The Signs of Death
Pontifical Academy of Sciences, Scripta Varia 110, Vatican City 2007
www.pas.va/content/dam/accademia/pdf/sv110/sv110-puybasset.pdf

THE ASSESSMENT OF COMA OUTCOME BY THE USE OF MULTIMODAL MR AND PROPORTIONALITY OF CARE IN NEURO-INJURED PATIENTS*

LOUIS PUYBASSET

Thank you for giving me the opportunity to be here and to discuss this topic with you. For myself there are not that many ethical issues regarding brain death, it is pretty clear as soon as the diagnosis is perfectly made. We have more ethical issues regarding the way we deal with families, and this is where we should concentrate our work. However, as science goes on I will try to show you that we are confronted more with ethical issues regarding the treatment that we provide to patients in a coma and we have seen with Dr. Bernat that this might be related also to organ donation through the programme of non-heart beating donors, and I will try to discuss with you these issues.

As intensivists, what we have to deal with is to try to find out tests that give us the possibility of tailoring the intensity of care that we provide to each individual patient after major traumatic or non traumatic brain injury. We have to do that to avoid disproportionate care in patients that will end up in permanent vegetative state or minimally conscious state at one year but the opposite is also true, i.e. to provide major intensive care in patients for whom we expect a good recovery, even though it is two or three months later. So it is our duty to develop tools in order to assess prognosis and to proportionate care accordingly. There are many ways to do that and I will try to show you what we do in Paris in my hospital and what we have developed there.

The first thing is to look at the anatomical pathways of consciousness that rely on, let us say, a very basic appreciation of two systems. First of all, it has been called by Parvizi and Damasio the *protoself*, and it is based on the ascending reticular activating system in the upper pons, the midbrain, the intralaminar nuclei and the reticular nucleus of the thalamus, the hypo-

* The views expressed with absolute freedom in this paper should be understood as representing the views of the author and not necessarily those of the Pontifical Academy of Sciences. The views expressed in the discussion are those of the participants and not necessarily those of the Academy.

thalamus and the basal forebrain. All this is connected to the cortex and some areas of the cortex are more important than others, especially the cingulated areas (Figure 1, see page 432).

One hypothesis is to say that poor outcome regarding recovery of consciousness is linked to specific alterations of the protoself network or to diffuse alteration of both hemispheres. What is so complicated is that we have to consider the symmetry of a lesion and this complicates the picture a lot, especially when we think of a bilateral lesion. We have to take that into account, whether bilateral lesions are symmetrical or asymmetrical.

We made different attempts to try to assess recovery of coma in those patients with severe head trauma and I will show you some of these attempts. Here we studied with morphological sequences 73 patients with MRI and we distinguished two groups of patients, those who will die or stay in a permanent vegetative or minimally conscious state at one year and those who will have a good recovery. In this series we had 32 patients with a good recovery and 41 patients with a bad recovery, so to say.

Weiss et al, submitted – n = 73 TBI patients

Table 1. Baseline Characteristics of the Patients.

	All patients n = 73	GOS 1-3 n = 41	GOS 4-5 n = 32	*P*
Age (years)	36 ± 14	40 ± 15	31 ± 13	<0.02
Sex (M/F)	58 / 15	37 / 4	21 / 11	NS
Mydriasis at scene	31 (42%)	22 (54%)	9 (28%)	NS
GCS at admission	6.1 ± 3.0	5 ± 3	7 ± 3	<0.01
Subdural hematoma	20 (27%)	17 (41%)	3 (9%)	<0.003
Epidural hematoma	12 (16%)	8 (20%)	4 (13%)	NS
Hypertonic saline use	36 (49%)	21 (51%)	15 (47%)	NS
Norepinephrine use	65 (89%)	37 (90%)	28 (88%)	NS

Figure 2.

We determined cluster analyses just to show you that it is possible, analysing the FLAIR images, to ponder each lesion and in doing that to have a prognosis likeliness regarding the outcome of the patient. Nowadays we have some tools that will provide us with more and more information regarding recovery.

Weiss et al, submitted – n = 73 TBI patients

Table 4. Independent risk factor for poor outcome – logistic regression analysis

	Odds Ratio	[95% CI]	*P*
MRI approach			
Right upper pons and right lower midbrain	5.1	1.8-14.5	<0.003
Hypothalamus and basal forebrain	2.3	1.2-4.3	<0.02
Left parietal, left temporal, left occipital lobes and left insula	3.3	1.4-7.9	<0.009
Combined clinical to MRI approach			
Right upper pons and right lower midbrain	4.7	1.2-18.1	<0.03
Hypothalamus and basal forebrain	2.6	1.2-5.7	<0.03
Left parietal, left temporal, left occipital lobes and left insula	4.0	1.3-11.8	<0.02
Grasping	21.2	1.7-271.2	<0.02
Chewing	26.9	3.7-197.5	<0.002

OR are given per one lesion increase for the different clusters.

Figure 3.

And these are the results regarding the assessment of outcome with the MRI plus the clinical symptoms that the patient presented, such as grasping or chewing.

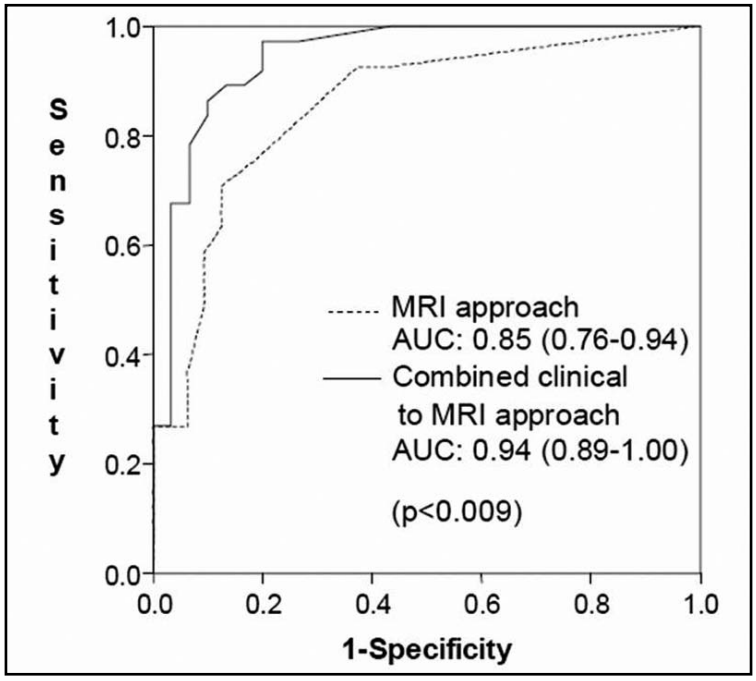

Figure 4.

The picture has changed a lot with the use of spectro-MR and diffusion tensor and I will now show you this type of analyses. Here we go from a purely morphological approach to a biochemical approach of the function of a pons. This is the normal aspect of a pons and the normal spectra with a first peak that is choline, a second that is creatine and a third that is n-acetyl-aspartate. The normal ratio for NAA/Cr is 2.33.

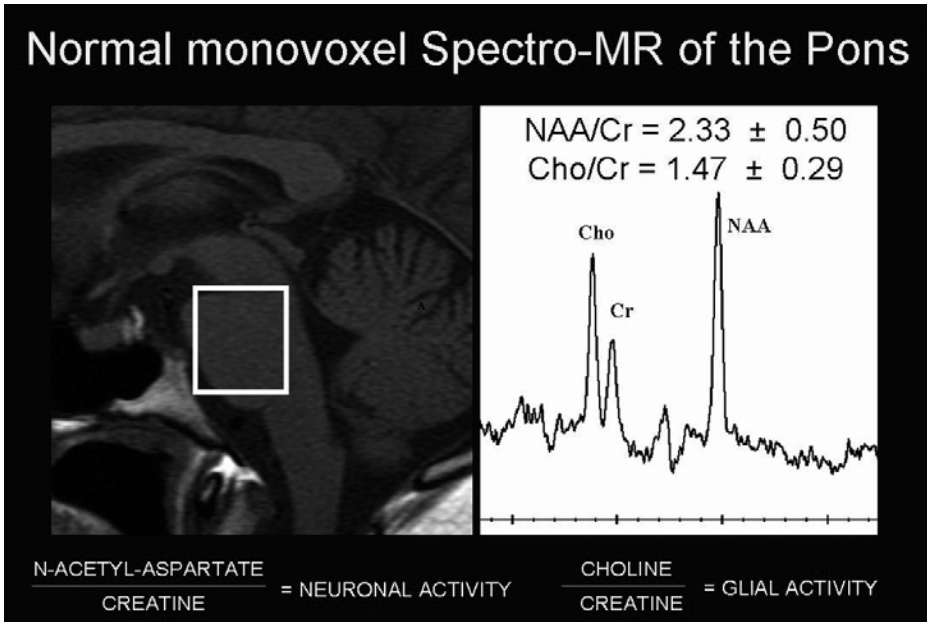

Figure 5.

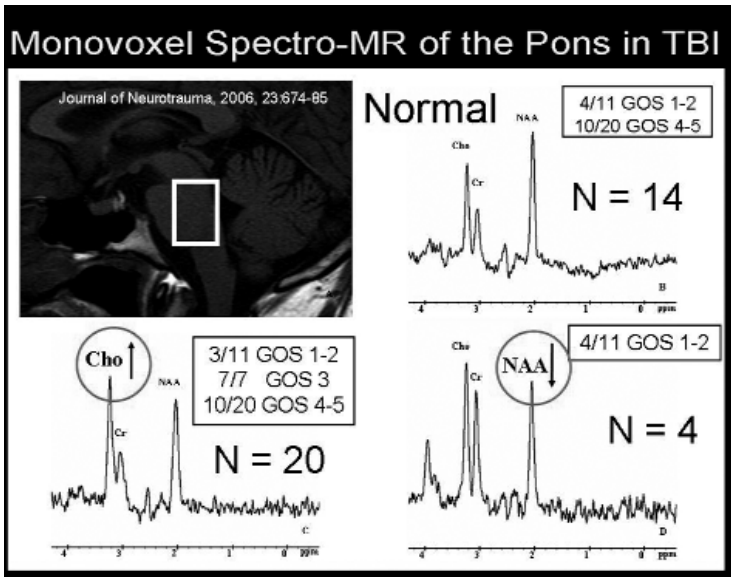

Figure 6.

This is a first study that we published in the *Journal of Neurotrauma*, showing the different aspect that we observed in the pons of traumatic patients and, as you see, 14 of these 48 patients had a normal aspect. Most of the patients had a cholinergic reaction, which does not mean that they will not end up in a bad clinical state, but all of the patients that presented a profound decrease in n-acetyl-aspartate over creatine ratio ended either in PVS or dead.

There are clear correlations between the number of lesions in FLAIR in traumatic brain injury and the disability rating scale at 18 months, so that we can somehow predict the outcome (Figure 7, see page 430).

Figure 8 (see page 433), shows a 4D Principal Component Analysis that we did. We analysed the FLAIR lesions in the hemispheres and combined that with the spectro-MR analysis of the pons. You can see that, in doing so, we were able to distinguish very clearly the group of patients that would have a good recovery, the group of patients that would stay in MCS and the group of patients that would either die or stay in PVS. That is another example of predictability of outcome. I have to specify that all these MRI were performed after the second to third week of insult. It is not done early because it is impossible to transport these patients to the MRI early, due of the increased intracranial pressure.

Another major issue is the use of diffusion tensor. For those who are not aware of this technique, Figure 9 (see page 433) shows a typical FLAIR image and a typical corresponding diffusion tensor. These techniques give you the major axonal routes in the brain.

Figure 10 (see page 434) shows the 3D images of a brain with diffusion tensor and this is now a sequence that we use in every comatose patient to see exactly where the white fibres insult is located. So here you have the typical brain stem with the four spinothalamic and the pyramidal signals, then we have the peduncles, and then we have all the hemispheric white fibres, and this is the normal assessment of the brain with diffusion tensor.

Another thing that we do on a systematic basis is the analysis of spectrometry on a section that goes through the basal ganglia. Figure 11 shows the normal aspects of the lenticular nuclei, of the insula, of the posterior thalamus, the parieto-occipital white matter, and the occipital cortex. With this technique you can put the voxel wherever you want and have an analysis of the biochemistry of the brain. As you see, usually the NAA is twice the creatine peak.

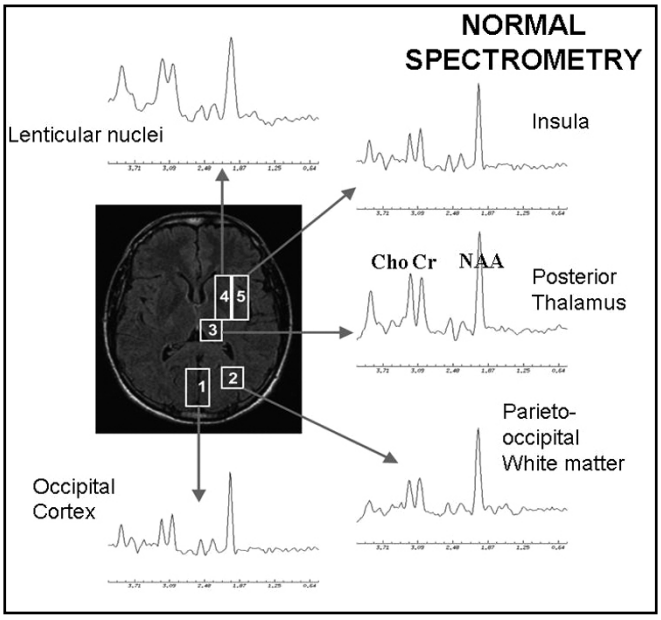

Figure 11.

Figure 12 (see page 434) is just to show you how efficient this imaging really is. This is what a totally destroyed brain stem looks like. This is not a brain death patient, these are patients who will end up either in permanent vegetative state, or in minimally conscious state. This destruction can be seen without any lesions on the FLAIR sequences. Here you have the destruction of all the white descending fibres in the pons and look also at the peduncles, at the mid brain, which is totally atrophic. And we see more and more of these diffusion tensor imaging abnormalities although FLAIR images might be normal.

Very interestingly, the usefulness of MRI goes in both directions, meaning that we can have patients with a very severe clinical state and good MRI and, therefore, good prognosis. The patient in figure 13 (see page 435) was a real cornerstone in our practice, he was 36 years old, he shocked us a lot. He had an initial Glasgow of 3 and was referred with a bilateral decerebration. I examined him myself so I know this is true. He had no increased ICP so we were able to reduce sedation very quickly and to have a real neurological examination. He stayed in decerebration for 15 days. He also had a neurovegetative crisis; we were very aware of this very poor clinical condition and went to the MRI quickly. We were surprised to see a normal MRI. This is a normal spectra for the pons and this is a normal aspect of the diffusion tensor in the pons.

These were the aspects of the diffusion tensor in the hemispheres, while figure 14 (see page 435) shows a spectro for the posterior thalamus on the right side. In fact, this patient recovered completely, even though we had to wait a long period of time, meaning that, with these types of techniques, we can clearly distinguish patients that have very severe clinical conditions and in whom we should continue care for weeks or months if necessary, because at the end they will wake up since they have a normal brain on the MRI. This could be apparented to a kind of stunned brain.

Another thing that we use a lot is what we call 'Cognitive EEG' (figure 15, see page 436). I will not go into detail here but it is the assessment of the response to two different auditory stimuli. It is a summation of the EEG answers to the stimuli. This is a normal aspect, with this well-known mismatched negativity operating between 200 and 300 milliseconds. The P3A indicates a preconscious state and the P3B indicates a conscious state. In this patient, we had a delayed mismatched negativity and a P3A, meaning that he was in a preconscious state. We usually combine this MRI approach with this electrophysiological approach to further determine the prognosis.

I will just show you some other images. You see, for example (figure 16, see page 436), in this patient who has a severe head trauma patient, he had

a subdural hematoma on the right side here and a subsequent extradural hematoma on the left side, he was operated twice. You see the profound discrepancy that we observed in the FLAIR image, it looks pretty normal on the left side compared to the total destruction of the white fibres using diffusion tensor. In this case the right side seems to be more diseased than the left side but, in fact, regarding the diffusion tensor imaging and the axons themselves, it is exactly similar.

Figure 17 is another example. This is an SAH patient, 60 years old, she was found a long time after the SAH, she had a major increase in ICP. This patient finally died and, when we look at the FLAIR, we see these hyper intense signals on the basal ganglia.

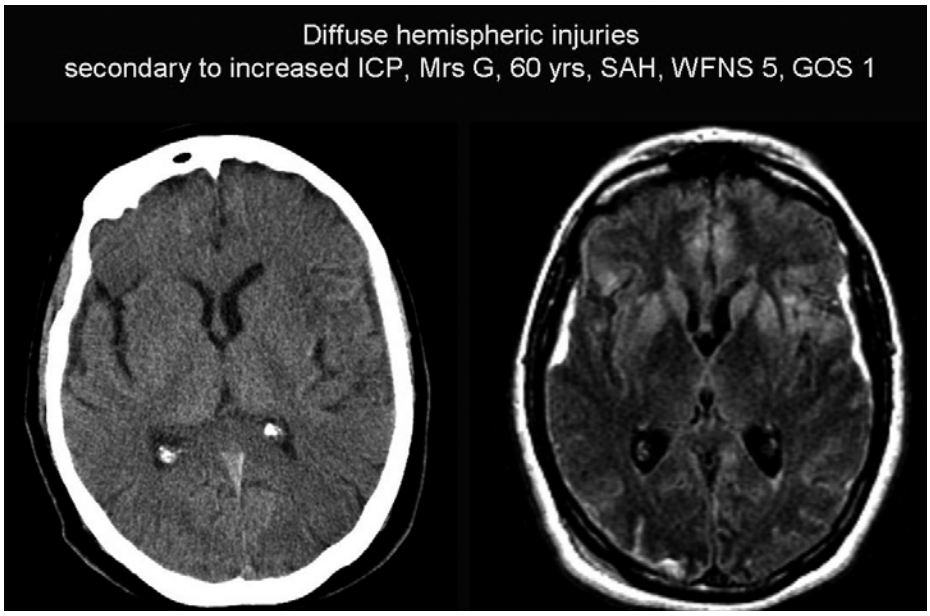

Figure 17.

However, when we look at the diffusion tensor (figure 18, see page 437), it is clear that there are no more white fibres in this brain and that ICU is helpless here.

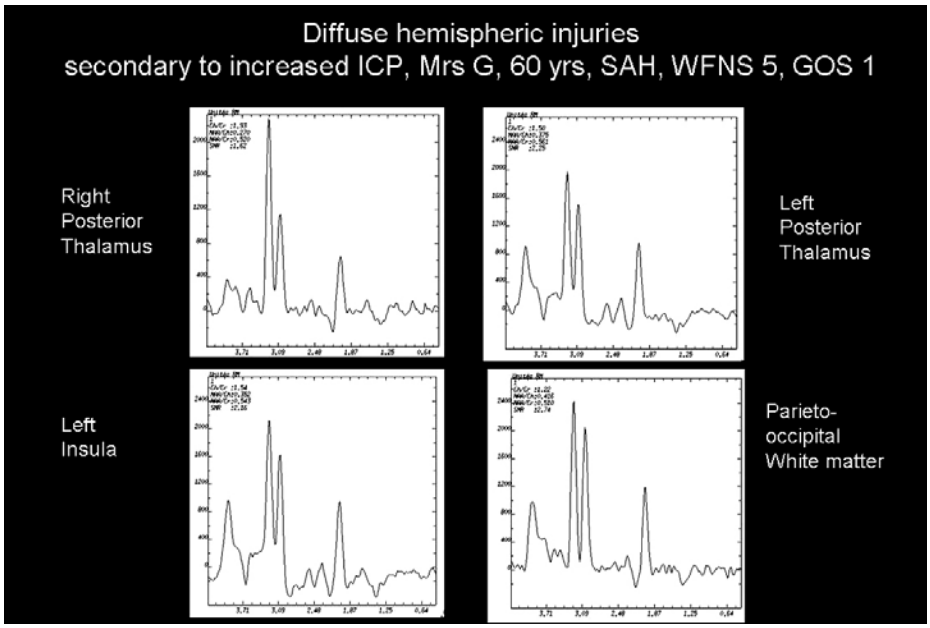

Figure 19.

This was confirmed by the spectro analysis of these different parts of basal ganglia (figure 19), showing a total destruction as assessed by the major reduction in the NAA / creatine ratio of about 0.5.

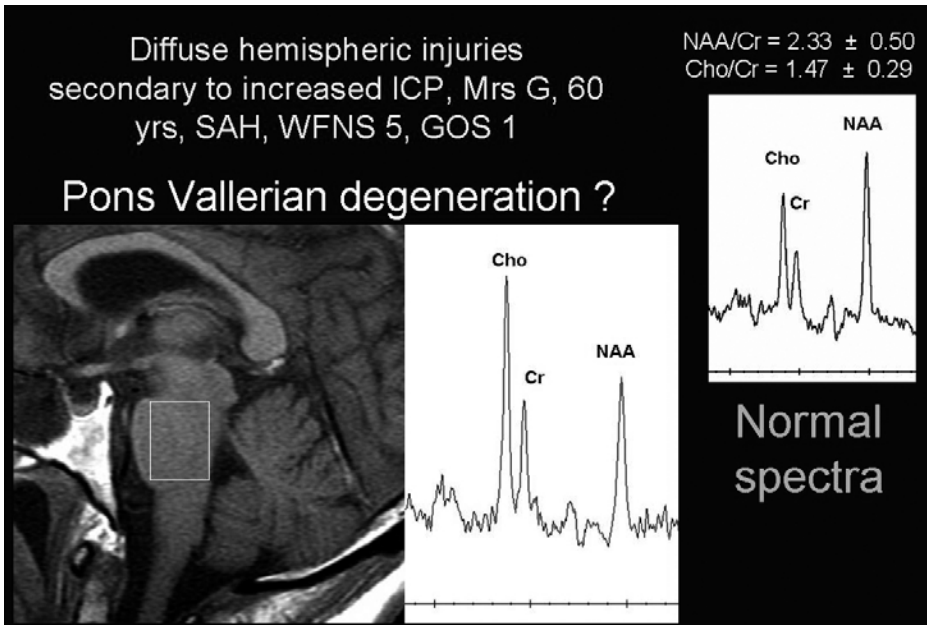

Figure 20.

One of the things that we discussed yesterday is the Wallerian degeneration of the pons. For example, in the patient I showed you before, who had a SAH, there was no primary insult to the pons, but when we look at the spectra of the pons (figure 20), we see a tremendous decrease in NAA / creatine ratio, meaning that we probably had a descending degeneration.

And when we look at the cognitive EEG (figure 21, see page 437), we see no answer, there is no mismatch, no P3A. All that is concordant to inform us that this patient will never wake up and will never recover consciousness, so maybe it is better if we stop the ICU care and let her die. We should go in this case from a curative logic to a palliative one.

We know today that quantitative assessment of spectrometry on the basal ganglia slice combined with fractional anisotropy measure allow a very good prediction of coma outcome.

Right now we are designing a study in France – I am the principal investigator – that will look at 400 severe TBI patients in 10 French centres and will do all these MRI analyses in a statistical blinded way and in a multicentre trial, to make sure that this is a relevant matter. But our goal is obviously to provide a hard scientific basis for withholding or withdrawing care in neurotrauma patients and to help in the decision-making process.

On a final note, I would like to go back to the issue of organ donation. As I told you, I have no ethical concern with brain death. I often, unfortunately, have this discussion with families and I think that ethics lies in the way we deal with families, but I have no ethical problem or issue with the diagnosis of brain death because brain death is diagnosed in France only by EEG or DSA, it is not based solely on clinical examination. So diagnosis is not a concern to me. My concern is much more the issue of the Class III Maastricht patients, and I wanted to take a few minutes to present that.

You know that, because of a shortage of organs, there are a lot of programmes coming now from the US, and especially from England and from the Netherlands, that try to harvest kidneys from people who are dead. We have three classes here. Class I are patients that are brought in dead, so you take the tissue in these patients; Class II are brought in dead, cardiac resuscitation is a failure, the patient does not recover cardiac rate, so we turn on extracorporeal circulation and then speak to the families. If they accept, there can be a kidney donation. For me, the major problem is with Class III patients.

I would say that we are going to have a major problem because the more we develop diagnostic tools to predict the outcome of a patient, the more often these questions will arise. Because of the family or because of a patient's previous wish or because of the pressure of a surgeon, we might be asked to harvest the kidneys of such patients. This question is particularly relevant to neuro ICU, because it is in these neurological patients that death occurs without any major organ dysfunction.

Thank you for your attention.

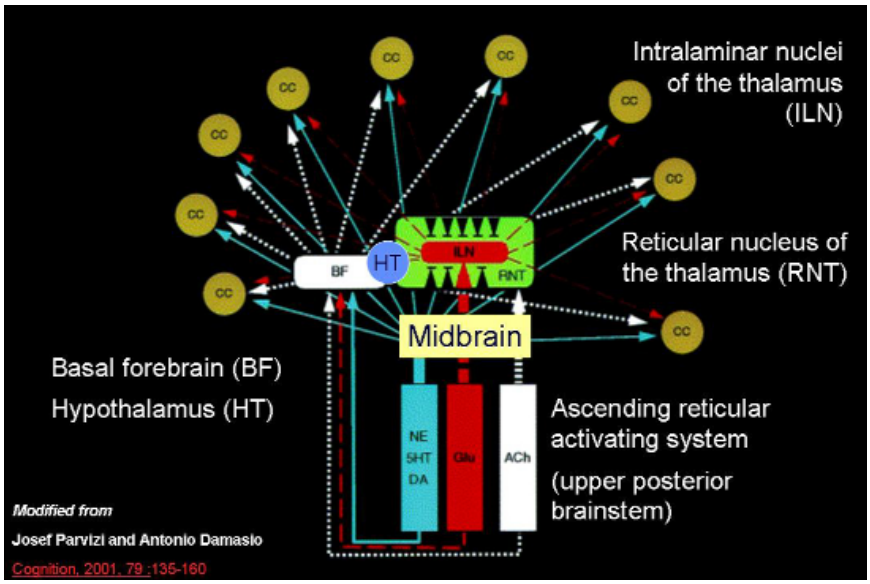

Figure 1.

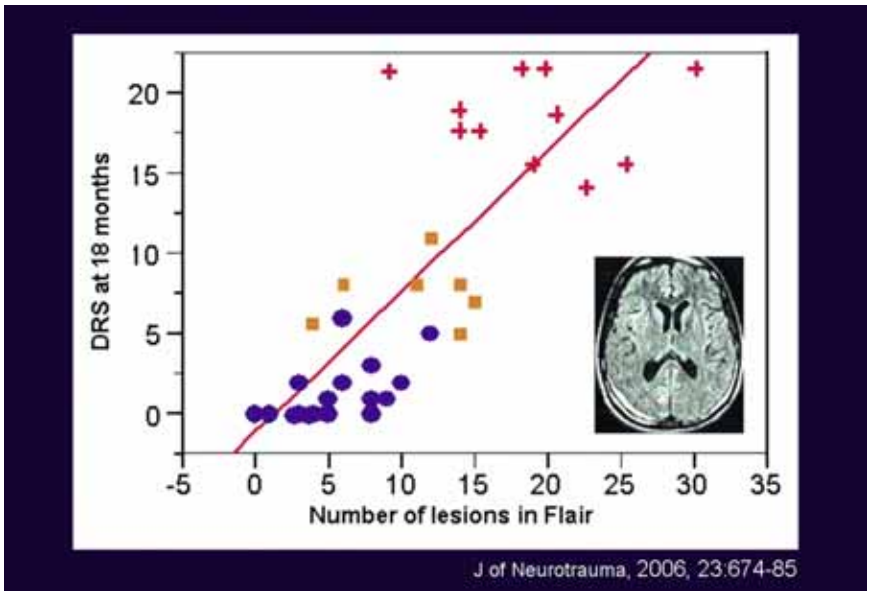

Figure 7.

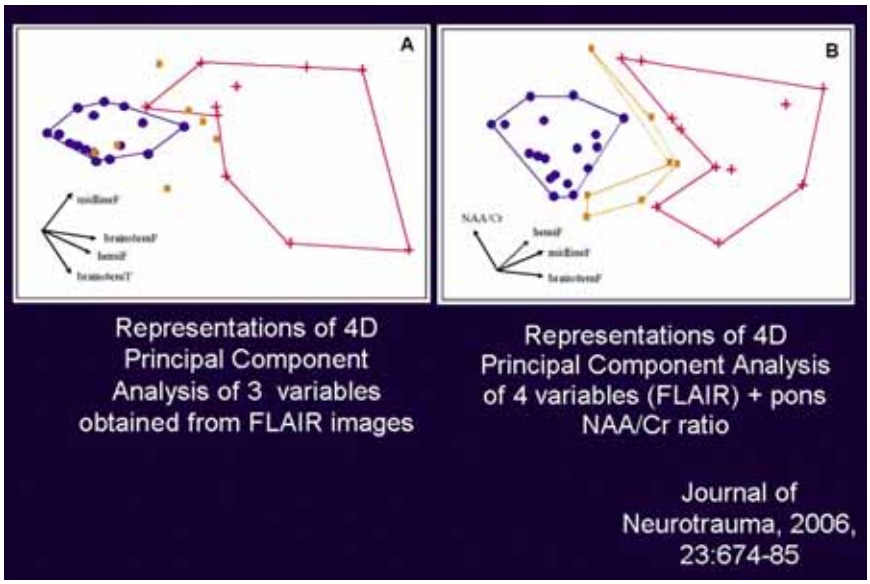

Figure 8.

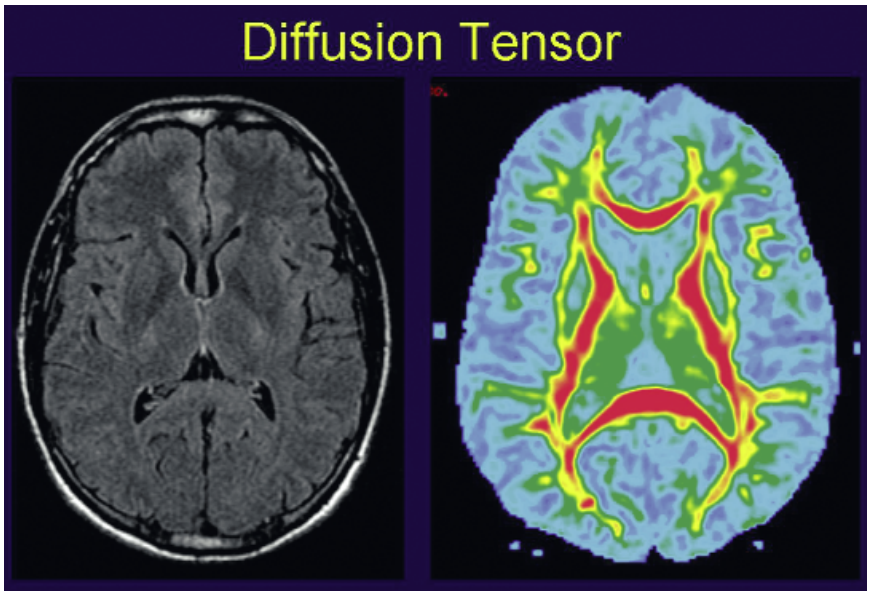

Figure 9.

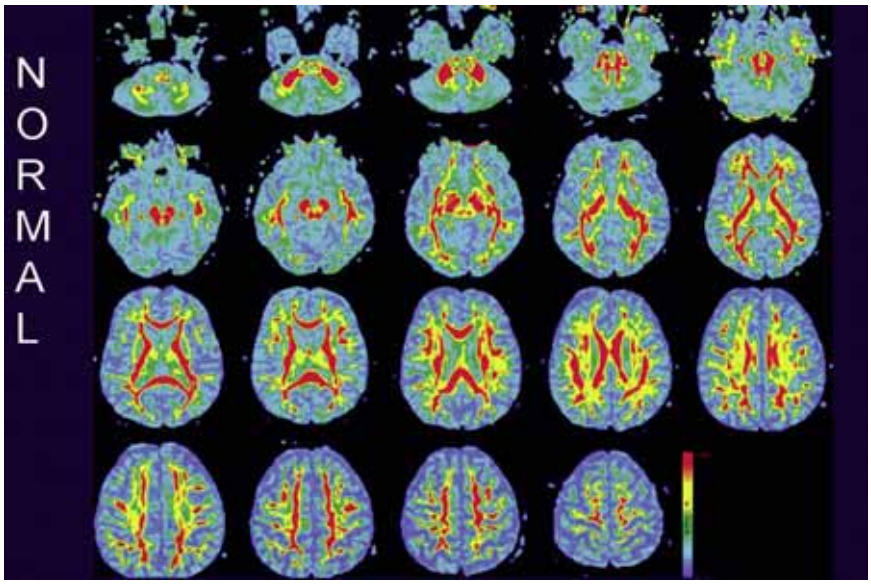

Figure 10.

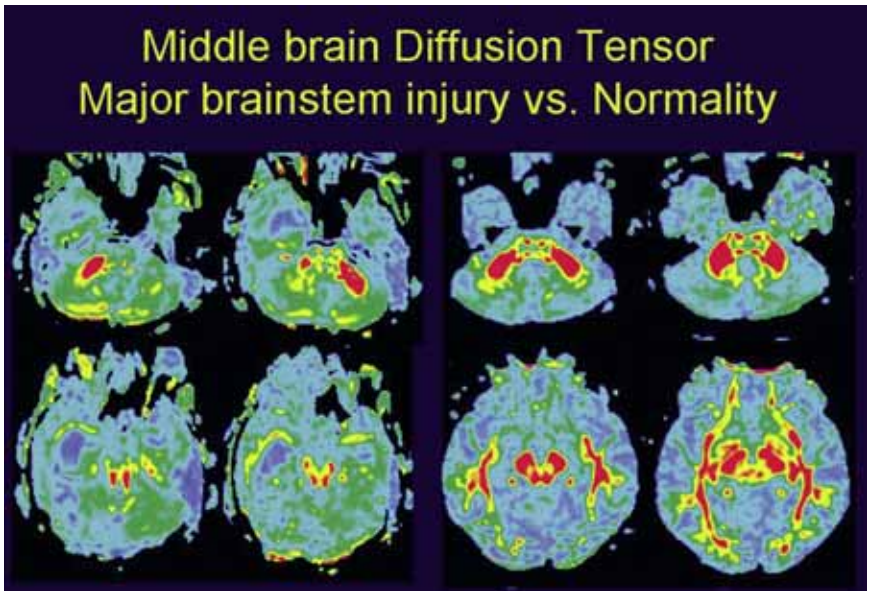

Figure 12.

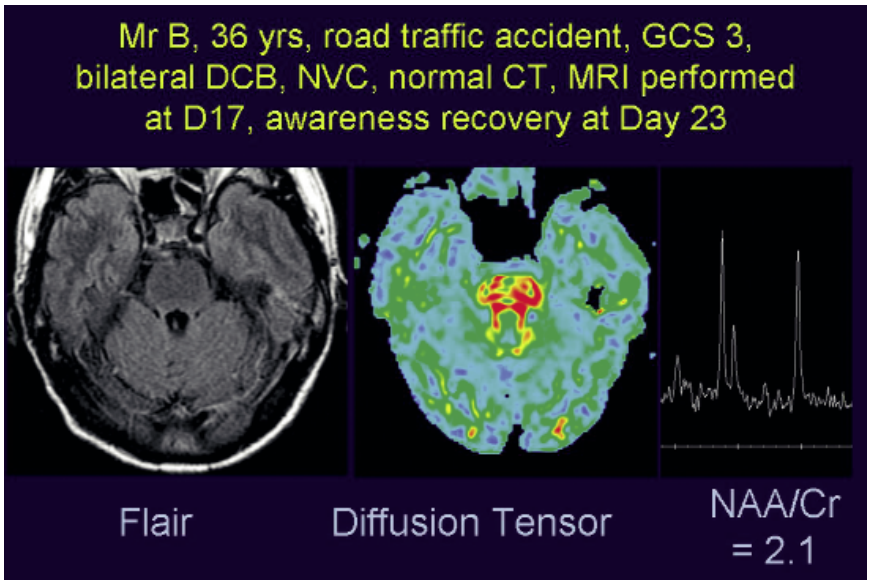

Figure 13.

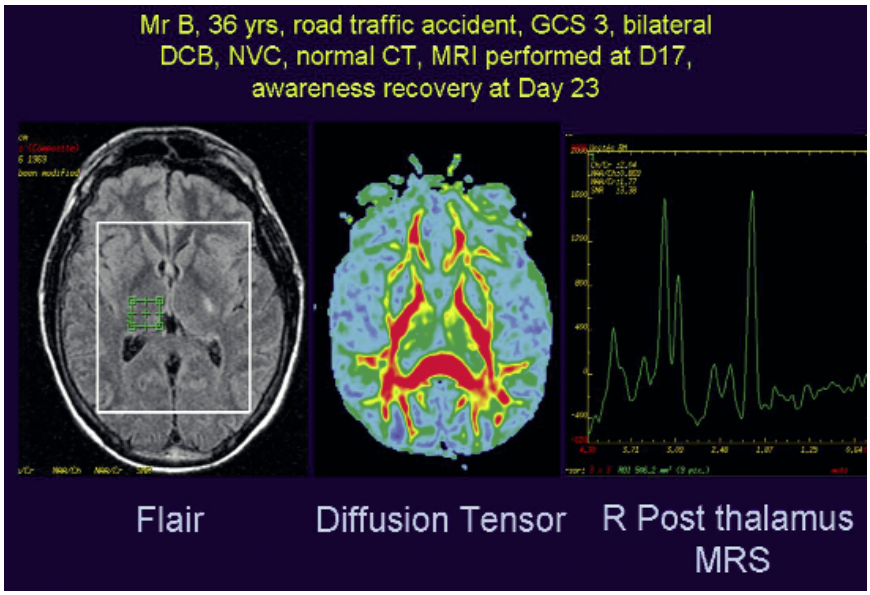

Figure 14.

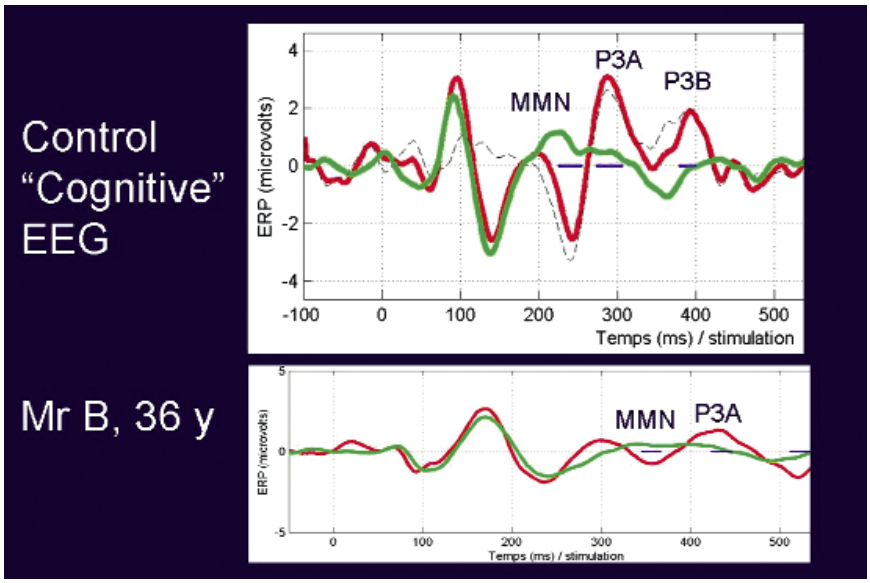

Figure 15.

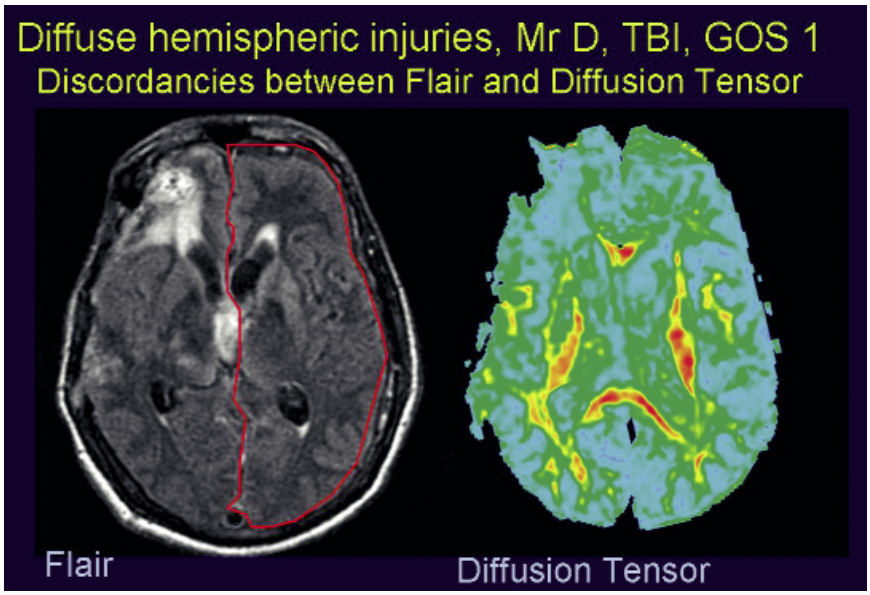

Figure 16.

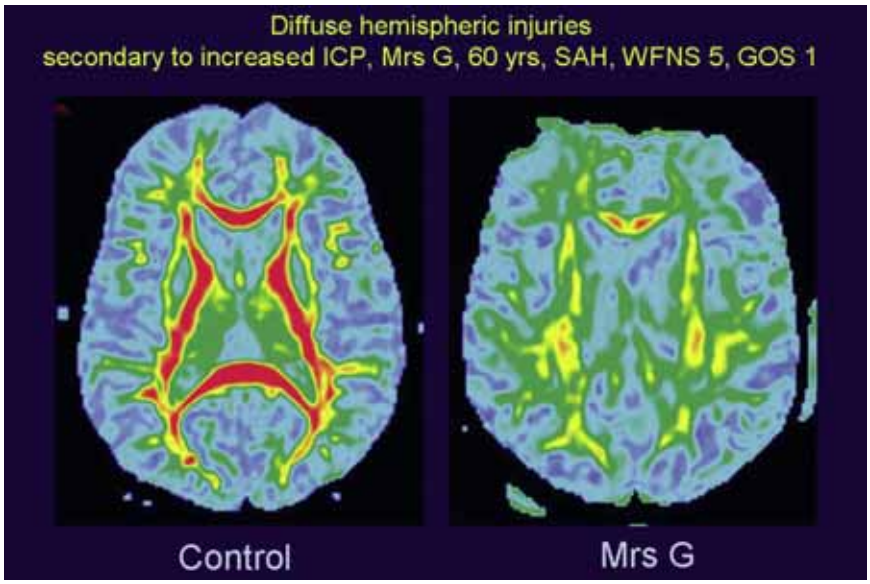

Figure 18.

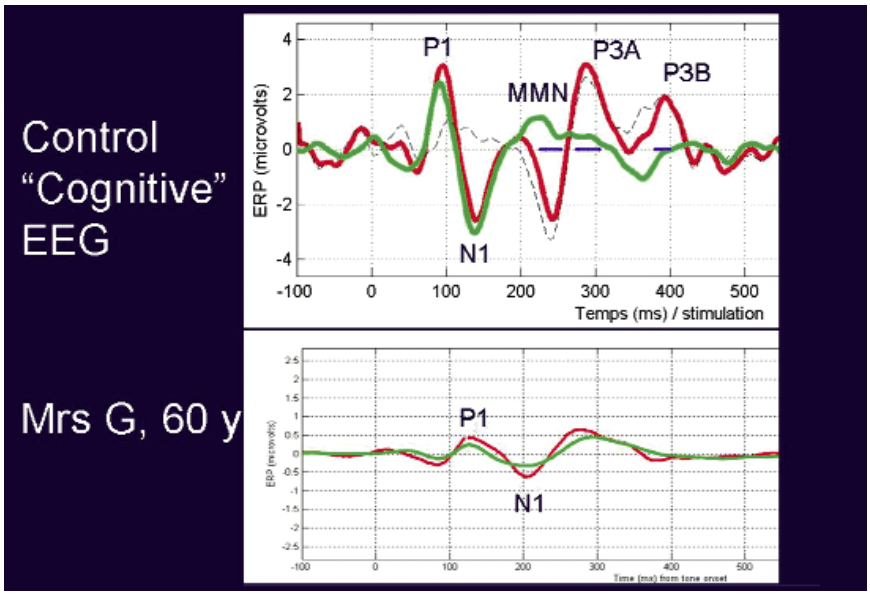

Figure 21.