Neurology, cognition and brain injury

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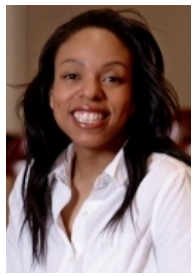
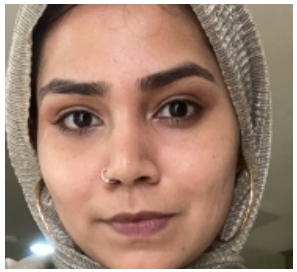
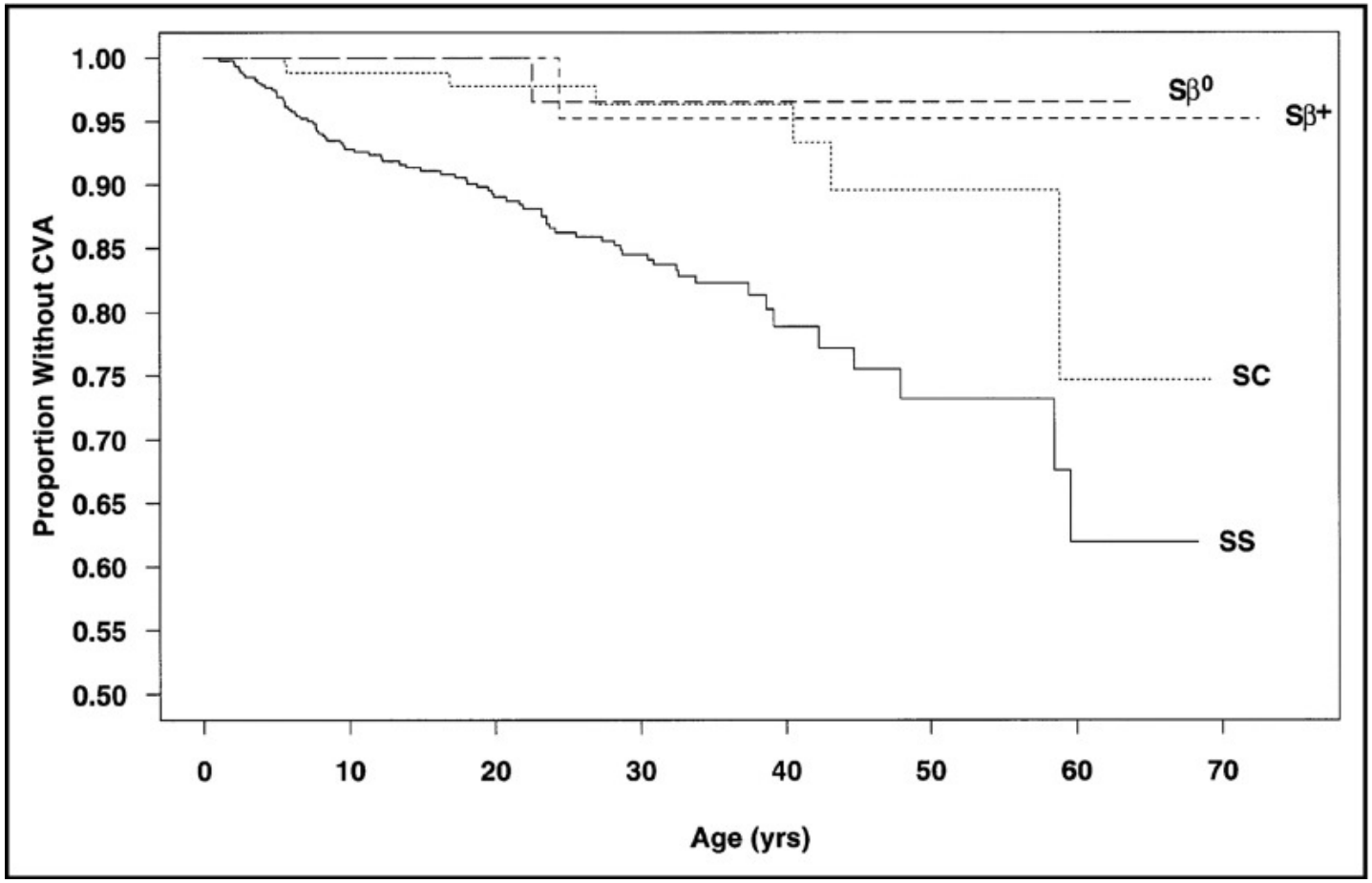






Long term risk of stroke by genotype CSSCD

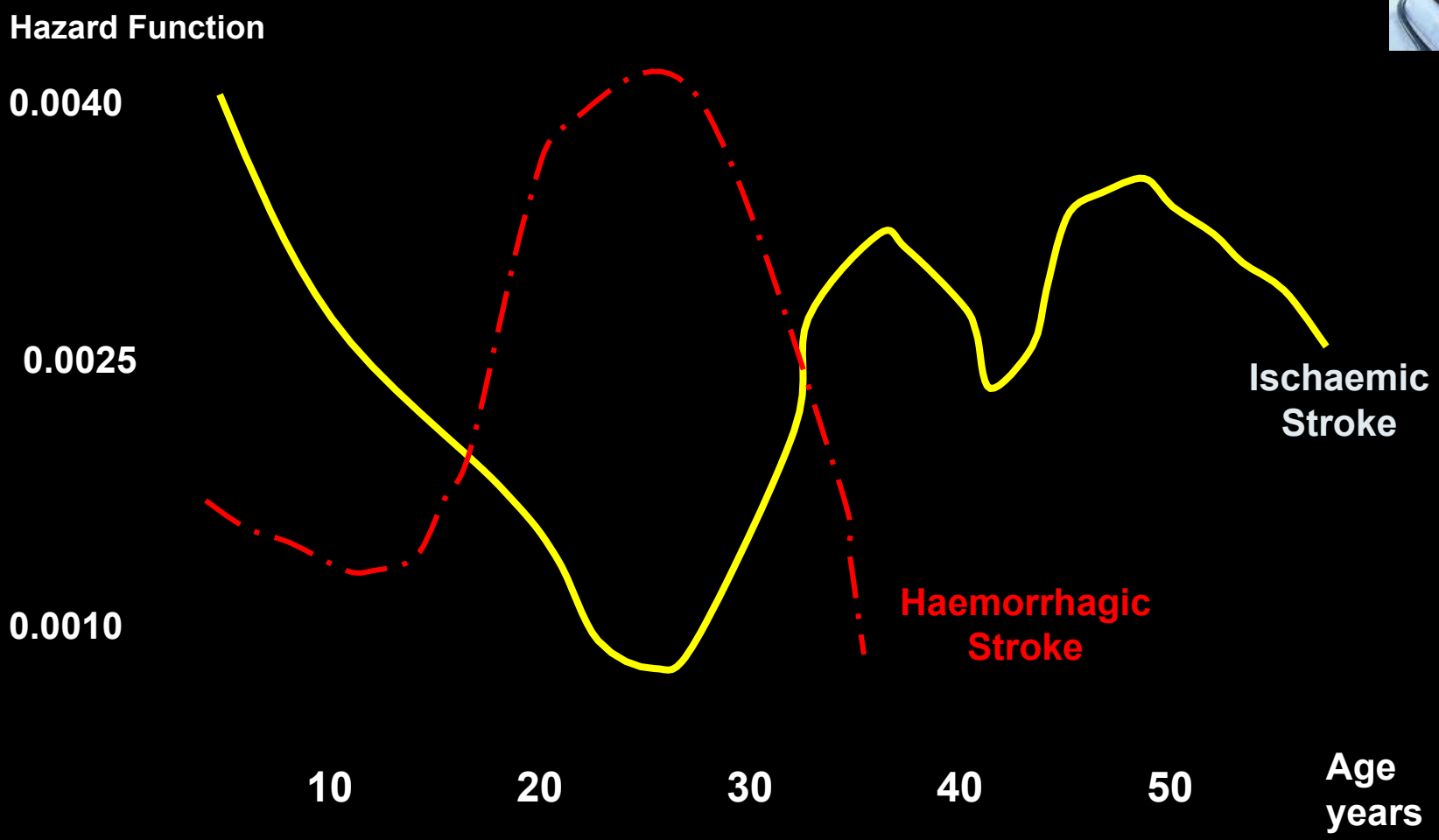
Ohene-Frempong 1998



Rates of infarctive and haemorrhagic stroke in HbSS patients by age

Ohene-Frempong 1998

25% by age 40



What clinical neurological syndromes do we recognise in 2022?

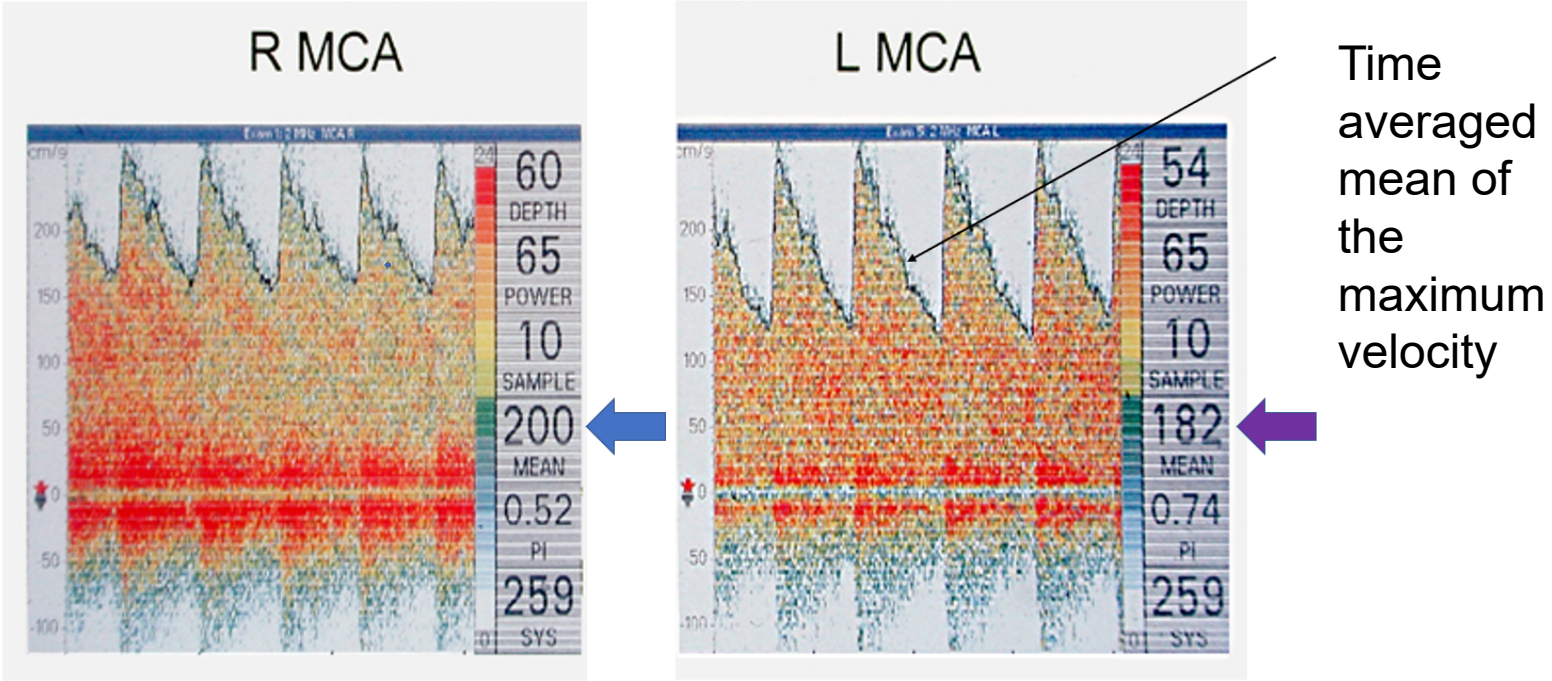
Less arterial ischaemic stroke

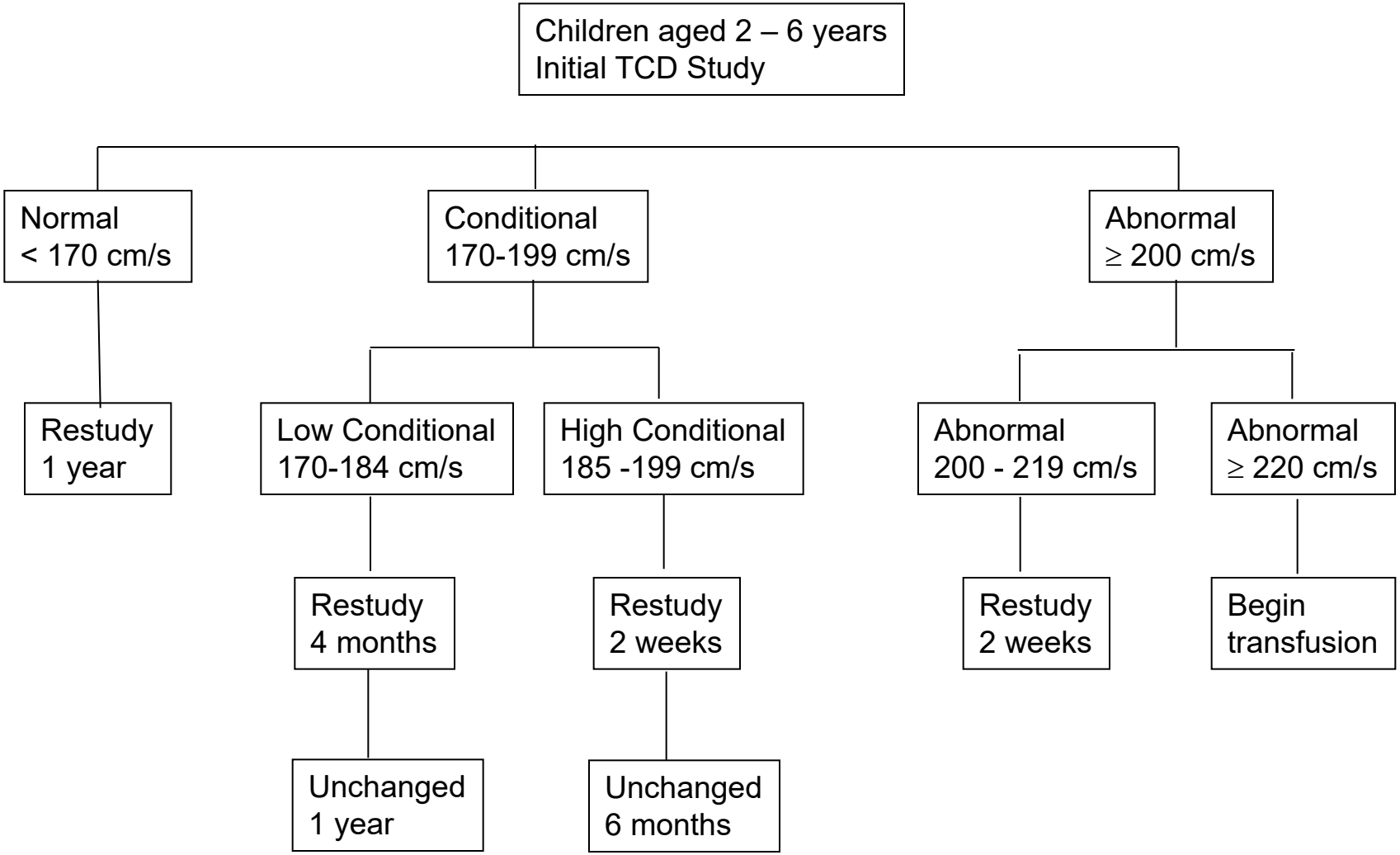
BUT

Stotesbury, Adams, Kirkham 2021 in Gladwin et al book

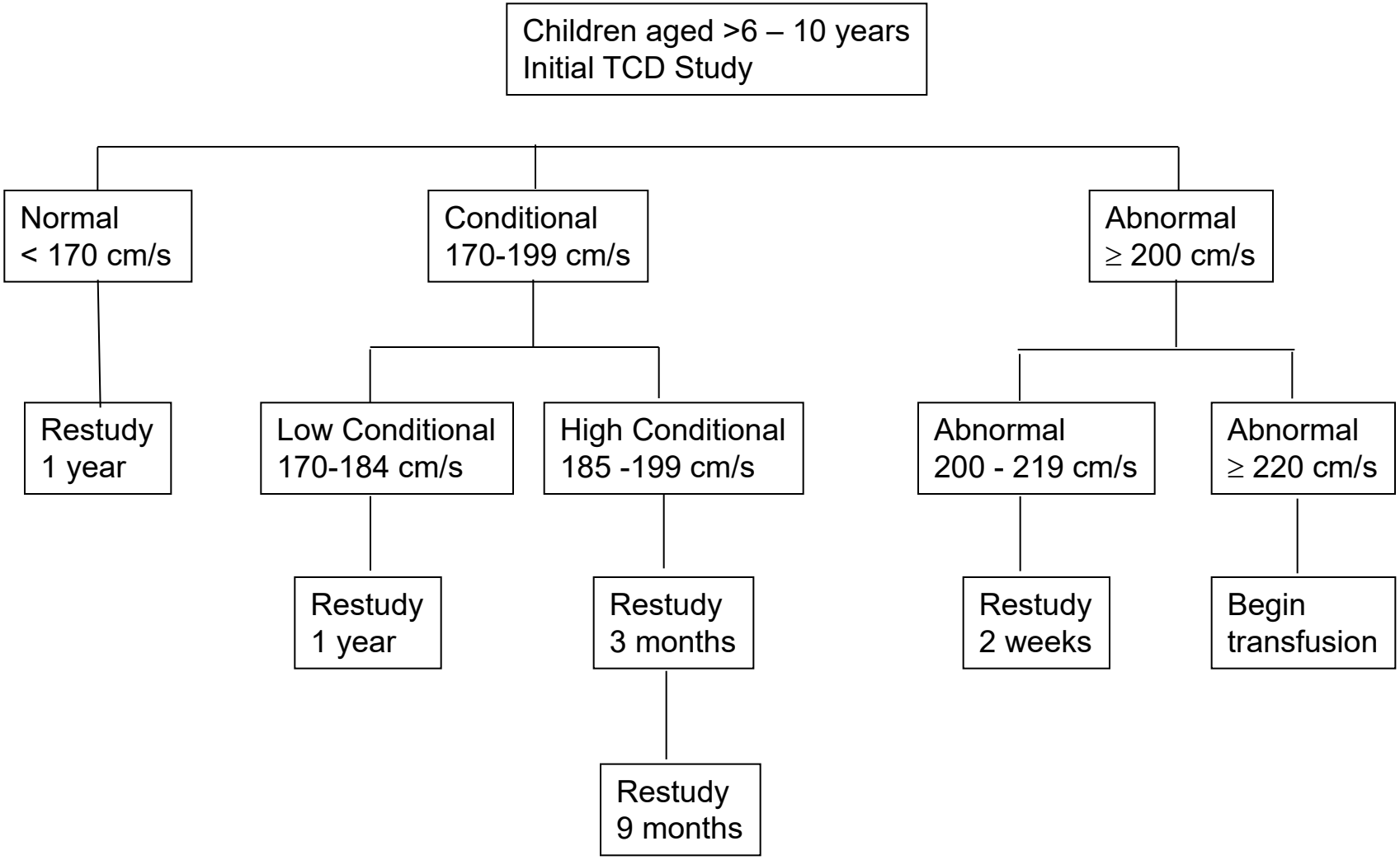
Transcranial Doppler: endpoint for STOP

TWiTCH
SPRING
HOPE



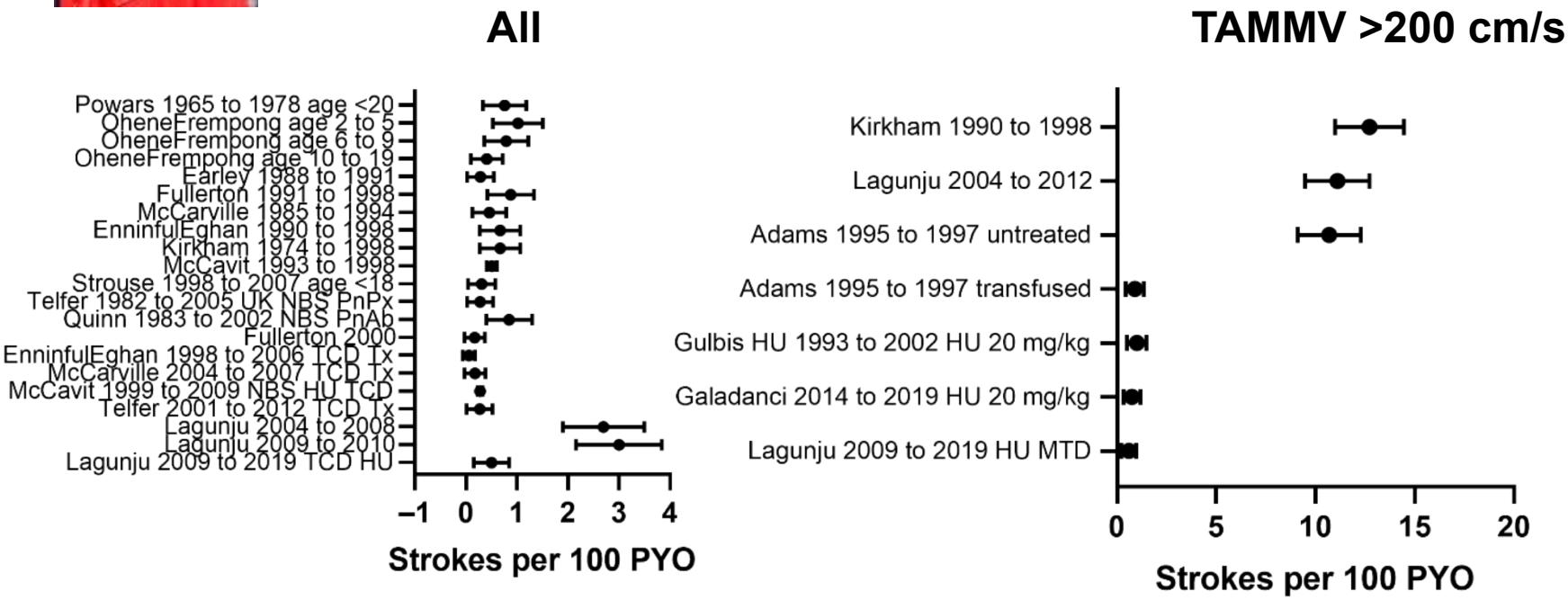


TCD (non-imaging) blood velocity action limits and follow up protocols for sickle cell children aged between 2 and 6 years. (Time-averaged maximum mean blood velocities) The action limits could be 10% lower when using TCDi to allow for the reported differences between imaging and non-imaging techniques.

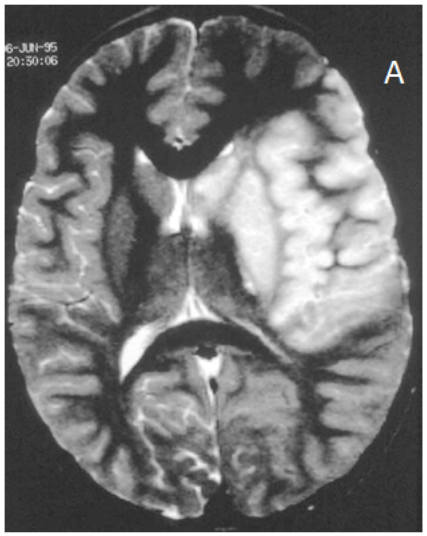


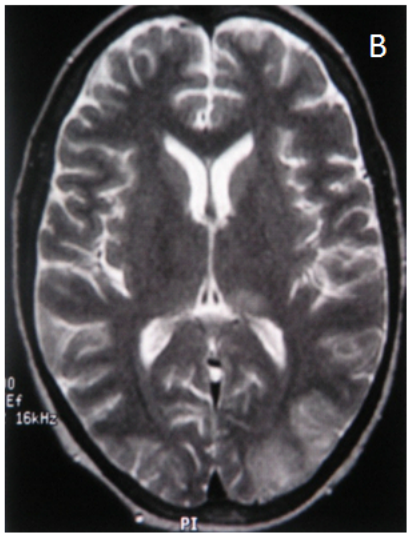
TCD (non-imaging) blood velocity action limits and follow up protocols for sickle cell children aged between 6 and 10 years. (Time-averaged maximum mean blood velocities) The action limits could be 10% lower when using TCDi to allow for the reported differences between imaging and non-imaging techniques.

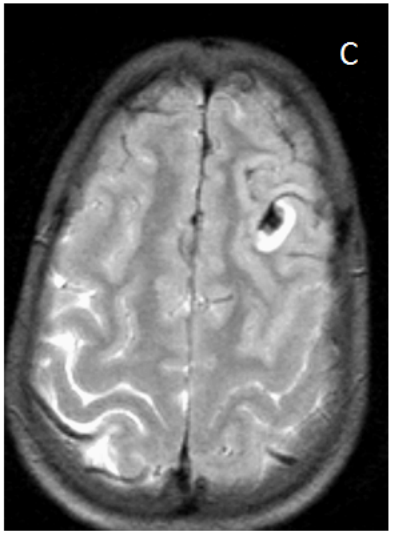
Epidemiology of stroke in SCD *Kirkham & Lagunju 2021*

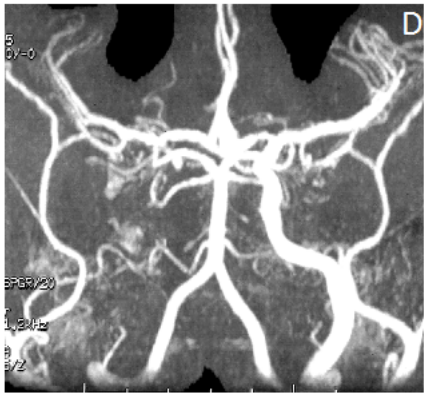


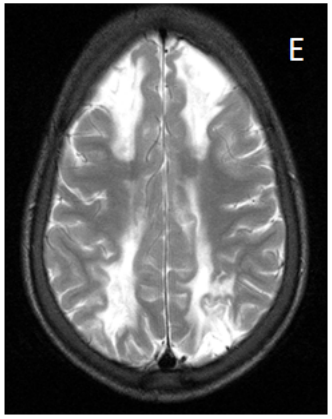
Kirkham & Lagunju 2021

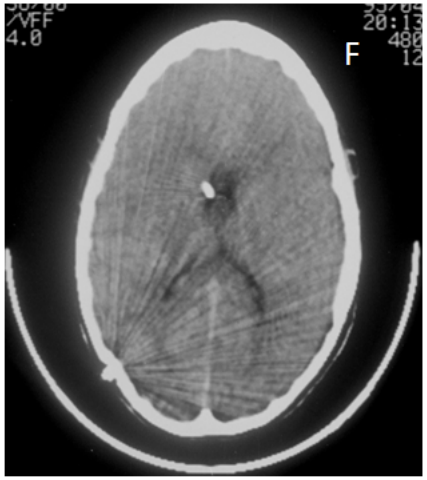












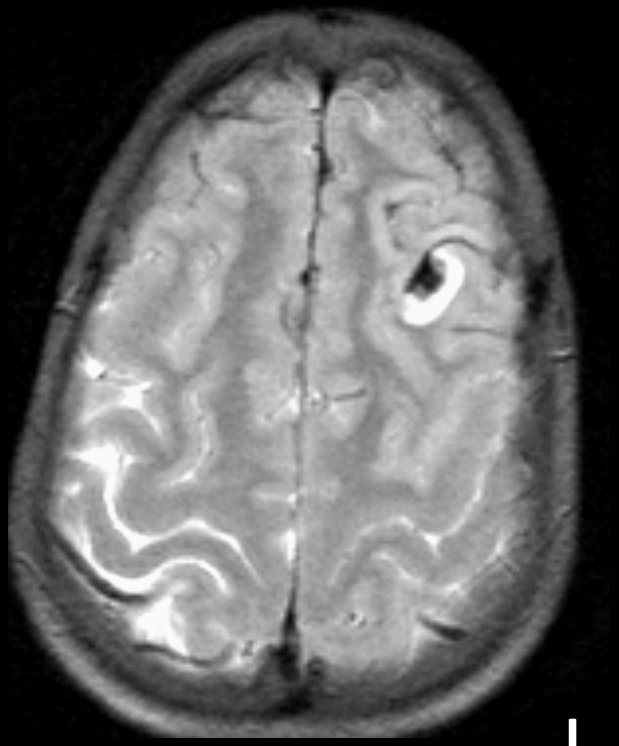
Acute severe headache

Haemorrhagic stroke on CT scan

Subdural

Post minor trauma

Intracerebral



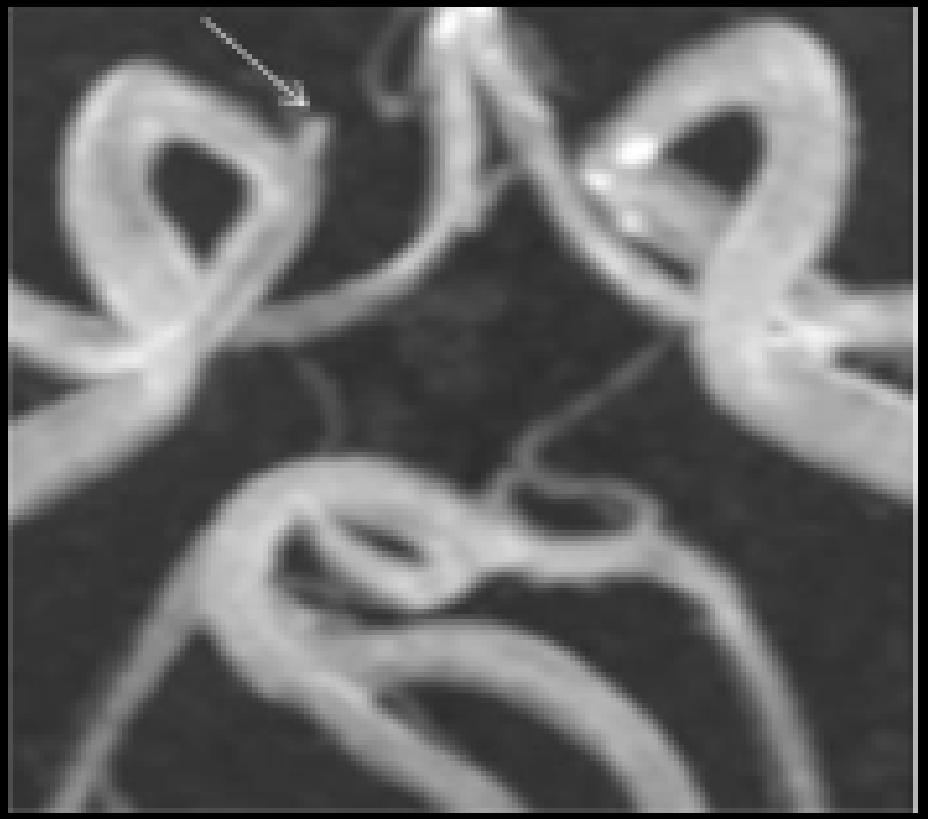
R L

Spontaneous

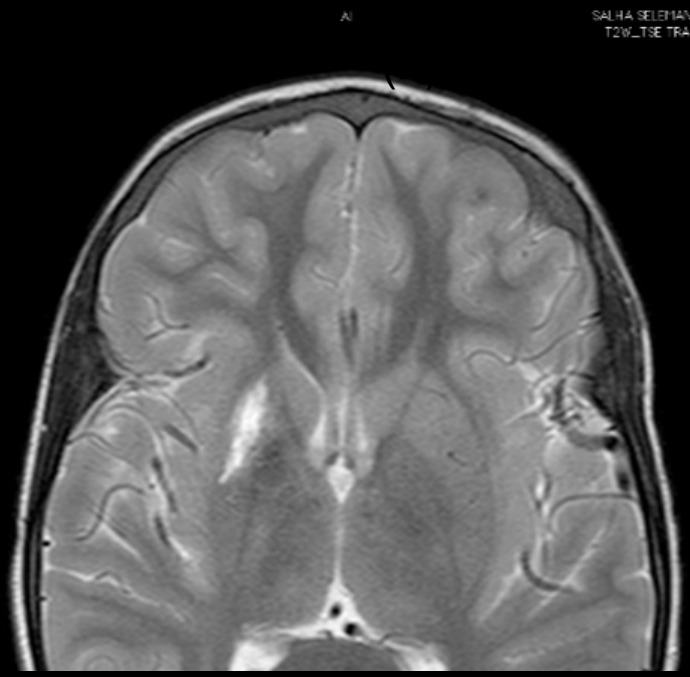
Subarachnoid

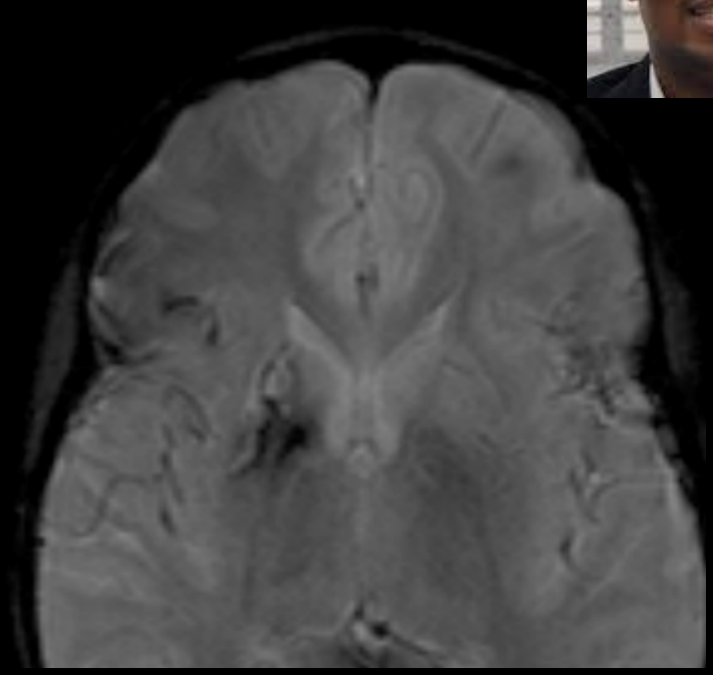
Post rapid transfusion for chest crisis

Cerebral aneurysm

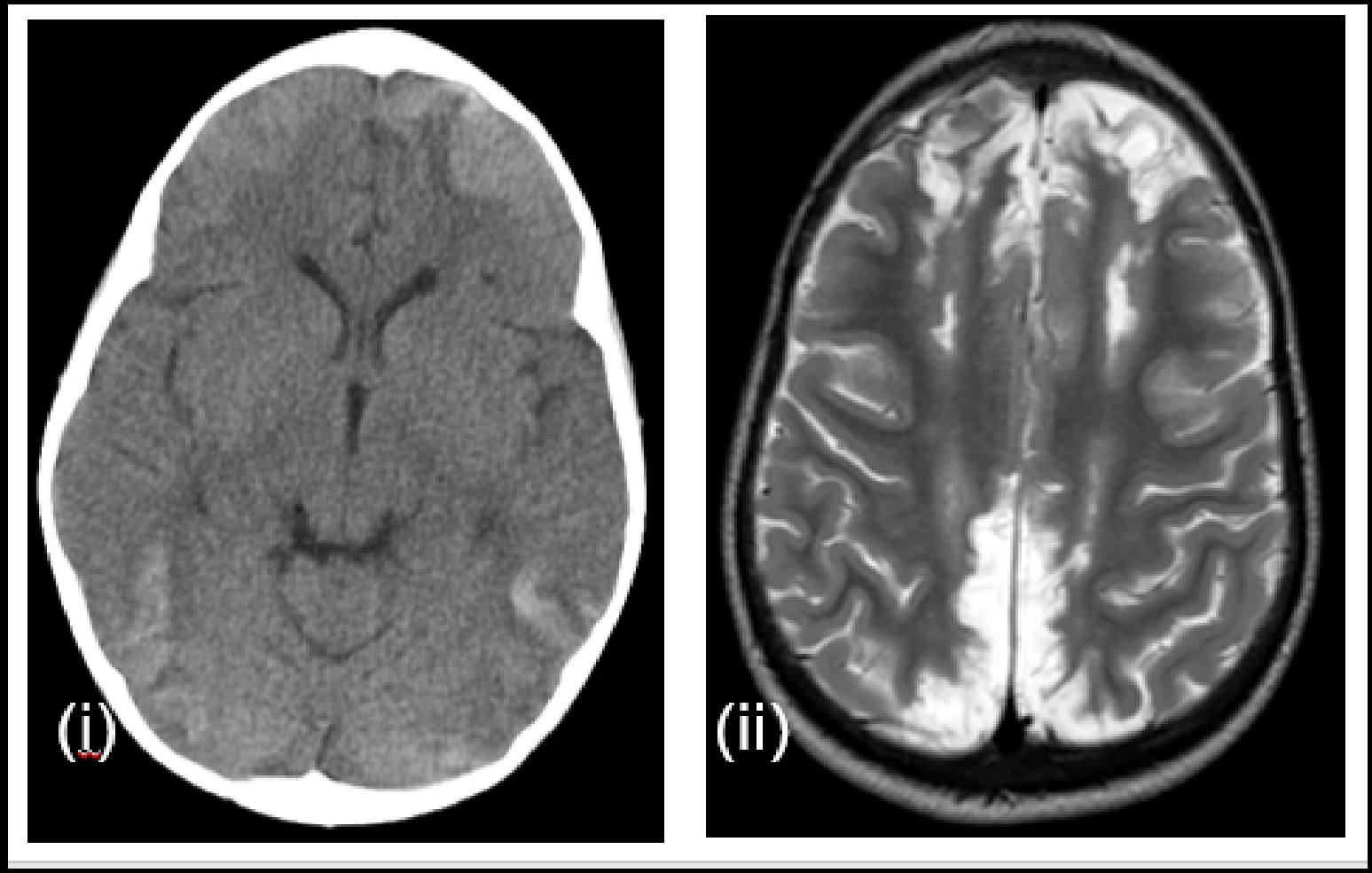


Ischaemic stroke then haemorrhage on gradient ECHO MRI





Haemorrhage then ischaemia post chest crisis



DO NOT TRANSFUSE TOO FAST **DO NOT REDUCE BLOOD PRESSURE**

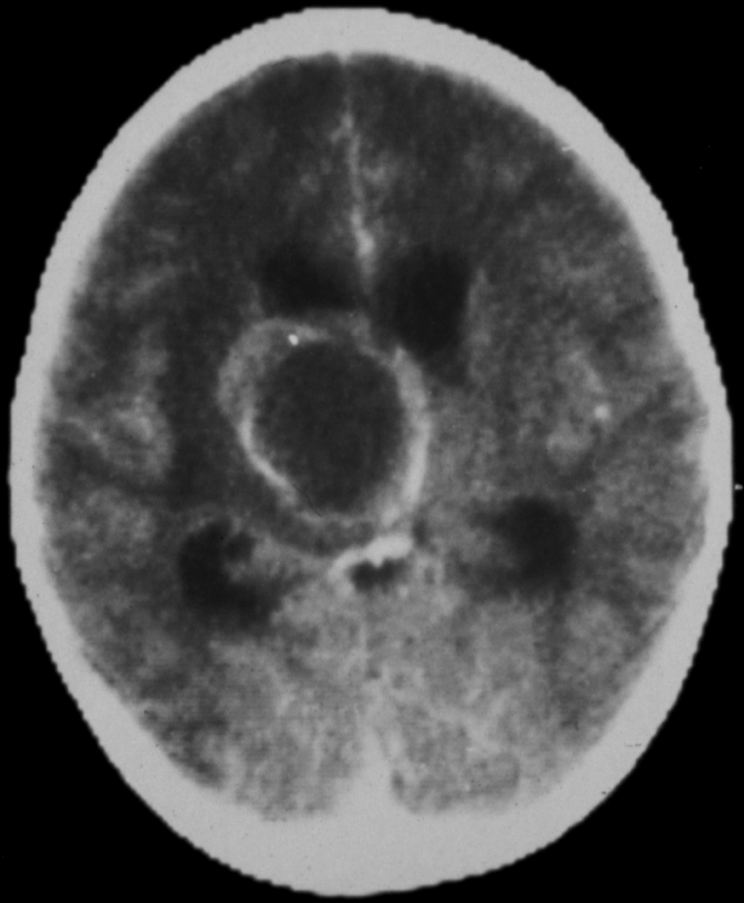
1st acute severe headache in SCD

- Manage as a neurological emergency
- Urgent neuroimaging
  - CT
  - MRI with gradient ECHO/ SWI and MRA
- If haemorrhage contact
  - neurosurgical unit
  - Paediatric or adult neurologist
- If infarct emergency transfusion
- If no haemorrhage/infarct ?migraine

Acute seizures

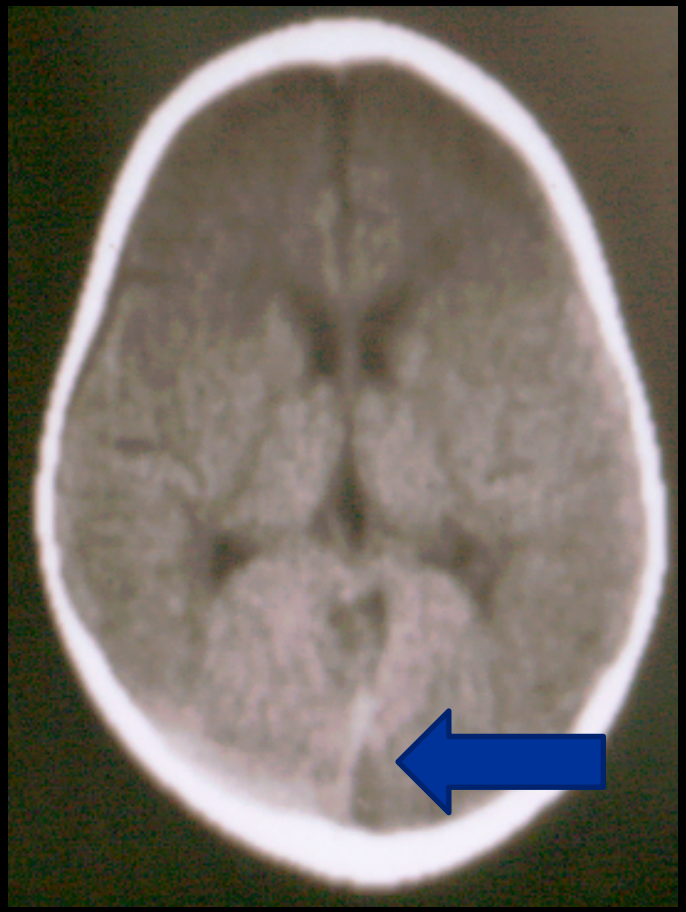
18 months ‘febrile convulsion’

Cerebral abscess



Sagittal sinus thrombosis

Pneumococcal meningitis, longstanding epilepsy



Straight sinus thrombosis

HbSC, unexplained hydrocephalus in infancy, headache, seizures, coma

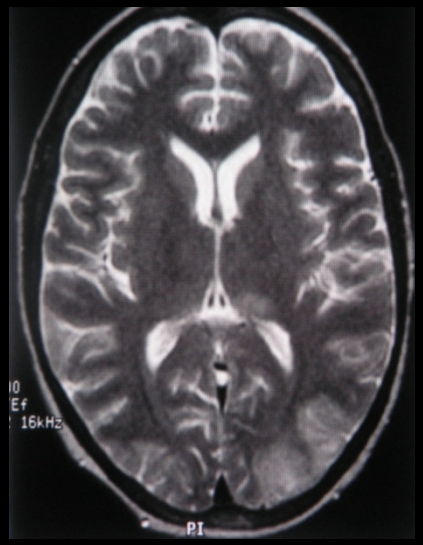
Straight sinus thrombosis

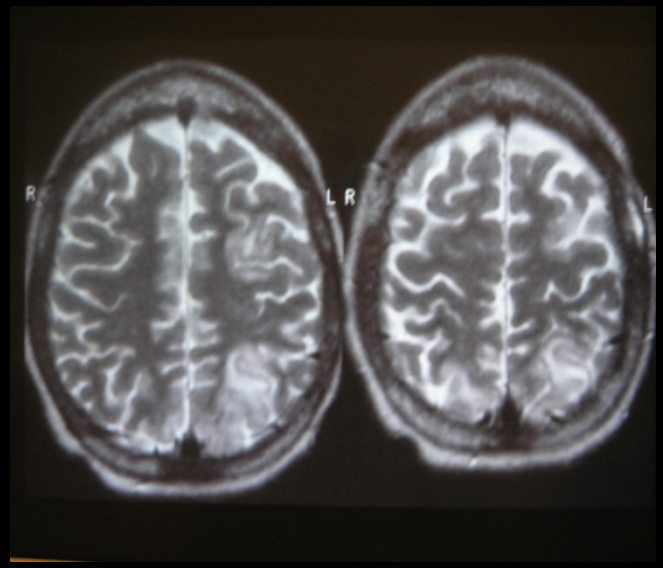
Sébire 2005

‘Reversible posterior leukencephalopathy’

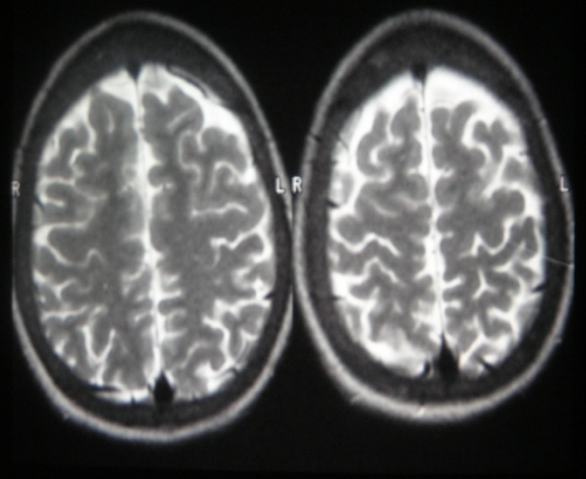
Henderson 2003, Solh 2016

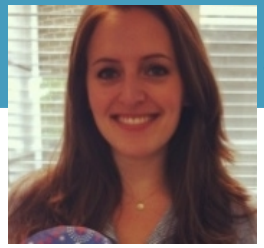
Chest crisis
Seizures
Coma





Chronic epilepsy

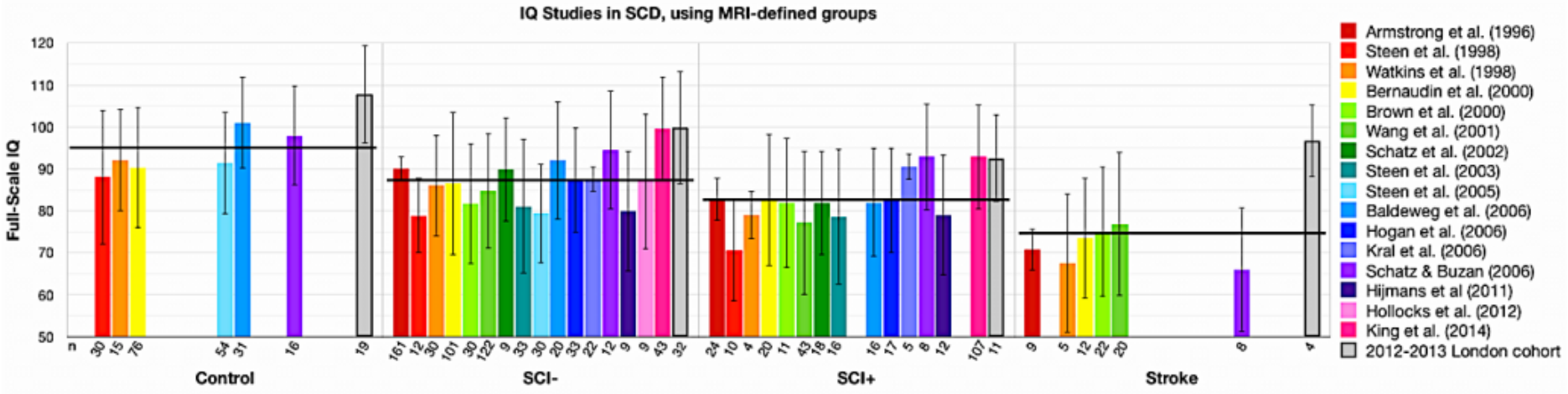


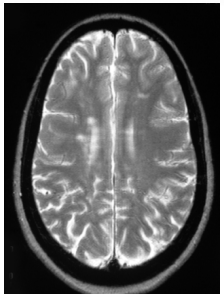


Neuropsychological functioning

Kawadler et al 2016

- Meta-analysis from all studies using Wechsler full-scale IQ and MRI to distinguish SCI- and SCI+





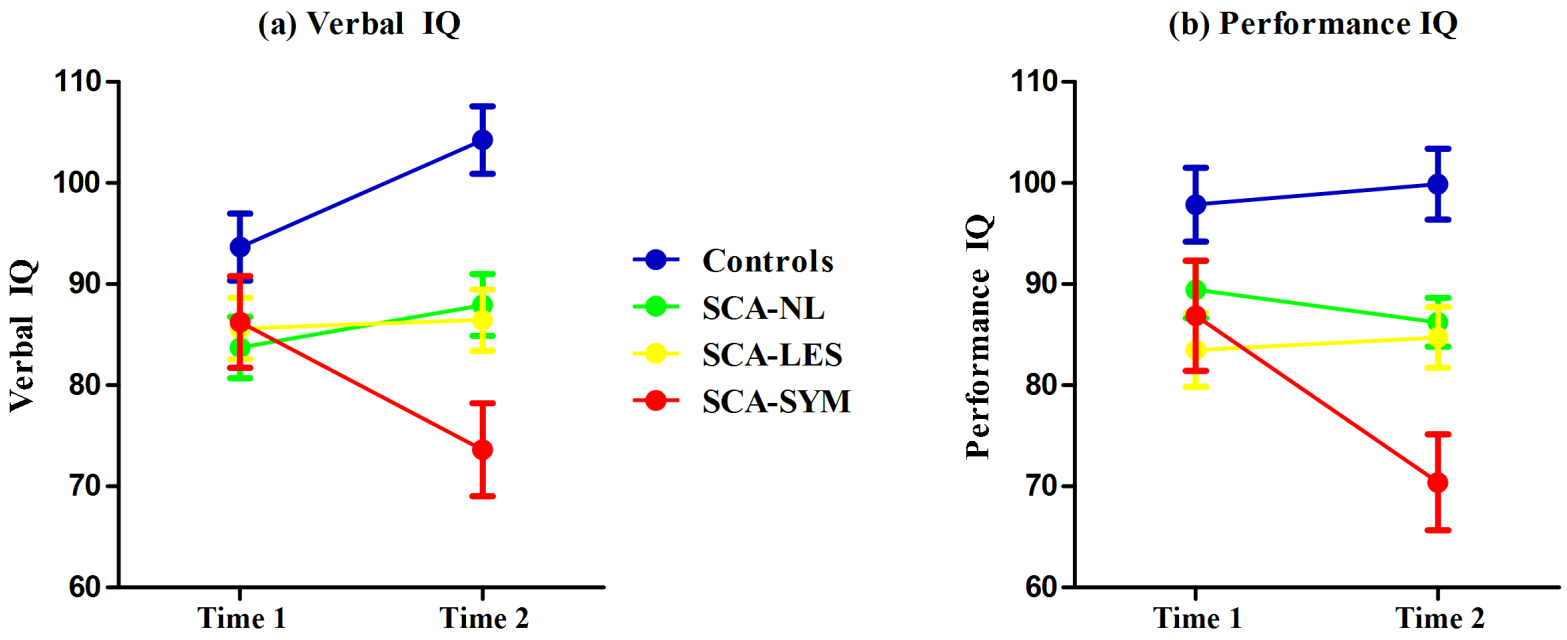
SCD: Decline in IQ with age

Wang et al 2001 (CSSCD)

- Children with HbSS with normal MRI (without SCI)
  - Central over-read of MRI (?field strengths)
  - SCI: abnormal T2-weighted signal intensity
  - Change from WISC-R to WISC-III
  - Statistically significant decline in
    - Verbal IQ 0.5 points/year
    - Coding 0.2 points/year
    - **Maths 0.9 points/year**
  - But not in digit span or reading

East London longitudinal IQ
44 SCA, 15 controls 9+/-2 years after initial IQ at 8+/-2 years (74% retention)

Hogan 2008

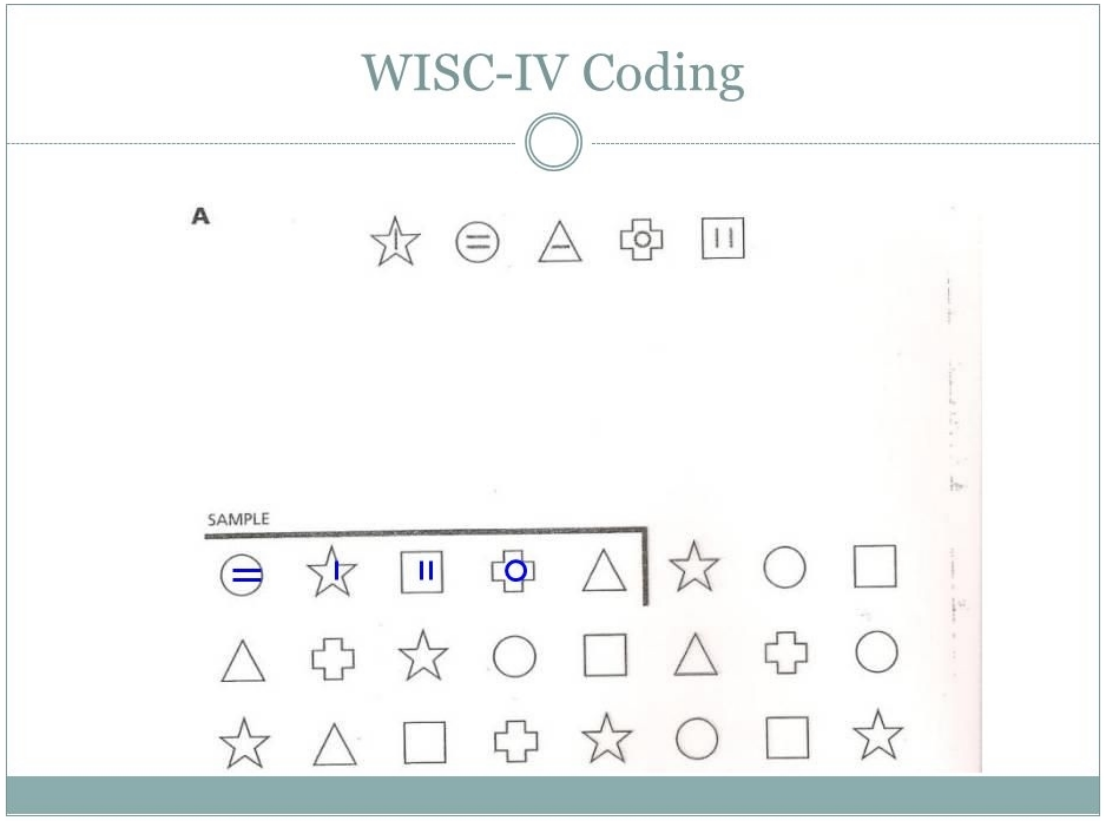


Cognitive decline in adults?

Ampomah et al 2022

Test	Baseline Raw Mean (SE)	Follow up Raw Mean (SE)	P value	Mean Difference (Decline)
RQCST				
Verbal	24.22 (1.03)	22.50 (.88)	0.66	-1.72 (0.72)
Non -Verbal	24.06 (0.70)	17.63 (0.73)	<.01	-6.44 (0.79)
Global Scores	59.78 (1.24)	51.09 (1.22)	0.14	- 8.69 (1.07)
Trail Making Test				
TMTa	81.03 (9.12)	67.55 (5.78)	0.04	-13.49 (10.46)
TMTb	197.42 (15.30)	173.21 (15.1)	0.14	-24.21 (18.00)
TMT(b-a)	118.22 (15.46)	109.63 (14.47)	0.84	-8.59 (21.84)
Modified Card Sorting				
Task category	3.79 (0.34)	3.04 (0.34)	0.08	-0.75 (0.30)
% Perseverative	28.69 (4.18)	39.28 (5.23)	0.07	10.59 (5.62)
WAIS-R-NI				
Digit Symbol Substitution	30.72 (1.60)	29.13 (1.53)	0.01	-1.59 (1.22)
Block design	10.97 (1.35)	21.85 (1.63)	0.047	10.88 (1.65)
Digit span	12.53 (0.47)	11.75 (0.56)	0.43	-0.78 (0.53)
Spatial span	10.76 (0.55)	10.07(0.42)	0.19	-0.69 (0.51)
Rey-Osterrieth				
Rey Copy	33.16 (0.82)	20.69 (0.95)	<0.01	-12.47 (0.92)
Immediate Recall	19.77 (1.24)	11.02 (0.73)	<0.01	-8.75 (1.20)

Processing speed

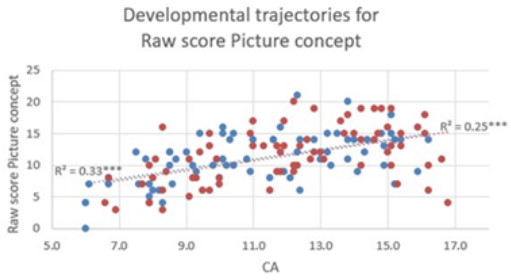


Cognitive function differences between children with SCD and controls in Dar es Salaam

Jacob et al 2022

Mean (SD)	Mean difference from controls		ANOVA F	P	Post-hoc (Dunnett's)
	SCI- (n=48)	SCI+ (n=21)			
Raven's	0.388	-1.211	0.344	.710	
PSI	-4.303	-9.303	3.690	.028	SCI+<Control
PRI	-1.77	-5.677	2.175	.118	
WMI	-1.819	-7.420	2.235	.111	

Difference in trajectory for Processing speed? *Jacob 2022*



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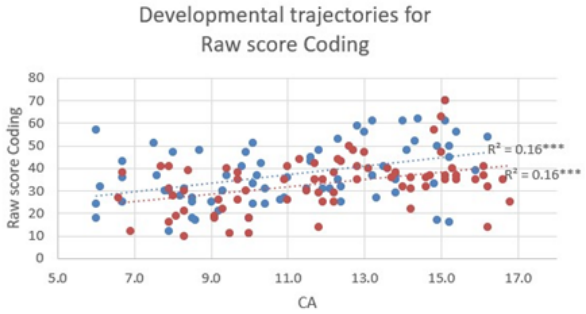

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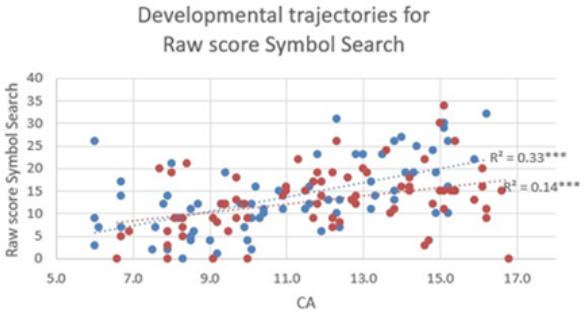

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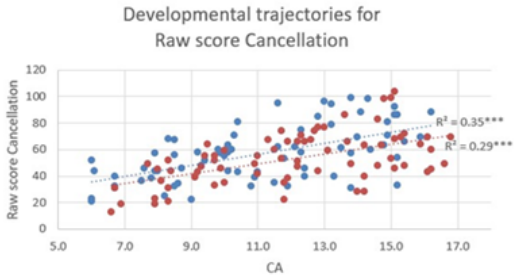
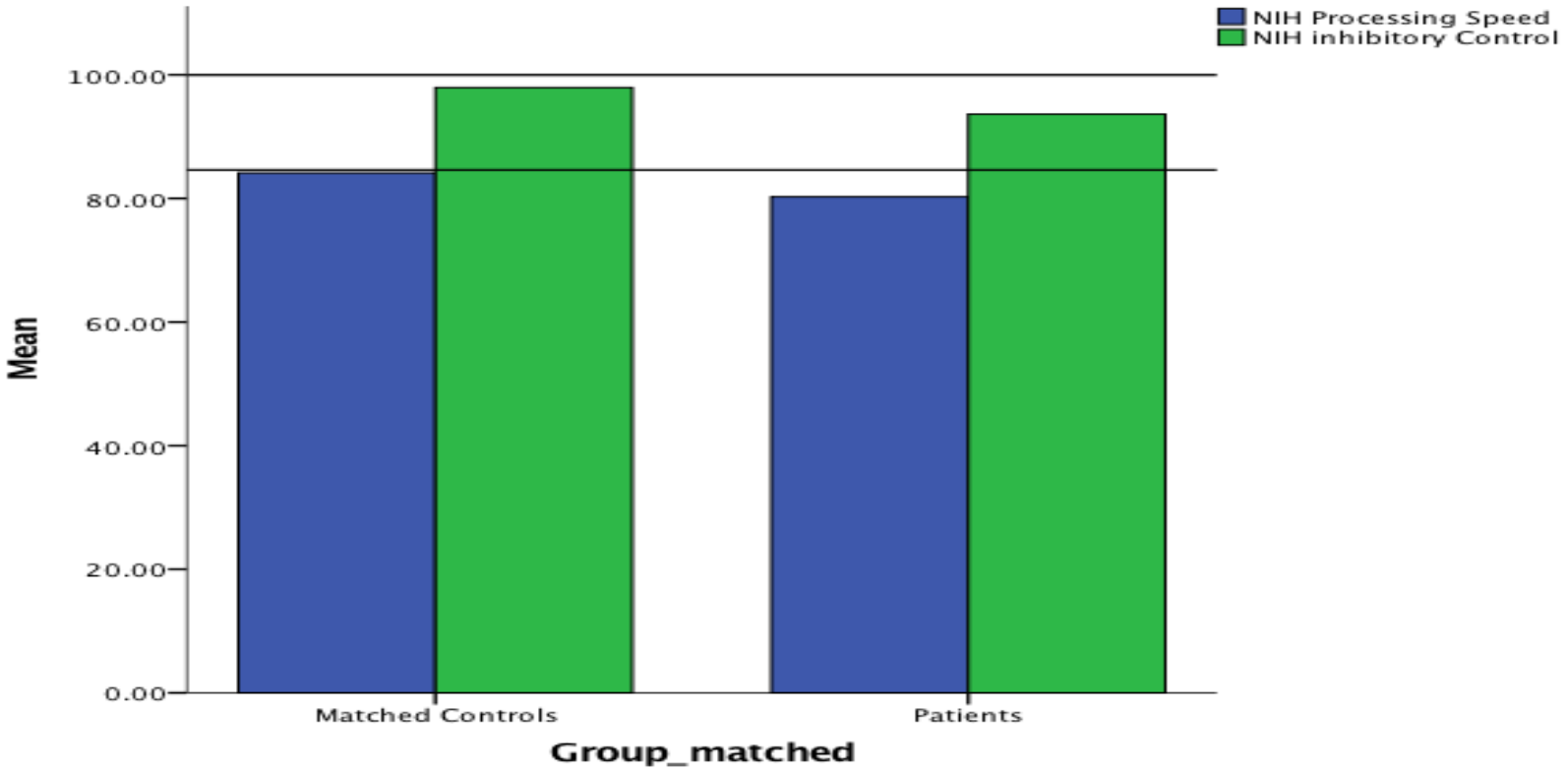


D

Processing Speed (NIH toolbox) in preschool children with and without sickle cell anemia

Downes et al 2016

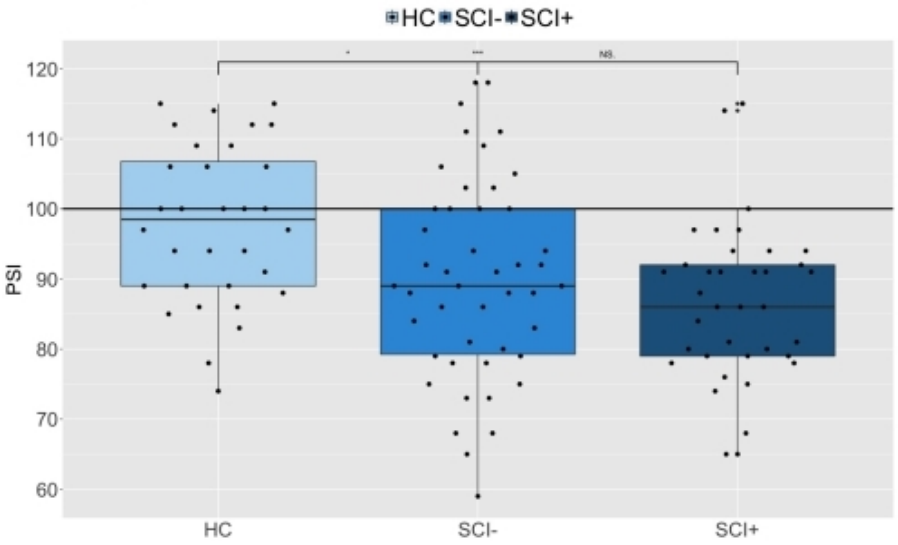
- Relatively intact processing speed and inhibitory control at this early stage in SCA



PSI in 84 young people with SCA

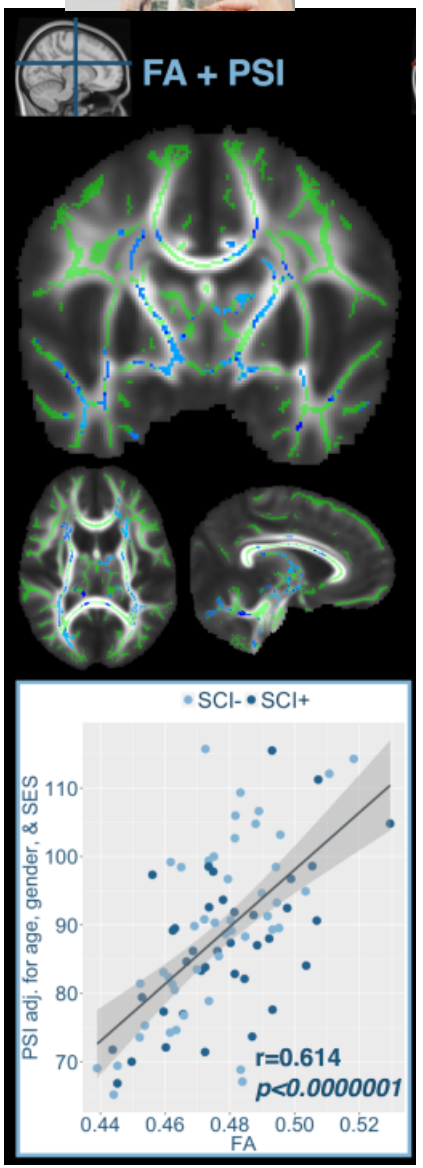
Stotesbury 2018

- Patients had significantly lower PSI than controls by 9.34 points
- Trend for lower FSIQ abolished when PSI included as a covariate.
- Patients with and without SCI had significantly lower PSI than controls



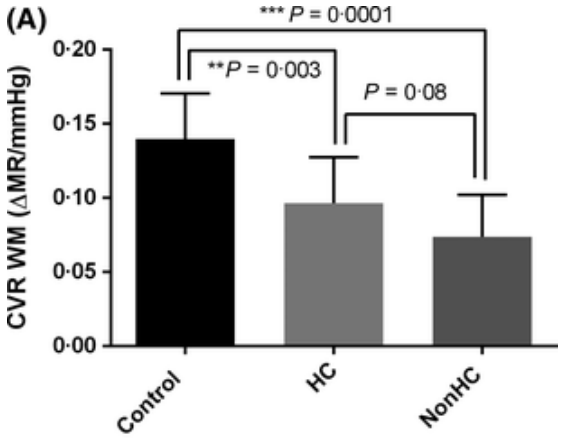
Diffusion tensor imaging TBSS and PSI *Stotesbury 2018*

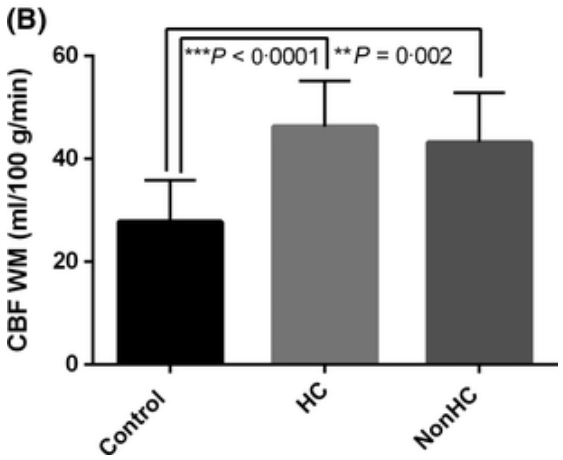
- Positive correlations of Fractional Anistropy & Processing speed index across the internal capsule and corpus callosum
- Correlations remained significant when examined in SCI+ and SCI- groups separately.

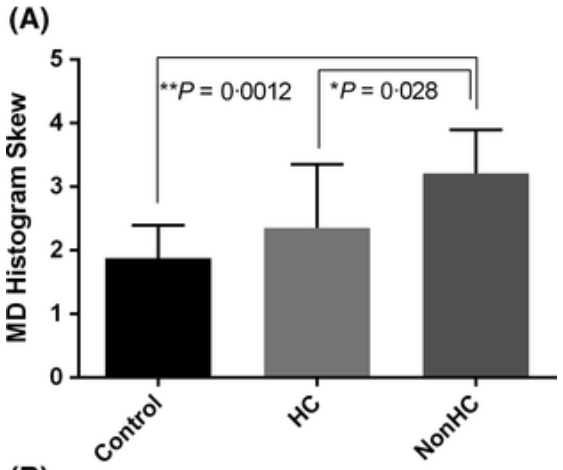


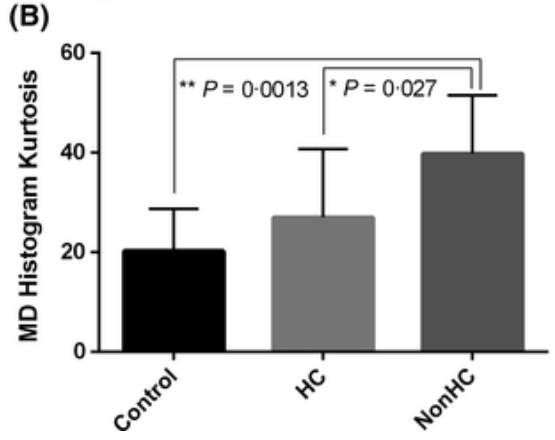
Diffusion Tensor Imaging
Effect of hydroxyurea on quantitative WM MRI

Kapustin et al 2019









Blood transfusion and cognitive function

-Anna Hood, Washington University, St Louis (now UCL)

- Children with SCD undergoing transfusion
- NIH toolbox
  - Executive: flanker, working memory
    - Improved near transfusion (higher scores than HU)
    - Declined far from transfusion (lower scores than HU)
    - Change in hemoglobin was significantly related to change in executive function in patients receiving transfusion
  - Processing speed: pattern comparison
    - Practice effect – for children with SCD and controls

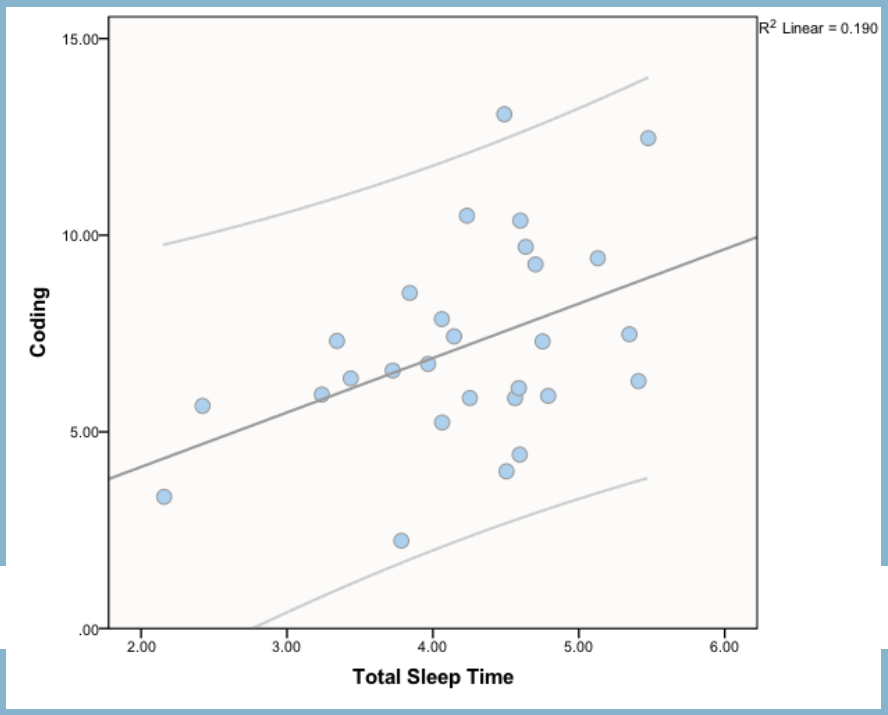
Effect of BMT on processing speed

	PSI pre BMT	PSI post BMT
Prussien	79.81 (12.29)	86.31 (14.04)

Hsieh et al – increase in PSI in patients with SCD undergoing BMT and controls

Coding and total sleep time during IP PSG

Koelbel 2017



***p* = 0.02**
r= 0.44

Controlled for Age, Gender, BMI

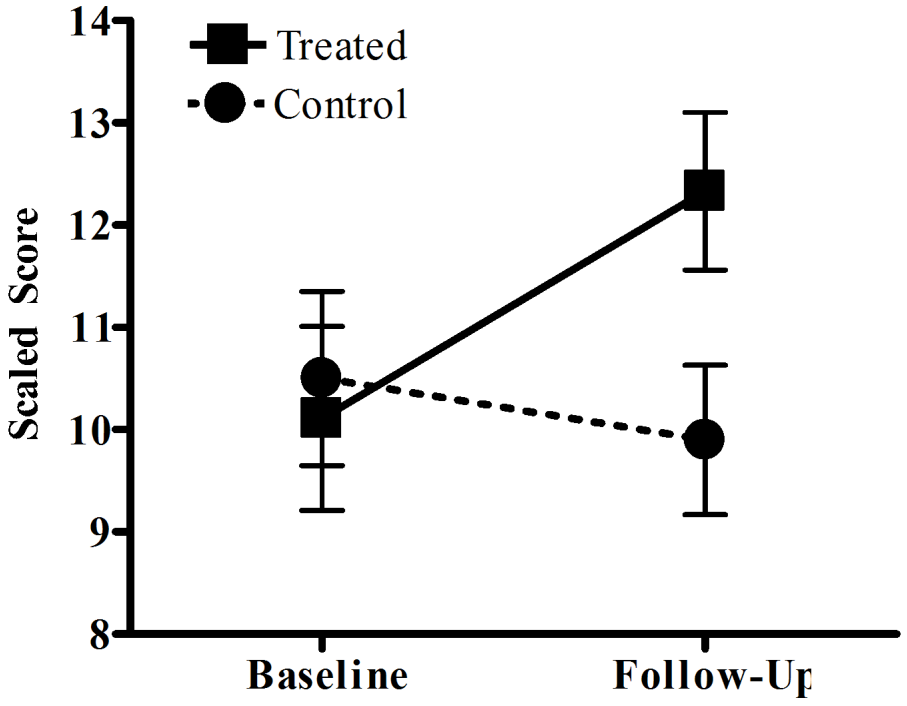
Cancellation (Wechsler)
-test of attention and processing speed

Overnight Auto-adjusting Positive Airway Pressure (APAP)

POMS1 pilot: Processing speed and Cancellation in those on APAP vs standard care *Marshall et al 2009*

Treated
Controls

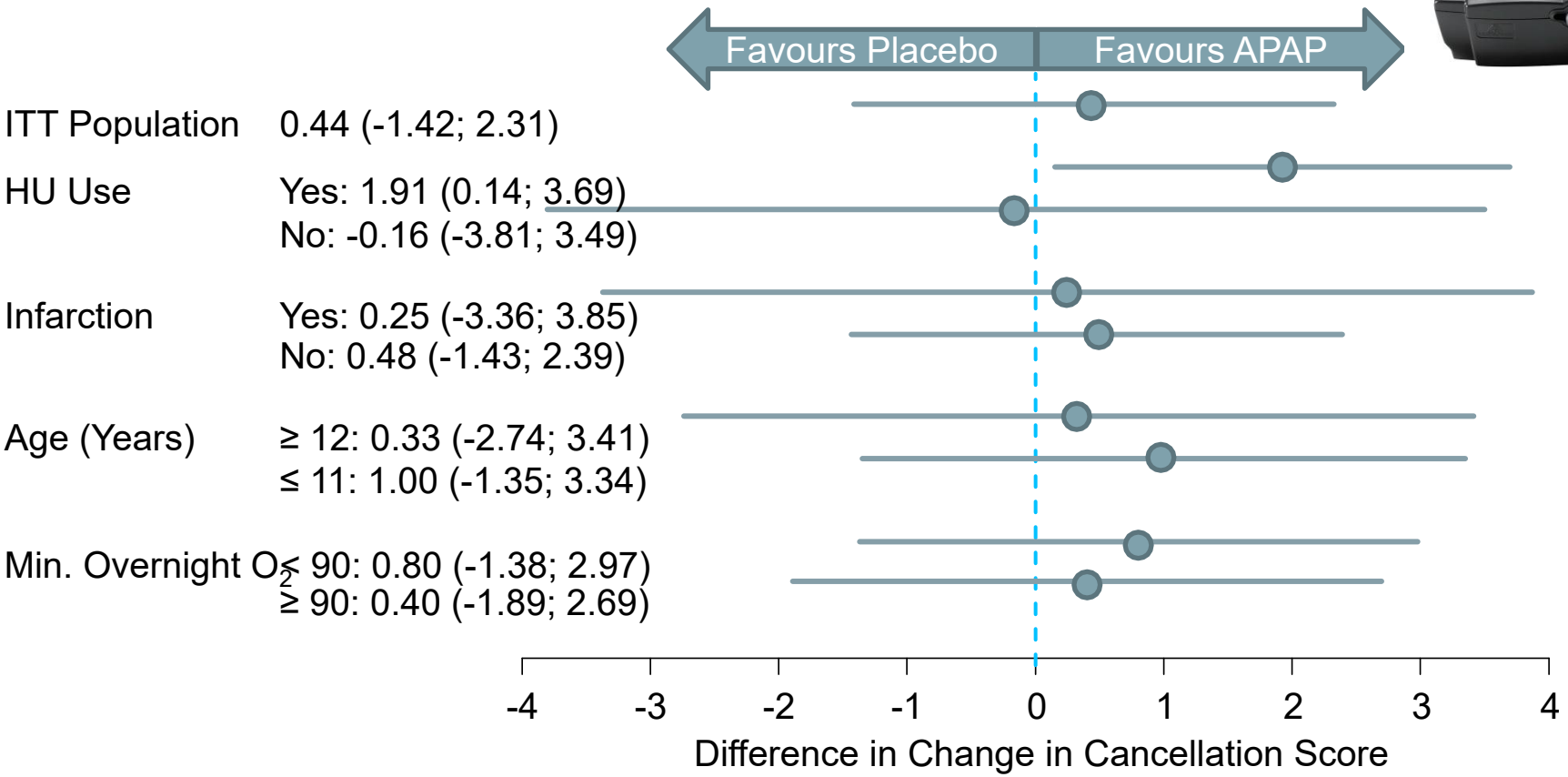
Scaled Score



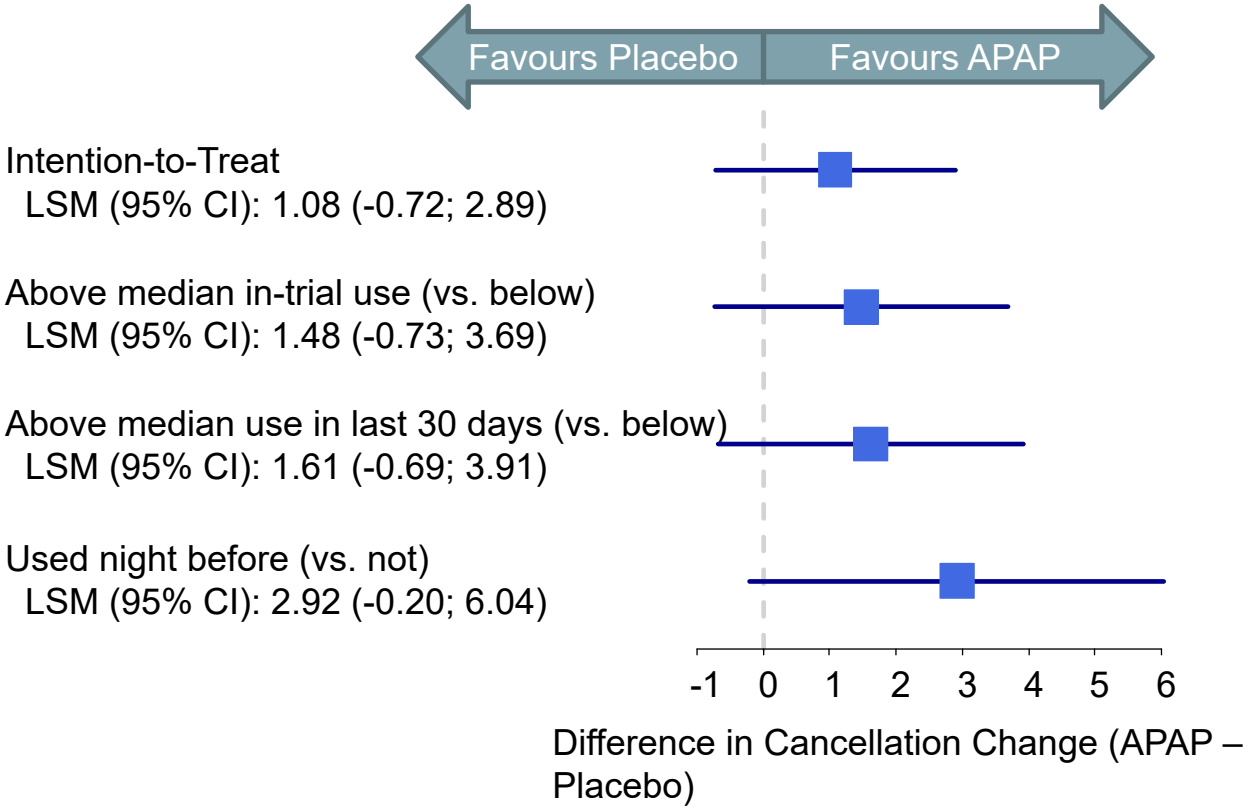
Processing speed

Cancellation

POMS2B APAP vs Standard care
Differences in Cancellation Scores Baseline to 6m



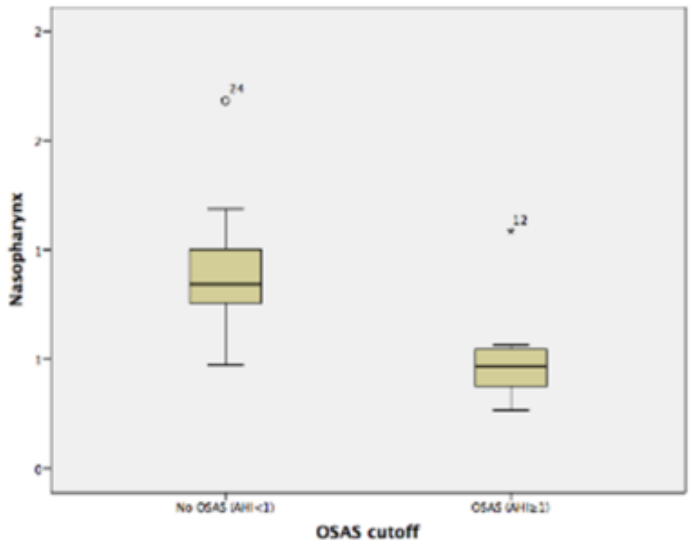
POMS2B Cancellation by Compliance

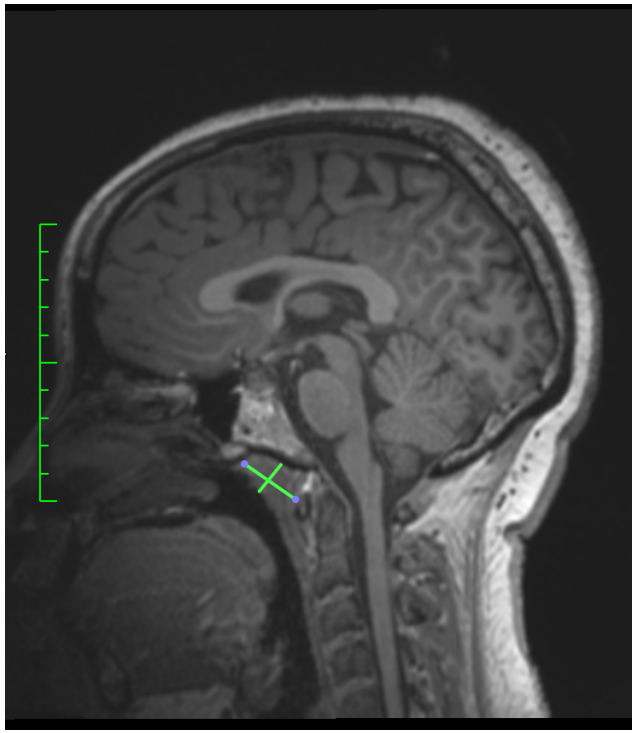


Cognition in preschool children with sickle cell anemia with and without previously diagnosed obstructive sleep apnoea *Downes 2022*

Follow-up Measure	SCA+OSA (n=3) Mean (SD)	SCA-OSA (n=7) Mean (SD)	p-value
WPPSI FSIQ	93.33(8.5)	99.28(10.9)	.42
WPPSI Coding	6.33 (1.5)	10.43 (2.2)	.02
NIH Processing Speed	68.41(7.4)	86.17(11.2)	.05
NIH Inhibitory Control	77.97(10.1)	93.59(24.3)	.41
BRIEF GEC	60.33(15.9)	55.6(18.9)	.73

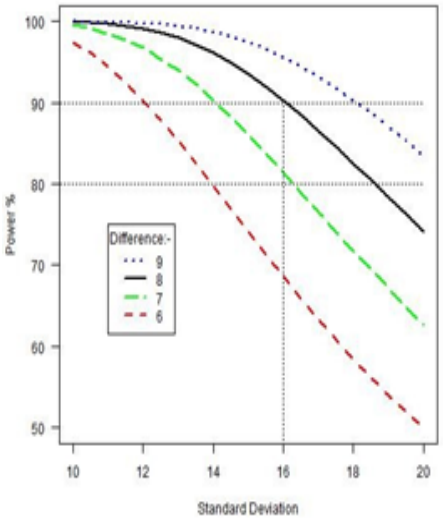
Nasopharynx smaller and adenoids larger in children with SCA and OSA





SMILES Study Design

SMILES
Study of Montelukast in Children with Sickle Cell Disease



Up to 180 children with sickle cell anaemia and sleep-disordered breathing (snoring and any degree of abnormal overnight oximetry)

NIH toolbox processing speed and executive composite (inhibition and switching); sleep and asthma questionnaires; MRI adenoids and brain for tract-based spatial statistics

Randomisation

Montelukast < 6 years 4mg; > 6 years 5mg

Placebo

NIH toolbox processing speed and executive composite (inhibition and switching); sleep and asthma questionnaires; MRI adenoids and brain for tract-based spatial statistics

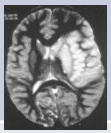
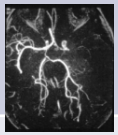
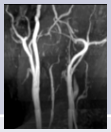
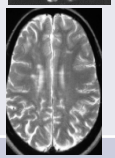
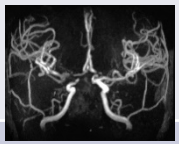
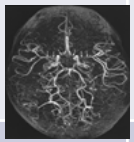
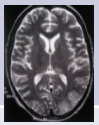
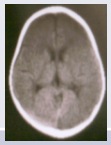
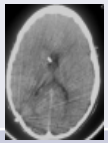
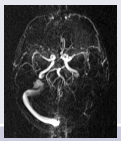
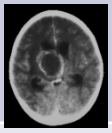
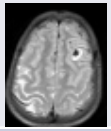
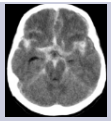
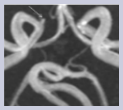
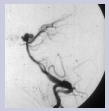
Prevention of neurological complications in SCD

- All stroke syndromes seen in SCD
  - Less ischaemic stroke with TCD screening and primary prevention
  - Recommendation is to *not* exclude children with SCD from traditional evaluation, including:
    - Imaging of cerebral vasculature
    - Echocardiogram
- Cognitive compromise in patients with SCD and
  - Some domains, e.g. processing speed, may improve with effective treatment
  - ?Benefit of
    - Blood transfusion
    - Hydroxyurea
    - Bone marrow transplant
    - Voxelator
    - Better sleep (nutrition/social support)

Publish!

- Frontiers in Neurology
- Frontiers in Stroke
- F1000

Stroke medicine for non-neurologists ;-) *Stotesbury et al chapter*

MRI	Vascular: MRA/MRV	Clinical and pathological findings	Treatment
	 	Sudden onset **stroke** with arterial territory infarct: stenosis, occlusion, dissection ICA, MCA, moyamoya. Exclude shunting	Transfuse, O2, Intensive care Stroke Unit -TL
	 	**Silent cerebral infarction**: no stroke but may have had seizures. Stenosis, occlusion, moyamoya ICA,MCA. Shunt	?Transfuse; ?Hydroxyurea
		**PRES: Posterior reversible encephalopathy syndrome** after rapid transfusion, acute chest, hypertension	Treat seizures, hypertension, hypoxia
	 	**Venous sinus thrombosis**: presents c hemiplegia, seizures, coma. CT : empty delta, thrombus, CTV /MRV	?Transfuse; rehydrate, anticoagulate
		**Abscess:** seizures, headaches, coma, raised intracranial pressure, fever	Antibiotics Neurosurgeon Intensive care
		**Intracerebral haemorrhage:** sudden onset very severe headache, coma. Venous , hypertension, aneurysm	Neurosurgeon Intensive care
	 	**Subarachnoid haemorrhage:** sudden onset very severe headache, coma . Aneurysm, venous , hypertension	Neurosurgeon Intensive care
		**Subdural haemorrhage:** headache, coma, raised intracranial pressure, skull infarction. Exclude trauma /NAI	Neurosurgeon Intensive care
		**Extradural haemorrhage:** headache, coma, raised intracranial pressure, skull infarction. Exclude trauma /NAI	Neurosurgeon Intensive care