Fronto-parietal and white matter haemodynamics predict cognitive outcome in children with moyamoya independent of stroke

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Supplementary table 1. CVR regional *f*neg from normative samples

	P1	P2	P3	P4	P5
*f*neg in the left grey matter (%)	10.0	10.2	9.6	3.0	3.0
*f*neg in the right grey matter (%)	9.4	9.7	7.9	4.1	4.1
*f*neg in the left white matter (%)	9.9	15.9	13.5	3.7	3.7
*f*neg in the right white matter (%)	10.3	17.1	11.2	6.8	6.8

The preliminary data from five healthy controls in our institution demonstrated 7 ± 3% (mean±SD) of voxels with negative CVRs in the left grey matter, 7 ± 2% in the right grey matter, 9 ± 5% in the left white matter and 9 ± 4% in the right white matter.

Supplementary Table 2. Detailed demographics and medical history in each case

Patient ID	Age at presentation	Age at diagnosis	Age at scan	Sex	ethnicity	other medical conditions_from initial abstraction	Other Medical conditions	Post surgery cases	Periods after surgery (years)
P01	5.37	6.81	10.13	0	East-Asian	ADHD, TIC, Migraine	ADHD, TIC, Migraine	1	3.13
P02	13.91	13.91	14.12	1	Caucasian	Diagnosed with new onset diabetes	Diabetes	0	N/A
P03	9.08	9.08	9.12	0	South-African	Initial presentation of TIA consisting of R facial droop with drooling, c, and R index finger paresthesia lassting ten minutes in June 2016.		0	N/A
P04	16.67	16.75	16.72	1	Caucasian	Hx of non-postural syncope beginning in March 2017, longstanding bifrontal HA (tension type and migrainous), depression.	Depression	0	N/A
P05_1	4.68	5.71	8.78	1	East-Asian	Adopted at age 18 months. Not much background history is noted. Hx of crying spells intially thought to be night terrors and longstanding HA.		1	0.71
P05_2	4.68	5.71	12.59	1	East-Asian	Adopted at age 18 months. Not much background history is noted. Hx of crying spells intially thought to be night terrors and longstanding HA.		1	4.53
P06	10.54	10.54	17.00	1	East-Asian	Migraine HA since the age of 3 years, learning difficulties, and bilateral TIA, mainly affecting the right side of body sensori-motor in nature (tingling), R>L.	Migraine, right-sided sensory-motor symptoms	1	6.25
P07	5.04	6.02	14.27	1	East-Asian	Diagnosed at six y.o but history predates to age 12 months involving "shuddering spells" and TIA (Left sided sensory and motor sx).	Left-sides sensory-motor symptoms	1	6.73
P08	5.64	6.78	9.32	1	Caucasian	headache /diagnosed Moya Moed/postop stroke	headache	1	3.24
P09	4.50	5.72	6.49	0	East-Asian	Familial Moya Moya (mat uncle affected but genetic testing could not be done)/ post b/l synangiosis		1	0.62
P10	4.99	8.05	8.85	0	Caucasian	Migraine headaches from the age of four.	Migraine	0	N/A
P11_1	9.23	9.23	9.52	0	South-African	B/L Moya Moya disease/ B/l pial synangliosis		0	N/A
P11_2	9.23	9.23	11.49	0	South-African	B/L Moya Moya disease/ B/l pial synangliosis		1	0.68
P12	4.46	4.46	14.86	1	Caucasian	L sided stroke followed by pial synangiosis/ did well for next 8 years/impaired CVR in 2014 followed by posterior revascularisation		1	9.41
P13	7.30	14.95	15.56	1	Caucasian	Initial stroke -L MCA first occurred in 2008-thought to be caused by presumed		0	N/A

						transient cerebral arteriopathy-but new MRI in 2016 showed new stenosis.			
P14	8.54	9.87	12.18	0	Caucasian	Presented in March 2012 hand paresthesias, slurred speech lasting approx. ten minutes.	NF1	1	2.15
P15	8.30	8.30	15.27	0	Caucasian	NF1, left pial synangiosis Oct 21, 2008, clinically asymp pre and post surgery,.	NF1	1	1.92
P16	10.52	10.52	12.64	0	Caucasian	Familial NF1 (mother)/ R optic glioma/ R Moya Moya -> maybe wrong and Left moyamoya correct?	NF1	1	0.64
P17	9.72	9.72	13.00	1	Caucasian	Hx of NF1, multiple NF related intracranial hamartomas, autism and hx of infantile spams.	NF1, Autism	0	N/A
P18	10.94	10.94	12.00	0	South-African	NF1 , L optic glioma/ L moya moya	NF1,	0	N/A
P19	7.66	7.66	9.10	0	East-Asian	NF1	NF1,	0	N/A
P20	10.66	10.66	11.09	1	Caucasian	NF1 familial, developmental delay, learning disability, Kawasaki disease,	NF1, Developmental delay, learning disability, Kawasaki disease	0	N/A
P21	1.54	4.53	14.20	0	East-Asian	NF1, optic pathway glioma	NF1, optic pathway glioma	1	8.75
P22	9.33	10.33	17.13	1	African	Sickle cell disease	Sickle cell disease	0	N/A
P23	6.58	6.58	14.60	1	African		Sickle cell disease	1	5.48
P24	11.84	11.84	17.08	1	South east-Asian	NF1 /Moya moya s/p revascularization, recent hypertension/ Sibling has Klinefelter syndrome	NF1, sibling has Klinefelter syndrome	#NULL!	N/A
P25	7.90	7.90	9.91	0	African	Scikle cell	Sickle cell disease	0	N/A
P26	15.91	15.91	16.38	1	Caucasian	NF1 / R Moya Moya/ no stroke/ bilat optic nerve glioma	NF1, optic pathway glioma	0	N/A
P27_1	8.12	8.12	9.01	1	East-Asian	Hemolytic Anemia (dx Dec 2014), Lupus (2015-05-06), NF1(strong family hx), optic pathway glioma. Scoliosis.	NF1	0	N/A
P27_2	8.12	8.12	14.00	1	East-Asian	Hemolytic Anemia (dx Dec 2014), Lupus (2015-05-06), NF1(strong family hx), optic pathway glioma. Scoliosis.	NF1	0	N/A

Supplementary table 3. Descriptive statistics for CVR estimates

		HM	CVR estimates	No stroke group			Stroke group		
				Mean±SD	Median	Range	Mean±SD	Median	Range
Brain tissue	Grey matter	L	Mean CVR_{pos}	0.67 ± 0.13	0.69	0.44 - 0.91	0.69 ± 0.20	0.69	0.39 - 1.03
			Mean CVR_{neg}	-0.26 ± 0.08	-0.25	-0.40 - -0.17	-0.29 ± 0.14	-0.26	-0.60 - -0.15
			Mean $CVR_{combined}$	0.46 ± 0.20	0.52	0.12 - 0.81	0.46 ± 0.23	0.50	0.11 - 0.90
			*f*pos	0.75 ± 0.13	0.77	0.56 - 0.90	0.74 ± 0.11	0.77	0.56 - 0.88
			*f*neg	0.19 ± 0.12	0.14	0.05 - 0.39	0.19 ± 0.11	0.17	0.06 - 0.41
		R	Mean CVR_{pos}	0.65 ± 0.12	0.66	0.45 - 0.86	0.66 ± 0.17	0.69	0.37 - 0.98
			Mean CVR_{neg}	-0.23 ± 0.08	-0.20	-0.41 - -0.13	-0.29 ± 0.14	-0.26	-0.56 - -0.14
			Mean $CVR_{combined}$	0.47 ± 0.14	0.51	0.25 - 0.73	0.42 ± 0.16	0.42	0.13 - 0.69
			*f*pos	0.78 ± 0.10	0.81	0.54 - 0.88	0.72 ± 0.10	0.75	0.54 - 0.83
			*f*neg	0.15 ± 0.10	0.11	0.05 - 0.39	0.20 ± 0.09	0.17	0.08 - 0.32
	White matter	L	Mean CVR_{pos}	0.51 ± 0.09	0.49	0.37 – 0.69	0.57 ± 0.18	0.60	0.28 - 0.95
			Mean CVR_{neg}	-0.21 ± 0.07	-0.20	-0.38 - -0.12	-0.25 ± 0.14	-0.20	-0.66 - -0.09
			Mean $CVR_{combined}$	0.35 ± 0.12	0.32	0.14 - 0.51	0.37 ± 0.18	0.35	0.05 - 0.75
			*f*pos	0.77 ± 0.12	0.76	0.59 - 0.92	0.76 ± 0.11	0.78	0.54 - 0.88
			*f*neg	0.21 ± 0.11	0.21	0.07 - 0.38	0.23 ± 0.12	0.21	0.10 - 0.49
		R	Mean CVR_{pos}	0.52 ± 0.14	0.49	0.34 - 0.92	0.59 ± 0.17	0.60	0.27 – 0.95
			Mean CVR_{neg}	-0.18 ± 0.06	-0.16	-0.26 - -0.10	-0.25 ± 0.15	-0.21	-0.70 - -0.11
			Mean $CVR_{combined}$	0.39 ± 0.15	0.39	0.19 - 0.75	0.38 ±0.16	0.39	0.08 - 0.68
			*f*pos	0.80 ± 0.10	0.84	0.61 - 0.91	0.75 ± 0.10	0.76	0.58 - 0.89
			*f*neg	0.18 ± 0.10	0.13	0.05 - 0.36	0.22 ± 0.10	0.20	0.09 - 0.38
Brain region	Frontal	L	Mean CVR_{pos}	0.60 ± 0.25	0.65	0.17 - 1.02	0.54 ± 0.26	0.44	0.26 - 1.11
			Mean CVR_{neg}	-0.21 ± 0.08	-0.20	-0.39 - -0.11	-0.25 ± 0.10	-0.22	-0.46 - -0.10
			Mean $CVR_{combined}$	0.39 ± 0.30	0.42	-0.23 - 0.70	0.30 ± 0.25	0.21	-0.08 - 0.85
			*f*pos	0.66 ± 0.21	0.72	0.20 - 0.86	0.63 ± 0.13	0.65	0.29 - 0.83
			*f*neg	0.24 ± 0.20	0.19	0.06 - 0.69	0.27 ± 0.12	0.27	0.08 - 0.54
		R	Mean CVR_{pos}	0.54 ± 0.21	0.54	0.16 - 0.83	0.46 ± 0.18	0.49	0.20 - 0.85
			Mean CVR_{neg}	-0.18 ± 0.08	-0.15	-0.37 - -0.10	-0.22 ± 0.10	-0.18	-0.37 - -0.08
			Mean $CVR_{combined}$	0.36 ± 0.26	0.39	-0.25 - 0.68	0.25 ± 0.18	0.25	-0.04 - 0.56
			*f*pos	0.68 ± 0.21	0.75	0.14 - 0.83	0.63 ± 0.14	0.66	0.34 - 0.81
			*f*neg	0.22 ± 0.21	0.16	0.05 - 0.78	0.25 ± 0.13	0.22	0.06 - 0.47
	Parietal	L	Mean CVR_{pos}	0.64 ± 0.18	0.68	0.32 - 0.95	0.64 ± 0.30	0.65	0.24 - 1.41
			Mean CVR_{neg}	-0.17 ± 0.05	-0.17	-0.31 - -0.10	-0.22 ± 0.10	-0.21	-0.46 - -0.09
			Mean $CVR_{combined}$	0.52 ± 0.20	0.51	0.18 - 0.88	0.48 ± 0.31	0.38	-0.02 - 1.12
			*f*pos	0.81 ± 0.12	0.81	0.55 - 0.95	0.77 ± 0.16	0.80	0.41 - 0.94
			*f*neg	0.16 ± 0.12	0.17	0.04 - 0.43	0.20 ± 0.15	0.14	0.06 - 0.57
		R	Mean CVR_{pos}	0.61 ± 0.16	0.62	0.36 - 0.92	0.60 ± 0.25	0.60	0.28 - 1.27
			Mean CVR_{neg}	-0.16 ± 0.07	-0.15	-0.36 - -0.09	-0.23 ± 0.11	-0.20	-0.43 - -0.07
			Mean $CVR_{combined}$	0.51 ± 0.16	0.49	0.31 - 0.84	0.45 ± 0.23	0.45	0.10 - 1.02
			*f*pos	0.85 ± 0.06	0.87	0.77 - 0.94	0.78 ± 0.10	0.80	0.53 - 0.94
			*f*neg	0.12 ± 0.06	0.12	0.04 - 0.22	0.18 ± 0.11	0.16	0.04 - 0.43
	Temporal	L	Mean CVR_{pos}	0.61 ± 0.14	0.64	0.28 - 0.80	0.72 ± 0.30	0.66	0.36 - 1.52
			Mean CVR_{neg}	-0.23 ± 0.07	-0.23	-0.38 - -0.13	-0.33 ± 0.21	-0.30	-0.96 - -0.09
			Mean $CVR_{combined}$	0.41 ± 0.17	0.42	0.05 - 0.64	0.43 ± 0.25	0.39	0.03 - 0.85
			*f*pos	0.70 ± 0.10	0.71	0.47 - 0.84	0.68 ± 0.14	0.72	0.38 - 0.89
			*f*neg	0.17 ± 0.09	0.16	0.05 - 0.38	0.20 ± 0.12	0.17	0.06 - 0.45
		R	Mean CVR_{pos}	0.67 ± 0.21	0.59	0.45 - 1.19	0.70 ± 0.25	0.65	0.43 - 1.18
			Mean CVR_{neg}	-0.22 ± 0.07	-0.21	-0.34 - -0.11	-0.30 ± 0.24	-0.23	-1.12 - -0.11
			Mean $CVR_{combined}$	0.48 ± 0.16	0.45	0.29 - 0.86	0.41 ± 0.21	0.35	0.09 - 0.83
			*f*pos	0.75 ± 0.06	0.76	0.61 - 0.82	0.68 ± 0.11	0.71	0.50 - 0.83
			*f*neg	0.12 ± 0.04	0.12	0.06 - 0.19	0.17 ± 0.09	0.15	0.06 - 0.40
	Occipital	L	Mean CVR_{pos}	0.75 ± 0.13	0.72	0.50 - 1.04	0.96 ± 0.28	0.91	0.55 - 1.70
			Mean CVR_{neg}	-0.22 ± 0.10	-0.19	-0.46 - -0.12	-0.25 ± 0.15	-0.22	-0.76 - -0.12
			Mean $CVR_{combined}$	0.61 ± 0.23	0.61	-0.01 - 0.97	0.82 ± 0.25	0.81	0.34 - 1.44
			*f*pos	0.84 ± 0.13	0.89	0.45 - 0.95	0.87 ± 0.06	0.89	0.72 - 0.95
			*f*neg	0.12 ± 0.13	0.07	0.02 - 0.49	0.09 ± 0.06	0.08	0.03 - 0.26
		R	Mean CVR_{pos}	0.79 ± 0.14	0.80	0.52 - 0.98	0.97 ± 0.33	1.02	0.40 - 1.79
			Mean CVR_{neg}	-0.20 ± 0.09	-0.18	-0.45 - -0.11	-0.29 ± 0.15	-0.25	-0.65 - -0.11
			Mean $CVR_{combined}$	0.66 ± 0.15	0.64	0.44 - 0.92	0.81 ± 0.34	0.86	0.18 - 1.52
			*f*pos	0.87 ± 0.07	0.90	0.74 - 0.94	0.87 ± 0.10	0.88	0.64 - 0.97
			*f*neg	0.09 ± 0.08	0.07	0.02 - 0.24	0.11 ± 0.09	0.08	0.02 - 0.33

Mean $CVR_{pos,}$ The mean of all positively reacting voxels; Mean CVR_{neg}, The mean of all negatively reacting voxels; Mean $CVR_{combined}$, weighted average of positive- and negative-reacting voxels; *f*pos, The fraction of positively reacting voxels; *f*neg, The fraction of negatively reacting voxels

Supplementary Table 4. Description of NF1 with moyamoya but no stroke

	Previous NF1 studies			Our no stroke cohort		
Patient characteristics	Hyman et al., (2005) N=81	Pride et al., (2010) N=46	Plasschaert et al., (2016) (N=46)	NF1 with MM (N=7)	Idiopathic MM (N=6)	p-value*
Age at scan (years)	11.52 (8.0 to 16.75)	12.5 ± 1.8 (10.0 to 16.7)	12.48 ± 3.08	12.18 ± 1.88	11.91 ± 3.14	-
Females (%)	38 (47%)	19 (43%)	16 (35%)	2 (28.6%)	4 (66.7%)	-
Intelligence Test	WICS-III	WICS-III	WISC-II-NL or WAIS-III-NL	WISC-III, IV, WAIS-IV		
FSIQ	90.6 (13.3)	89.7 (14.1)	89.73 ± 12.16	85.43 ± 7.68	103.0 ± 5.02	0.005
VCI	92.2 (14.2)	90.4 (15.4) (VIQ)	91.93 ± 13.64 (VIQ)	91.29 ± 10.00	105.00 ± 6.23	0.008
PRI	91.5 (13.5)	92.0 (14.0) (PIQ)	87.52 ± 13.87 (PIQ)	84.33 ± 10.67	108.30 ± 8.54	0.009
WMI	-	-	-	89.43 ± 8.22	95.17 ± 8.66	0.23
PSI	-	-	-	89.14 ± 12.90	95.83 ± 8.09	0.30
Executive Functioning Test	TOL, CCT	BRIEF	BRIEF but raw scores	BRIEF-T scores		
p value (comparison with healthy control)	P<0.0001 (TOL), p<0.003 (CCT)	P=0.006 (GEC)	P<0.001	-	-	
% of NF1 <1SD below mean	71.3% (TOL), 33.3% (CCT)	-	-	-	-	
BRIEF-BRIS	-	59.2 (12.6)	-	52.00 ± 13.27	55.60 ± 13.28	0.53
BRIEF-MI	-	60.3 (13.1)	-	61.33 ± 14.95	63.30 ± 17.10	0.79
BRIEF-GEC	-	60.6 (12.8)	-	59.67 ± 14.84	61.40 ± 15.37	0.93

*Mann-Whitney U Test

The effect of comorbidity on cognitive outcome was examined by comparison of the children with MMD and MMS in the no stroke group. Between group comparisons revealed significant differences in the following IQ indices: FSIQ, U=2.0, p=0.005; VCI, U=3.0, p=0.008; PRI, U=1.5, p=0.009. Executive function scores were not different in the MMD group (mean BRIEF-GEC=61.40, SD=15.37) compared with the NF-1 group (Mean BRIEF-GEC=59.67, SD=14.84; p=0.93).

Supplementary Table 5. Correlations between regional CVR negativity and cognitive outcomes in the whole group

	Spearman's rho	IQ				EF			
		FSIQ	VCI	PRI	WMI	PSI	BRIS	MI	GEC
Left frontal fneg	Correlation Coefficient	**-.506***	-.415	-.278	-.325	-.408	.131	.103	.181
	$p_{corrected}$	**0.03**	0.10	0.27	0.16	0.10	0.64	0.71	0.53
Right frontal fneg	Correlation Coefficient	**-.496***	**-.569***	-.334	-.262	-.327	.127	.300	.322
	$p_{corrected}$	**0.03**	**0.02**	0.16	0.27	0.17	0.63	0.28	0.27
Left parietal fneg	Correlation Coefficient	-.357	-.170	-.196	-.402	-.344	.089	-.186	-.065
	$p_{corrected}$	0.13	0.48	0.45	0.10	0.15	0.72	0.53	0.79
Right parietal_fneg	Correlation Coefficient	**-.550***	**-.621****	-.418	**-.455***	-.114	.401	.311	.418
	$p_{corrected}$	**0.02**	**0.01**	0.10	**0.05**	0.64	0.13	0.28	0.13
Left temporal fneg	Correlation Coefficient	-.361	-.263	-.203	**-.536***	-.137	.082	-.261	-.103
	$p_{corrected}$	0.13	0.27	0.44	**0.02**	0.57	0.73	0.36	0.70
Right temporal fneg	Correlation Coefficient	-.374	**-.482***	-.239	-.327	.138	.370	.223	.332
	$p_{corrected}$	0.12	**0.04**	0.34	0.16	0.58	0.17	0.44	0.25
Left occipital fneg	Correlation Coefficient	-.376	-.258	-.258	**-.498***	-.185	.109	-.183	-.037
	$p_{corrected}$	0.12	0.28	0.29	**0.03**	0.45	0.68	0.53	0.88
Right occipital fneg	Correlation Coefficient	**-.503***	**-.500***	-.417	**-.542***	-.202	.304	.092	.215
	$p_{corrected}$	**0.03**	**0.03**	0.10	**0.02**	0.42	0.27	0.72	0.45
Left white matter fneg	Correlation Coefficient	**-.562***	-.394	-.323	**-.576***	-.443	.133	.012	.120
	$p_{corrected}$	**0.02**	0.10	0.18	**0.02**	0.06	0.64	0.96	0.67
Right white matter fneg	Correlation Coefficient	**-.629****	**-.635****	**-.488***	-.400	-.391	.214	.402	.431
	$p_{corrected}$	**0.01**	**0.01**	**0.04**	0.09	0.10	0.45	0.14	0.12

The correlations between regional CVR negativity and cognitive outcomes in the whole group were presented. Different IQ measures were correlated with CVR negativity of multiple cortical and white matter regions, which remained significant with multiple comparison correction, while any of EF measures did not survive with multiple comparison correction.

Supplementary Table 6. Relative effects of regional negative CVRs and cognitive outcomes before adjusting for covariates

Cognitive outcomes		Effect	B	SE	Beta	95% CI		$P_{corrected}$	R^2
						LL	UL		
IQ	FSIQ	Intercept	106.95	5.41		95.88	118.02	<0.001	0.31
		Right white matter	-85.11	24.21	-0.55	-134.70	-35.53	0.01	
	VCI	Intercept	106.21	4.82		96.34	116.08	<0.001	0.29
		Right white matter	-73.11	21.58	-0.54	-117.31	-28.91	0.005	
	PRI	Intercept	100.95	4.71		91.27	110.63	<0.001	0.22
		Right occipital lobe	-97.88	35.81	-0.47	-171.49	-24.27	0.022	
	WMI	Intercept	108.21	4.61		98.76	117.66	<0.001	0.36
		Right white matter	-44.01	20.34	-0.37	-85.74	-2.28	0.048	
		Right occipital lobe	-55.75	26.74	-0.35	-110.61	-0.88	0.047	
	PSI	Intercept	105.00	6.18		92.33	117.67	<0.001	0.16
		Left white matter	-59.23	25.37	-0.40	-111.20	-7.27	0.027	
EF	BRIS	Intercept	43.57	4.13		35.01	52.13	<0.001	0.31
		Right parietal lobe	70.81	22.78	0.55	23.57	118.06	0.005	
	MI	Intercept	47.36	5.61		35.67	59.06	<0.001	0.19
		Right white matter	55.06	25.37	0.44	2.14	107.98	0.042	
	GEC	Intercept	46.56	5.4		35.30	57.82	<0.001	0.22
		Right white matter	57.79	24.44	0.47	6.81	108.77	0.046	

Without controlling for covariates, three measures (FSIQ, VCI, WMI) in IQ and two measures (MI, GEC) in EF were explained by the CVR negativity in the right white matter, suggesting this region may be affected by the disease in general and linked to these cognitive outcomes. The PRI in IQ was associated with CVR negativity in the right occipital lobe, while the PSI in IQ with CVR negativity in the left white matter. The BRIS in EF was associated with the CVR negativity in the right parietal lobe.

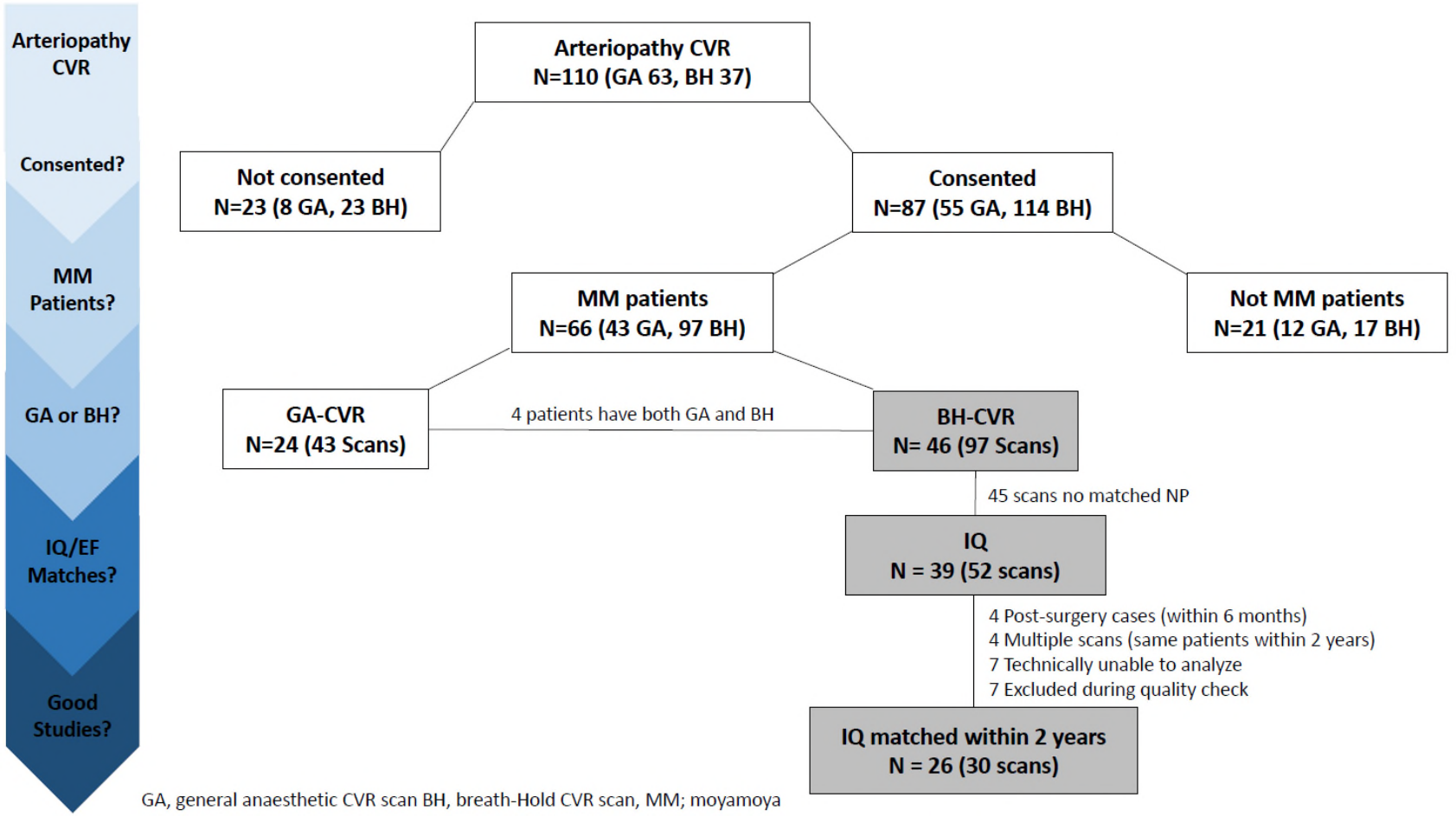
Supplementary Table 7. Relative effects of regional negative CVRs and cognitive outcomes in MMD and MMS groups

Cognitive outcomes		MMD							MMS-NF1							
		Effect	B	SE	Beta	95% CI		p	R^2	Effect	B	SE	Beta	95% CI		p	R^2
						LL	UL							LL	UL		
IQ	FSIQ	Intercept	103.91	3.35		96.67	111.15	<0.001	0.32	Intercept	105.58	6.74		90.57	120.60	<0.001	0.52
		R parietal lobe	-52.51	21.13	-0.57	-98.15	-6.88	0.027		**L white matter**	-88.88	27.25	-0.72	-149.59	-28.17	0.009	
	VCI	Intercept	111.81	3.99		103.13	120.49	<0.001	0.65	Intercept	104.75	4.95		93.73	115.77	<0.001	0.53
		Stroke	-12.37	3.72	-0.59	-20.47	-4.27	0.006		**R occipital lobe**	-99.82	29.92	-0.73	-166.48	-33.16	0.008	
		R white matter	-49.96	21.00	-0.42	-95.71	-4.20	0.035									
	PRI	Model not significant	-	-	-	-	-	-	-	Intercept	99.48	6.76		84.18	114.78	<0.001	0.37
										R occipital lobe	-94.09	40.67	-0.61	-186.08	-2.09	0.046	
	WMI	Intercept	106.83	4.37		97.38	116.28	<0.001	0.32	Intercept	105.14	5.38		93.15	117.12	<0.001	0.47
		L parietal lobe	-44.80	17.99	-0.57	-83.67	-5.93	0.027		**L temporal lobe**	-80.80	27.29	-0.68	-141.60	-20.00	0.014	
	PSI	Model not significant	-	-	-	-	-	-	-	Intercept	107.36	9.47		86.25	128.46	<0.001	0.35
										L white matter	-88.98	38.29	-0.59	-174.30	-3.66	0.043	
EF	BRIS	Intercept	43.19	4.75		32.74	53.65	<0.001	0.42	Model not significant	-	-	-	-	-	-	-
		R parietal lobe	83.58	29.37	0.65	18.93	148.23	0.016									
	MI	Model not significant	-	-	-	-	-	-	-	Model not significant	-	-	-	-	-	-	-
	GEC	Intercept	41.39	7.42		24.86	57.92	<0.001	0.33	Model not significant	-	-	-	-	-	-	-
		R white matter	88.15	39.48	0.58	0.17	176.12	0.05									

Exploratory analysis was conducted of each moyamoya group (MMD and MMS-NF1) separately, to determine the relative effect of comorbidity on the observed association between CVR estimates and cognitive outcomes. The main differences were found in the relative effects of cortical regional negative CVR on the IQ indices. In the separated analysis of MMS-NF1, the association between occipital lobe CVR negativity and IQ indices was pronounced. This association was not observed in the separated analysis of MMD. Instead, the hypothesised effects of parietal lobe CVR negativity was prominent in explaining both IQ and executive function scores in MMD.

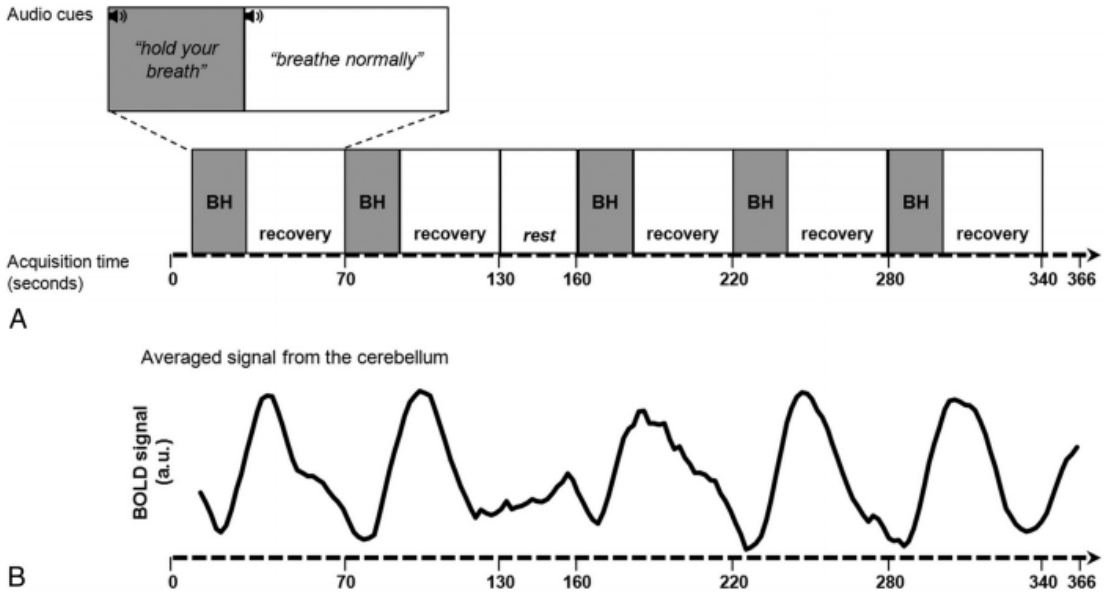
Supplementary Table 8. Main use of acronyms

NF1	Neurofibromatosis type 1
SCD	Sickle cell disease
MMS	Moyamoya syndrome
MMD	Idiopathic moyamoya disease
TIA	Transient ischaemic attacks
CBF	Cerebral blooe flow
CPP	Cerebral perfusion pressure
BH-CVR	Breath-hold cerebrovascular reactivity
fneg	Fractional voel counts of nagatively reacting voxels in CVR
FSIQ	Full-scale IQ
VCI	Verbal comprehension index
PRI	Perceptual reasoning index
WMI	Working memory index
PSI	Processing speed index
BRIS	Behavior Regulation/Inhibitory Self-Control
MI	Metacognitive Index
GEC	Global executive composite
BRIEF	Behavior Rating Inventory of Executive Function
MM/stroke	In moyamoya condition with stroke presentation
MM/no stroke	In moyamoya condition without stroke presentation
MMS-NF1	Syndromic moyamoya with comorbid NF1
MMS-SCD	Syndromic moyamoya with comorbid SCD



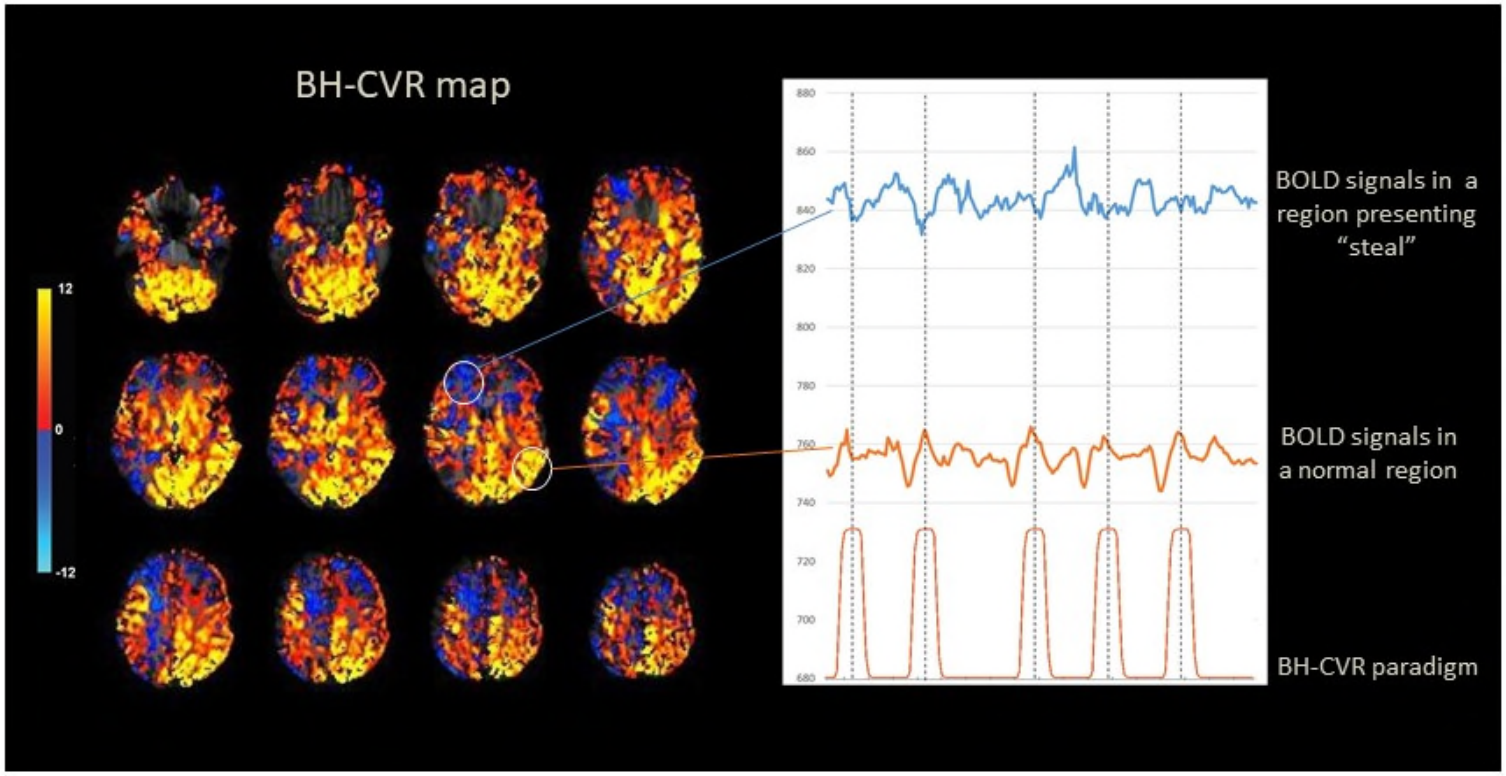
Supplementary Figure 1. Consort chart for study population

CVR, Cerebrovascular Reactivity; GA-CVR, General Anaesthesia Cerebrovascular Reactivity; BH-CVR, Breath-Hold Cerebrovascular Reactivity; NP, Neuropsychological data

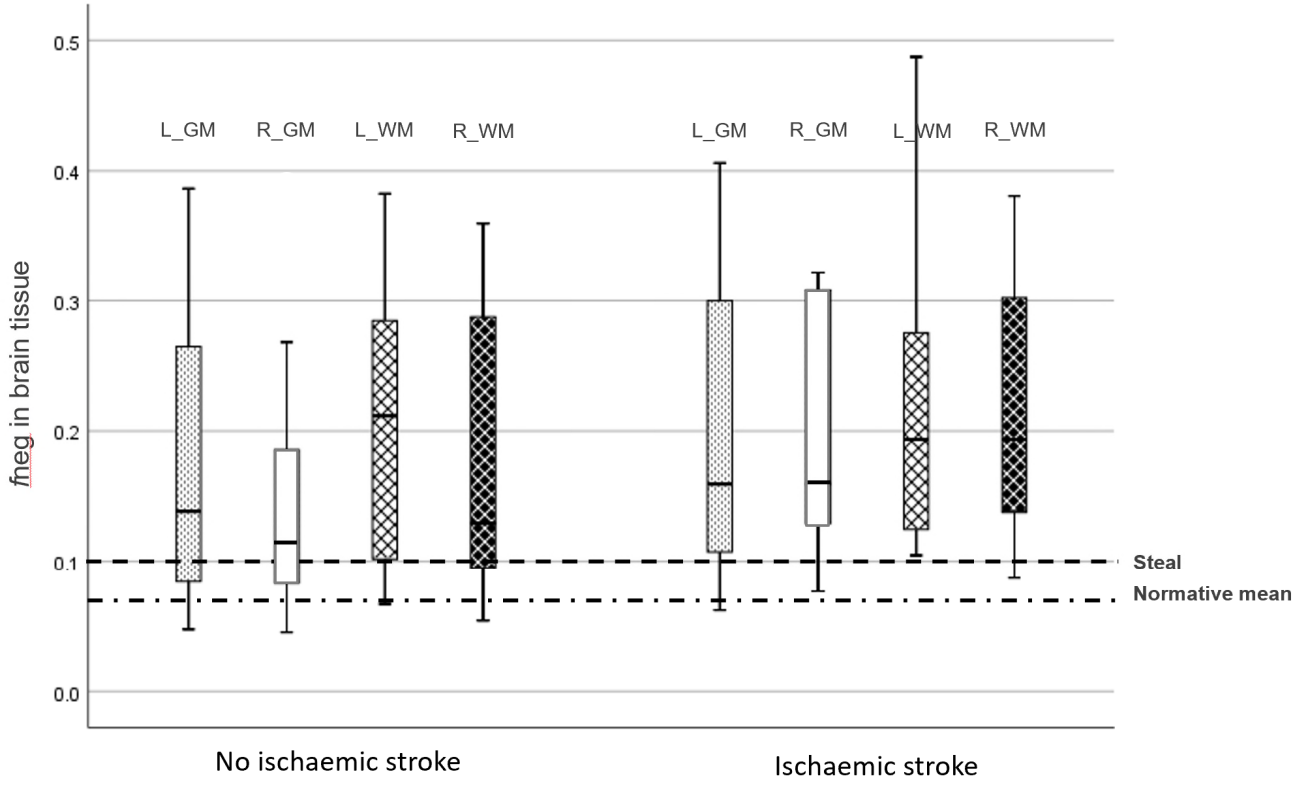


Supplementary Figure 2. Schematic of breath-hold paradigm (A) and cerebellar BOLD signal time course (B). a.u. indicates arbitrary units.

(Taken from Dlamini et al., 2018)



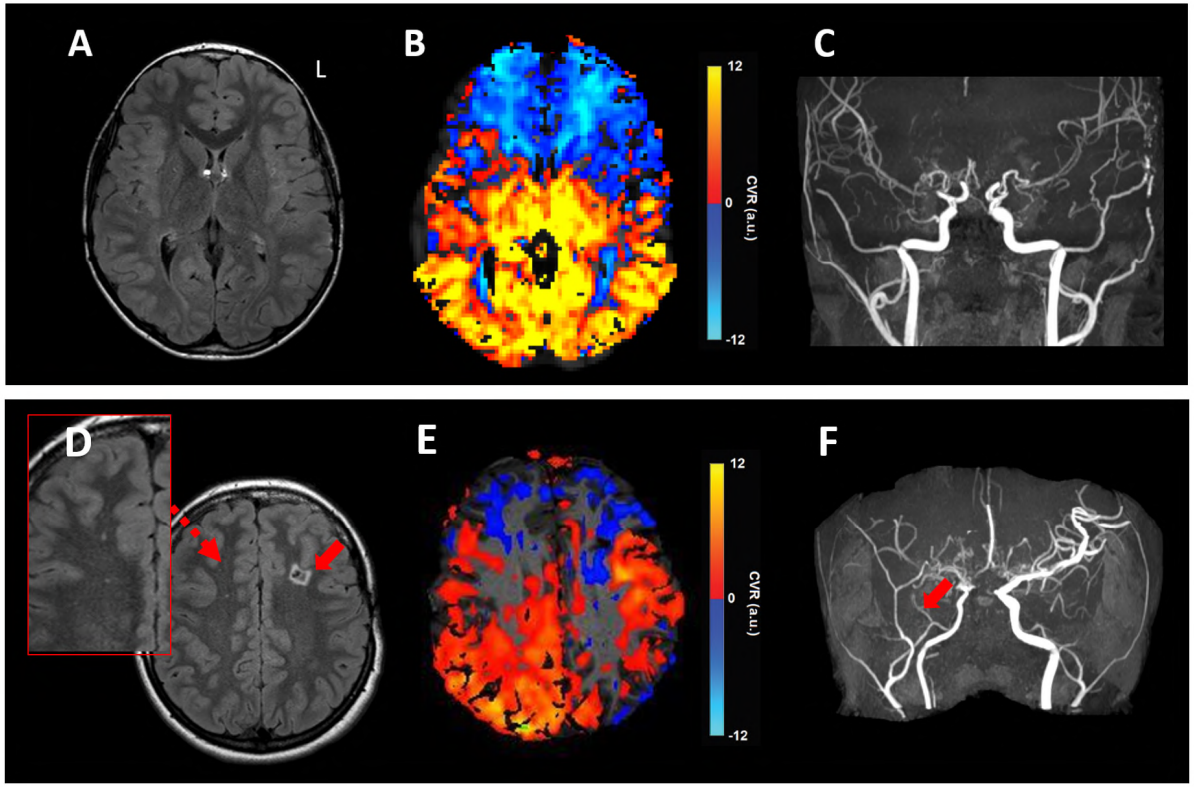
Supplementary Figure 3. CVR maps demonstrating positively (red-yellow) and negatively (blue) reacting voxels. Negative β weights describing an inverse relationship with the regressor represented the steal phenomenon



L_GM: left grey matter; R_GM: right grey matter; L_WM: left white matter; R_WM: right white matter

Supplementary Figure 4. CVR regional summaries by brain tissue in stroke and no stroke group

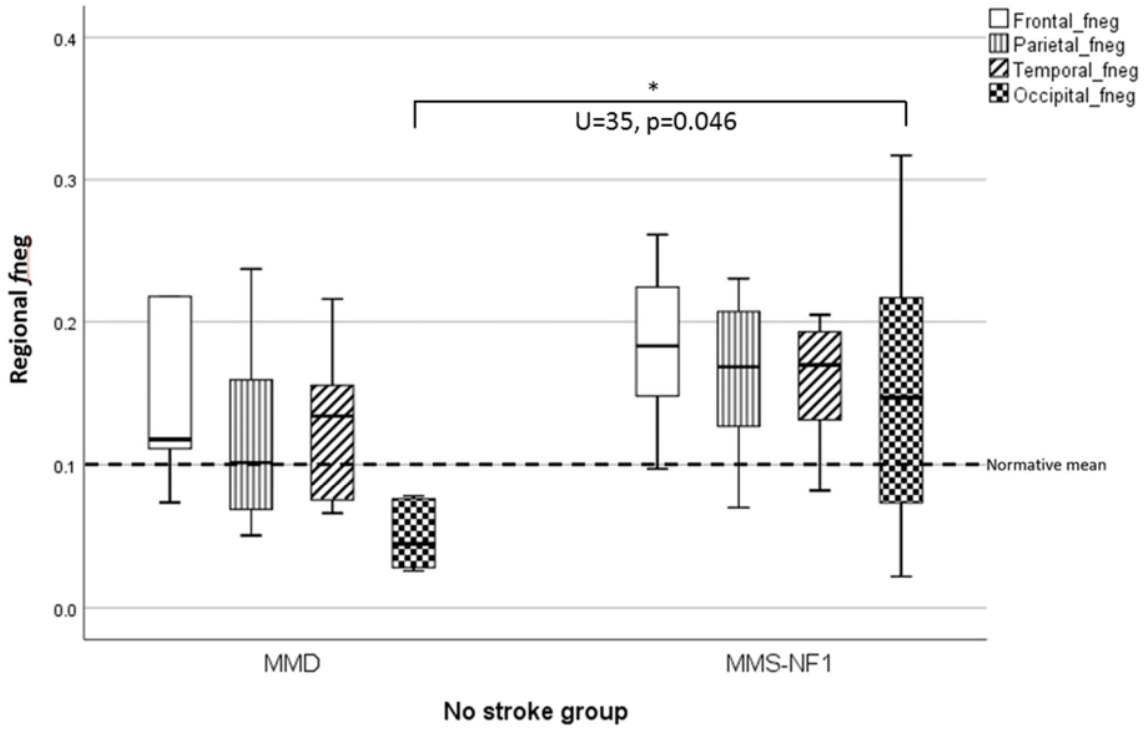
Regional fneg values in summaries of brain tissue were higher in children with MM/stroke and MM/no stroke when compared to the normative means. Children with MM/stroke tended to havehigher fneg values compared to children MM/no stroke. However, these differences did not reach statistical significance.



Supplementary Figure 5. Illustrative images of no stroke and stroke cases in moyamoya condition

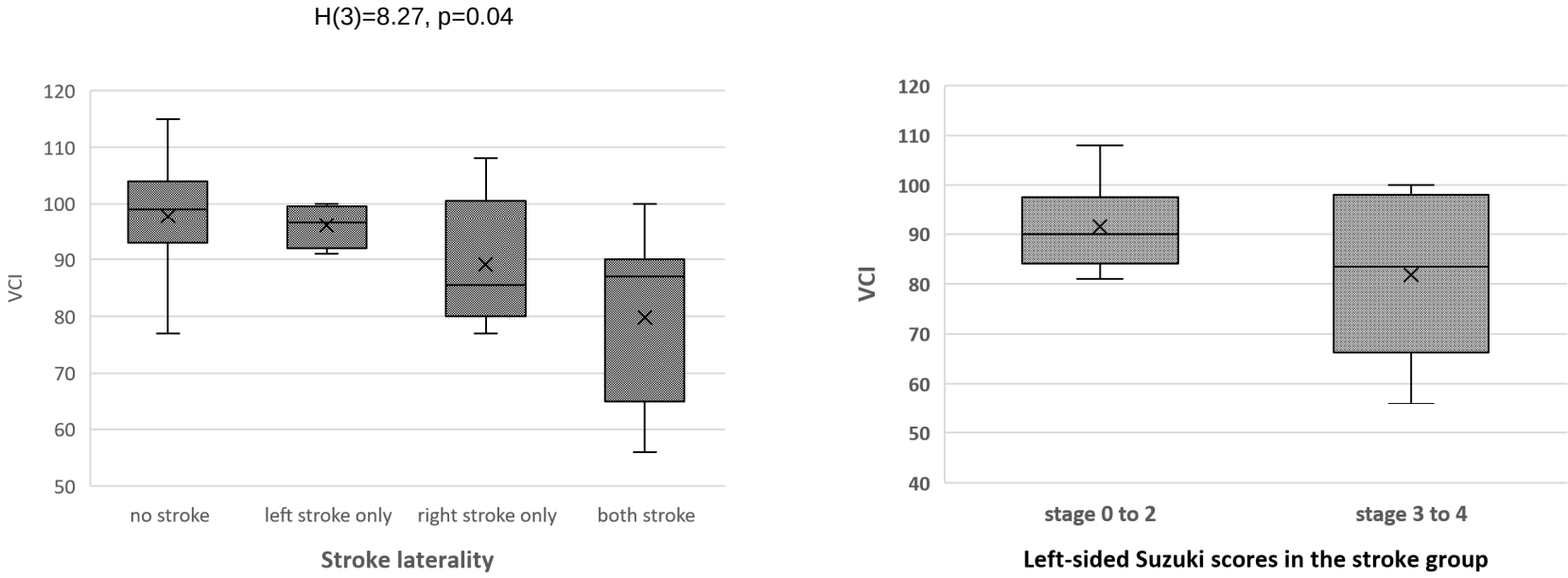
No stroke case (12-year-old, MMS-NF1, bilateral MM, TIA) (A-C): (5A) Normal appearing axial T2-FLAIR; (5B) BH-CVR maps demonstrating negative (blue scale) reactivity in the frontal region; (5C) Time-of-flight magnetic resonance angiography suggestive of bilateral severe stenosis of the supraclinoid internal carotid arteries and the proximal anterior cerebral arteries.

Stroke case (14-year-old girl, MMD, bilateral MM, with bilateral infarcts) (D-F): (5D) Axial T2-FLAIR images showing left MCA-ACA territory and right deep watershed infarcts (insert: dashed arrow) (5E) BH-CVR maps demonstrating negative (blue scale) reactivity in the frontal region; (5F)



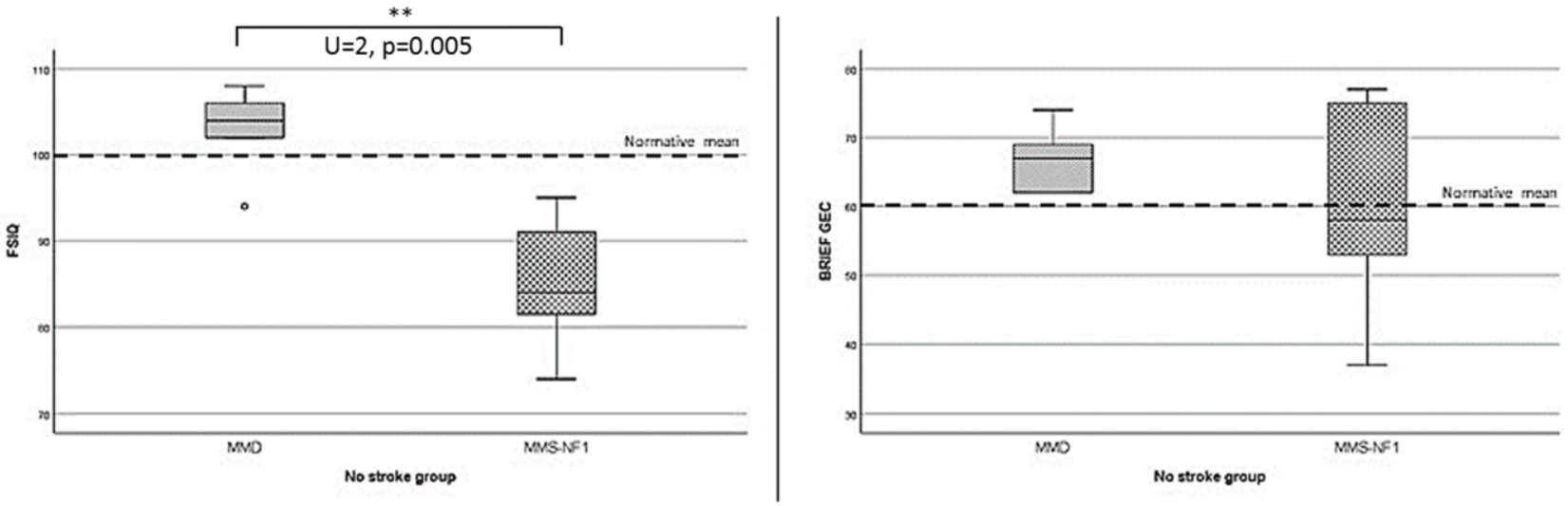
Supplementary Figure 6. Regional fneg comparisons between MMD and MMS-NF1 in no stroke group

The effect of comorbidity was examined in thirteen children with MM/no stroke (MMD=6, MMS-NF1=7). Children with MMD and MMS-NF1 demonstrated elevated CVR negativity predominantly in the frontal region. In addition, *f*neg values were significantly higher in children with NF1 compared to children with MMD, in the right occipital lobe.



Supplementary Figure 7. The association between the stroke laterality and the VCI

Significantly lower Verbal Comprehension Index (VCI) was observed in children with unilateral and bilateral stroke. In addition, children with moderate severity (Suzuki stage 3 and 4) in the left hemisphere revealed mean VCI scores, about 10 points lower (Mean=91.44, SD=8.68) than children with mild severity (Suzuki stage 0 to 2) in the left hemisphere (Mean=81.75, SD=17.04).



Supplementary Figure 8. Cognitive outcomes in children with MMD and MMS-NF1 in no stroke group

The effect of comorbidity on cognitive outcome was examined by comparison of the children with MMD and MMS in the no stroke group. Executive function scores were abnormal (one SD above the normative means) in children with MMD, while IQ scores were in the normal range. Children with MMS-NF1 deviated approximately one SD from the normative means in the majority of IQ and EF scores.