WEB APPENDIX

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INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria

All of the following 4 criteria must be satisfied for trial eligibility:

1. Age ≥18 years.
2. Cardiac arrest in the last 7 days.
3. Admission to an intensive care unit.
4. Persisting unconsciousness at day 7 defined as the inability to obey verbal commands not attributed to sedation or aphasia.

Exclusion criteria

1. Obvious or suspected pregnancy.
2. Coma explained by sedation
3. MRI contraindication (e.g., pace maker, medical device incompatible with MRI, intraocular or cerebral metallic cluster).
4. Cardiac arrest caused by trauma.
5. Previous or additional neurological history (e.g., intracranial bleeding, stroke, tumor) susceptible to interference with the clinical outcome.
6. Severe hemodynamic failure precluding transport and MR scanning.
7. Severe respiratory failure precluding transport and MR scanning.
8. Confluent leukoaraiosis (defined on Fazekas scale ≥ grade 4; see the Web Appendix additional files 7 pp 31).
9. Patient with severe impairment of vital functions and/or potentially life-threatening with a handicap prior to the event.
10. Refusal of the family.
11. Patient protected by the law (under supervision or trusteeship).

DATA TRANSPARENCY

Fifty patients examined with multimodal magnetic resonance imagery by Luyt et al[1] and van der Eerden et al[2] were part of the derivation cohort of this study. Analysis process was different and data recomputed in the present paper with a different methodology.

DETAILS OF CONVENTIONAL MR IMAGING ACQUISITION

The following conventional MR sequences were performed:

(i) 3D inversion recovery fast spoiled gradient recalled echo (FSPGR) or magnetization-prepared rapid acquisition gradient echo (MP RAGE) T1-weighted images;

(ii) Axial T2-weighted fluid-attenuated inversion recovery (FLAIR) images;

(iii) Axial $T2^*$-weighted gradient-recalled echo (GRE) or susceptibility-weighted imaging (SWI);

(iv) Diffusion-weighted imaging (DWI).

The protocol for the MR varied slightly by institution, reflecting a pragmatic approach to acquisition of imaging data. The precise parameters of each sequence were adapted to the individual scanner type, field strength, coil used, and departmental protocol (Table S1; appendix pp18).

DIFFUSION TENSOR IMAGING (DTI) ACQUISITION AND PROCESSING

There were minimum requirements for diffusion tensor imaging (DTI) acquisition. Whole-brain DTI was acquired in an axial plane perpendicular to the main field B0 using diffusion-encoding gradient pulses (b ranges from 700 to 1000 sec/mm^2) applied along at least 11 orientations (range 11 to 64; Table S1) isotropically distributed over the surface of a sphere with electrostatic repulsion, a maximum slice thickness of 3 mm (range 2 to 3 mm) with no gap between slices, a 96 x 96 matrix, and a field of view (FOV) of 300 mm. At least two additional volumes (range 2 to 4) were acquired with b = 0 sec/mm^2. Parallel imaging was employed with a maximal acceleration factor of 2.

All DTI image-processing steps were performed in a fully automated processing pipeline. The pipeline involved:

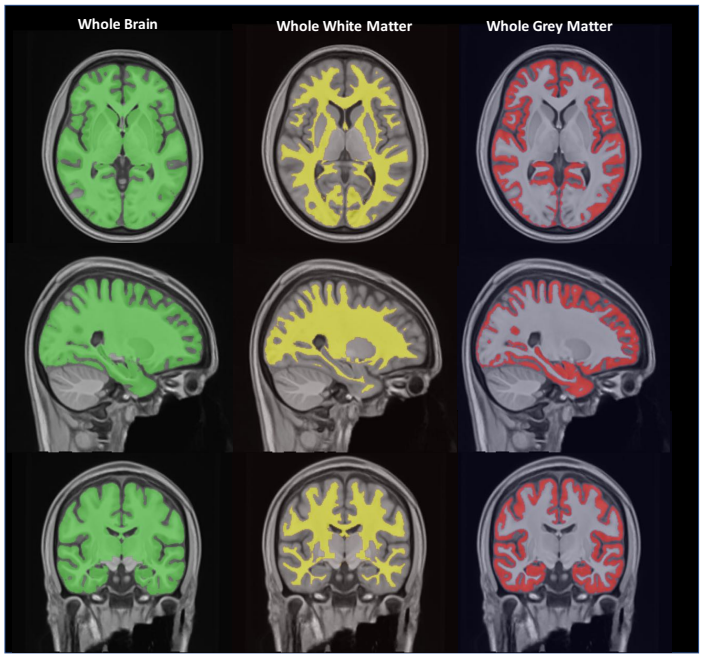
(i) Correction for motion and distortions caused by Eddy currents using the Functional MRI of the Brain (FMRIB) software library package 5.0 (www.fmrib.ox.ac.uk/fsl/);[3]

(ii) Computing the fractional anisotropy (FA) and the average diffusion coefficient (aDC) maps[4] using the diffusion tensor model with the FMRIB's DTIFIT algorithm;[5]

(iii) Linear and nonlinear registration of the FA and aDC maps on the T1 with the University College London's NiftyREG tool (cmictig.cs.ucl.ac.uk/research/software/22-niftyreg);[6]

(iv) Masking of the white and gray matter using segmented anatomical MRI of the subject with the Freesurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/). [7]

(v) Averaging FA and aDC values within segmented whole brain (WB), white matter (WWM) and gray matter (WGM) masks (see next figure).



Brain segmentations of 3DT1-weighted MRI template. Whole Brain mask, in green; Whole White Matter mask, in yellow; and Whole Grey Matter mask in red.

Given the variability in FA and aDC of healthy volunteers values between centers (Table S2; appendix pp19), which arises because of differences in scanner types and acquisition parameters, a normalization procedure was performed. That is, the raw value of each derived diffusion measure was divided by the mean of this measure across control subjects acquired in the same scanner with the same sequence.

PROTON MAGNETIC RESONANCE SPECTROSCOPY (^{1}H-MRS) DATA ACQUISITION AND PROCESSING

Proton magnetic resonance spectroscopy (^{1}H-MRS), was acquired on all MR scanners using the point-resolved proton spectroscopy sequence (PRESS) with TR=1500 ms, TE=135 ms. Single-voxel spectroscopy was acquired in the posterior two-thirds of the pons (matrix, 1x1; voxel thickness, 15 mm; frequency direction, S/I; 96 averages with water suppression). The axial chemical shift imaging (CSI) was performed at the level of the two thalami (matrix, 18 x 18; field of view, 24 x 24 cm; slice thickness, 10 to 20 mm; number of excitation, 1).

^{1}H-MRS data processing was performed by expert neuroradiologists using standard manufacturer software dedicated to MR spectroscopy post-processing (Advantage Windows for General Electric; Spectra, Syngo MR for Siemens; and Achieva software for Philips). For CSI data, the volume of interest in the thalamus was placed on non-angled FLAIR images after coregistration of spectroscopic data and FLAIR volume. The quality of the selected spectra was inspected by experts (N.A., and D.G.) and was considered acceptable only if choline (Cho) and creatine (Cr) signals were clearly separated. The spectra were analyzed for the concentration of metabolites in the thalamus and pons: N-acetylaspartate (NAA; at 2 ppm), choline (Cho; at 3.2 ppm), creatine and phosphocreatine (Cr; at 3 ppm). For pons, the voxel was positioned on the 2/3 posterior part of the pons, covering all its height. For thalami, the NAA/Cr ratio was computed as (NAA left thalamus + NAA right thalamus)/(Cr left thalamus + Cr right thalamus), except in cases where some voxels were not interpretable. In this case, only the side with spectra of good quality was taken into account.

CALCULATION OF ODDS RATIOS

Because there were categorical and continuous variables with different units, odds ratios (with 95% CI) were computed by taking the exponent of the absolute value of the estimated parameters (and 95% CI), the latter being multiplied by a factor that accounts for the unit used (*i.e.*, 0.1 in the case of ^{1}H-MRS parameters). We tested the null hypothesis of an estimated parameter being equal to zero with the use of Wald's test with one degree of freedom. This corresponds to the null hypothesis of an odds ratio being equal to 1, *i.e.*, no predictive value. Hence, a variable was considered to be predictive if $P<0.05$.

MULTIVARIATE LOGISTIC-REGRESSION MODELS

A forward stepwise variable selection was performed with Akaike information criterion, alpha-to-enter equal to 0.15 and alpha-to-exit equal to 0.20, as described by Hosmer and Lemeshow.[8]

First model

In the first model, only the following were considered: standard predictive variables (i.e., motor response no better than extensor at MRI day), OHCA score, and the predictive EEG variables (i.e., the Synek score and the absence of reactivity).

Second model

In the second model, qualitative MRI variables (FLAIR, DWI) were added to those in the first model.

Third model

In the third model, predictive quantitative MRI variables (WWM-FA, whole brain FA, gray matter aDC, whole brain aDC, thalamus and pons NAA/Cr ratio) were added to the second model.

SUPPLEMENTARY FIGURES AND TABLES

Figure S1: Scatter plot of whole white matter fractional anisotropy (FA) versus whole brain average diffusion coefficient (aDC) for all patients in the derivation cohort and healthy volunteers. Subjects status are in color, MRI delays are represented by symbols.

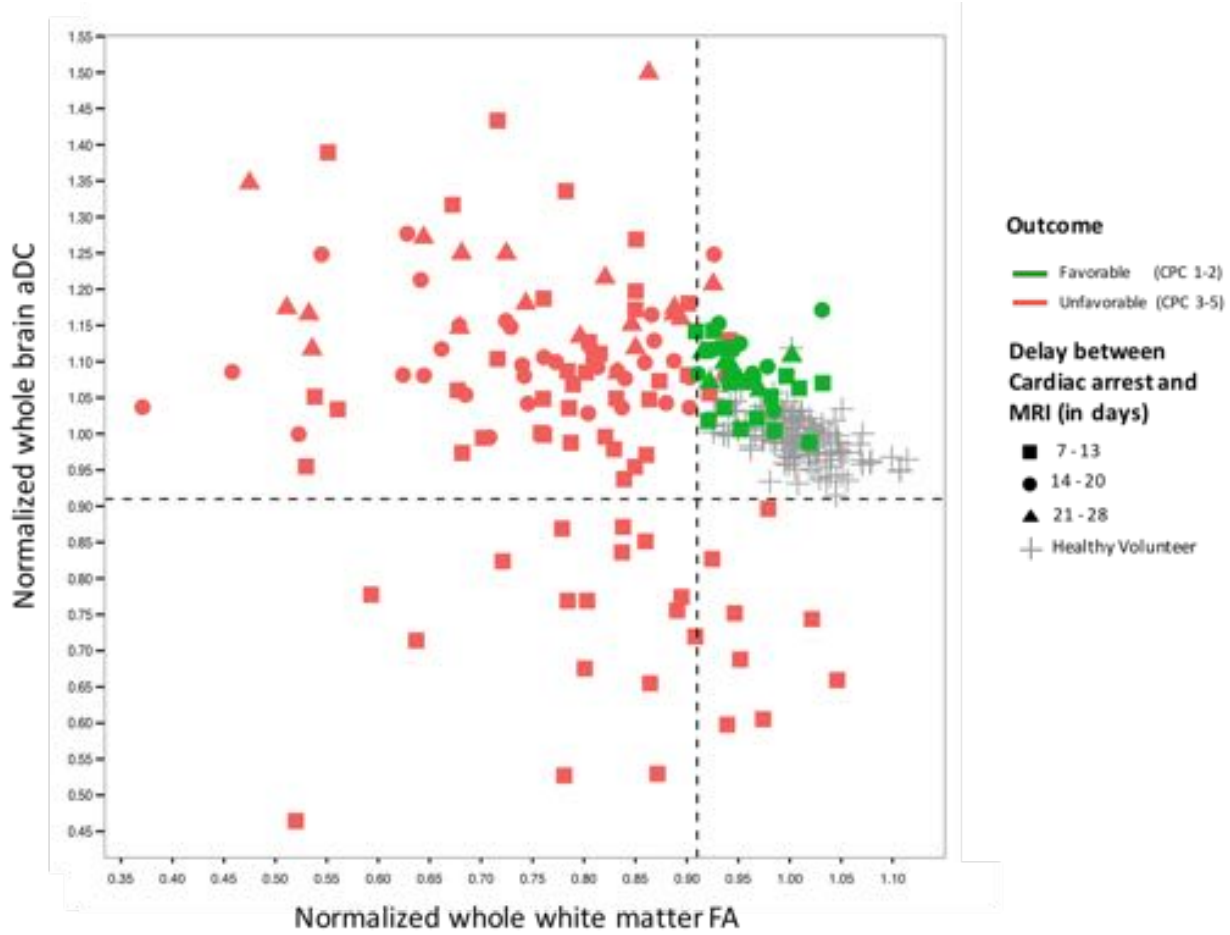


Figure S2: Receiver-Operating-Characteristic curves for standard criteria (panel A), qualitative magnetic qualitative resonance imaging (MRI; panel B), and quantitative MRI biomarkers (panel C) for unfavorable outcome in the subpopulation of patients without a limitation or withdrawal of care in the derivation cohort.

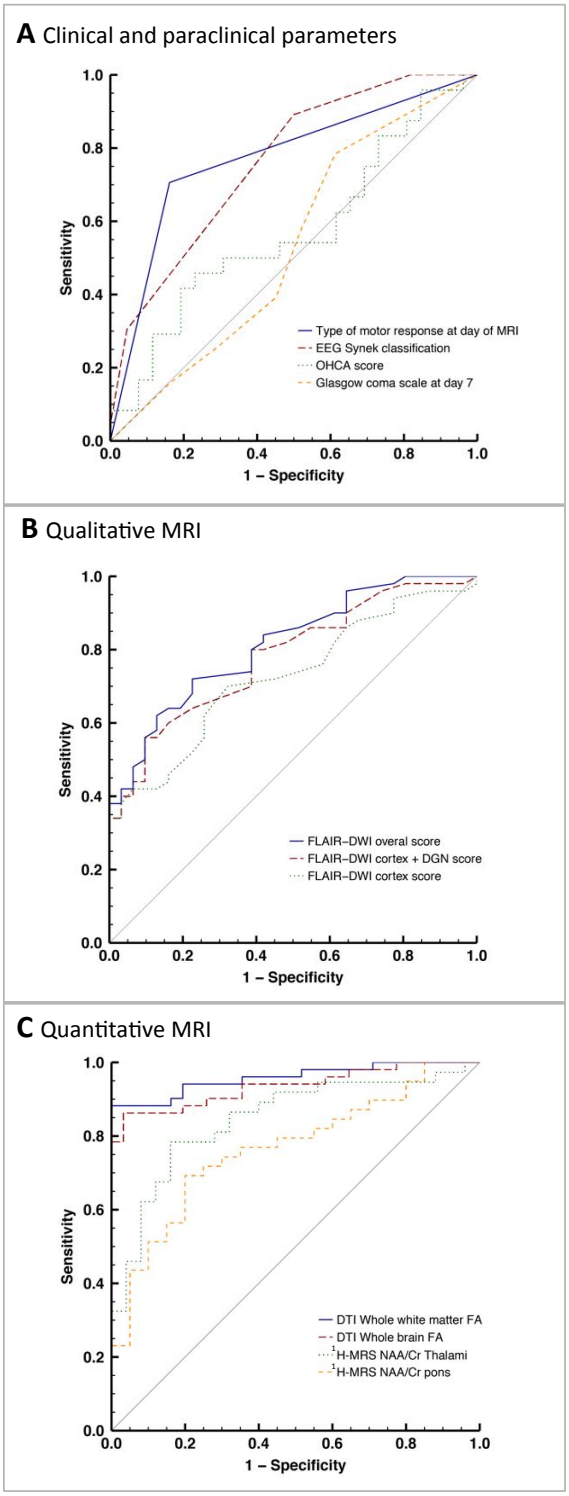


Figure S3: Probability of unfavorable outcome according to whole white matter fractional anisotropy (WWM-FA) in the derivation cohort. Estimate of the probability of unfavorable outcome at a given value of WWM-FA. Fitted logistic function over the patients without low average diffusion coefficient (aDC). The gray zone corresponds to the 95% confidence interval of the estimated probability. The dots represent the patients, being placed at y-axis equal to 1 if the outcome is unfavorable, and 0 on the contrary.

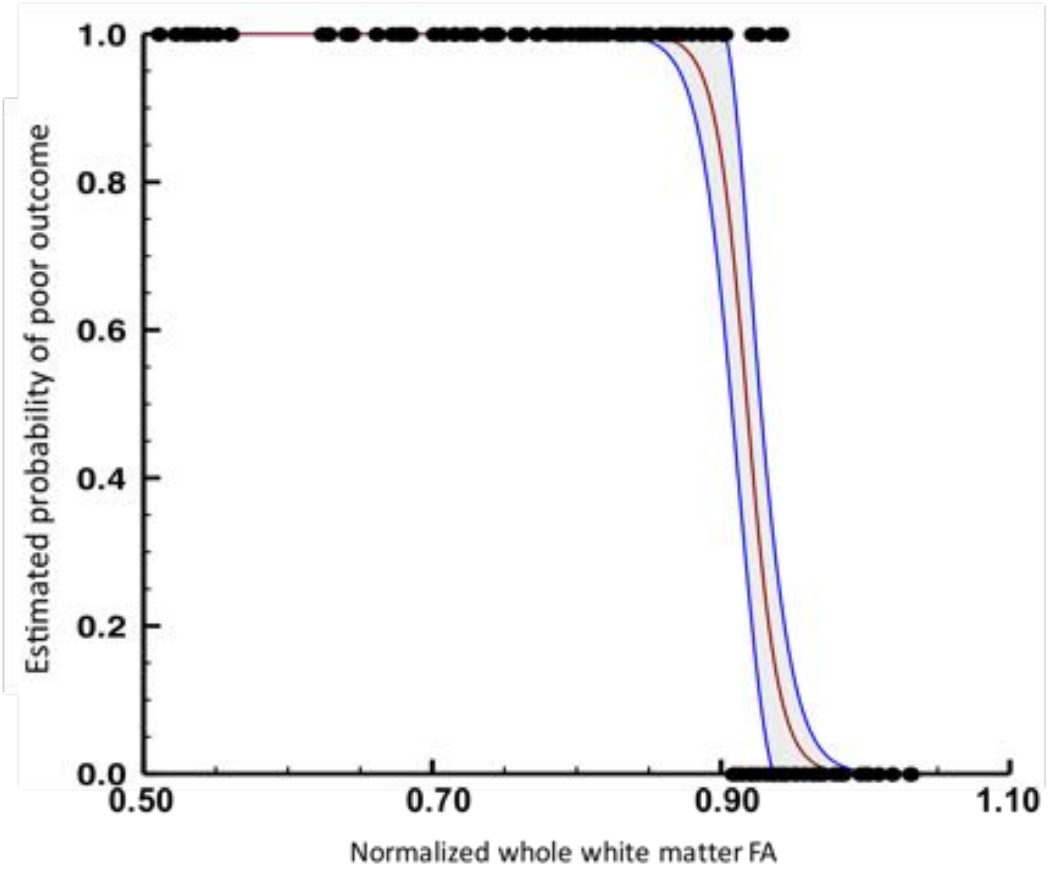
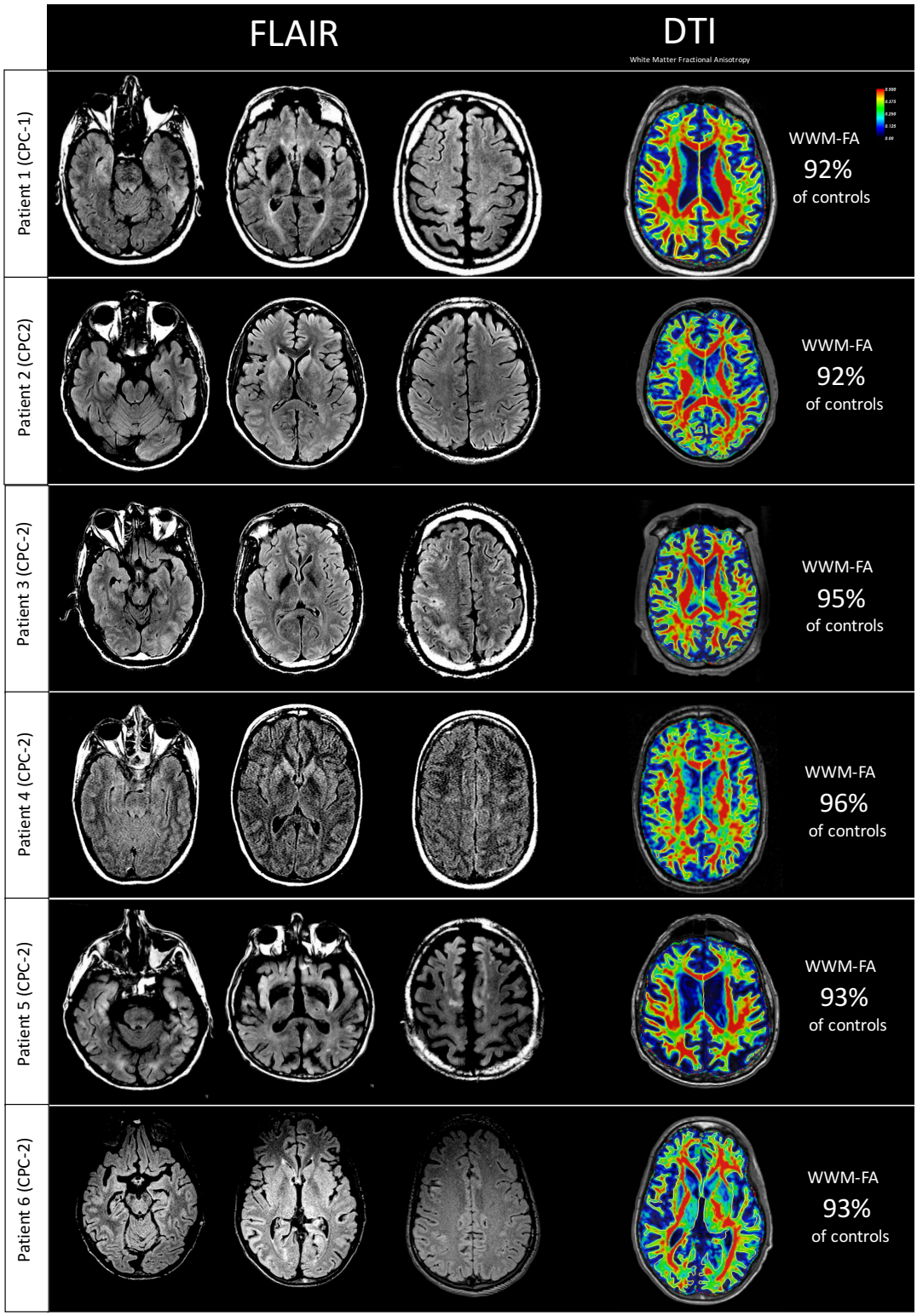


Figure S4: Maps of fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) and color-coded raw values of whole white matter fractional anisotropy (WWM-FA) map of patient 1 to 6 from the 12 patients that had favourable outcome despite mild-to-severe signal abnormalities in basal ganglia or cortex.



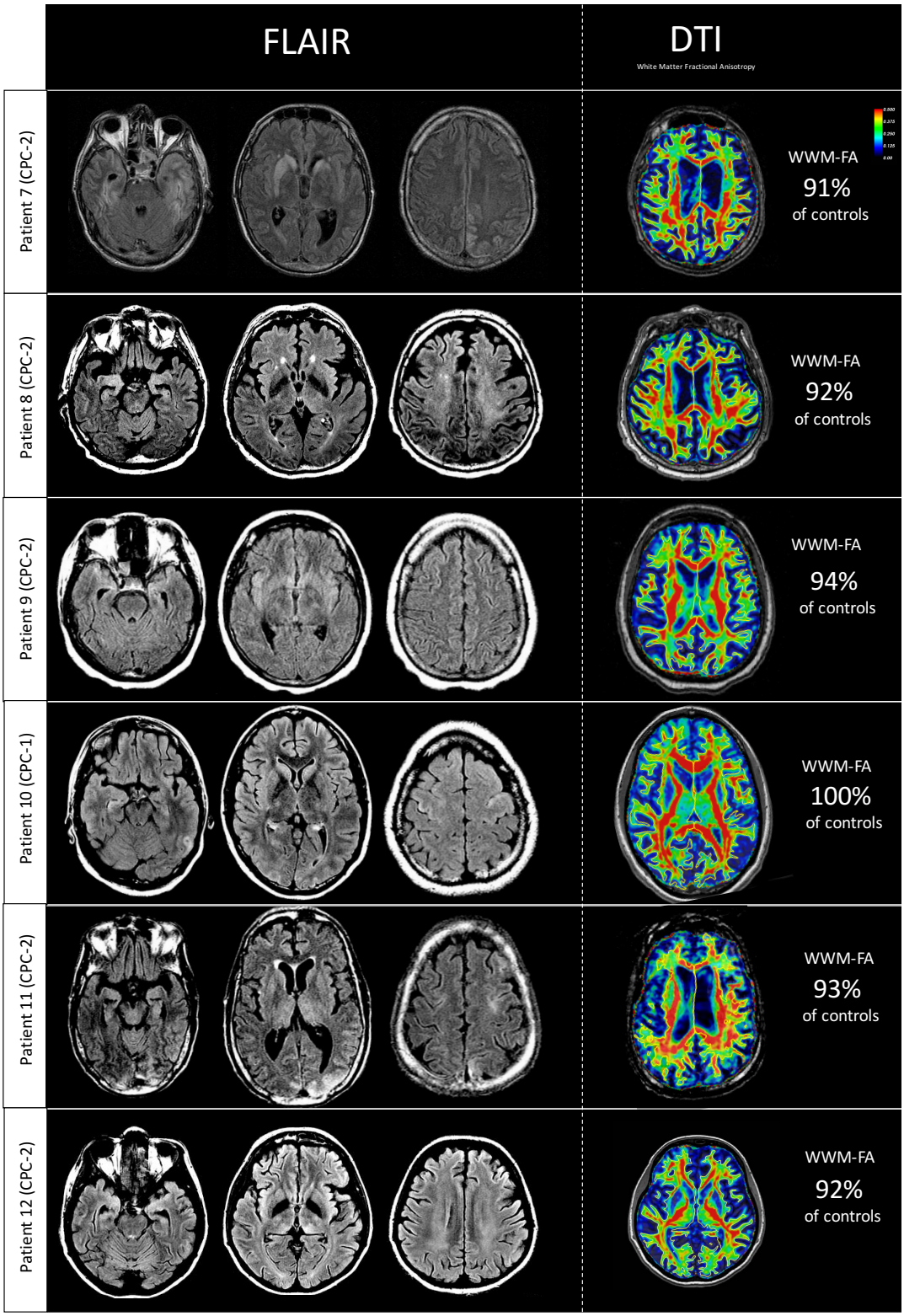

FLAIR
DTI
White Matter Fractional Anisotropy
Patient 7 (CPC-2)
WWM-FA
91%
of controls
Patient 8 (CPC-2)
WWM-FA
92%
of controls
Patient 9 (CPC-2)
WWM-FA
94%
of controls
Patient 10 (CPC-1)
WWM-FA
100%
of controls
Patient 11 (CPC-2)
WWM-FA
93%
of controls
Patient 12 (CPC-2)
WWM-FA
92%
of controls

Table S1: Acquisition parameters for each MR scanner

Radiologic center	Center number Location	CENTER 2 Marseille, France		CENTER 29 Paris, France		CENTER 28 Paris, France	CENTER 1 Paris, France			CENTER 11 Liege, Belgium	CENTER 16 Monza, Italia	CENTER 30 Clermont-Ferrand, France	CENTER 10 Bordeaux, France	CENTER 08 Rouen, France		CENTER 35 Toulouse, France
MR Scanner	Manufacter	Siemens	Siemens	GE Medical Systems	GE Medical Systems	GE Medical Systems	GE Medical Systems	GE Medical Systems	GE Medical Systems	Siemens	Philips Medical Systems	GE Medical Systems	Philips Medical Systems	Siemens	Siemens	Philips Medical Systems
	Model	Aera	Skyra	Signa HDxt	Signa HDxt	Optima MR450w	Signa HDx	Signa EXCITE	Genesis Signa	TrioTim	Achieva	Discovery MR750	Achieva	SymphonyTim	Avanto	Achieva
	Software version	syngo MR D13	syngo MR D13	HD23.0_V01_1210.a	15.0_M4_0910.a	DV23.1_V02_1317.c	14.0_M5_0737.f	11.1_M4_0818.a	11	syngo MR B15	2.6.3.6	DV22.0_V02_1122.a	2.6.3.1	syngo MR B13	syngo MR B17	3.2.2.0
	Head coils (elements)	Head Matrix Coil (12)	Head Matrix Coil (12)	8ch HR BRAIN (8)	8ch HR BRAIN (8)	Head coil (24)	8ch HR BRAIN (8)	Head coil (8)	Head coil (8)	Body coil (6)	SENSE-Head coil (8)	HNS-Head coil (29)	SENSE-head coil (8)	Head Matrix Coil (12)	Head Matrix Coil (12)	SENSE-head coil (32)
	Magnetic Field Strength (tesla)	1.5	3	3	3	1.5	3	1.5	1.5	3	1.5	3	1.5	1.5	1.5	3
T1 3D	Orientation plane (type)	Axial	Axial	Sagital	Axial	Axial	Axial	Axial	Axial	Axial	Sagital	Sagital	Axial	Axial	Axial	Sagital
	Slices (n)	160	160	146	154	528	154	156	124	120	175	176	150	384	384	170
	Thickness (mm)	1	1	1.2	1.2	1,2	1.2	1	1,2	1.2	1	1	1	1	1	1
	Number of averages (n)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	TR/TE/TI (ms)	1880/2.62/1100	1900/2.49/993	7.14/3.09/380	7.124/3.1/380	9.14/4.3/25	7.224/3.1/380	10.5/2.2/600	10.5/2.2/600	2300/2.47/900	25/3,803/0	8.16/3.18/400	7.37/3.6/0	2120/4.1/1100	2120/4.07/1100	8.33/3.86/0
	Bandwidth (Hz)	160	180	122	122	97	122	97	97	220	192	244	207	159	159	191
	Matrix	256 x 256	256 x 256	288 x 224	288 x 224	320 x 224	288 x 224	256 x 256	256 x 256	256 x 240	240 x 240	256 x 256	256 x 256	320 x 220	320 x 220	232 x 232
	FOV (cm)	25 x 25	25 x 25	14 x 11	14 x 11	15 x 11	14 x 11	24 x 24	24 x 24	26 x 24	23 x 23	26 x 26	26 x 26	32 x 22	32 x 22	21 x 21
	Flip angle (°)	15	9	15	15	15	15	10	10	9	30	11	8	15	15	8
T2	Orientation plane	Axial	Axial	Sagital	Axial	Axial	Axial	Axial	Axial	Coronal	Axial	Axial	Axial	Axial	Axial	Axial
	Slices (n)	30	32	392	61	45	61	45	40	25	46	40	40	46	46	40
	Thickness (mm)	4	4	1	2	3	2	3	3	5	2	2	3	3	3	3
	Number of averages (n)	1	1	1	3	2	3	2	3	1	6	1	4	2	2	4
	TR/TE (ms)	7130/126	5700/84	2500/69.6	6340/98	3340/105.5	6340/98	3340/105.5	3320/103.6	6000/91	4633/100	6462/105.6	4857/100	5850/130/0	5850/130	4857/100
	Bandwidth (Hz)	190	225	244	195	122	195	122	122	200	330	195	212	195	195	212
	Matrix	384 x 243	448 x 273	256 x 256	512 x 288	256 x 256	512 x 288	256 x 256	256 x 256	320 x 320	256 x 273	512 x 320	256 x 203	256 x 192	256 x 192	256 x 203
	FOV (cm)	19 x 23	19 x 23	13 x 13	28 x 16	12 x 12	28 x 16	12 x 12	12 x 12	22 x 22	10 x 11	24 x 15	11 x 9	24 x 18	24 x 18	11 x 9
	Flip angle (°)	160	150	90	90	90	90	90	90	120	90	90	90	180	180	90
T2 GRE or SWI	Orientation plane (type)	Axial (GRE)	Axial (GRE)	Axial (SWI)	Axial (GRE)	Axial (GRE)	Axial (GRE)	Axial (GRE)	Axial (GRE)	Axial (GRE)	Axial (GRE)	Axial (SWI)	Axial (GRE)	Axial (GRE)	Axial (GRE)	Axial (GRE)
	Slices (n)	25	36	112	30	30	30	29	28	20	22	108	25	31	31	24
	Thickness (mm)	5	4	2.6	5	5	5	5	5	5	5	3	5	5	5	4
	Number of averages (n)	1	1	0.69	1	1	1	1	1	1	2	0.7	2	1	1	1
	TR/TE (ms)	520/13.6	500/9	47.3/25	782.5/12.6	778/12.6	778/12.6	300/15	500/15	700/6	707.8/23	40.6/25	755/23	1090/26/0	1090/26	721.92/16
	Bandwidth (Hz)	100	250	244	162	162	162	97	122	400	109	244	109	80	80	217
	Matrix	320 x 168	320 x 173	320 x 224	320 x 200	320 x 200	320 x 200	256 x 256	256 x 256	448 x 350	256 x 205	320 x 256	224 x 146	256 x 192	256 x 192	232 x 184
	FOV (cm)	18 x 24	16 x 22	13 x 9	15 x 9	15 x 9	15 x 9	24 x 24	24 x 24	20 x 16	23 x 18	15 x 12	20 x 13	12 x 9	12 x 9	10 x 8
	Flip angle (°)	20	20	20	20	20	20	30	30	20	18	15	18	15	15	18
T2 FLAIR	Orientation plane	Axial	Axial	Axial	Axial	Sagital	Axial	Axial	Axial	Axial	Axial	Axial	Axial	Axial	Axial	Sagital
	Slices (n)	30	46	45	30	240	27	28	24	176	22	46	25	31	31	160
	Thickness (mm)	4	4	3	5	1.4	5	5	5	1	5	3	5	5	5	2
	Number of averages (n)	1	1	1	1	1	1	0.5	0.5	2	1	1	2	1	1	1
	TR/TE/TI (ms)	900/78/2500	8370/104	9000/152.5/2250	9002/152.74/2250	8000/158.36/2187	9002/154.5/2250	10002/145.1/2200	10004/159.5/2200	6000/388/2100	6000/100/2000	11000/141.9/2350	11000/140/2800	8000/112/2200	8000/112/2200	8000/343.79/2400
	Bandwidth (Hz)	180	225	139	139	122	139	97	244	750	563	139	226	195	195	486
	Matrix	320 x 168	320 x 230	352 x 224	352 x 224	224 x 224	352 x 224	320 x 192	320 x 192	256 x 258	240 x 186	320 x 320	256 x 160	256 x 192	256 x 192	240 x240
	FOV (cm)	17 x 23	17 x 24	16 x 10	16 x 10	12 x 12	16 x 10	15 x 9	30 x 18	25 x 25	21 x 17	15 x 15	23 x 14	12 x 9	12 x 9	24 x 24
	Flip angle (°)	150	150	90	90	90	90	90	90	160	90	90	90	150	150	90
DTI	Orientation plane	Axial	Axial	Axial	Axial Axial	Axial	Axial Axial	Axial Axial	Axial	Axial Axial	Axial	Axial	Axial	Axial	Axial	Axial
	Slices (n)	3720	4680	2856	2550 637	648	2601 572	564 564 648	480	2835 5980	2040	2915	2040	2444	2444	3230
	Gradient directions (n)	30	64	50	50 12	30	50 12	11 11 23	23	20 64	32	50	32	12	12	30
	Baseline scans at b = 0	2	1	2	1 1	2	1 1	1 1 1	1	3 2	1	3	1	4	4	3
	B-value (s/mm2)	1000	1000	1000	1000 1000	1000	1000 1000	900 900 700	700	1000 1000	1000	1000	1000	900	900	1000
	Thickness (mm)	2,2	2	2.5	2.5 3	2.5	2.5 3	3 3 5	3	3 3	2	2.5	2	3	3	2
	Number of averages (n)	1	1	1	1 1	1	1 1	4 4 2	5	1 1	1	2	1	1	1	2
	TR/TE (ms)	9200/82	9800/82	14000/85	14000/85 1400/81.9	12000/94.7	14000/74.5 12000/73,1	13000/81 13000/85.9	8000/79,5 8000/84.9	5700/87 5700/87	15395/60	6000/78	15395/60	8400/120/0	8400/120	7000/77
	Bandwidth (Hz)	1470	1030	1953	1953 1953	1953	1953 1953	1953 1953 1953	882	1500 1500	2100	1953	2100	179	179	2438
	Matrix	100 x 100	128 x 128	128 x 128	128 x 128 128 x 128	128 x 96	128 x 128 96 x 96	96 x 96 96 x 96	128 x 128 128 x 128	128 x 128 128 x 128	128 x 128	96 x 96	128 x 128	96 x 96	96 x 96	112 x 109
	FOV (cm)	18 x 18	23 x23	14 x 14	14 x 14 14 x14	14 x 10	13 x 13 11 x 11	10 x 10 10 x 10 16 x 16	16 x16	23 x 23 23 x 23	24 x 24	9 x 9	24 x 24	5 x 5	5 x 5	22 x 22
	Flip angle (°)	90	90	90	90 90	90	90 90	90 90 90	90	90 90	90	90	90	90	90	90

DTI denotes Diffusion Tensor Imaging; FLAIR, Fluid-Attenuated Inversion Recovery; FOV, Field Of View; GRE, Gradient-Recalled Echo; SWI, Susceptibility-Weighted Imaging; MR, Magnetic Resonance

Table S2: Diffusion tensor imaging healthy volunteer results for each MR scanner

	Healthy volunteers (N=131)	Fractional Anisotropy (FA)			average Diffusion Coefficient (aDC)		
		Whole Brain	Whole White Matter	Whole Gray Matter	Whole Brain	Whole White Matter	Whole Gray Matter
					$10^{-4}\ mm^2/s$		
CENTER 01 (GE-Signa EXCITE; 1.5 Tesla) 11 Directions Te 81	5	0.251±0.010	0.362±0.015	0.142±0.005	8.01±0.29	7.25±0.24	8.75±0.41
CENTER 01 (GE-Signa EXCITE; 1.5 Tesla) 11 Directions Te 85.9	7	0.250±0.014	0.369±0.016	0.140±0.020	9.11±0.37	8.10±0.09	10.05±0.71
CENTER 01 (GE-Signa EXCITE; 1.5 Tesla) 23 Directions Te 79.5	5	0.243±0.005	0.337±0.006	0.152±0.011	8.43±0.16	7.58±0.10	9.26±0.40
CENTER 01 (GE-Genesis Signa; 1.5 Tesla) 23 Directions Te 84.9	10	0.226±0.015	0.317±0.19	0.137±0.11	9.24±0.36	8.37±0.25	10.04±0.45
CENTER 01 (GE-Signa HDx; 3 Tesla) 50 Directions Te 74.5	5	0.292±0.013	0.423±0.014	0.174±0.006	8.61±0.26	8.08±0.17	9.09±0.34
CENTER 01 (GE-Signa HDx; 3 Tesla) 12 Directions Te 73.1	5	0.269±0.015	0.387±0.018	0.162±0.008	8.65±0.33	7.99±0.19	9.25±0.45
CENTRE 02 (Siemens-Aera; 1.5 Tesla) 30 Directions	5	0.253±0.005	0.369±0.008	0.142±0.003	8.52±0.24	7.90±0.22	9.08±0.26
CENTRE 02 (Siemens-Skyra; 3 Tesla) 64 Directions	9	0.270±0.010	0.392±0.016	0.142±0.006	8.60±0.34	7.72±0.29	9.51±0.42
CENTER 08 (Siemens-Avanto; 1.5 Tesla) 12 Directions	5	0.271±0.009	0.381±0.009	0.158±0.010	9.10±0.09	7.87±0.17	10.35±0.16

CENTER 08 (Siemens-Symphonytim; 1.5 Tesla) 12 Directions	7	0.291±0.011	0.401±0.12	0.187±0.10	8.91±0.25	7.73±0.22	10.00±0.32
CENTER 10 (Philips-Achieva; 1.5 Tesla) 32 Directions	7	0.260±0.016	0.348±0.028	0.164±0.008	8.73±0.32	8.07±0.32	9.41±0.34
CENTER 11 (Siemens-TrioTim; 3 Tesla) 20 Directions	5	0.279±0.008	0.398±0.010	0.154±0.014	8.40±0.27	7.49±0.27	9.37±0.33
CENTER 11 (Siemens-TrioTim; 3 Tesla) 64 Directions	9	0.267±0.018	0.380±0.030	0.146±0.007	8.36±0.36	7.63±0.32	9.15±0.47
CENTER 16 (Philips-Achieva; 1.5 Tesla) 32 Directions	6	0.276±0.009	0.393±0.105	0.170±0.004	8.42±0.20	7.79±0.13	8.98±0.27
CENTRE 28 (GE-Optima MR450w; 3 Tesla) 30 Directions Te 94	5	0.269±0.015	0.387±0.108	0.162±0.008	8.65±0.33	7.99±0.19	9.25±0.45
CENTRE 29 (GE-Signa HDxt; 3 Tesla) 12 Directions Te 81.9	5	0.238±0.015	0.357±0.007	0.124±0.005	8.95±0.15	8.25±0.18	9.64±0.16
CENTER 29 (GE-Signa HDxt; 3 Tesla) 50 Directions Te 85	16	0.274±0.009	0.403±0.012	0.149±0.007	8.90±0.24	8.20±0.22	9.57±0.38
CENTER 30 (GE-Discovery MR750; 3 Tesla) 50 Directions	9	0.253±0.010	0.384±0.10	0.135±0.008	8.93±0.53	7.99±0.32	9.79±0.77
CENTER 35 (Philips-Achieva; 3 Tesla) 30 Directions	6	0.300±0.004	0.434±0.005	0.174±0.005	8.18±0.17	7.45±0.10	8.82±0.22

GE, General Electric.
Results are means ±SD.

Table S3: Outcomes in the derivation and validation cohorts

	Developmental cohort			Validation cohort		
	All patients	**Favorable outcome (CPC 1-2)**	**Unfavorable outcome (CPC 3-5)**	**All patients**	**Favorable outcome (CPC 1-2)**	**Unfavorable outcome (CPC 3-5)**
	(N = 150)	(N = 33)	(N = 117)	(N = 50)	(N = 11)	(N = 39)
Variables						
Best numerical, Cerebral Performance Categories (CPC) during trial						
Category — no. (%)						
1	12 (24)	12 (36)	0 (0)	1 (2)	1 (9)	0 (0)
2	21 (14)	21 (64)	0 (0)	10 (20)	10 (91)	0 (0)
3	11 (7)	0 (0)	11 (9)	7 (14)	0 (0)	7 (18)
4	106 (76)	0 (0)	106 (91)	32 (64)	0 (0)	32 (82)
5	NA	NA	NA	NA	NA	NA
CPC at follow-up*						
Category — no. (%)						
1	12 (8)	12 (36)	0 (0)	1 (2)	1 (9)	0 (0)
2	16 (11)	16 (49)	0 (0)	9 (18)	9 (82)	0 (0)
3	6 (4)	1 (3)	5 (4)	6 (12)	0 (0)	6 (15)
4	10 (7)	0 (0)	10 (9)	4 (8)	0 (0)	4 (10)
5	106 (71)	4 (12)	102 (87)	30 (60)	1 (9)	29 (75)
Modified Rankin scale score at follow-up*						
Score — no. (%)						
0	2 (1)	2 (6)	0 (0)	1 (2)	1 (9)	0 (0)
1	8 (5)	8 (24)	0 (0)	0 (0)	0 (0)	0 (0)

2	6 (4)	6 (18)	0 (0)	8 (16)	8 (73)	0 (0)
3	12 (8)	12 (36)	0 (0)	1 (2)	1 (9)	0 (0)
4	4 (3)	1 (3)	3 (3)	6 (12)	0 (0)	6 (15)
5	12 (8)	0 (0)	12 (10)	4 (8)	0 (0)	4 (10)
6	106 (71)	4 (12)	102 (87)	30 (60)	1 (9)	29 (75)
Cause of death — no. (%)						
Brain death	6 (4)	0 (0)	6 (5)	1 (2)	0 (0)	1 (3)
Cerebral	64 (43)	0 (0)	64 (56)	34 (68)	0 (0)	34 (89)
Cardiovascular	5 (3)	1 (3)	5 (4)	2 (4)	0 (0)	2 (5)
Respiratory	14 (9)	1 (3)	14 (12)	1 (2)	0 (0)	1 (3)
Multiple organ dysfunction syndrome	5 (3)	1 (3)	5 (4)	1 (2)	0 (0)	1 (3)
Other or undetermined	8 (5) †	1 (3)	8 (7) †	1 (2) †	1 (9) †	0 (0)
Time of survival if dead						
Median		62	19		128	19
Interquartile range		47-89	13-32		128-128	16-45

The neurologic follow-up was specified in the protocol to be at 180±14 days, but the time to follow-up was in some cases several weeks longer for logistic reasons. † Cause of death missing in four cases in the derivation cohort and in one case in the validation cohort.

Table S4: Reasons for withdrawal or limitation of life sustaining therapy in the derivation cohort †

	All (N=150)	Favorable outcome (CPC 1-2) (N=33)	Unfavorable outcome (CPC 3-5) (N=117)
Total no. of WLLST	72	2	70
Brain dead	6	0	6
Neurological reasons	66	2	64
MOF and hemodynamic failure	0	0	25
Comorbidity	17	1	16
Ethical reason	6	1	5

WLLST denotes withdrawal or limitation of life sustaining therapy of any reason.
†More than one reason could be registered for each patient. MOF denotes multi organ failure. Brain death was defined as having fulfilled criteria of brain death as per individual countries legislation. Neurological reasons were as defined in the trial protocol and above in this document.

Table S5: Criteria of poor outcome fulfilled or not by the 33 patients with favourable outcome.

	Motor response <3 at day 7	No pupillary or corneal reflexes	High NSE or S100B levels †	Status myoclonus	Unreactive burst-suppression on EEG	Status epilepticus on EEG	Diffuse anoxic injury on MRI
Patient 1	-	-		-	-	-	-
Patient 2	-	-		-	-	-	-
Patient 3	-	-		-			-
Patient 4	+	-	-	-			-
Patient 5	+	-		-	-	-	-
Patient 6	-	-		-	-	-	-
Patient 7	-	-		-	-	-	-
Patient 8	-	-		-	-	-	-
Patient 9	+	-	-	-	+	-	-
Patient 10	+	-		-	-	-	-
Patient 11	-	-	-	-	-	-	-
Patient 12	-	-		-	-	-	-
Patient 13	+	-		-	-	-	-
Patient 14	+	-		-	-	-	-
Patient 15	+	-		-	-	-	-
Patient 16	-	-	-	-	-	-	-
Patient 17	-	-		-			-
Patient 18	-	-	+ (S100B)	-	-	-	+
Patient 19	+	-		-	-	-	-
Patient 20	-	-	-	-	-	-	-
Patient 21	-	-	-	-			-
Patient 22	-	-	-	-	-	-	+
Patient 23	-	-		-			+
Patient 24	-	-		-	-	-	-
Patient 25	+	-		-	-	+	+
Patient 26	-	-		-	-	-	+
Patient 27	-	-		-	-	-	+
Patient 28	+	-	+ (NSE)	-	-	-	+
Patient 29	-	-	-	-	-	-	+
Patient 30	+	-		-	-	-	+
Patient 31	-	-	-	-	-	-	+
Patient 32	+	-	+ (S100B)	-	-	-	+
Patient 33	+	+		-			+

EEG denotes electroencephalography; MRI, magnetic resonance imaging; NSE, neuron specific enolase and S100B, protein S-100B. ''+'' indicates the criterion was present, "-" it was absent and a blank cell indicates the test was not performed. † Only high NSE levels are considered as a biological criterion of poor outcome according to the ERC/ESICM guidelines[9]

Table S6: Prognostic values of significant variables of the patients without a limitation or withdrawal of care decision in the derivation cohort

Variables	ROC_{AUC} *(95% Confidence Interval)*	Optimal cutoff	Specificity	Sensitivity	Predictive Positive Value	Negative Predictive Value
			Expressed in percent (95% Confidence Interval)			
Clinical and electroencephalography (EEG) variables						
OHCA score	0.57 (0.41–0.74)†	≥58	100 (87–100)	8 (1–27)‡	100 (16–100)	54 (39–69)
EEG Synek classification	0.76 (0.65–0.87)†	≥5	100 (85–100)	4 (1–15)‡	100 (16–100)	33 (22–46)
Qualitative Magnetic Resonance Imaging (MRI) variables						
FLAIR-DWI overall score	0.81 (0.72–0.90)†	≥42	100 (89–100)	38 (25–53)‡	100 (82–100)	50 (37–63)
FLAIR-DWI cortex score	0.73 (0.62–0.84)†	≥30	100 (89–100)	34 (21–49)‡	100 (80–100)	48 (36–61)
FLAIR-DWI cortex + deep gray nuclei score	0.78 (0.68–0.88)†	≥42	100 (89–100)	34 (21–49)‡	100 (80–100)	48 (36–61)
Quantitative MRI variables						
Whole white matter FA	0.96 (0.92–1.00)	<0.91	100 (89–100)	88 (76–96)	100 (92–100)	84 (68–94)
Whole brain FA	0.94 (0.88–0.99)	<0.91	100 (89–100)	78 (65–89)	100 (91–100)	74 (58–86)
NAA/Cr Thalami	0.85 (0.75–0.94)†	<0.9	100 (86–100)	32 (18–50)‡	100 (74–100)	50 (36–64)
NAA/Cr Pons	0.77 (0.64–0.89)†	<1.6	100 (83–100)	23 (11–39)‡	100 (66–100)	40 (26–55)
Combination of (Multivariate models)						
Standard criteria– OHCA score – EEG Synek classification	0.84 (0.74–0.94)†	-	100 (85–100)	4 (1–15)‡	100 (16–100)	33 (22–46)
Standard criteria – OHCA score – EEG Synek classification – qualitative MRI	0.84 (0.74–0.94)†	-	100 (85–100)	54 (39–61)‡	100 (86–100)	51 (35–67)
Standard criteria – OHCA score – EEG Synek classification – qualitative MRI – quantitative MRI	0.99 (0.98–1.00)	-	100 (85–100)	93 (82–99)	100 (92–100)	88 (69–97)

ROC_{AUC} denotes area under the receiver operating characteristic curve; DWI, Diffusion Weighted Imaging; FA, Fractional Anisotropy; FLAIR, Fluid-Attenuated Inversion Recovery and NAA/Cr, N-acetyl aspartate over creatinine ratios. OHCA score calculation, FLAIR-DWI scoring system and EEG Synek classification are described in additional files 2, 3 and 4 of the Supplementary Appendix, respectively. † ROC_{AUC} significantly different than the one of the WWM-FA ($P<0.05$). ‡ Sensitivity significantly different than the one of the WWM- FA *(*$P<0.05$).

Table S7: Multivariate analysis in the derivation cohort

		Multivariate logistic regression			
	Unit (UI)	Estimated Coefficient	Standard Error	Odds Ratio *(95% Confidence Interval)*	P Value
Standard criteria – OHCA score – EEG variables					
Motor response no better than extensor day MRI	Absent vs. Present	2.05	0.61	7.8 (2.5–29.5)	<0.001
EEG Synek classification	Per UI increase	1.23	0.40	3.4 (1.6–8.1)	0.002
Standard criteria – OHCA score – EEG variables – qualitative MRI					
Motor response no better than extensor day MRI	Absent vs. Present	1.91	0.65	6.7 (2.0–27.5)	0.003
EEG Synek classification	Per UI increase	0.85	0.43	2.3 (1.1–5.8)	0.047
FLAIR-DWI overall score	Per UI increase	0.07	0.03	1.1 (1.0–1.2)	0.007
Standard criteria – OHCA score – EEG variables – qualitative MRI – quantitative MRI					
Motor response no better than extensor day MRI	Absent vs. Present	2.18	1.37	8.8 (1.2–241.3)	0.111
EEG Synek classification	Per UI increase	1.24	0.94	3.5 (1.6–29.4)	0.002
FLAIR-DWI overall score	Per UI increase	0.15	0.06	1.2 (1.1–1.3)	0.014
NAA/Cr Pons	Per 0.1 UI decrease	0.37	0.14	1.4 (1.1–2.3)	0.048
Whole white matter FA	Per 0.01 UI decrease	0.55	0.20	1.7 (1.3–2.9)	0.005

DWI denotes Diffusion Weighted Imaging; FA, Fractional Anisotropy; and FLAIR, Fluid-Attenuated Inversion Recovery. OHCA score calculation, FLAIR-DWI scoring system and EEG Synek classification are described in additional files 2, 3 and 4 of the Supplementary Appendix, respectively.

Table S8: Multivariate analysis of the patients without withdrawal or limitation of life sustaining therapy in the derivation cohort

		Multivariate logistic regression			
		Estimated	Standard	Odds Ratio	
	Unit (UI)	Coefficient	Error	*(95% Confidence Interval)*	P Value
Standard criteria – OHCA score – electroencephalography (EEG) variables					
Motor response no better than extensor day MRI	Absent vs. Present	1.77	0.68	5.9 (1.6–25.0)	0.009
EEG Synek classification	Per 1 UI increase	1.35	0.52	3.8 (1.5–12.1)	0.010
Standard criteria – OHCA score – EEG variables – qualitative MRI					
Motor response no better than extensor day MRI	Absent vs. Present	2.08	0.80	8.0 (1.8–45.1)	0.009
EEG Synek classification	Per UI increase	1.40	0.58	4.1 (1.4–14.7)	0.016
FLAIR-DWI interpretation: hyperintensity in deep grey nuclei	Yes vs. No	2.30	0.77	10.0 (2.4–53.4)	0.002
Standard criteria – OHCA score – EEG variables – qualitative MRI – quantitative MRI					
EEG Synek classification	Per UI increase	5.51	2.38	246.1 (9.3–231274.3)	0.021
Whole white matter FA	Per 0.01 UI decrease	1.38	0.63	4.0 (1.8–27.7)	0.029

*DWI, diffusion weighted imaging; FA, fractional anisotropy and FLAIR, fluid-attenuated inversion recovery. OHCA score calculation, FLAIR-DWI scoring system and EEG Synek classification are described in additional files 2, 3 and 4 of the Supplementary Appendix, respectively.

SUPPLEMENTARY ADDITIONAL FILES

Additional file 1: Glasgow Coma Scale (GCS)[10]

	Score
Eyes	
Spontaneous opening	4
Open in response to sound	3
Open in response to pressure	2
None	1
Verbal	
Orientated	5
Confused	4
Inappropriate words	3
Sounds	2
None	1
Motor	
Obeys commands	6
Localizes painful stimuli	5
Normal flexion/withdrawal	4
Abnormal flexion	3
Extension	2
None	1

Additional file 2: Equation for the OHCA cardiac arrest score[11]

−13 if the initial recorded rhythm is VF or ventricular tachycardia

+6×ln (no-flow interval)*a*

+9×ln (low-flow interval)*b*

−1434/(serum creatinine)*c*

+10×ln (arterial lactate)*d*

The score is computed as sum of the five parameters.

a Natural logarithm of the no-flow interval (min), the lowest possible value being 0.5.

b Natural logarithm of the low-flow interval (min), the lowest possible value being 0.5.

c Plasma creatinine expressed in μmol per liter.

d Natural logarithm of plasma lactate (in mmol per liter) on admission.

Additional file 3: EEG pattern according to the Synek classification system[12,13]

Grade		Description
1	(optimal)	Dominant reactive alpha activity with some theta activity.
2	(benign)	Dominant theta activity, preservation of normal sleep features, and with frontal monorhythmic delta activity.
3	(uncertain)	Small amplitude, diffuse, irregular, non reactive delta activity.
4	(malignant)	Burst suppression, epileptiform discharges, and low-output nonreactive activity or Alpha/theta coma.
5	(fatal)	Isoelectric.

Additional file 4: Qualitative brain FLAIR and DWI MRI scoring system[14]

			FLAIR signal	DWI signal
Supratentorial				
Gray matter	Cortex	Frontal		
		Parietal		
		Temporal		
		Occipital		
		Insula		
		Hippocampus		
	Deep gray nuclei	Caudate		
		Putamen		
		Globus pallidus		
		Thalamus		
White matter		Frontal		
		Parietal		
		Temporal		
		Occipital		
		Corpus Callosum		
Infratentorial	Brainstem	Midbrain		
		Pons		
		Medulla		
	Cerebellum	Cortex		
		White matter		
		Dentate nuclei		
	Total			

All 21 brain regions were scored using fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) sequences according to the severity of signal abnormality on a 5-point scale:

0: no abnormality

1: possibly abnormal

2: mildly abnormal

3: moderately abnormal

4: severely abnormal

The overall score, used for analyses, consisted of all points given to all brain regions on FLAIR and DWI.

Additional file 5: Glasgow-Pittsburgh Cerebral Performance Categories (CPC)[15, 16]

Score		Description
1	(Good Cerebral Performance)	Conscious. Alert, able to work and lead a normal life. May have minor psychological or neurological deficits (mild dysphasia, non-incapacitating hemiparesis, or minor cranial nerve abnormalities).
2	(Moderate Cerebral Disability)	Conscious. Sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life (dressing, traveling by public transportation, and preparing food). May have hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory or mental changes.
3	(Severe Cerebral Disability)	Conscious. Dependent on others for daily support because of impaired brain function (in an institution or at home with exceptional family effort). At least limited cognition. Includes a wide range of cerebral abnormalities from ambulatory with severe memory disturbance or dementia precluding independent existence to paralytic and able to communicate only with eyes, as in the locked-in syndrome.
4	(Coma, Vegetative State)	Not conscious. Unaware of surroundings, no cognition. No verbal or psychological interactions with environment.
5	(Death)	Certified brain dead or dead by traditional criteria.

Additional file 6: Modified Rankin Scale[17, 18]

Score	Description
0	No symptoms at all.
1	No significant disability despite symptoms; able to carry out all usual duties and activities.
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance.
3	Moderate disability; requiring some help, but able to walk without assistance.
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention.
6	Dead.

Additional file 7: Fazekas visual scale score[19]

Periventricular white matter

0: Absence

1: “Caps” or “pencil lining”

2: Smooth “halo”

3: Irregular periventricular hyper-intensity extending into deep white matter

Deep white matter

0: Absence

1: Punctate foci

2: Beginning confluence of foci

3: Large confluent areas

REFERENCES

1. Luyt CE, Galanaud D, Perlbarg V, et al. Diffusion tensor imaging to predict long-term outcome after cardiac arrest: a bicentric pilot study. *Anesthesiology* 2012; **117**:1311-21.
2. van der Eerden AW, Khalilzadeh O, Perlbarg V, et al. White matter changes in comatose survivors of anoxic ischemic encephalopathy and traumatic brain injury: comparative diffusion-tensor imaging study. *Radiology* 2014; **270**:506-16.
3. Smith SM, Zhang Y, Jenkinson M, et al. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *Neuroimage* 2002; **17**:479-89.
4. Basser PJ, Mattiello J, LeBihan D. Estimation of the effective self-diffusion tensor from the NMR spin echo. *J Magn Reson B* 1994;**103**:247-54.
5. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 2004; **23** Suppl 1:S208-S219.
6. Modat M, Ridgway GR, Taylor ZA, et al. Fast free-form deformation using graphics processing units. *Comput Methods Programs Biomed* 2010; **98**:278-84.
7. Dale, A.M., Fischl, B., Sereno, M.I., Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* 1999; **9**:179-94.
8. Hosmer DW, Jr., Lemeshow S, Sturdivant RX. Applied Logistic Regression. 3rd Edition ed. Hoboken, NJ, USA: John Wiley & Sons; 2013.
9. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. *Intensive care medicine* 2015; **41**: 2039-56.
10. Teasdale G, Gentleman D. The description of 'conscious level': a case for the Glasgow Coma Scale. *Scott Med J* 1982; **27**:7-9.
11. Adrie C, Cariou A, Mourvillier B, et al. Predicting survival with good neurological recovery at hospital admission after successful resuscitation of out-of-hospital cardiac arrest: the OHCA score. *Eur Heart J* 2006; **27**:2840-5.
12. Synek VM. EEG abnormality grades and subdivisions of prognostic importance in traumatic and anoxic coma in adults. *Clin Electroencephalogr* 1988; **19**:160-6.
13. Synek VM. Prognostically important EEG coma patterns in diffuse anoxic and traumatic encephalopathies in adults. *J Clin Neurophysiol;* 1988; **5**:161-74.
14. Hirsch KG, Mlynash M, Jansen S, et al. Prognostic value of a qualitative brain MRI scoring system after cardiac arrest. *J Neuroimaging* 2015; **25**:430-7.
15. Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. Brain Resuscitation Clinical Trial I Study Group. *N Engl J Med* 1986; **314**:397-403.
16. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet* 1975; **1**:480-4.
17. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. *Prognosis. Scott Med J* 1957; **2**:200-15.
18. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van GJ. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988; **19**:604-7.
18. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol* 1987; **149**:351-6.