DEVELOPMENT OF BIOMARKERS OF CEREBRAL CONNECTIVITY ASSESSED BY MAGNETIC RESONANCE DURING RECOVERY AND REHABILITATION OF PATIENTS WITH CEREBRAL INFARCTION

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*The coordinating investigator and the research centre of this project proposed to the Board of the Fundació La Marató de TV3 to waive the funding of two years of one of the co-ordinated subprojects and to adapt the work plan, without prejudice to the research. At the meeting of the Board held on 27 May 2021 it was agreed to amend the original sum.

1. Abstract

Approximately 33% of patients die and 33% have persistent disability after stroke, placing a burden on society. The mechanisms involved in recovery of function are not well understood. Both structural and functional brain reorganization contribute to recovery and are enhanced by rehabilitation, a complex programme of interacting therapies that promote recovery and independence. Conclusive data to define the optimal intensity of training strategies are lacking. MRI techniques have revolutionized our understanding of connectivity: diffusion tensor imaging (DTI) reveals the macro- and micro-structure of the brain, and functional MRI (fMRI) shows specific cognitive and behavioral networks. Pre-existing functional/structural connections and the impact of lesion onto them are the most important determinants of outcome. The primary objective was to determine the value of MRI markers of brain connectivity (MRI-BBC) in predicting stroke patients' functional outcomes after rehabilitation. Secondary objectives were (S1) to determine whether combining MRI-BBC and clinical scores can predict functional outcomes better than either approach alone and (S2) whether MRI-BBC can identify patients who will respond better to higher rehabilitation intensities. We designed a prospective observational cohort of 82 consecutive patients with moderate-to-severe acute stroke. MRI examinations were done using 1.5T or 3T scanners; anatomical sequences, DTI, and resting state-fMRI will be acquired. Several clinical scales will provide comprehensive information about biological, psychological, and social factors through the evaluation of motor function, emotional state, cognitive status, and ability to perform activities of daily living at admission and 6-month follow-up. Fifty-one patients received standard rehabilitation treatment (i.e. physiotherapy, occupational therapy, and speech therapy sessions aimed at treating specific deficits). As a pilot study, 31 patients received intense rehabilitation (≥3hours/day) in an inpatient rehabilitation facilities scenario. After imaging preprocessing, we used a whole-brain mask to calculate the correlation coefficient matrices for every paired region using the Harvard-Oxford probabilistic atlas. To evaluate functional outcome, we applied the modified Rankin Scale at 90 days. We used region of interest analyses to explore the functional connectivity between regions and graph-computation analysis to detect differences in functional connectivity between patients with good functional outcome (modified Rankin Scale score, mRS ≤2) and those with poor outcome (mRS>2). Structural connectivity alterations were assessed using TBSS (Tract-Based Spatial Statistics) to detect differences in fractional anisotropy (FA) values in the white

matter tracts. We found that patients with good outcome had greater functional connectivity than patients with poor outcome. Higher values in FA mean values were demonstrated in patients with good outcome. Although mRS at discharge and baseline National Institutes of Health Stroke Scale score was the most accurate independent predictor of 90-day mRS, adding structural and functional connectivity increased accuracy to 96%. Preserved bilateral interhemispheric connectivity had greater impact in favoring good prognosis.

2. Results

Figure 1. Lesion topography for the cohort of patients with standard rehabilitation**.**

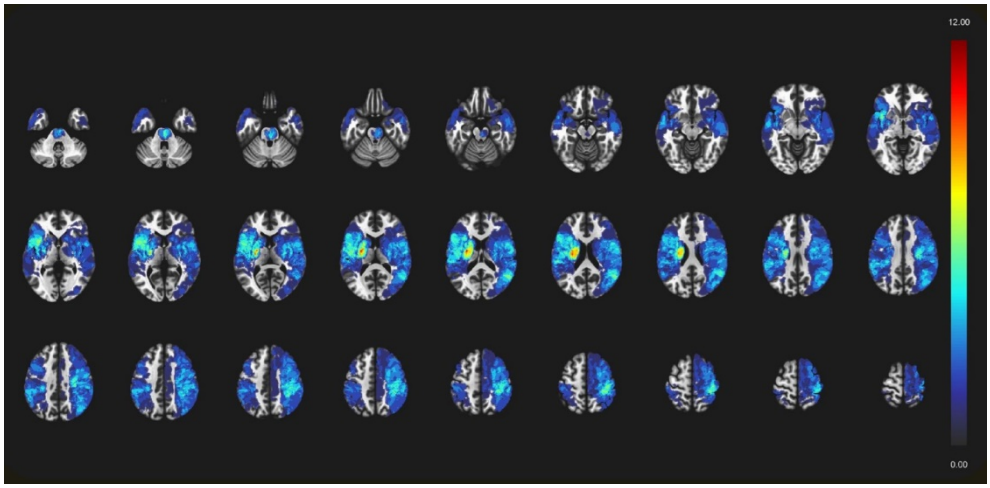


Figure 2. Lesion topography for the cohort with intensive rehabilitation.

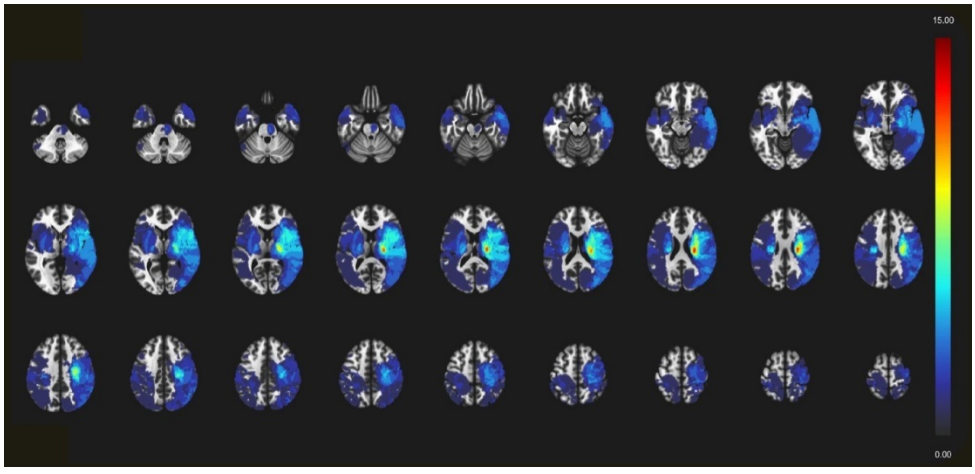


Table 1. Characteristics of both cohorts of patients treated with standard or intensive rehabilitation.

	Standard rehabilitation n=51	**Intensive rehabilitation n=31**	**p-value**
Age	64 (57.5-70)	75 (61-81)	0.012
Location of lesion			
Hemispheric	43;61.4%	27;38.6%	1.000
Cerebellum	0;0%	0;0%	
Brainstem	8;66.7%	4;33.3%	
Etiology of stroke			
Undetermined	7;46.7%	8;53.3%	0.091
Cardioembolic	21;80.8%	5;19.2%	
Atheromatosis	10;62.5%	6;37.5%	
Small vessel	13;52%	12;48%	
Laterality			
Right	22;51.2%	21;48.8%	0.081
Left	27;73%	10;27%	
Both	1;100%	0;0%	
Level of vascular occlusion			
Middle cerebral artery	43;64.2%	24;35.8%	0.343
Anterior cerebral artery	0;0%	1;100%	
Posterior cerebral artery	1;50%	1;50%	
Vertebrobasilar	7;63.6%	4;36.4%	
NIHSS score at baseline	9 (7-10)	5 (4-6)	<0.001
Infarct volume at baseline [mL]	9.77 (3.05-38.76)	2.92 (1.14-21.395)	0.805
Infarct volume at 6 months [mL]	13.825 (1.771-40.605)	2.810 (0.423-23.52)	0.580
Modified Rankin Score at discharge	4 (3-4)	4 (3-4)	0.602
Modified Rankin Score at discharge categorized			
Functionally independent	6;60%	4;40%	1.000
Functionally dependent	44;62%	27;38%	
Modified Rankin Score at 3 months	3 (2-3)	2 (1-2)	<0.001
Modified Rankin Score at 3 months categorized			
Functionally independent	24;49%	25;51%	0.003
Functionally dependent	26;81.2%	6;18.8%	
Barthel Index at 3 months	75 (46.25-90)	95 (85-100)	<0.001
Barthel Index at 3 months categorized			
Functionally independent	10;43.5%	13;56.5%	0.033
Functionally dependent	40;69%	18;31%	
Motricity Index mean value at baseline	26 (0-95)	68.5 (50.5;86.75)	0.013
Fugl-Meyer total, upper extremity at baseline	7 (0.5-60)	53 (30.5-60.5)	0.004
Fugl-Meyer total, lower extremity at baseline	17 (9.5-31)	25 (16-31)	0.071
Montreal Cognitive Assessment at baseline	10 (4-17)	21 (13-24)	<0.001
Motricity Index mean value at 3m	96 (82-99)	84.5 (76-100)	0.731
Fugl-Meyer total, upper extremity at 3m	53.5 (32.5-66)	63 (58-66)	0.099
Fugl-Meyer total, lower extremity at 3m	32 (27-34)	34 (32-34)	0.242
Montreal Cognitive Assessment at 3 months	15 (9.25-23)	25.5 (18.75-28)	<0.001
Motricity Index mean value at 6m	99 (75.5-99)	96 (84.5-100)	0.437
Fugl-Meyer total, upper extremity at 6m	52 (39-63.5)	66 (60.5-66)	0.055
Fugl-Meyer total, lower extremity at 6m	33 (30-34)	34 (31.5-34)	0.483
Montreal Cognitive Assessment at 6 months	17.5 (11.25-26)	26 (25-28.75)	<0.001

Table 2. Characteristics of the cohorts of patients according to functional outcome at 3 months.

	Standard rehabilitation n=51			**Intensive rehabilitation n=31**		
	Functionally independent (mRS 0-2)	**Functionally dependent (mRS 3-5)**	**p-value**	**Functionally independent (mRS 0-2)**	**Functionally dependent (mRS 3-5)**	**p-value**
Age	63 (57.5-79.5)	77 (65.5-82)	0.067	62 (55-68)	71 (63.5-75.5)	0.099
Location of lesion						
Hemispheric	17; 40.5	25;59.5	0.021	22;81.5%	5;18.5%	1.000
Cerebellum				0;0%	0;0%	
Brainstem	7;87.5	1; 12.5		3;75%	1;25%	
Etiology of stroke						
Undetermined	1;16.7%	5;83.3%	0.399	7;87.5%	1; 12.5%	0.925
Cardioembolic	10;46.6%	11;52.4%		4;80%	1;20%	
Atheromatosis	5;50%	5;50%		5;83.1%	16.7%	
Small vessel	8;61.5%	5;38.5%		9;75%	3;25%	
Laterality						
Right	8;36.4%	14;63.6%	0.252	18;85.7%	3;14.3%	0.358
Left	14;53.8%	12;46.2%		7:70%	3;30%	
Both	1; 100%	0;0%		0;0%	0;0%	
Level of vascular occlusion						
Middle cerebral artery	17;40.5%	25;59.5%	0.025	19;79.2%	5;20.8%	1.000
Anterior cerebral artery	0;0%	0;0%		2;100%	0;0%	
Posterior cerebral artery	1;100%	0;0%		1;100%	0;0%	
Vertebrobasilar	6;85.7%	1;14.3%		3;75%	1;25%	
NIHSS score at baseline	7 (6-9)	10 (9-11.75)	0.001	4 (4-5)	8.5 (8-11.25)	0.012
Infarct volume at baseline [mL]	11.66 (2.808-36.128)	8.62 (5.66-50.18)	0.278	2.345 (1.11-21.898)	3.63 (1.62-6.24)	0.996
Infarct volume at 6 months [mL]	2.32 (0.99-30.825)	28.13 (4.2-46.95)	0.233	2.81 (0.288-20.92)	12.09 (6.625-17.555)	0.601
Modified Rankin Score at discharge	3 (2.75-3)	4 (4-4)	<0.001	3 (3-4)	4 (4-4)	<0.001
Modified Rankin Score at discharge categorized						
Functionally independent	6;100%	0;0%	0.008	4;100%	0;0%	0.561
Functionally dependent	18;40.9%	26;59.1%		21;77.8%	6;22.2%	
Barthel Index at 3 months	92.5 (80-100)	47.5 (35-75)	<0.001	100 (90-100)	80 (76.25-80)	0.004
Barthel Index at 3 months categorized						
Functionally independent	10;100%	0;0%	<0.001	13;100%	0;0%	0.028
Functionally dependent	14;35%	26;65%		12;66.7%	6;33.3%	
Motricity Index mean value at baseline	54 (21-99)	0 (0-12.75)	0.003	75.5 (59.5-93)	18.75 (5.125-59.75)	0.033
Fugl-Meyer total, upper extremity at baseline	26 (2-63)	1.5 (0-5.5)	0.012	56 (48-62)	9.5 (4.25-37.25)	0.012
Fugl-Meyer total, lower extremity at baseline	20 (13-33)	7.5 (1.75-13)	0.004	28 (20-33)	12.5 (5.7-17-75)	0.018
Montreal Cognitive Assessment at baseline	14.5 (4-21.25)	7 (3-16)	0.231	21.5 (13-25)	20 (18-21)	0.617
Motricity Index mean value at 3m	99 (91.5-99)	61.5 (49.25-71.25)	0.135	88.25 (76-100)	79.5 (55.5-92.5)	0.323
Fugl-Meyer total, upper extremity at 3m	57 (42.5-66)	27 (9-33)	0.084	65 (60-66)	50 (8-59)	0.144
Fugl-Meyer total, lower extremity at 3m	32(29-34)	27 (25-33)	0.303	34 (32-34)	32 (29-32)	0.386
Montreal Cognitive Assessment at 3 m	18.5 (13.5-25.75)	10 (6.75-13.5)	0.015	25 (19.5-28)	26 (19-26)	0.883
Motricity Index mean value at 6m	99 (92-99)	0 (0-38)	0.114	96 (84.875-100)	70.5 (48.25-81.25)	0.285
Fugl-Meyer total, upper extremity at 6m	60.5 (47.75-64.5)	39 (23.5-39)	0.114	66 (63.5-66)	59 (33.5-62)	0.416
Fugl-Meyer total, lower extremity at 6m	33 (30.5-34)	31 (27.5-32.5)	0.544	34 (31.75-34)	34 (26-34)	0.529
Montreal Cognitive Assessment at 6 m	21 (14-27)	14 (9-21)	0.108	26 (23.5-28.5)	26 (26-27.5	0.185

Table 3. Microstructural analysis of the white matter tracts in patients treated with standard rehabilitation according to the functional outcome at 3 months using fractional anisotropy.

	Functionally independent (mRS 0-2)	**Functionally dependent (mRS 3-5)**	**p-value**
Anterior corona radiata, left	0.38; (0.35,0.43)	0.36; (0.34,0.38)	0.041
Anterior corona radiata, right	0.40; (0.34,0.44)	0.35; (0.32,0.39)	0.007
Anterior limb of internal capsule, left	0.47; (0.43,0.51)	0.44; (0.40,0.47)	0.092
Anterior limb of internal capsule, right	0.49; (0.44,0.52)	0.44; (0.40,0.47)	0.003
Body of corpus callosum	0.47; (0.44,0.49)	0.43; (0.41,0.45)	0.010
Cingulum, left	0.39; (0.36,0.41)	0.37; (0.33,0.39)	0.049
Cingulum, right	0.39; (0.35,0.43)	0.35; (0.34,0.38)	0.040
Cingulum (Hippocampus), left	0.40; (0.37,0.41)	0.37; (0.36,0.39)	0.080
Cingulum (Hippocampus), right	0.40; (0.37,0.41)	0.37; (0.36,0.40)	0.306
Cerebral peduncle, left	0.55; (0.53,0.57)	0.54; (0.53,0.56)	0.291
Cerebral peduncle, right	0.55; (0.52,0.57)	0.53; (0.50,0.54)	0.021
Corticospinal tract, left	0.53; (0.52,0.54)	0.51; (0.50,0.52)	0.034
Corticospinal tract, right	0.52; (0.50,0.53)	0.51; (0.47,0.53)	0.267
External capsule, left	0.37; (0.31,0.41)	0.33; (0.31,0.37)	0.176
External capsule, right	0.37; (0.33,0.38)	0.31; (0.30,0.35)	0.043
Fornix	0.27; (0.23,0.35)	0.25; (0.23,0.28)	0.231
Fornix / Stria terminalis, left	0.43; (0.41,0.45)	0.40; (0.38,0.43)	0.019
Fornix / Stria terminalis, right	0.40; (0.35,0.43)	0.35; (0.34,0.37)	0.060
Genu of corpus callosum	0.43; (0.38,0.46)	0.39; (0.37,0.42)	0.064
Inferior cerebellar peduncle, left	0.45; (0.43,0.46)	0.43; (0.40,0.45)	0.015
Inferior cerebellar peduncle, right	0.46; (0.44,0.47)	0.43; (0.42,0.46)	0.037
Inferior fronto-occipital fasciculus, left	0.42; (0.39,0.45)	0.40; (0.36,0.42)	0.106
Inferior fronto-occipital fasciculus, right	0.44; (0.40,0.46)	0.41; (0.35,0.42)	0.059
Middle cerebellar peduncle	0.46; (0.44,0.47)	0.43; (0.42,0.45)	0.013
Medial lemniscus, left	0.52; (0.50,0.54)	0.51; (0.49,0.53)	0.143
Medial lemniscus, right	0.52; (0.50,0.55)	0.52; (0.50,0.53)	0.289
Posterior corona radiata, left	0.44; (0.41,0.45)	0.42; (0.39,0.43)	0.009
Posterior corona radiata, right	0.43; (0.42,0.45)	0.42; (0.40,0.42)	0.002
Pontine crossing tract	0.52; (0.49,0.53)	0.51; (0.50,0.54)	0.751
Posterior limb of internal capsule, left	0.55; (0.54,0.58)	0.55; (0.51,0.56)	0.165
Posterior limb of internal capsule, right	0.55; (0.53,0.58)	0.54; (0.49,0.56)	0.029
Posterior thalamic radiation, left	0.48; (0.46,0.51)	0.45; (0.44,0.48)	0.033
Posterior thalamic radiation, right	0.49; (0.46,0.51)	0.45; (0.43,0.47)	0.012
Retrolenticular part of internal capsule, left	0.51; (0.49,0.53)	0.48; (0.46,0.50)	0.139
Retrolenticular part of internal capsule, right	0.52; (0.49,0.53)	0.48; (0.46,0.51)	0.011
Splenium of corpus callosum	0.50; (0.48,0.55)	0.48; (0.47,0.49)	0.030
Superior cerebellar peduncle, left	0.48; (0.46,0.49)	0.46; (0.44,0.48)	0.078
Superior cerebellar peduncle, right	0.48; (0.47,0.49)	0.47; (0.44,0.48)	0.025
Superior corona radiata, left	0.45; (0.43,0.47)	0.42; (0.40,0.44)	0.037
Superior corona radiata, right	0.45; (0.43,0.47)	0.43; (0.40,0.44)	0.005
Superior fronto-occipital fasciculus, left	0.41; (0.34,0.45)	0.35; (0.30,0.42)	0.106
Superior fronto-occipital fasciculus, right	0.46; (0.42,0.49)	0.42; (0.37,0.43)	0.009
Superior longitudinal fasciculus, left	0.43; (0.40,0.44)	0.40; (0.38,0.42)	0.063
Superior longitudinal fasciculus, right	0.43; (0.41,0.44)	0.40; (0.39,0.42)	0.006
Sagittal stratum, left	0.47; (0.46,0.49)	0.45; (0.44,0.47)	0.079
Sagittal stratum, right	0.47; (0.46,0.50)	0.45; (0.42,0.47)	0.021
Tapatum, left	0.32; (0.22,0.35)	0.25; (0.23,0.30)	0.132
Tapatum, right	0.35; (0.29,0.43)	0.31; (0.25,0.36)	0.337
Uncinate fasciculus, left	0.40; (0.37,0.42)	0.39; (0.36,0.40)	0.123
Uncinate fasciculus, right	0.41; (0.38,0.44)	0.38; (0.33,0.41)	0.032

Table 4. Predictive models of functional outcome at 3 months based on mRS in the cohort of patients with standard rehabilitation.

Univariate analysis	AUC	Sensibility	Specificity	PPV	NPV	cut-off value
Modified Rankin Score at discharge	0.865	0.833	0.885	0.870	0.852	4
Fugl-Meyer total, lower extremity at baseline	0.836	0.857	0.700	0.857	0.700	11
Motricity Index at baseline	0.807	0.762	0.800	0.889	0.615	17
NIHSS score at baseline	0.782	0.792	0.654	0.679	0.773	10
Fugl-Meyer total, upper extremity at baseline	0.745	0.619	0.800	0.867	0.500	9
External capsule, right mean FA	0.798	0.550	0.950	0.917	0.679	0.435
Medial lemniscus, left mean FA	0.775	0.500	0.900	0.833	0.643	0.427
Genu of corpus callosum, mean FA	0.755	0.800	0.600	0.667	0.750	0.489
Inferior fronto-occipital fasciculus, right mean FA	0.752	0.800	0.650	0.696	0.765	0.431
Anterior limb of internal capsule, left mean FA	0.744	0.500	0.950	0.909	0.655	0.489
Bivariate analysis						
Age + Modified Rankin Score at discharge	0.904	0.917	0.808	0.815	0.913	
Fugl-Meyer total, upper extremity at baseline + External capsule, left mean FA	0.926	0.765	1.000	1.000	0.600	
Modified Rankin Score at discharge + Anterior corona radiata, right mean FA	0.914	0.900	0.950	0.947	0.905	
NIHSS score at baseline + Modified Rankin Score at discharge	0.899	0.750	1.000	1.000	0.812	
Modified Rankin Score at discharge + Anterior limb of internal capsule, left mean FA	0.884	0.850	0.900	0.895	0.857	
Modified Rankin Score at discharge+ Montreal Cognitive Assessment at baseline	0.882	0.909	0.783	0.800	0.900	
Age + Motricity Index at baseline	0.879	1.000	0.700	0.875	1.000	
Age + Fugl-Meyer total, lower extremity at baseline	0.879	0.762	0.900	0.941	0.643	
Infarct volume at baseline + Modified Rankin Score at discharge	0.878	0.833	0.880	0.870	0.846	
Modified Rankin Score at discharge + Corticospinal tract, right mean FA	0.820	0.800	0.900	0.889	0.818	
Trivariate analysis						
Age + Fugl-Meyer total, lower extremity at baseline + External capsule, right mean FA	0.951	1.000	0.833	0.944	1.000	
Age + Fugl-Meyer total, lower extremity at baseline + Anterior limb of internal capsule, left mean FA	0.941	1.000	0.833	0.944	1.000	
Infarct volume at baseline + Modified Rankin Score at discharge + Corticospinal tract, right mean FA	0.912	0.800	0.900	0.889	0.818	
Age + Fugl-Meyer total, lower extremity at baseline + Corticospinal tract, right mean FA	0.926	0.822	0.833	0.938	0.714	
NIHSS score at baseline + Modified Rankin Score at discharge + Anterior limb of internal capsule, left mean FA	0.916	0.800	1.000	1.000	0.833	
NIHSS score at baseline + Modified Rankin Score at discharge + External capsule, right mean FA	0.926	0.900	0.850	0.857	0.895	

Table 5. Predictive models of functional outcome at 3 months based on mRS in the cohort of patients with intensive rehabilitation.

Univariate	AUC	Sensibility	Specificity	PPV	NPV	cut-off value
NIHSS score at baseline	0.923	0.833	0.960	0.833	0.960	6
Fugl-Meyer total, upper extremity at baseline	0.913	0.667	0.760	0.400	0.905	44.5
Fugl-Meyer total, lower extremity at baseline	0.850	0.667	0.800	0.444	0.909	19
Motricity Index mean value at baseline	0.827	0.667	1.000	1.000	0.926	35
Modified Rankin Score at discharge	0.800	1.000	0.600	0.375	1.000	4
Bivariate						
NIHSS score at baseline + Infarct volume at baseline	0.964	1.000	0.800	1.000	1.000	
NIHSS score at baseline + Modified Rankin Score at discharge	0.957	1.000	1.000	0.545	1.000	
Modified Rankin Score at discharge + Fugl-Meyer total, upper extremity at baseline	0.953	1.000	0.880	0.667	1.000	
Age+ NIHSS score at baseline	0.947	0.833	0.800	0.500	0.952	
NIHSS score at baseline + Fugl-Meyer total, upper extremity at baseline	0.943	0.833	0.960	0.833	0.960	
Fugl-Meyer total, upper extremity at baseline + Montreal Cognitive Assessment at baseline	0.942	0.800	0.958	0.800	0.958	
NIHSS score at baseline + Motricity Index mean value at baseline	0.940	0.833	0.960	0.833	0.960	

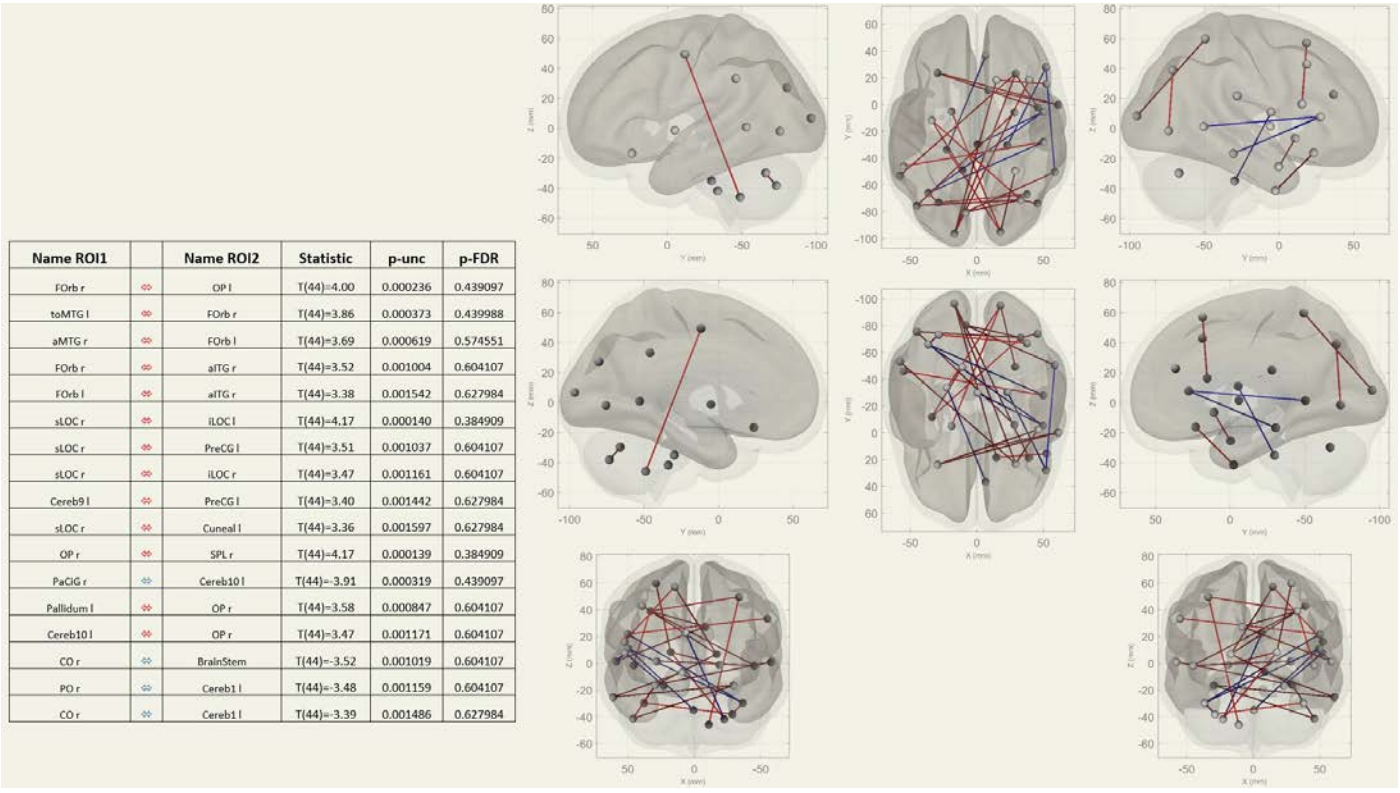
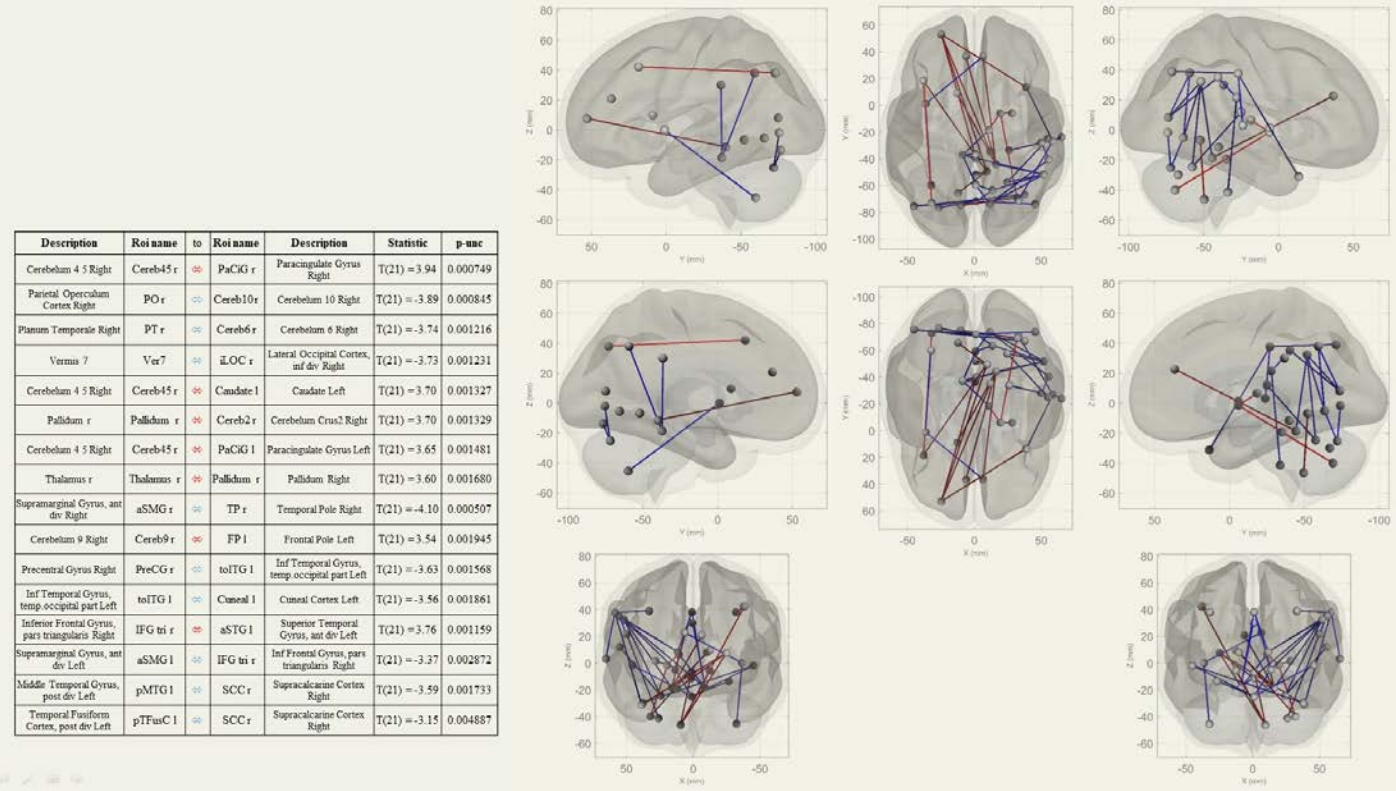


Figure 3. Patients treated with standard rehabilitation. Regions of interest (ROI)-based analysis for patients with favourable (mRS ≤2) and unfavorable (mRS >2) functional outcome. Left; significant functional connectivity ROI-to-ROI relationships with uncorrected p-value.



Description	Roi name	to	Roi name	Description	Statistic	p-unc
Cerebelum 4 5 Right	Cereb45 r	↔	PaCiG r	Paracingulate Gyrus Right	T(21) = 3.94	0.000749
Parietal Operculum Cortex Right	PO r	↔	Cereb10r	Cerebelum 10 Right	T(21) = -3.89	0.000845
Planum Temporale Right	PT r	↔	Cereb6 r	Cerebelum 6 Right	T(21) = -3.74	0.001216
Vermis 7	Ver7	↔	iLOC r	Lateral Occipital Cortex, inf div Right	T(21) = -3.73	0.001231
Cerebelum 4 5 Right	Cereb45 r	↔	Caudate l	Caudate Left	T(21) = 3.70	0.001327
Pallidum r	Pallidum r	↔	Cereb2 r	Cerebelum Crus2 Right	T(21) = 3.70	0.001329
Cerebelum 4 5 Right	Cereb45 r	↔	PaCiG l	Paracingulate Gyrus Left	T(21) = 3.65	0.001481
Thalamus r	Thalamus r	↔	Pallidum r	Pallidum Right	T(21) = 3.60	0.001680
Supramarginal Gyrus, ant div Right	aSMG r	↔	TP r	Temporal Pole Right	T(21) = -4.10	0.000507
Cerebelum 9 Right	Cereb9 r	↔	FP l	Frontal Pole Left	T(21) = 3.54	0.001945
Precentral Gyrus Right	PreCG r	↔	toITG l	Inf Temporal Gyrus, temp.occipital part Left	T(21) = -3.63	0.001568
Inf Temporal Gyrus, temp.occipital part Left	toITG l	↔	Cuneal l	Cuneal Cortex Left	T(21) = -3.56	0.001861
Inferior Frontal Gyrus, pars triangularis Right	IFG tri r	↔	aSTG l	Superior Temporal Gyrus, ant div Left	T(21) = 3.76	0.001159
Supramarginal Gyrus, ant div Left	aSMG l	↔	IFG tri r	Inf Frontal Gyrus, pars triangularis Right	T(21) = -3.37	0.002872
Middle Temporal Gyrus, post div Left	pMTG l	↔	SCC r	Supracalcarine Cortex Right	T(21) = -3.59	0.001733
Temporal Fusiform Cortex, post div Left	pTFusC l	↔	SCC r	Supracalcarine Cortex Right	T(21) = -3.15	0.004887

Figure 4. Patients treated with intensive rehabilitation. Regions of interest (ROI)-based analysis for patients with favourable (mRS ≤2) and unfavorable (mRS >2) functional outcome. Left; significant functional connectivity ROI-to-ROI relationships with uncorrected p-value.

3. Relevance and future implications

Early accurate prediction of functional outcome would enable patients, family, and carers to know what to expect after stroke. Incorporating MRI markers of brain connectivity (MRI-BBC) into decision-making algorithms for rehabilitation might help more patients benefit from therapy and select the most appropriate type and intensity of rehabilitation strategy, because evidence-based evaluation of rehabilitation treatment approaches might help determine whether potential recovery through stimulating neuroplasticity would justify rehabilitation processes even if the prognosis were weak. The results of this project would enable clinicians and researchers to stratify patients into more homogeneous prognostic groups for experimental trials, and also to measure and compare costs of rehabilitation. Reliable and valid instruments of measurement can be used to guide stroke rehabilitation and can provide opportunities to evaluate the quality of care. Our results may direct functional prognosis and allow health professionals to improve their clinical decision-making and establish realistic,

attainable treatment goals. MRI-BCC also allows for monitoring recovery in patients within a specific treatment as well as within regional stroke services, and provides transparency across stroke services. Our work will continue with the aim to offer novel biomarkers based on advanced MRI techniques by assessing structural and functional brain connectivity to predict long-term functional outcome after stroke, not merely motor recovery but also other important clinical variables (language and cognition) and patient's dependence. Although there is evidence of a dose-dependent relationship between intensity of therapies and functional outcomes, there is a lack of conclusive data to define the optimal intensity of training strategies for specific disabilities.

4. Bibliography and papers

Sartor MM, Grau-Sánchez J, Guillén-Solà A, Boza R, Puig J, Stinear C, Morgado-Perez A, Duarte E. Intensive rehabilitation programme for patients with subacute stroke in an inpatient rehabilitation facility: describing a protocol of a prospective cohort study. BMJ Open. 2021 Oct 18;11(10):e046346.