacob)

このレポートは、2012 年 11 月 19 日　東京、帝国ホテルにおいて行なわれた第 33 回本田賞授与式記念講演の要旨をまとめたものです。

This report is the gist of the commemorative lecture at the 33rd Honda Prize Award Ceremony at the Imperial Hotel, Tokyo on 19th November 2012.

Ecotechnology of the Water Molecule in the Human Brain

Dr. Denis Le Bihan

It is an immense honor for me to receive this prestigious award. Of course, it is because of my work, which you have found important for society, but I am extremely pleased that this award comes from Japan, a country which I deeply affectionate. I have many friends in Japan, and some of them are here today. I am also very pleased that my daughter, Armelle, could join me. Unfortunately, however, my wife, Christiane, could not attend this ceremony because today, at the same time, my second daughter, Carolyn, is graduating from a university in London. Therefore, our family had to split so that everybody could celebrate.

I would like to truly thank the Honda Foundation, Mr. Ishida and the selection committee, for selecting me for this award. I also would like to convey my sincere appreciation to Mr. Ito, President and CEO of Honda Motor Co., Ltd., with whom I had such a wonderful discussion this morning.

This award is not solely "my" award, as it is also an award for my family: my parents, especially my father who passed away a little bit too early, one month ago, he was so proud of me receiving this prize; my wife and my daughters, and, of course, my many colleagues in France and around the world.

Today, I would like to give you the highlights of my work and some explanations about what I have done. The Honda Award is bound to the concept of ecotechnology and emphasizes how society can benefit from engineers' work, inventions, and discoveries. This is a key point. It is not good to advance something and keep it for yourself. You are really happy, at least this is my case, only if you can see that your inventions and your work could be useful for society. Also, this award for me is a tremendous encouragement to continue my research, as I still have many ideas to pursue. So this award gives me a lot of energy to continue my work.

■ Progress of Imaging

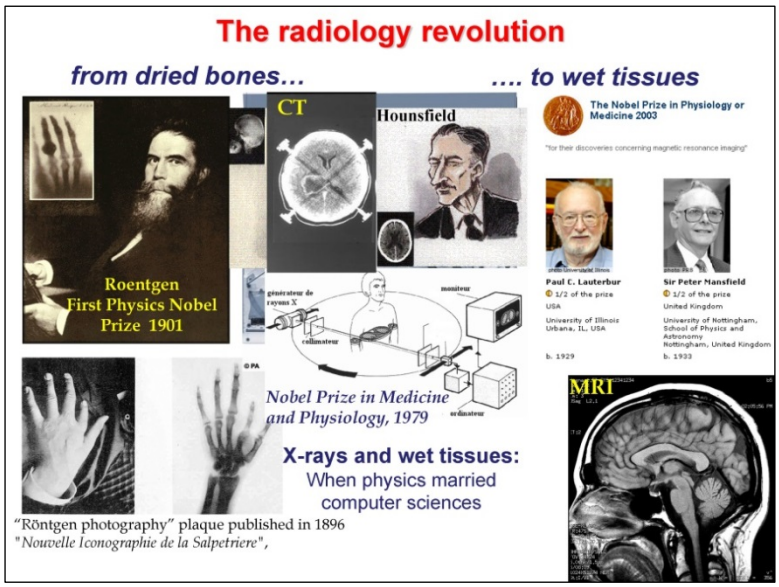

Fig 1

〈Fig 1〉　My work has been dedicated to imaging of the body, mainly the brain. Imaging started with this man, Dr. Roentgen, who got the first Nobel Prize in Physics in 1901 for the discovery of the X-ray. With radiography, we can obtain images, but they are mainly of bones. It was, of course, a big discovery because we could see into the body for the first time, but the limitation of radiography is that we cannot really see the organs very well.

The second big discovery came when it became possible to see "wet" tissues, organs of the body, not only dry bones by combining X-ray systems with sensors and computers, so-called "computed tomography" or CT. It was invented by Dr. Hounsfield and Dr. Cormack, who got the Nobel Prize in 1979. That was, however, still not enough. Although it was possible to see some diseases, such as tumors in the brain, the structure of the brain itself could not be seen with great details.

Then came two men, Dr. Paul Lauterbur, a chemist, and Sir Peter Mansfield, a physicist. They got the Nobel Prize in Physiology or Medicine in 2003 for their invention of MRI, Magnetic Resonance Imaging. With MRI, we can see the brain in great detail because the brain is made out of water and MRI is especially sensitive to water. Over the last 100 years, water has become very important for the radiologist. To produce images, we started from the electrons of calcium with X-rays, and now, with MRI, we depend on the hydrogen nucleus, the proton, which is at the heart of the water molecule.

■ Mechanism and Characteristics of MRI

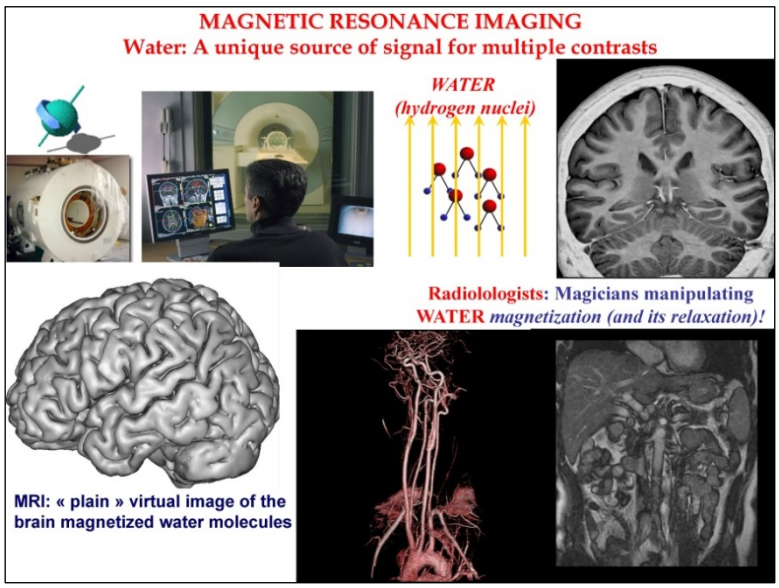

Fig 2

〈Fig 2〉　What is MRI? MRI consists in using a very strong magnetic field produced by a magnet to magnetize water molecules. More precisely, we magnetize the protons, the nuclei of the hydrogen atoms. The magnetization of water in the brain is not the same for white matter, grey matter, blood vessels, and skin, for instance. By manipulating the magnetization of water molecules, using radio waves, radiologists are like magicians which can create at will contrasts between those tissues within the brain.

Engineers improved the technique a lot, so it is common nowadays to see the vessels coming from the aorta going to the brain, or, thanks to very fast imaging methods, to see heart beats and respiration, and of course, my main subject of interest, to see the brain in great detail. However, what we see on MRI images is not really a brain. We have to understand that this is in fact a magnetic image of the water molecules in the brain. Therefore, we have to keep in mind that what we have to see is not really the brain, but a virtual copy of the brain through the magnetization of its water molecules.

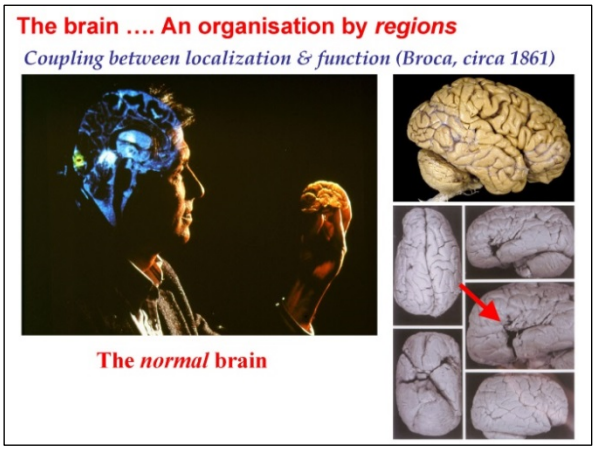

Fig 3

〈Fig 3〉　Let's see now what the brain looks like. We all have a brain, but they are all different. The brain weights a little more than 1 kg. There was a French surgeon, Mr. Broca whose patient, Mr. Leborne, could not speak. He was aphasic. If you asked him, "What is your name?" he would say, "Tan, tan tan" "What is the year?" "Tan, tan, tan", so his nickname was "Tan". Soon this patient died, and Broca took the brain for study, and he made two major discoveries.

There are two hemispheres in the brain. Broca had the intuition that his patient could not speak because the lesion was in the left hemisphere, first discovery. Second, he realized that the lesion was in front of the brain. If the lesion were located somewhere else in the brain, the patient could have other symptoms but not a language problem.

That was a very visionary idea. For more than 150 years, this is how we learned how the brain works: taking the brain of people after their death and trying to correlate their disease with a location in the brain. We learned a lot, but of course it was difficult to find normal volunteers!

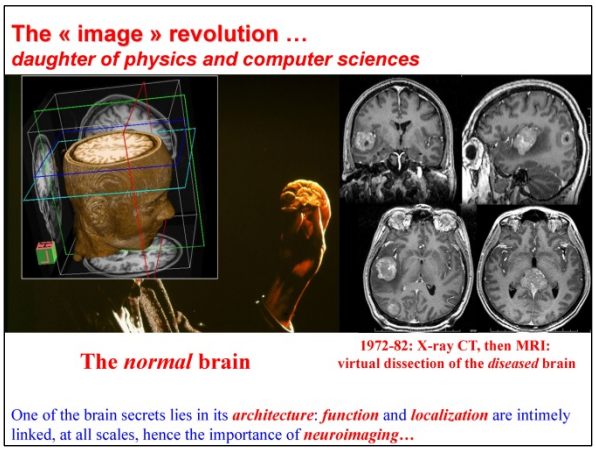

Fig 4

〈Fig 4〉 Subsequently, everything changed when CT and MRI came, as it became possible to obtain patients' images where they were still alive. This was a revolution for health care, of course. With those images, we do not need dissection to see the brain of patients or normal people. Also the link between a lost function and the localization of a lesion could be immediately found. This possibility which started about 30 years ago has completely changed the way we can study the brain.

■ Plasticity of Human Brains with MRI

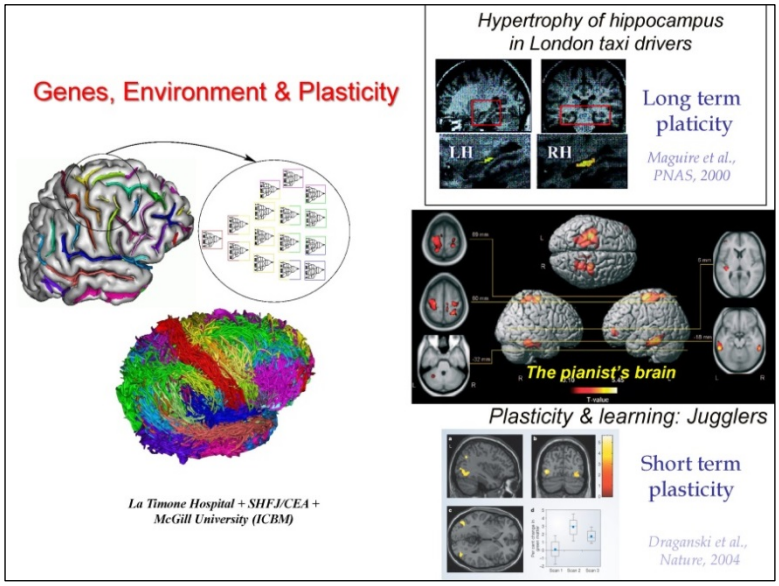

Fig 5

〈Fig 5〉 Let us see some examples. We all have brains that look very similar in shape. However, there are huge differences between people if we look at details. For example, look at the red line of this structure (left). Its location and shape can change a lot between people. The location can vary by as much as 1.5 cm, but we still do not understand today the reasons of this

variability. Our genes are probably responsible, partly, but there could also be mechanical reasons occurring during brain development. Imaging is clearly a way to get clues about brain development.

Let's take another example. This is a study that was performed on London taxi drivers. London taxi drivers are very high-skilled although I know Japanese taxi drivers are even better. The drivers are trained for two years, navigating in the streets of London. Please look at this part of the brain with a red square (upper right), which is called the hippocampus and is like our GPS in the brain. Its size in taxi drivers from London is bigger than in normal people. It means that by learning how to navigate as a taxi driver, they have increased this region of their brain, the hippocampus. As for bus drivers, there is no difference because bus always uses the same routes.

Pianists are also very interesting "animals" to study, and so am I. By looking at the images at the middle on the right, we cannot see the differences by eyes, but with computer software, we can detect that those regions of the brain are a little bit thicker than in ordinary people. For instance, coordination between the two hands is very important, and pianists have a little more grey matter, more neurons, in the related parts of the brain. From those studies, we can say that we model our brains ourselves depending on our life.

Here is another example to show you that this plasticity can, indeed, be very fast. Young people were trained to juggle balls for a few weeks. In just a few weeks, we can see that some parts of the brain have developed as you develop your muscles by exercise (image on the lower right). Those regions of the brain are involved in visualizing movement in space.

We can really modify our brain, and this plasticity is especially important when the brain develops, which starts when we are fetuses growing in the uterus of our mother. Because MRI does not use any ionizing radiation, we can obtain images without any danger of fetuses during pregnancy.

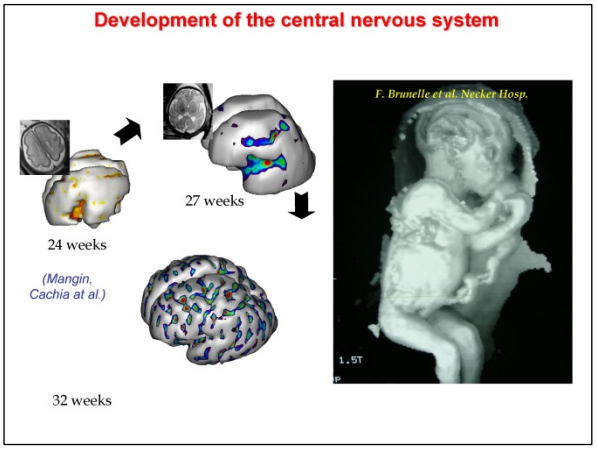

Fig 6

〈Fig 6〉　Why are we so interested in doing MRI of fetuses and embryos? These are images obtained at 24th, 27th, and 32nd weeks of pregnancy. Just to remind you, a normal pregnancy is 39 weeks. You can see that the brain is becoming more and more complicated over the development of the brain.

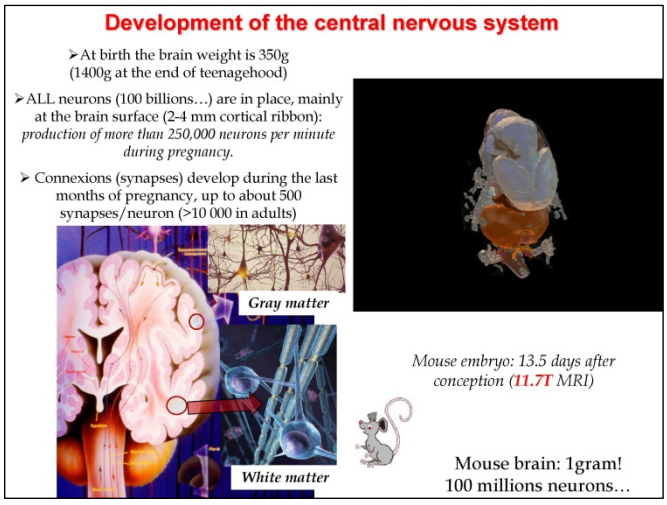

Fig 7

〈Fig 7〉　Here is an image (left) which depicts the organization of the brain. The brain is made of neurons, and the neurons are produced at a very high rate during pregnancy, up to 250,000 neurons per minute. When we are born, we have a capital of 100 billion neurons. After that, we lose our neurons day after day. In short, we have our capital of neurons at birth. Neurons are produced in the center of the brain. At the beginning, the future brain is just a tube with water inside. The neurons are produced at its periphery, at the surface of the tube. Then, they will migrate to the future surface of the brain which becomes more and more complex, as it must accommodate such a large number of neurons. It is a little bit like Japan: The many beaches allow extent the surface of Japan, the brain is doing the same. All the

neurons will migrate, and they will be installed in a thin ribbon of 2 to 4 mm on the brain surface which is called gray matter. Then, there is also white matter, which is made of the connections which the neurons share through extensions called axons.

We can also obtain images of embryos in mice with MRI to see their structure with even more details to study brain development. This is an image of a mouse fetus (right). Pregnancy for mice is 21 days, and this image was obtained at 11 days. I am always amazed by all these stunning images which we can see with MRI.

■ Brain Function with functional MRI (fMRI)

We have seen examples of what MRI can show us about brain's anatomy, but what about brain function? When you look at this screen here, or when you hear me, there are many things going on in your brain. How could we make images of our working brain? For many years, one way to see the brain working was through awake patients in the neurosurgery suit, and to excite parts of the brain through electrodes. This sounds like a joke, but it is still used today, for neurosurgeon to very precisely determine the location to perform their surgery to avoid functional damages. The brain is not sensitive to pain, so patients do not suffer going out of anesthesia for a while.

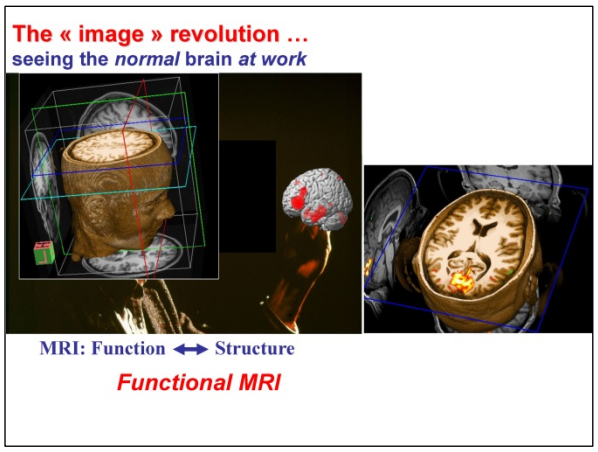

Fig 8

〈Fig 8〉　Looking at activity of brain regions without opening the skull has been a dream. This dream has come true with MRI which can give images of our working brain. This is called functional MRI. When we look at something, this region of the brain at the back, called the visual cortex, is very active. This is like the back of a camera, and the world perceived through our eyes (the lenses) is projected here. How is it possible to make such images?

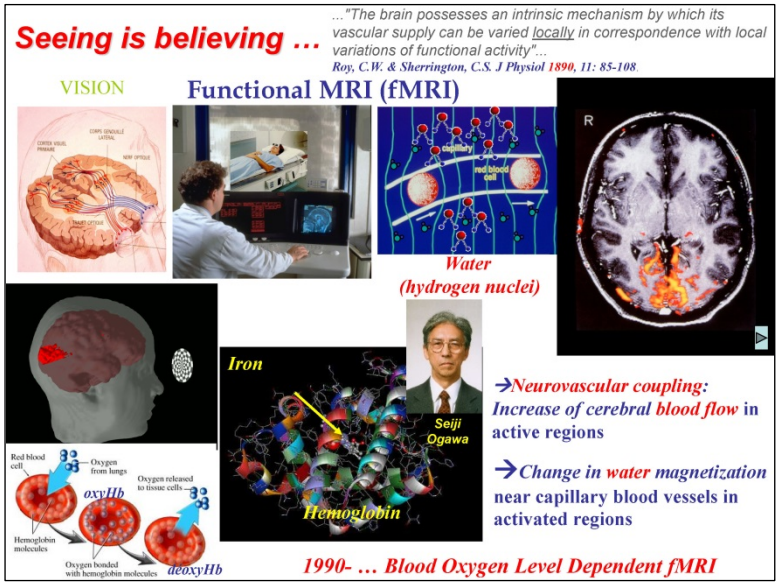

Fig 9

〈Fig 9〉 This is my great privilege to explain the work of Prof. Ogawa because he is the pioneer who developed this method, this concept. Prof. Ogawa made the hypothesis that perhaps if we can look at changes in brain blood flow with MRI, which would reveal brain function. The concept that brain activity and blood flow are related was suggested long ago in an article published in the 1890s by Dr. Roy and Dr. Sherrington: Regions of the brain where there is activity have an increased energy demand and increased blood flow. It is a little bit similar to Tokyo: If there is one area which becomes very active, more taxis will come in. So if we have a way to see blood flow in the brain, we will have a chance to see its activity.

Then, what Prof. Ogawa noticed was MRI could be made very sensitive to blood flow variations. Blood contains red blood cells, and that is why blood is red. But the reason why red blood cells are red is that they contain hemoglobin. Hemoglobin carries oxygen from the lungs to the organs. Hemoglobin is a complex molecule which hides an atom of iron inside. This iron atom can get magnetized depending on the oxygen load of hemoglobin. In short, one may consider that hemoglobin-filled red blood cells travelling in the small blood vessels in the magnetic field of the MRI magnet are tiny magnets which will change locally the magnetic field around small vessels. The water molecules nearby are sensitive to those changes in the magnetic field, which will change their magnetization. The effect is tiny, but with computer software, one can produce images reflecting those changes in the water magnetization near the vessels in the regions where the brain has been activated. Hence, when we look at a screen in the magnet, there are changes in the magnetization of water in the visual cortex, and we can follow in great detail what is going on. This is really a wonderful discovery that Prof. Ogawa made, and his method, called BOLD for Blood Oxygen Level Dependent, is now used everywhere in the world.

■ Applications of functional MRI

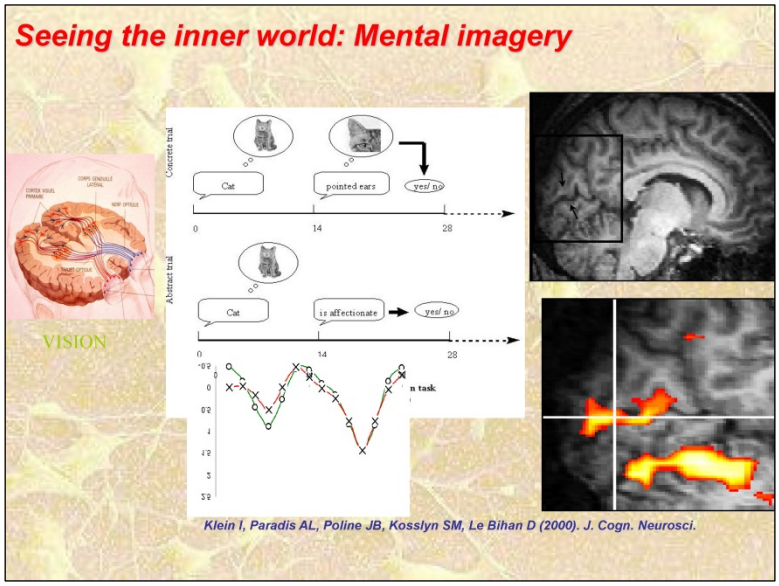

Fig 10

〈Fig 10〉 It is now time to see examples of what we can see with functional MRI. You understood that that there is activation at the back of your brain when you see the world. Now, please close your eyes and think about a cat. The question is "where is the cat in your brain?" The response can be obtained with MRI. When we say "cat," the person in the magnet, in complete darkness, will think about a cat. What do we see on the images? This image (lower right) is a zoom of the back of the brain, the visual cortex, and we see that the magnetization of the water molecules has changed there, just by thinking about a cat. It shows that this part of the brain, which we use to see the real world, is also used to see the "inner" world, our mental images. That was a big discovery. If you ask to the person in the magnet, "Could you see whether the cat has pointed ears?" he has to look back at his mental image, and we see that there is an even bigger response (figure at the bottom), a bigger change in the magnetization of the water molecules.

Consequently, the obvious question that Prof. Sadato, who is also here today, asked was "what about blind people, people who have never seen in their life?" They have a visual cortex, but what do they do with it? The result he showed (although using another method, not MRI), was that when people who are congenitally blind read Braille with their fingers, they activate the visual cortex. Literally they see and read with their fingers. From this result, we can just think that it is good that nature is able to recycle a little bit of the brain circuits, but I have another hypothesis. My idea is that there are some tiny circuits in the brain that are genetically programmed to perform basic tasks. Yet, the way we use them varies from person to person, depending on how those basic circuits are connected. Blind people also have the circuits,

and their circuits are working normally, but they are connected differently because they do not receive visual inputs. For normal people, the connections are with the eyes, while for blind people the connections are with other senses; touches of the fingers, audition, etc. A group from Israel has recently shown that blind people trained to make mental images from sounds also activate the visual cortex as well. This is also a great discovery.

We can see even further into our brain and get close to mind reading. Our visual cortex is "retinotopic" which means it is a little bit like a camera, in short, at the back of the brain, what we see up is projected down, what is left goes to right, and so on. Then, if we look at a vertical bar, we activate the visual cortex in a particular way, different from the way activated by looking at a horizontal object. We can also see that in our MRI images.

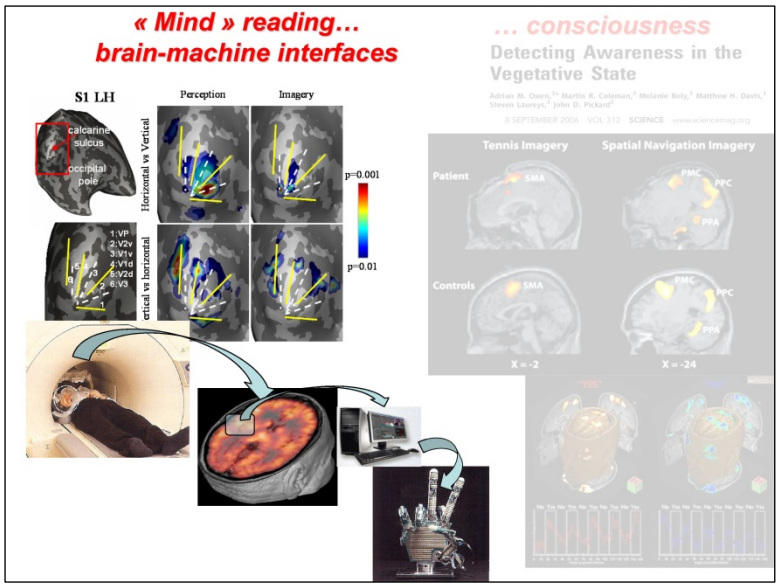

Fig 11

〈Fig 11〉 The experiment we did consisted in having people in the total darkness, and we asked them just to think about a vertical or horizontal flashing bar without telling us. Then by looking at the images (upper left), we could predict with high success rate which orientation people were thinking about, horizontal or vertical. Some experiments we have done recently at NeuroSpin with Dr. Bertrand Thirion and Dr. Stanislas Dehaene showed that we could even predict letters imagined by subjects placed in the MRI magnet. We ask them in the darkness, "Could you think about big 'H,' big 'M, and big 'R'?" and based on the MRI images we could determine very accurately which letters they were thinking about. Yes, we can read the mind, to some extent.

The potential of this "mind reading" ability could be very useful. I have been amazed to see the performances of the Honda robot ASIMO. Could we, someday, pilot such skillful robots with our mind? Just consider handicapped people, this would change their life. Of course current

MRI scanners would not be convenient at all, too heavy and cumbersome, but it could be done with lighter technologies, such as EEG, electroencephalograph. The activity of the brain could be monitored, and the signal transformed to drive a robot, an artificial hand, just by thought.

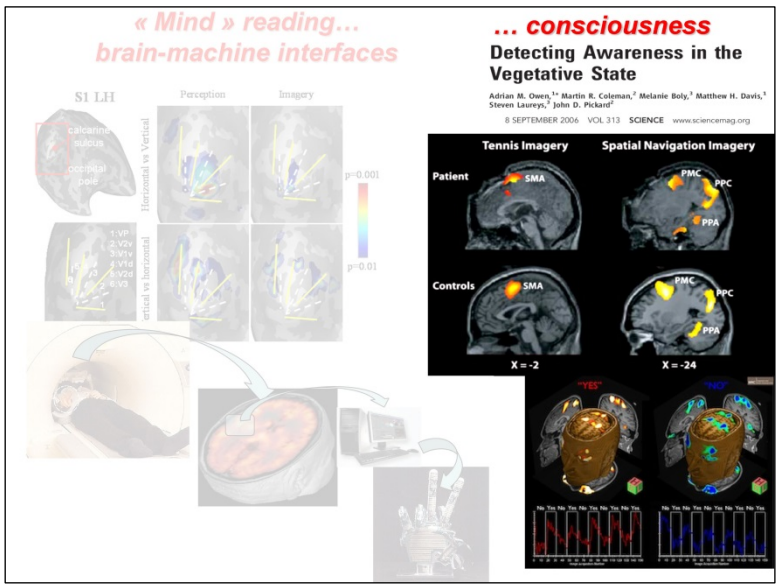

Fig 12

〈Fig 12〉　functional MRI can do even more. Those images (upper right) have been obtained in a young lady who is in a comatose state because of a car accident, so she cannot move and does not react to any stimulus. Dr. Owen suggested putting this patient in the MRI scanner. Once installed in the scanner, they asked the patient "What is your name?" Of course, as the lady is in a coma, nothing happened physically, but on the MRI images, her Broca's area which is linked to language lighted up! In short, this lady understood the question and was responding in mind, what MRI images could show us. Next, the doctors asked her "Could you think that you are playing tennis?" Again, as the lady is in a coma, nothing happens physically. However with MRI, we can see that the regions that are now activated in the patient are the same that are those activated in normal people thinking about playing tennis. Following that, they asked, "Could you think that you are moving in your house and are looking at different things?" And again, you see this network of regions which got activated are the same regions activated by normal, conscious people. The BOLD fMRI method of Prof. Ogawa's is now opening a huge field, as it is now becoming possible to communicate with some patients in a coma. I do not want to say all of them, because so far, apparently, it works in about 15% to 20% of them. One way to communicate with them is to say, for instance, "To answer a question 'Yes,' just think you are playing tennis. If you want to say 'No,' think you are moving in your house." Then, we can see the differences in images, very quickly. I have heard about one patient in a coma state who is now writing a book that way.

■ Invention of diffusion MRI (dMRI)

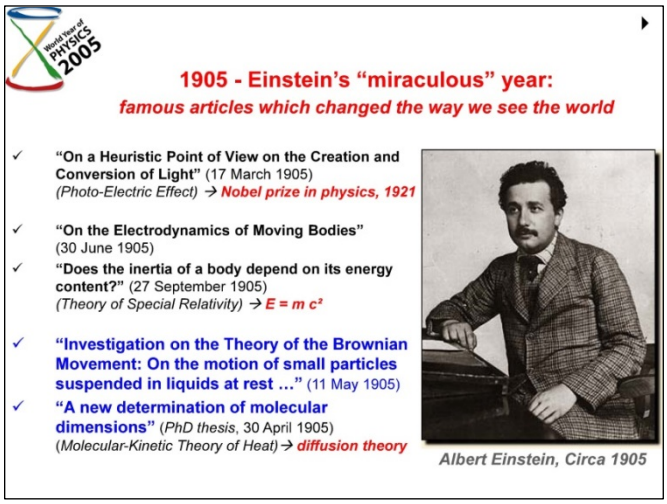

Fig 13

〈Fig 13〉 Now I will switch to what I have invented: diffusion MRI. The roots of diffusion MRI, in fact, started very early in the work of Einstein. In 1905, he published several papers: one paper on the photoelectric effect for which he got a Nobel Prize many years later. He also published papers on the relativity theory with the very famous equation, $E = mc^2$. At the same time, he was just finishing his PhD thesis in physics which was on molecular diffusion. To begin with, what is diffusion exactly?

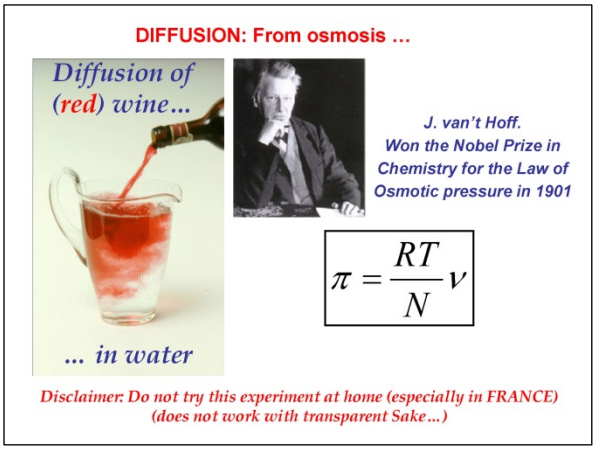

Fig 14

〈Fig 14〉 Before Einstein, what people considered as diffusion was very advanced science, as J. van't Hoff got a Nobel Prize for this work. If you mix up two liquids with different colors like water and red wine, after some time they get completely mixed. This is what was called diffusion. Equations were written to describe the effect, but the reason for this mixing was not known at that time. This reason is Brownian motion. Brownian motion was discovered by Mr.

Brown, a botanist, who observed pollen in water under his microscope. He could see that all particles were shaking all the time. This phenomenon is called Brownian motion and is true for any atom or molecule in the universe. However, the existence of atoms was not yet established in 1905.

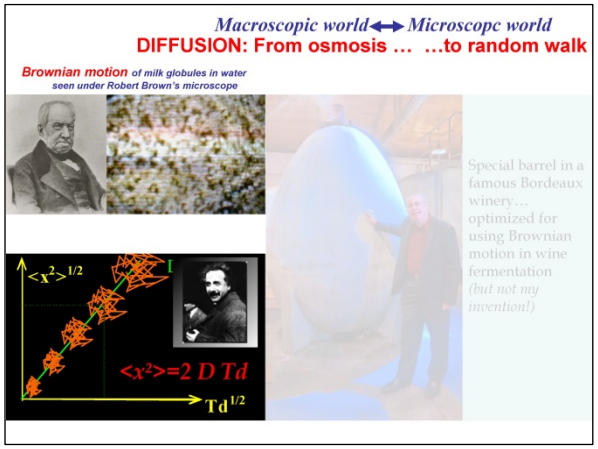

Fig 15

〈Fig 15〉 If we drink the wine a little bit too much, we may experience random walk. The idea of Einstein's was that perhaps the random walk of atoms or molecules could explain diffusion, and he wrote this equation that links the displacement of the molecules with time (lower left). If his equation could predict diffusion well, then it would be established that atoms and molecules do exist and are responsible for the diffusion process. If we give molecules a short time to diffuse, they will not go very far. If you give them more time, they will go further and further away. Statistically, in fact, they individually explore more and more space, but the average center of their position (if one considers millions of molecules) will not move, staying in the same place. That is the diffusion theory set up by Einstein.

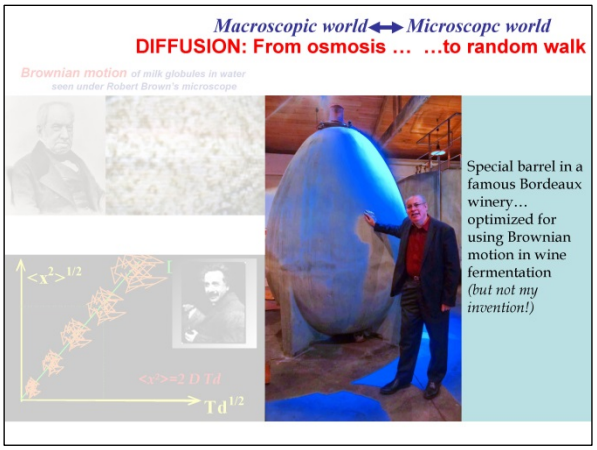

Fig 16

〈Fig 16〉 Brownian motion has been used in many different ways. I was very surprised last year when I visited a very fine wine maker in Bordeaux. The owner paid a very expensive price to buy this barrel, which is supposed to improve Brownian motion and make good wine. I do not believe it, but the owner did, apparently. This is the power of marketing.

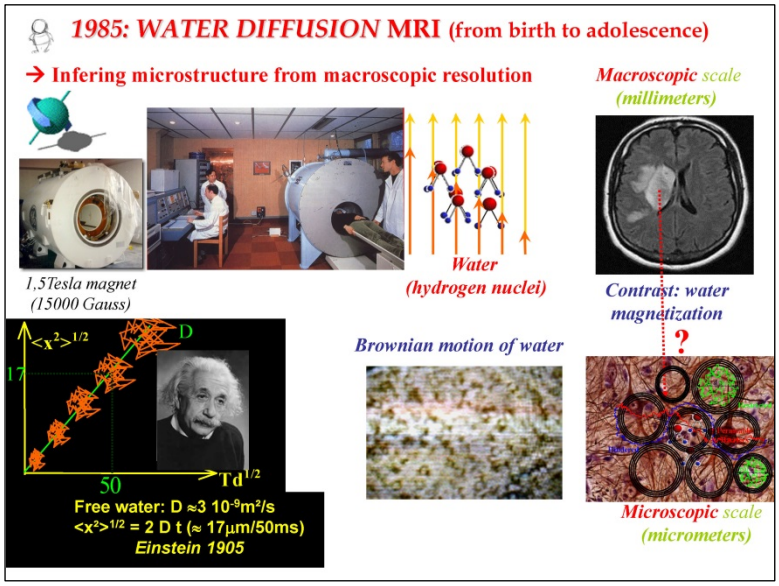

Fig 17

〈Fig 17〉 When I was young, circa 1985, I had the idea that perhaps diffusion could be used with MRI, a little bit like Einstein who used diffusion to prove the existence of atoms or molecules which nobody could see. Look at this image (upper right): there is a lesion there, and even if you are not a doctor you know well that there is something abnormal. Yet, the resolution of the images is only millimeters. To get some information on the nature of this lesion, one needs to see the lesion at a much finer scale so as to see individual cells, which are 100 to 1,000 times smaller. My idea was that perhaps water molecules diffusing in the tissues and the lesions could hit obstacles such as cell membranes, fibers, etc. By watching their diffusion, one

could get precious information on what water molecules have encountered in the tissue, acting as spies or probes for us. We are very lucky because in 50 thousands of a second (time interval used with MRI), at the brain temperature (37℃), water molecules diffuse on distances in the order of 15 ㎛, 15 millionths of a meter, based on Einstein's equation. We are at the right scale, about the size of cells in tissues. The concept behind diffusion MRI is that although the images have a coarse resolution, like millimeters, we can provide information about the microscopic world and the structure of the tissues.

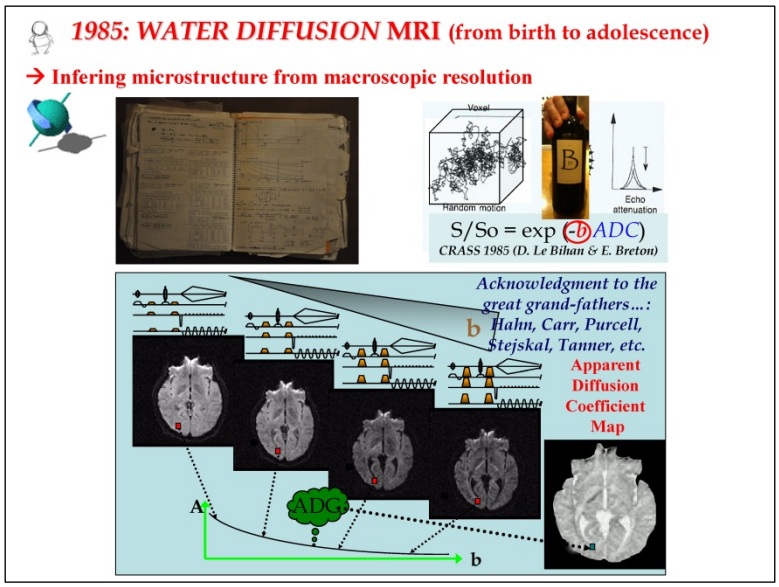

Fig 18

〈Fig 18〉 This is how diffusion started. I do not want to bother you with physics details about the method but just mention that for normal MRI, you have to use a very strong and homogeneous magnetic field. For diffusion MRI, in order to label the random walk of water molecules, we have to vary the magnetic field from left to right or from top to bottom. When we make the field change in space, and if the molecules move due to diffusion, we will have some kind of way to label their displacements. This is what I invented in 1985 with one of my colleagues, Dr. Eric Breton. I simplified the theory to keep simple equations and gave the letter "b", following my name, to one of the parameter inside the equation which everybody is using today for diffusion MRI, although many of my colleagues do not know it! Indeed, Dr. Stejskal and Dr. Tanner pioneered the field, showing in 1965 how diffusion could be measured. My contribution was to incorporate their idea with MRI, so as to make, for the first time, images of diffusion, which is maps of organs in our body, notably the brain, where the diffusion coefficient is shown using a gray scale or color scale in each point of the image.

This image below is a slice of the brain obtained by normal MRI. When we add variations in space of the magnetic field, for instance from left to right, the MRI signal goes down due to

diffusion. This effect is different for each point within the brain, and we can get images for each point of the Brownian motion of water molecules.

■ Applications of diffusion MRI ①: Acute Stroke Diagnosis

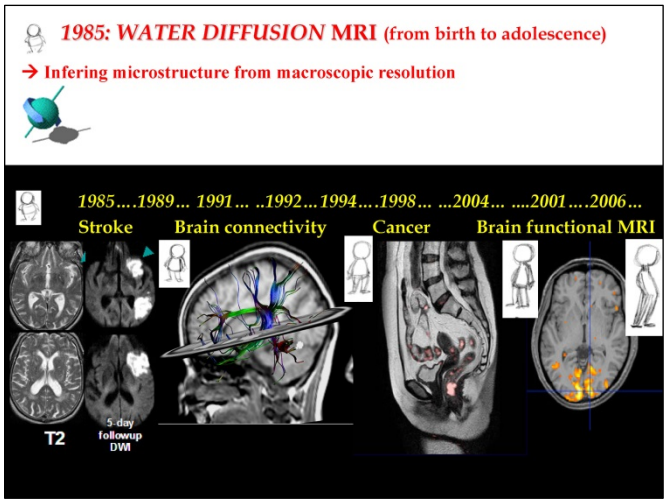

Fig 19

〈Fig 19〉 Now, what do we do with diffusion MRI? We can diagnose stroke at the acute phase, make images of the connections within the brain, diagnose cancer… applications are many!

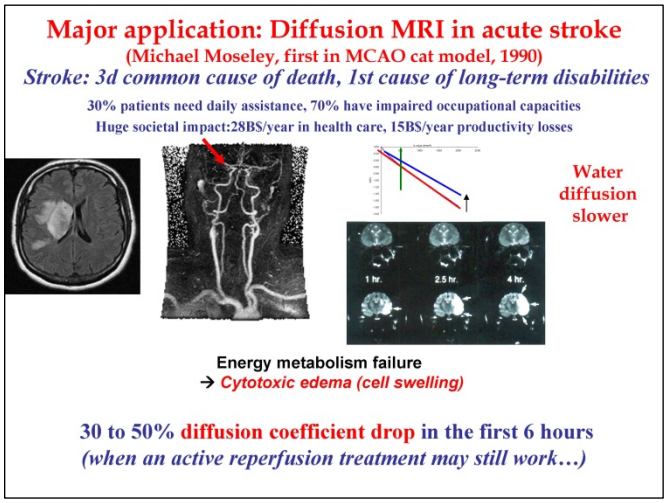

Fig 20

〈Fig 20〉 Let's start with the very first major application of diffusion MRI. The lesion of the patient I showed you earlier (Fig 17) is in fact a stroke. The patient had a clot in an artery, so the neurons depending on this artery there do not get blood supply anymore, and they are dying. Stroke is the third common cause of death and the first cause of long-term disability by far. After stroke, 30% patients who survive need daily assistance, and 70% have impaired

occupational capacity. The societal cost is huge for healthcare, but also for productivity loses. You can see how terrible this disease is.

In 1990, my colleague Dr. Michael Moseley in the United States was working on a model of stroke in the cat. He was using my new diffusion MRI method and discovered that the diffusion coefficient of water was going down during stroke at the acute phase (image on the right). In short, in the regions of the brain where neurons are dying, the diffusion of water molecules slowed down. Because I had just invented diffusion MRI, it was possible to obtain such images fort the first time. Nowadays, this is done in common practice in hospitals, but at that time there was no way to diagnose stroke at the acute stage, when treatment might still be possible. With the CT scanner it takes many hours before stroke lesions become visible.

If you have symptoms such as difficulty in speaking, moving your arms and legs, feeling dizzy or something wrong with your vision, or having a very strong, unusual headache, then maybe you are undergoing a stroke. During a stroke, millions of neurons are dying every minute. After six hours, it is too late. The neurons are dead; they will never recover again. However, if you can go to the emergency room of a stroke center and get an emergency MRI, it is possible to save your neurons, and your life, because we can give some drugs that will dissolve the clot instantaneously. Once the blood clot goes away, the neurons get the oxygen and sugar they need, and then all of a sudden the symptoms disappear, for ever. The patient is definitely cured.

This is how we can save the lives of people undergoing stroke, but only 1% of them benefit today from this technique so far. In modern countries like Japan and France, we have MRI systems and emergency departments, but most people do not realize when they are suffering from a stroke, until too late. Thus, we have to educate the public. I think that the Honda Prize is definitely along this philosophy that society will benefit from invention if we educate and help people to understand it. I am very honored that the Honda Foundation recognizes this work because it can save the lives of people, and my hope is that it will save the lives of more and more people than today.

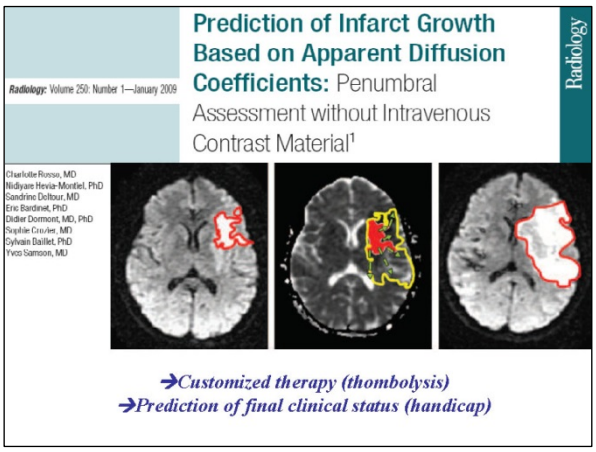

Fig 21

〈Fig 21〉 With diffusion MRI, we can also predict how these areas affected by stroke will change in time. We can predict that this patient, for instance, will get worse as the affected region will extend in a few days, and his MRI images will turn to like this image (right). We have to act promptly and aggressively to save this patient. In other patients, we can predict that the stroke will not evolve, so there is no need to do anything if the patient has no major symptom. With diffusion MRI, we can decide which patients need treatment or not in emergency.

■ Applications of diffusion MRI ②: Cancer Diagnosis

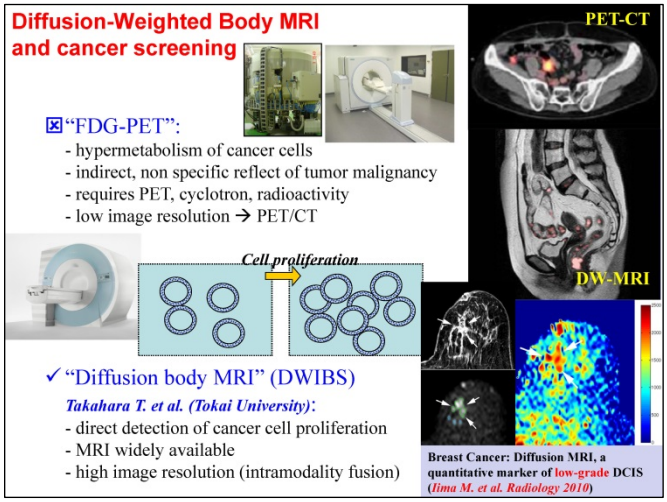

Fig 22

〈Fig 22〉 In cancer also, diffusion MRI is making a bigger and bigger impact. The diagnosis of cancer is not so easy so far. We usually rely on a radioactive false sugar (FDG) with positron-emission tomography (PET), another technique than MRI, to detect regions that are cancer lesions or metastases which consume a lot of the injected FDG. The problem is that specificity is not very high because banal inflammation lesions give positive results mimicking

cancer, although they are not. Besides, the images that are obtained with PET are not so crisp, so we often merge them with those acquired with CT scanners using combined PET-CT machines. Despite those limits, FDG-PET is working well and considered as the reference method.

However, Prof. Takahara in Japan showed that my method of diffusion MRI can be used instead of PET. He showed that in regions of the body where cells proliferate, as in cancer, Brownian motion decreases. Because the MRI images are very crisp, this method is getting more and more attention as a method to detect or monitor cancer. You can also use diffusion MRI to see whether chemotherapy works or not at an early stage. If the drug fails, it takes several weeks or months before we know if it is working or not, and then it might be too late to switch to another treatment. With diffusion MRI, one can see if the drug is working or not very early, and decide to switch immediately to another drug if necessary.

In breast cancer, with Dr. Iima from Kyoto University, we showed that some lesions diagnosed with cancer by mammography could be established with diffusion MRI not as cancer lesions in fact. Ladies sometimes get surgery or very invasive treatments for nothing because the lesion is, indeed, not a cancer or a cancer evolving very slowly in life which just requires monitoring. There was no need to remove the breast. This is a conceptual revolution: to make the diagnosis of "no cancer" instead of suspecting cancer each time a lesion is seen with mammography.

■ Applications of diffusion MRI ③: Mapping of Brain Connectivity

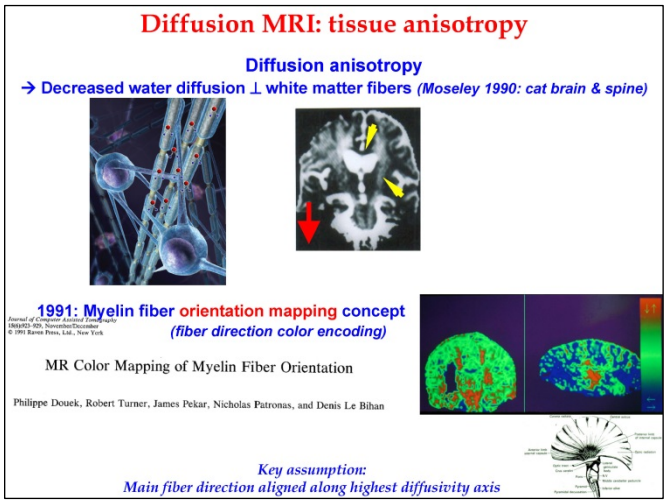

Fig 23

〈Fig 23〉 Another major application of diffusion MRI is that diffusion can be used to see the connections in the brain. I explained earlier that white matter was made of the connections between neurons. It has been established by Dr. Moseley that the Brownian motion of water molecules seen with diffusion MRI is faster along the fibers than perpendicular to the fibers.

This is exactly like when you have cars running on the highway, they go in the direction of the highway and not perpendicular to the highway. So in 1991, when I was in the United States, with my student, Dr. Philippe Douek, we showed that if we measure diffusion in two directions, we can determine the orientation is of the fibers in the brain. In the image (lower right), vertical direction is shown in red; horizontal in blue; or in-between in green. The images were very crude at that time, but it was the first time we could obtain images of the direction of the connection fibers in the brain, thanks again to diffusion MRI.

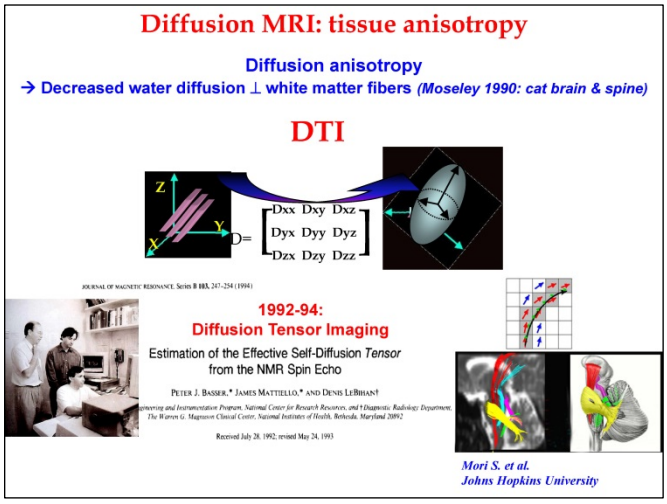

Fig 24

〈Fig 24〉　Soon after, with Dr. Peter Basser and Dr. James Mattiello you can see in this black and white photo from 1992, we developed the concept of diffusion tensor imaging, which fully exploits the sensitivity of diffusion MRI to orientation in space. With this framework, we can now obtain images of the brain connection fibers for each point of the image in all orientations. The next step came in 1998 as it was shown how to connect all those points together to make images of the connections themselves. This was first proposed by another Japanese scientist, Prof. Susumu Mori, who works at Hopkins University in the United States. By using a mathematical algorithm, he showed that it was possible to connect the points within the diffusion MRI images and obtain images of the connections like can be seen in this image (lower right).

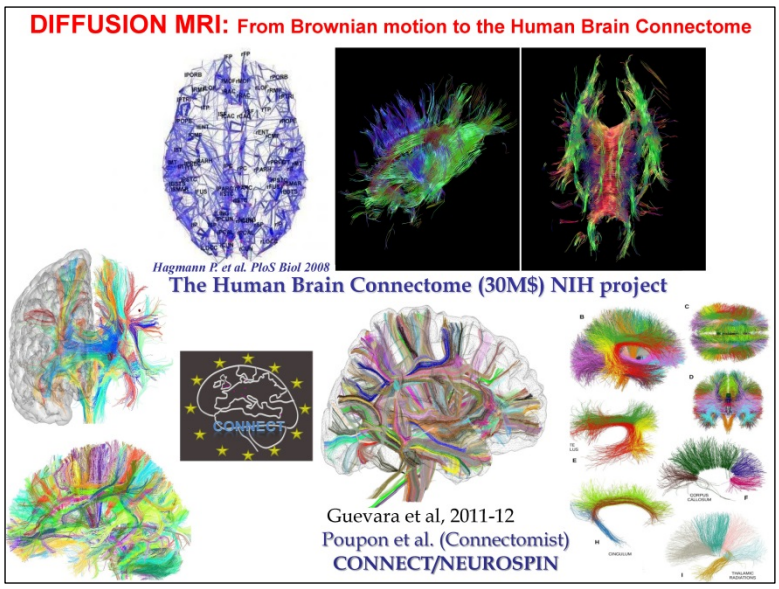

Fig 25

〈Fig 25〉　Look at those gorgeous images (foreside). They are examples of the connections of the human brain. The United States NIH have injected $30 million to make the first atlas of the connections within the brain. In Europe, we do not have so much money, but we have another project called the Connect Project (downside). We got only $2 million, but we have been the first to complete an atlas of human brain connections in a group of 80 subjects.

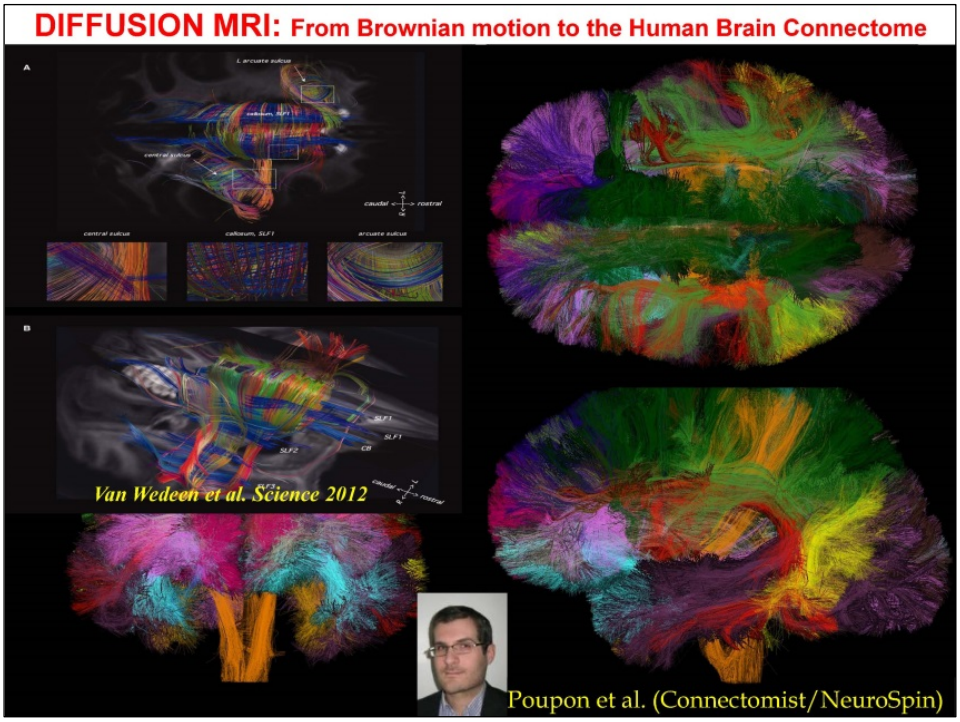

Fig 26

〈Fig 26〉 Those astonishing images (right) of the connections in the brain are part of this atlas, fruit of the work of my colleagues, especially Dr. Cyril Poupon at NeuroSpin. They are not artwork, but represent the real connections within the brain of a normal subject. It takes only 15 minutes to get such pictures of one's brain connections. Just go into the MRI scanner and wait… you can even sleep if you like. 15 minutes later, we have all the images required to map the connections like that. Dr. Van Wedeen at MIT just published an article a few months ago showing that inside the brain is like in a computer, with ribbons of fibers (left). Plasticity in the brain probably comes from the way those connections get established or disappear in time.

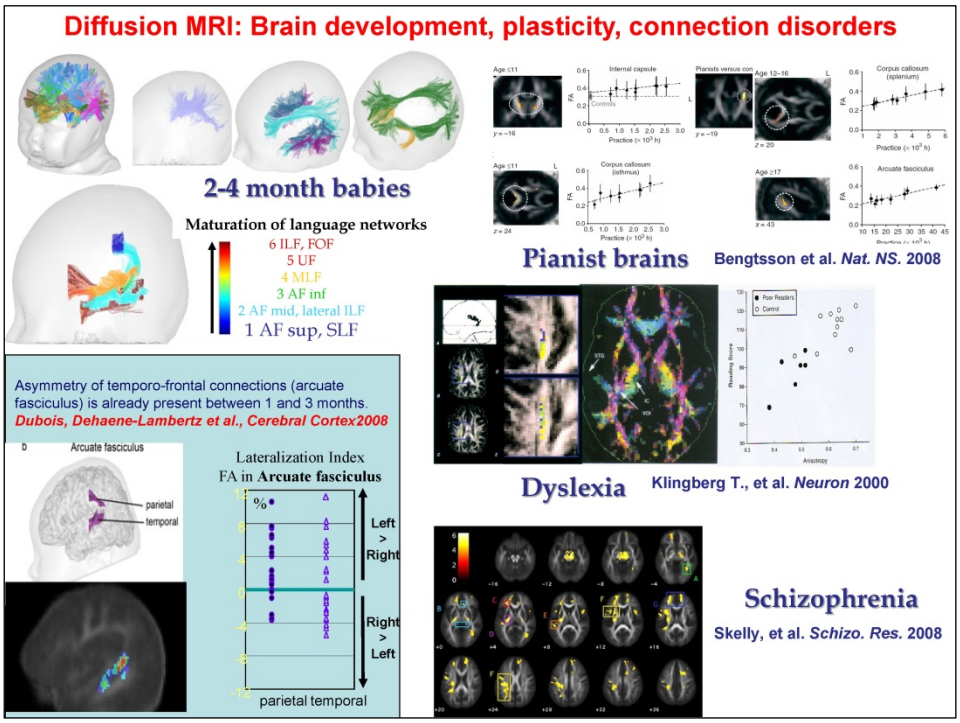

Fig 27

〈Fig 27〉 Let me give you some examples of plasticity in the brain and it can be seen from the connection maps obtained with diffusion MRI. I told you that language is generally in the left hemisphere of the brain. Babies, 2- 4-month-old babies, do not speak. However, we can see that their connection fibers are already asymmetric (upper left). The fibers are more developed in the left hemisphere, so the baby will be prepared to use the left hemisphere to speak.

This is work by Dr. Jessica Dubois, my former student (upper right). Pianists also develop connections in the brain depending on the number of hours spent practicing in their life. When they are children, a few thousand hours are enough to deeply modify connections. Between 11 and 17 years of age, it takes more hours of practice to modify them. By adult age, it is more and more difficult. Therefore, this is my advice, if you would like to play the piano, it is better to start early than late!

In dyslexia, it has been shown that some connections could be faulty. One can see from the image on the right middle that in dyslexic people, who are very bad at reading, the connections are bad in some parts of the brain involved with language and reading. However, when they improve their reading abilities thanks to some rehabilitation, one can see that the connections get better. Functional performance, and plasticity, is linked to brain connections.

And for schizophrenic patients, it has been shown recently that some connections in their brain were apparently wrong. Schizophrenic patients most often hear voices. Actually they do really hear voices, as we can see that from functional MRI (lower right). This is not a surprise. In fact, we always hear voices, we speak to ourselves, but we know that the voices come from us,

not from strangers. If some connections are faulty between frontal regions where thoughts originate and the temporal regions which make “inner sounds” (like mental images in the visual cortex), both may appear shifted in time, not related. It is a little bit like watching a movie with the sound and the images out of synchrony, which is very uncomfortable. This is, so far, a hypothesis for the symptoms of schizophrenia which may result indeed, as with other disorders, such as autism, abnormalities in the connections and the synchronization between brain regions.

■ Applications of diffusion MRI ④: Water Diffusion fMRI

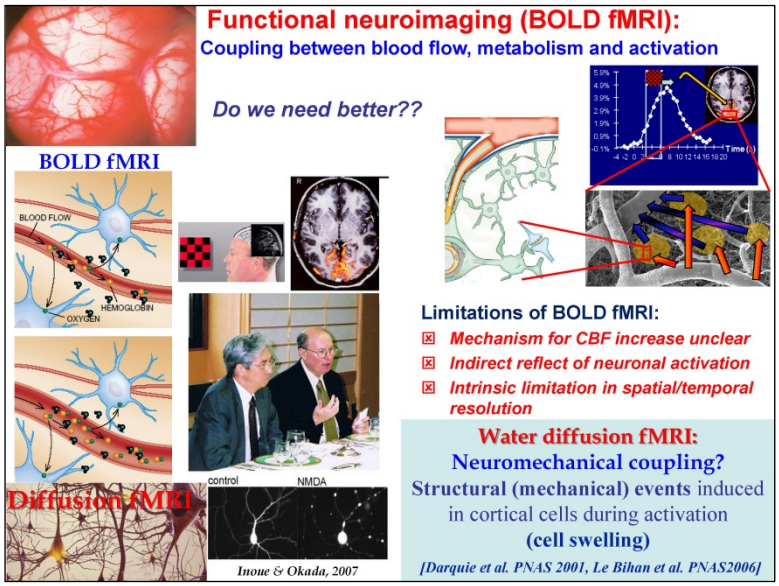

Fig 28

〈Fig 28〉 The last application of diffusion MRI which I want to introduce today is for imaging brain function. I explained that the method of Prof. Ogawa is great, so why do we need better? It works very well, but we know that sometimes there are limitations. If we look at how the brain works by looking at blood flow, we are not really looking at the neurons but looking at something indirect. Furthermore, mechanisms linking the change in blood flow with neuronal activity are not very well established. Also, we can think that there are different regions of the brain with different functions, but using the same vessels, this method cannot separate them.

Based on those points, we have discussed many times with Prof. Ogawa, and I have proposed another way: perhaps with diffusion MRI, we can also see how the brain works. My idea is that when neurons get activated, they change in shape. There is some swelling of brain cells, and diffusion MRI is very sensitive to the structure of the tissues. Then, this was my hypothesis: instead of looking at the increase in the blood flow from activation, maybe we can see how brain tissue structure is changing during activation through cell swelling.

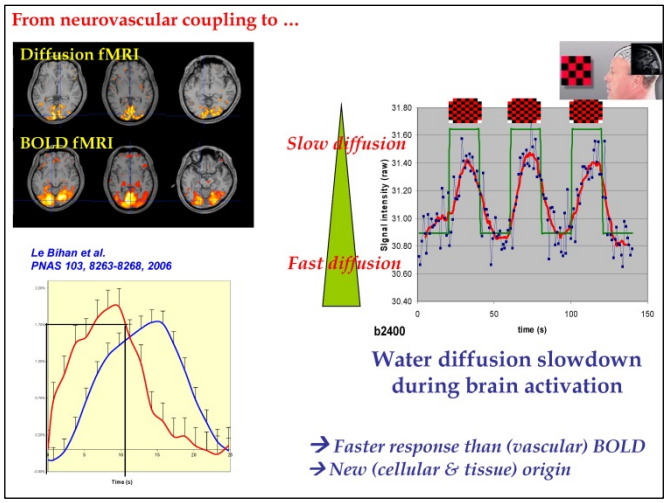

Fig 29

〈Fig 29〉　We did this experiment in Kyoto. In the images (upper left), the top is diffusion fMRI (DfMRI), and the down is BOLD fMRI. Both are working very well, and we can see the visual cortex. When the people are looking at flickering image, we see a very strong activation in the visual cortex. With BOLD fMRI, one sees the change in magnetization induced by the stimulation. However, the peak of the response occurs late, well after the end of the stimulation. This is because we are looking at the blood flow. The blood flow response is slow and is delayed compared to neuronal activity.

With DfMRI, what we could see from the figure (right) in the activated region is that the diffusion of water is slowing down just each time the visual system is stimulated. When the visual stimulus is off, water diffusion gets faster again. The main point is that we observed that this curve changed much faster than BOLD fMRI. There is a fast change in diffusion, and the maximal response, occurs right at the end of the simulation, which is what we expect from neuronal activity.

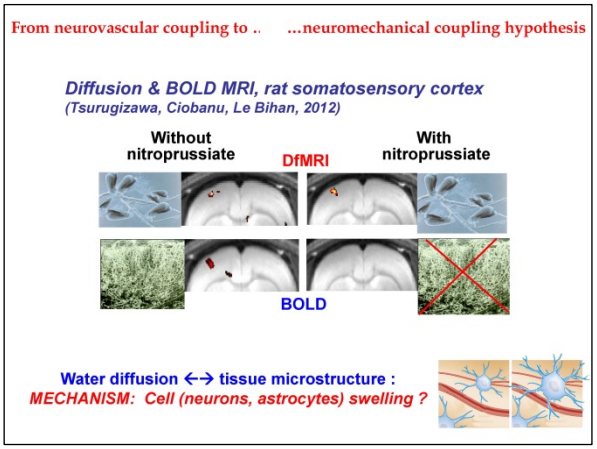

Fig 30

〈Fig 30〉 In short, diffusion fMRI is very different than BOLD, not vascular like, but is related to something going on in the tissue itself. We recently performed at experiment at NeuroSpin with Dr. Tsurugizawa to confirm this mechanism in rat brains. We stimulated the forepaw of the rats, which induced a brain response visible with diffusion fMRI and BOLD fMRI. However, after giving a drug called nitroprusside to the rats, drug which suppresses the increase in blood flow, we could see that response of the BOLD fMRI disappeared because it is linked to blood flow. However, the diffusion fMRI response remained unaffected. This experiment clearly shows that diffusion fMRI offers something new to make images of brain activation, directly linked to brain cells and not blood flow.

■ Importance of Mysterious Molecule: Water

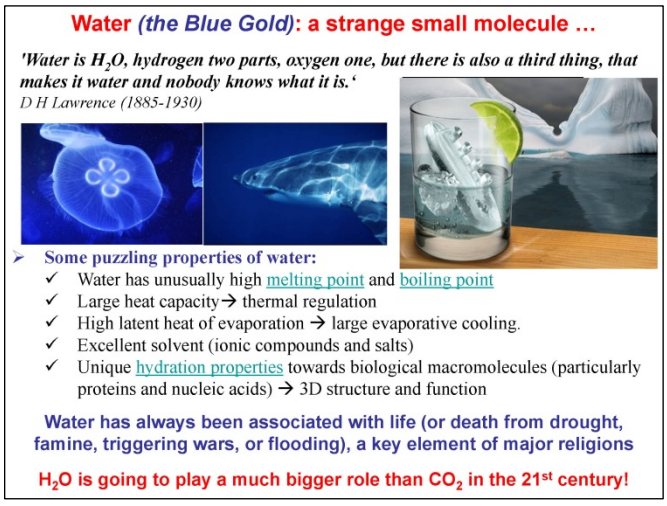

Fig 31

〈Fig 31〉 How could our thoughts alter Brownian motion of water? We need to explore water to explain it. Water is a wonderful, strange molecule with many special properties. There is one property of water that is unfortunately very famous, and that is that solid water, ice, floats on

top of water. It should not, as for other liquids, when cooled and turned to solid, their “ice” goes to the bottom because it is denser. It is the opposite for water. For the Titanic, this feature had turned to a disaster…. Lately we have started to understand the structure of water, but there are still many mysteries about water.

Water has been very important for life, but, unfortunately, may also lead to death by its absence, or its presence. The terrible tsunami you witnessed in Japan was clearly a dramatic example of the destructive power of water. But there is a lot to fear also from the lack of water which is essential to life. We always think about CO_2 as an important molecule to watch for the future. The water molecule has about the same size, tiny, but I believe that we will have more problems with H_2O than with CO_2 in the 30 to 50 years to come. In any case, both their fates are entangled through our planet climate.

Fig 32

〈Fig 32〉　Water is very important in Kyoto to such an extent that there are temples dedicated to water, and the water of Kiyomizu temple is especially pure. There are different kinds of water, depending on its content. The water in Kyoto is not the same as the water in Paris. When people drink it, it could be good for the brain. There are many temples where water is seen as a very important source to get a pure mind. Sake also requires very pure, very good water. So do Kimonos, also. To make the colors of the kimonos in Kyoto, the quality of the water in the rivers is very important.

So water is very important, and nature has developed many tricks around it. For instance, the lotus leaves are always very clean. The reason of its cleanliness is the structure of the surface of the leaves (lower right). In a normal plant (foreside), water will adhere to the leaves, slide and not take the dirt. However, the leaves of the lotus (downside) present a surface which makes the water molecules to roll, taking the dirt away. In today’s buildings, people use this

technology to make self-cleaning windows.

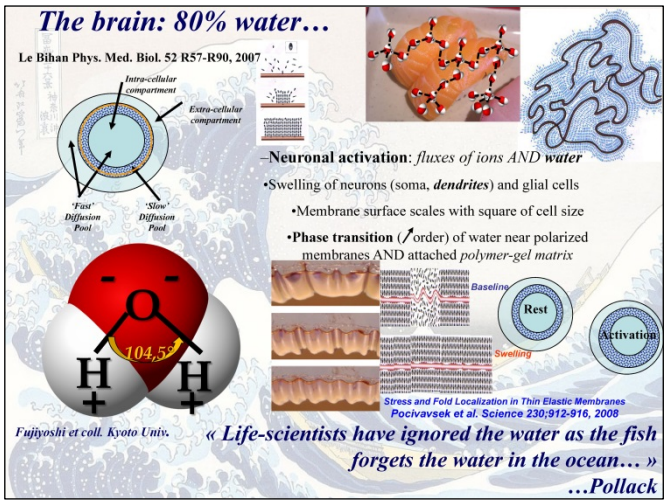

Fig 33

〈Fig 33〉　Brain contains 80% water. Nine molecules out of ten in the brain are water. Take this sushi for example (foreside), how do you know it is fresh? Take your chopsticks and press on the sushi, and then the water will come out. The fish is dead, so how is that possible? In fact, the water molecules are present, and they are glued to the proteins that are contained in the sushi, for many hours. This shows you that water molecules are not free in cells. Water molecules are most often bound to some structures such as proteins.

What I am proposing is that next to the surface of the membranes of the cells, some water molecules are glued to the membranes, and those water molecules are slower to diffuse. If the cell swells, its membrane surface increases and a quantity of water becomes bound to the membrane as well. This could explain why the Brownian motion of water in general is slowing down during activation. As cells swell when they get activated, the quantity of slow diffusing water in the activated region increases. This is just a hypothesis, but we should really pay more attention to water and its role in brain function.

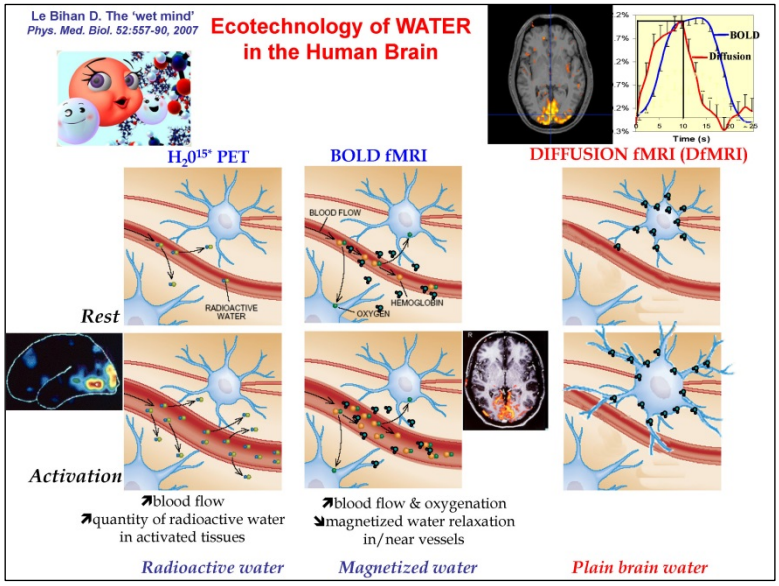

Fig 34

〈Fig 34〉　To summarize this part, we can look at brain function with BOLD fMRI very well, but we can also do it with diffusion fMRI. However, the mechanisms are completely different. I believe that water molecules are not just there in the brain to give us good or beautiful images. Water molecules may be a very important actor of the function of the brain. Perhaps shall we say that our ability to think may be dependent on water molecules?

■ Hypothesis from diffusion MRI

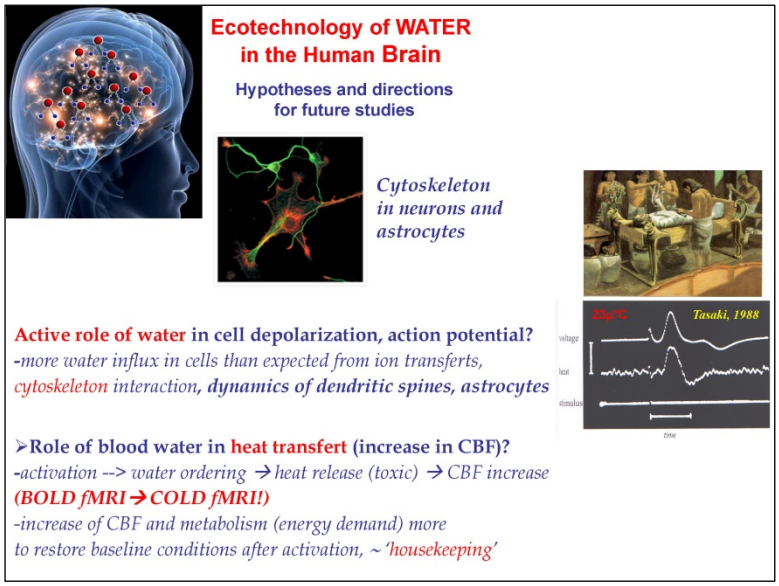

Fig 35

〈Fig 35〉 In summary, water molecules can help us to understand dynamic changes occurring in our brain, but many people perhaps do not know or tend to overlook that everything in our brain is dynamic in fact. Neurons parts called dendritic spines are dancing all the time. This movement is crucial to their function. I think that diffusion MRI is sensitive to the dance of the brain cells.

A second point is that I said that we do not know really well why there is increased blood flow during activation, which is used with BOLD fMRI. In the past, Egyptians, when they were preparing their mummies, were throwing away the brain because they considered the brain merely as a radiator, just to evacuate heat. They thought that emotions were coming from the heart, and that the brain was just there to cool down the blood. So is the expression, "cold blood". It is known that water has a very strong heat transfer capacity. One reason for the increase in blood flow during brain activation could perhaps be to cool down the regions of the brain that are activated. I saw ASIMO this morning, and he is using a lot of energy to "think" too, so there are fans to cool down ASIMO "brain". For the human brain, we use water to cool it down, which may overheat, as shown in the right figure by Dr. Tasaki. This is why, to tease Prof. Ogawa, I told him that his BOLD fMRI method should be called COLD fMRI instead because it is related to the variations of blood flow used to cool the activated brain tissue.

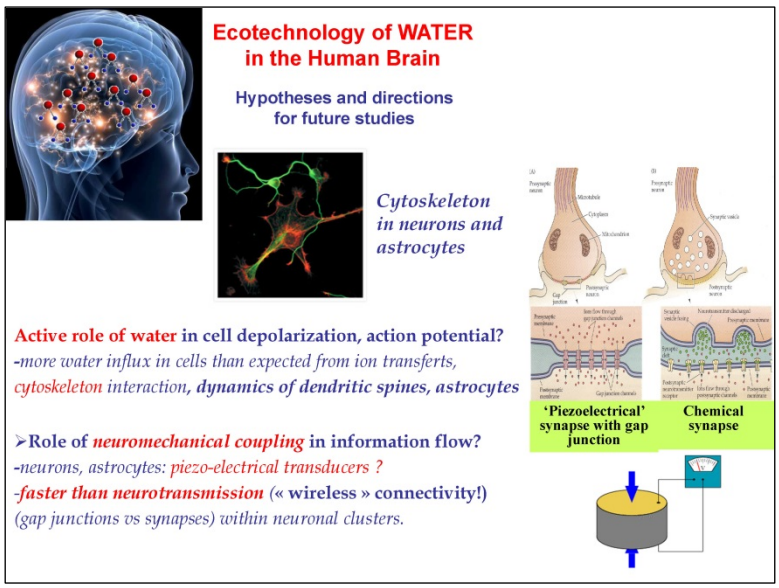

Fig 36

〈Fig 36〉　A last point is that all those changes in the shape of the neurons may reflect some transformation or transmission of information. Let's say I am in the Tokyo metro which is very crowded. If somebody is sneezing or coughing, everybody will feel something! That may happen in the brain. Brain cells, neurons or astrocytes, change shape all the time when they are activated, and the other cells nearby "feel" something, which, in turn, may activate them too. This is the same principle as piezoelectric transducers that we have in our quartz watches: mechanical variations are transformed into electrical potential. This mechanism will be much faster than the transmission mechanism we know today from synapses and the release of neurotransmitters. I call this new mechanism "wireless connectivity". Locally, neurons can communicate by touching each other, but once they are ready to export information to another cluster of neurons at a distance, then they use neurotransmission. Neurotransmission is very efficient to transmit information at a distance, but it is relatively slow and perhaps not optimized for information processing within clusters on neurons.

■ The Future of MRI

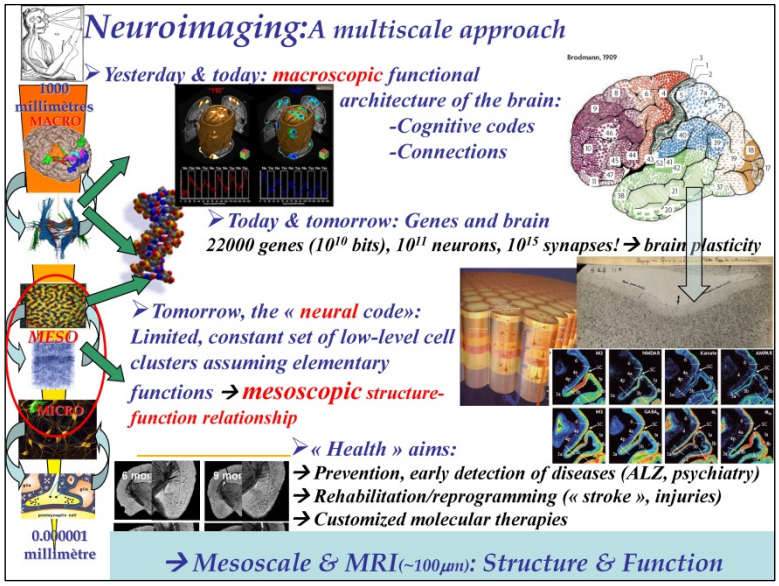

Fig 37

〈Fig 37〉　We are close to the end of my talk now, so let me introduce to you vision for the future. We have seen that we can look at brain function with the method of Prof. Ogawa, even of comatose patients. We can see connections in the brain with diffusion MRI, but we need to go further away. We have only about 20,000 genes, but neurons are 100 billion, and each neuron is connected to 10,000 more other neurons. This enables brain plasticity. In order to explain the brain more, we have to go to another scale.

My idea is that there is a neural code like a genetic code. Along the surface of the brain, there are small islands of neurons that are dedicated to specific tasks, and each task is probably determined by genes. You cannot modify them just overnight, but the way those small clusters of neurons are connected in time, and space is changing all the time. This is plasticity which makes up higher order cognitive functions. This is how we can speak French, Japanese, or English. In order to see those islands, we need to have a microscope in vivo. We need to see the brain at a different scale, which I call the mesoscale. Once we have understood this neural code, it would be possible for us to understand diseases such as Alzheimer's disease or psychiatric disorders. We may even think about ways to reprogram the brain.

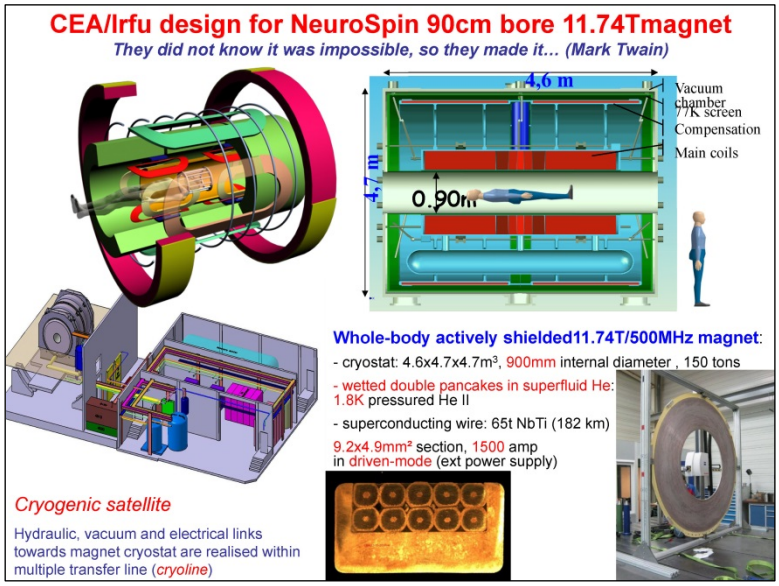

Fig 38

〈Fig 38〉 To do so, we need to improve the resolution of MRI, and the only way to do that is to increase even higher the magnetic field we use with MRI. This is the magnet that Prof. Ogawa mentioned in his speech. At CEA, we are very proud to have ingenious physicists who made the magnets in the LHC in Geneva; the magnets that have been used to discover the Higgs boson. The same technologies can be used to make magnets for MRI. Those people are also involved in the ITER project, as you know well because the head of ITER is Japanese, Dr. Osamu Motojima. It is in Cadarache in France and is also led by CEA. They will use very special magnets, too.

We are currently making this huge magnet for MRI, about 5 m in size. As you see, it is made of discs, like pancakes (lower right). We call them pancakes because we are French, I guess! There will be many of them, 170. The niobium-titanium superconducting material used to make up the wires comes from Japan. It is sent to the United States where it is formatted to the designed shape, 10 filaments in a U-shaped gutter, 9 mm by 4 mm. The accuracy for positioning this wire is within 25 μm, and there will be 182 km in total. Once we have all these pancakes aligned together, the magnetic force will reach 8,000 tons, and still, nothing should move within the magnet. You can understand that it is a beautiful piece of engineering that our colleagues from CEA are putting together in collaboration with Alstom, a French company located in Belfort.

Fig 39

〈Fig 39〉　With this device, we expect to be able to have a global picture, to understand how the brain works, and to understand how the brain is sometimes unfortunately affected by terrible diseases during development and aging. Japan and France are facing big problems with an aging population, the need for rehabilitation, psychiatric disorders, and so on. This should be also the spirit of Honda Foundation, to promote interaction between people, understand different cultures, and respect each other. We are also thinking about driving interfaces between our mind and objects around us. Can you think about driving your car by your mind without touching anything? For handicapped people, that would be a dream. I know that sometime this dream will come true. If, with diffusion MRI, we can contribute a little to this dream, I will be extremely happy.

■ Conclusion

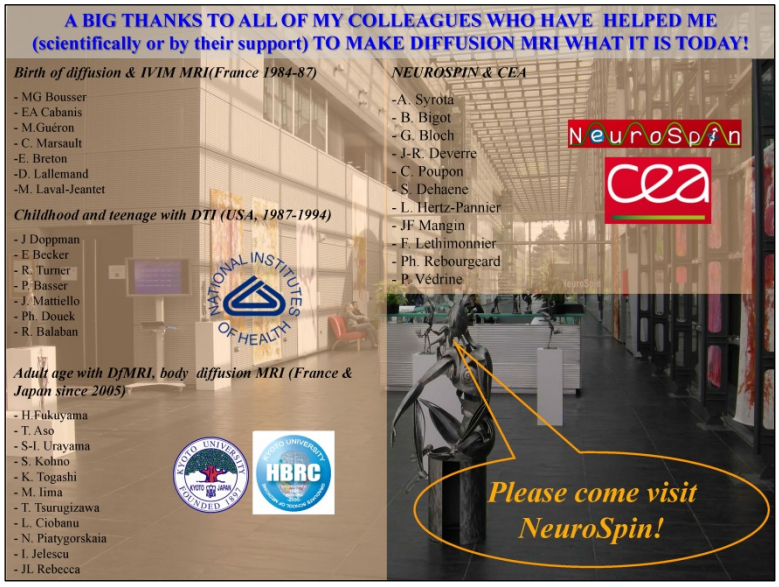

Fig 40

〈Fig 40〉　This is NeuroSpin. And again, diffusion MRI would not have been possible without the support, the help of many, many colleagues there. I could not put everybody on the slide, or I would need 10 slides. I would like to just mention a few colleagues through the history of diffusion MRI.
I started in France, and Prof. Bousser, a neurologist, introduced me to several key people so that I could start working on diffusion on my own. When I went on to diffusion MRI, I was still a resident and a PhD student in physics. I then moved to the United States and was also very lucky to be working with great people like Dr. Robert Turner and Dr. Peter Basser while we developed diffusion tensor imaging. And then, I went back to France and later started to collaborate with Japan and Kyoto University, so Prof. Hidenao Fukuyama, Dr. Toshihiko Aso, Mr. Shinichi Urayama, assistant proferror, Dr. Satoru Kohno, and many people who helped me develop functional MRI with diffusion. I also thank Prof. Kaori Togashi and Dr. Iima who are now using diffusion MRI in the body for clinical applications.

Of course, there are many people from CEA who really were supportive, responding to my project. To just name a few, when I talked about NeuroSpin, Prof. Andre Syrota who was my boss when I conceived NeuroSpin immediately understood that it was a great idea and made everything so that it could happen. Bernard Bigot, our general administrator, was and is still very supportive. Dr. Gilles Bloch, who is here, is an MRI and MR spectroscopy specialist by training, so he also understands me very well (we worked together in the past). Also, I want to thank all my many colleagues who are not here today. I hope that you will have a chance to visit NeuroSpin someday. Again, I am very thankful for Honda Foundation for giving me this award, which is a treasure for me. I thank you again very much.

⟨MEMO⟩

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