Last known normal:
The evolution of acute stroke imaging beyond the ‘normal’ head CT

Neurology Grand Rounds, December 14th, 2018

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Disclosures

◊ Please see http://cme.wustl.edu for my full disclosures.
◊ I have no current potential financial conflict of interest.
◊ Research Support Grants:
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  ◊ IBM, FAANG (through index funds)
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  ◊ Washington University School of Medicine
  ◊ Occasional expert witness consultations
Today’s talk

- Evolution of evidence based acute stroke imaging
- Current state and controversies
- A hypothesis
A brief history of evidence based stroke imaging
Acute stroke

Noncontrast head CT

0 – 3 hours since last known well

NINDS

1995
Noncontrast head CT is often ‘normal’ in the first 6 hours

Figure 1. Histogram of ASPECTS distribution in patients randomized to rt-PA treatment or placebo.
Acute stroke

0 – 4.5 hours since last known well

Noncontrast head CT

NINDS

1995

ECASS-3

2008
Acute stroke

0 – 4.5 hours since last known well

Noncontrast head CT

Endovascular Treatment for Acute Ischemic Stroke — Still Unproven
Marc I. Chimowitz, M.B., Ch.B.

NINDS 1995
ECASS-3 2008
2013
IMS-3 MR-RESCUE SYNTHESIS-Expansion
Acute stroke

Noncontrast head CT

0 – 4.5 hours since last known well

Recanalization and Clinical Outcome of Angiography in the Interventional Management of Acute Stroke

Andrew M. Domchuk, MD, Mayank Goyal, MD, Sharon D. Emmad Gazi, BSc, Michael D. Hill, MD, Tudor G. Jovic, MD, Donald Frei, MD, Rüdiger von Kummer, Prof Dr med, Kevin Liebeskind, MD, Thomas A. Tomsick, MD, Yuko Y. Palesch, Investigators

Figure 2: Diagram shows post hoc baseline CT angiography distribution of any visible occlusions. The mRS distribution was not significantly different (generalized Wilcoxon test, $P = .011$).
### Endovascular thrombectomy after large-vessel ischaemic stroke: Systematic literature review and meta-analysis of patient data from 10 randomised controlled trials

<table>
<thead>
<tr>
<th>Age (years) (P_{interaction} = 0.07)</th>
<th>n</th>
<th>cOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-49</td>
<td>158</td>
<td>1.36 (0.75-2.46)</td>
</tr>
<tr>
<td>50-59</td>
<td>218</td>
<td>2.85 (1.72-4.72)</td>
</tr>
<tr>
<td>60-69</td>
<td>333</td>
<td>2.58 (1.49-4.48)</td>
</tr>
<tr>
<td>70-79</td>
<td>371</td>
<td>2.41 (1.55-3.74)</td>
</tr>
<tr>
<td>80-89</td>
<td>1080</td>
<td>2.44 (1.70-3.50)</td>
</tr>
<tr>
<td>≥80</td>
<td>198</td>
<td>3.68 (1.95-6.92)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ASPECTS (P_{interaction} = 0.29)</th>
<th>n</th>
<th>cOR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>0-5</td>
<td>121</td>
<td>1.24 (0.62-2.49)</td>
</tr>
<tr>
<td>6-8</td>
<td>475</td>
<td>2.34 (1.68-3.26)</td>
</tr>
<tr>
<td>9-10</td>
<td>682</td>
<td>2.66 (1.61-4.40)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alteplase (P_{interaction} = 0.43)</th>
<th>n</th>
<th>cOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>1090</td>
<td>2.45 (1.68-3.57)</td>
</tr>
<tr>
<td>No</td>
<td>188</td>
<td>2.43 (1.30-4.55)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stroke location (P_{interaction} = 0.17)</th>
<th>n</th>
<th>cOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA</td>
<td>274</td>
<td>3.86 (1.65-9.48)</td>
</tr>
<tr>
<td>M1</td>
<td>887</td>
<td>2.29 (1.73-3.04)</td>
</tr>
<tr>
<td>M2</td>
<td>94</td>
<td>1.28 (0.51-3.21)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NIHSS score (P_{interaction} = 0.45)</th>
<th>n</th>
<th>cOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10</td>
<td>177</td>
<td>1.67 (0.80-3.50)</td>
</tr>
<tr>
<td>11-15</td>
<td>307</td>
<td>2.68 (1.39-5.19)</td>
</tr>
<tr>
<td>16-20</td>
<td>473</td>
<td>2.81 (1.80-4.38)</td>
</tr>
<tr>
<td>≥21</td>
<td>321</td>
<td>2.52 (1.40-4.54)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Onset to randomisation (P_{interaction} = 0.10)</th>
<th>n</th>
<th>cOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤300 min</td>
<td>1070</td>
<td>2.66 (1.83-3.87)</td>
</tr>
<tr>
<td>&gt;300 min</td>
<td>208</td>
<td>1.76 (1.05-2.97)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex (P_{interaction} = 0.34)</th>
<th>n</th>
<th>cOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>676</td>
<td>2.54 (1.92-3.36)</td>
</tr>
<tr>
<td>Female</td>
<td>601</td>
<td>2.38 (1.46-3.88)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tandem lesion (P_{interaction} = 0.17)</th>
<th>n</th>
<th>cOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>122</td>
<td>2.95 (1.38-6.32)</td>
</tr>
<tr>
<td>No</td>
<td>1132</td>
<td>2.35 (1.68-3.28)</td>
</tr>
</tbody>
</table>

**Total** 1278
ICA terminus occlusion
Thrombectomy
Acute stroke

0 – 4.5 hours since last known well

Noncontrast head CT

0 – 6 hours, NIHSS ≥ 6

Head/neck CTA

1995
NINDS

2008
ECASS-3

2013

2015

MR-CLEAN
ESCAPE
SWIFT-PRIME
REVASCAT
EXTEND-IA
(and others)

IMS-3
MR-RESCUE
SYNTHESIS-
Expansion
Acute stroke

0 – 4.5 hours since last known well

Noncontrast head CT

0 – 6 hours, NIHSS ≥ 6

Head/neck CTA

>6 hours?

Astrup et al. 1981

NINDS 1995

ECASS-3 2008

2013

2015

2017

MR-CLEAN
ESCAPE
SWIFT-PRIME
REVASCAT
EXTEND-IA
(and others)

IMS-3
MR-RESCUE
SYNTHESIS-
Expansion
Measures that maintain or raise the residual perfusion in the area of acute focal ischemia are probably all-important determinants of the final outcome in stroke. At present, such therapeutic intervention is "blind" since the effect on hemodynamics in the ischemic area cannot be monitored. This problem is, however, being approached by the development of instrumentation for repeatable non-invasive 3-dimensional imaging of regional cerebral blood flow and metabolism.

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WashU’s role in imaging stroke

The Effect of Hemorrhage on Neuroimaging: Radiology

Max Wintzen, MD
Roland Bauwens, MD
Geoffrey Marc
Werner Hacke
Walter K.
Ja
Alma G.

Abstract—The role of imaging in acute stroke has expanded
recently, with new techniques being developed and implemen-
ted in clinical practice. These techniques include diffusion-
weighted imaging, perfusion imaging, and functional imaging.
Magnetic resonance imaging (MRI) and computed tomogra-
phy (CT) are the most commonly used imaging techniques.
MRI is more sensitive than CT for detecting ischemic injury
and is also useful for evaluating hemorrhagic stroke. CT is
more sensitive than MRI for detecting intracerebral hemor-
rhage and is useful for evaluating patients with known hem-
orrhagic stroke.

MRI in acute stroke

Andria L. Ford, MD
Ronen R. Leker, MD

Correspondence to
Dr. Ford:
fordal@wustl.edu

When considering IV tissue plasminogen activator (tPA)
for ischemic stroke, acute imaging must ensure neuro-
logic deficits are not due to intracerebral hemor-
rhage and ascertain the presence of early ischemic brain
changes in the 3- to 4.5-hour window. The National Insti-
tute of Neurological Disorders and Stroke (NINDS)
European Cooperative Acute Stroke Study (ECASS) III trial
allowed both CT and MRI for screening and treatment
and showed a significant benefit of tPA in the 3- to
4.5-hour window.

Lateralization of Basilar Occlusion

Witte T. Cross III, MD;

Original Articles

Magnetic resonance imaging in hyperacute

Jin-Moo Lee MD, PhD,
Chung Y. Hsu MD, PhD

Predicting the ischemic core and penumbra

- **PET**: Accurate, Limited availability
- **Noncontrast head CT**: Poorly accurate, Highly available, easy to use, and fast
- **MRI**: Accurate, Available but not fast (~30 minute delay at BJH)
- **CTP**: Modestly accurate, Highly available, easy to use, and fast
The current ‘winners’

<table>
<thead>
<tr>
<th>ADC &lt; 620</th>
<th>rCBF &lt; 30%</th>
<th>Tmax &gt; 6 sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Apparent diffusion coefficient</td>
<td>• Relative cerebral blood flow</td>
<td>• Time to maximum of the residue curve</td>
</tr>
<tr>
<td>• Derived from routine DWI sequence</td>
<td>• Measured as compared to the contralateral side of the brain</td>
<td>• &gt;6 seconds considered to represent penumbra + ischemic core</td>
</tr>
<tr>
<td>• &lt;620 defines the ischemic core</td>
<td>• &lt;30% is considered to represent the ischemic core</td>
<td>• Sensitive to multiple factors</td>
</tr>
<tr>
<td>• Among most well validated measures of ischemic core</td>
<td></td>
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</tbody>
</table>
Acute stroke

0 – 4.5 hours since last known well
- Noncontrast head CT

0 – 6 hours, NIHSS ≥ 6
- Head/neck CTA

6 – 24 hours since last known well, NIHSS ≥ 6
- Brain CTP or MRI

Astrup et al. 1981
NINDS 1995
ECASS-3 2008
2013
IMS-3 MR-RESCUE SYNTHESIS-Expansion
2015
2017
MR-CLEAN ESCAPE SWIFT-PRIME REVASCAT EXTEND-IA (and others)
DAWN DEFUSE-3
Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct

DAWN Trial

- 6-24 hours from last known normal
- Adults only
- Large vessel occlusion on CTA
- **Ischemic core** = rCBF < 30% or ADC < 620
- **Penumbra** = NIHSS
  - < 80 years old
    - NIHSS ≥ 10 and ischemic core < 31 mL
    - NIHSS ≥ 20 and ischemic core < 51 mL
  - ≥ 80 years old
    - NIHSS ≥ 10 and ischemic core < 21 mL
DAWN Trial

- Stopped for efficacy after 206 patients
- Medical arm:
  - 13% achieved functional independence (mRS 0-2)
- Thrombectomy arm:
  - 49% achieved functional independence (mRS 0-2)
- Number needed to treat was ~3 for MAJOR improvement
- Number needed to treat was ~2 for ANY improvement
The DEFUSE-3 Trial

Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging

DEFUSE 3

- 6-16 hours
- Adults 18-90 yo
- NIHSS ≥ 6
- ICA or M1 occlusions
- **Ischemic core** = rCBF < 30% or ADC < 620
  - must be < 70 mL
- **Penumbra** = Tmax > 6 seconds
  - must be ≥ 15 mL
- Mismatch ratio must be ≥ 1.8
DEFUSE 3

- Stopped for efficacy after 182 patients
- Medical arm:
  - 17% functional independence (mRS 0-2)
- Treatment arm:
  - 45% functional independence (mRS 0-2)
- Number needed to treat was ~3 for MAJOR improvement
- Number needed to treat was ~2 for ANY improvement
50yo man, NIHSS 18, LKW 8 hours ago
CTA
Adding CTP

CBF < 30% volume: 20 ml
Mismatch volume: 52 ml
Mismatch ratio: 3.6
Tmax > 6.0 s volume: 72 ml
Where is the occlusion?

CBF<30% volume: 8 ml
Mismatch volume: 141 ml
Mismatch ratio: 18.6
Tmax>6.0s volume: 149 ml

Warning: review source data quality and bolus timing.
Basilar artery occlusion
Bottom Line

- **Level 1** multiple RCT evidence that:
  - Patients with stroke 6-24 hours from onset
    - Selected by advanced stroke imaging (CTP or MRI-DWI+PWI)
    - Found to have a large vessel occlusion on CTA or MRA
  - Benefit greatly (NNT 2-3) from thrombectomy
- New standard of care
  - Already in the American Stroke Association’s newest 2018 guidelines
- Degree of benefit:
  - Dozens of patients now live independently because of their treatment at MIR
Acute stroke

0 – 4.5 hours since last known well

Noncontrast head CT

0 – 6 hours, NIHSS ≥ 6

Head/neck CTA

6 – 24 hours since last known well, NIHSS ≥ 6

Brain CTP or MRI

Astrup et al.

1981

NINDS

1995

ECASS-3

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MR-CLEAN
ESCAPE
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REVASCAT
EXTEND-IA
(and others)

2015

IMS-3
MR-RESCUE
SYNTHESIS-Expansion

2017

DAWN
DEFUSE-3
Acute stroke

- 0 – 4.5 hours since last known well
- Noncontrast head CT
- 0 – 6 hours, NIHSS ≥ 6
- Head/neck CTA
- 6 – 24 hours since last known well, NIHSS ≥ 6
- Brain CTP or MRI
- 4.5+ hours since last known well
- Brain MRI

Astrup et al. 1981
NINDS 1995
ECASS-3 2008
IMS-3 2013
MR-CLEAN ESCAPE SYNTHESIS-Expansion
MR-RESCUE SWIFT-PRIME REVASCAT EXTEND-IA (and others) 2015
DAWN DEFUSE-3 2017
WAKE-UP 2018
MR WITNESS Trial

- Safety trial
- 14 U.S. sites, including Washington University
- Patients were 4.5-24 hours since last known well
- No contraindication to tPA
- Radiology inclusion criteria
  - DWI-FLAIR Mismatch
  - FLAIR in region of DWI+ infarct is <1.15 contralateral FLAIR
- If met criteria, got tPA
- Safety results: of 80 patients, 1 symptomatic ICH and 3 cases of symptomatic edema
WAKE-UP Trial

- Clinical inclusion criteria
  - Unknown time of onset (beyond 4.5 hours)
  - Adults only
  - Not a thrombectomy candidate
- Radiology inclusion criteria
  - **DWI-FLAIR** Mismatch
  - Defined as no ‘visible’ or ‘marked’ FLAIR hyperintensity in DWI+ infarct region
- 503 enrolled, 11.5% increase in good outcomes (MRS 0-1)
Figure S1. Examples of Patients With and Without DWI-FLAIR-Mismatch.
**Acute stroke**

- 0 – 4.5 hours since last known well
  - Noncontrast head CT
  - Head/neck CTA
  - Brain CTP or MRI
  - Brain MRI

- 0 – 6 hours, NIHSS ≥ 6

- 6 – 24 hours since last known well, NIHSS ≥ 6

- 4.5+ hours since last known well

**Timeline:**
- Astrup et al.: 1981
- NINDS: 1995
- ECASS-3: 2008
- IMS-3: 2013
- MR-CLEAN: 2015
- MR-RESCUE: 2017
- REVASCAT: 2018
- SYNTHESIS-Expansion: 2013
- DAWN: 2018
- DEFUSE-3: 2018
- WAKE-UP: 2018
The current state of acute stroke imaging and controversies
Current state of acute stroke imaging

Acute stroke

Noncontrast head CT

NIHSS < 6
Stroke onset known or clearly < 4.5 hours

NIHSS < 6
Stroke onset unknown and possibly < 4.5 hours

Brain MRI

NIHSS ≥ 6
LKN < 6 hours

NIHSS ≥ 6
LKN 6-24 hours

RAPID (CTA/CTP or Brain MRI/MRA/MRP)

Head/neck CTA

If no LVO and stroke onset unknown, possibly < 4.5 hours
Metabolic flux in cancer

Ma & Vosseller *Amino Acids* 2013
Imaging flux in stroke

EMS  OSH  CAR

Stroke Patient
Noncontrast head CT
Head/neck CTA
Brain MRI

Stroke Patient
Noncontrast head CT
Head/neck CTA
Brain CTP or MRI
Brain MRI

2013  2018
Controversies: Perfusion thresholds?

In patients achieving rapid reperfusion:

Ischemic core estimate based on rCBF < 30% 
overestimated 24 hour DWI infarct volume

Bivard, Parsons et al.  
*Ann Neurol* 2017
Controversies: Perfusion thresholds?

In HERMES and the tenecteplase trial:

Ischemic core based on rCBF < 30% underestimated 24 hour DWI infarct volume, regardless of time to reperfusion

Hoving et al. *Stroke* 2018
Controversies: CTA in first 6 hours?

Rocha & Jovin Stroke 2017
Controversies: CTA in first 6 hours?

Only patients with LVO were enrolled in this trial

Campbell et al. *NEJM* 2018
Going beyond 24 hours?

**Table 3** Outcomes

<table>
<thead>
<tr>
<th></th>
<th>DAWN eligible (≥24 hours since TLKW) n=21</th>
<th>DAWN trial intervention arm n=107</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procedural outcomes, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rates of TICI ≥2b</td>
<td>17 (81%)</td>
<td>90 (84%)</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>Efficacy outcomes, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early neurological recovery</td>
<td>6 (29%)</td>
<td>51 (48%)</td>
<td>0.10</td>
</tr>
<tr>
<td>mRS 0–2 at 90 days</td>
<td>9 (43%)</td>
<td>51 (48%)</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>Safety outcomes, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic deterioration</td>
<td>2 (10%)</td>
<td>15 (14%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>1 (5%)</td>
<td>6 (6%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Mortality</td>
<td>4 (19%)</td>
<td>20 (19%)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

ICH, intracranial hemorrhage; mRS, modified Rankin Scale; TICI, Thrombolysis in Cerebral Infarction; TLKW, time last known well.

Desai et al. *JNIS* 2018
A hypothesis
The elephant in the room

✧ ~50% of acute ischemic strokes have NIHSS < 4-6 (Dhamoon et al. *Stroke* 2009; Fonarow et al. *JAH A* 2012; Reeves et al. *Stroke* 2013)

✧ Of all acute ischemic stroke patients > 3-5:
  ✧ ~21% thrombectomy eligible in the first 6 hours (Vanacker et al. *Stroke* 2016)
  ✧ ~5.4% might meet DAWN and DEFUSE-3 (Jadhav et al. *Stroke* 2018)
  ✧ Of all undergoing thrombectomy, up to 50% achieve functional independence (mRS 0-2) at 3 months
  ✧ Of those not undergoing thrombectomy, a smaller percentage might benefit from natural history and/or IV thrombolysis

✧ Thus, a large number of stroke patients will still not achieve functional independence
Age is a major factor

Daniele et al. *AJNR* 2015

(Mayank Goyal—not me!)
Collaterals are a major factor

Clinical outcome vs. infarct growth

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Endovascular Therapy (N=92)</th>
<th>Medical Therapy (N=90)</th>
<th>Odds Ratio or Risk Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy outcome: median score on modified Rankin scale at 90 days (IQR)‡</td>
<td>3 (1–4)</td>
<td>4 (3–6)</td>
<td>2.77 (1.63–4.70)§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary efficacy outcome: functional independence at 90 days — no. (%)¶</td>
<td>41 (45)</td>
<td>15 (17)</td>
<td>2.67 (1.60–4.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Safety outcomes — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death at 90 days</td>
<td>13 (14)</td>
<td>23 (26)</td>
<td>0.55 (0.30–1.02)</td>
<td>0.05</td>
</tr>
<tr>
<td>Symptomatic intracranial hemorrhage §</td>
<td>6 (7)</td>
<td>4 (4)</td>
<td>1.47 (0.40–6.55)</td>
<td>0.75</td>
</tr>
<tr>
<td>Early neurologic deterioration</td>
<td>8 (9)</td>
<td>11 (12)</td>
<td>0.71 (0.30–1.69)</td>
<td>0.44</td>
</tr>
<tr>
<td>Parenchymal hematoma type 2</td>
<td>8 (9)</td>
<td>3 (3)</td>
<td>2.61 (0.73–14.69)</td>
<td>0.21</td>
</tr>
<tr>
<td>Imaging outcomes**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median infarct volume at 24 hr (IQR) — ml</td>
<td>35 (18–82)</td>
<td>41 (25–106)</td>
<td>—</td>
<td>0.19</td>
</tr>
<tr>
<td>Median infarct growth at 24 hr (IQR) — ml</td>
<td>23 (10–75)</td>
<td>33 (18–75)</td>
<td>—</td>
<td>0.08</td>
</tr>
<tr>
<td>Reperfusion &gt;90% at 24 hr — no./total no. (%)</td>
<td>59/75 (79)</td>
<td>12/67 (18)</td>
<td>4.39 (2.60–7.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complete recanalization at 24 hr — no./total no. (%)</td>
<td>65/83 (78)</td>
<td>14/77 (18)</td>
<td>4.31 (2.65–7.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TICI score of 2b or 3 — no./total no. (%)</td>
<td>69/91 (76)</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

Albers et al. NEJM 2018
Hypothesis and a proposal

- The value of reperfusion extends beyond preventing infarct growth, as it might also be important to facilitate stroke recovery.
- Heightened brain perfusion and metabolism are important for brain development.
Cerebral blood flow and metabolism during development

Brain CBF (yellow), CMRGlc (blue), and CMRO2 (red)

Goyal, Raichle et al. *Cell Metabolism* 2014
Brain metabolism decreases with age

Goyal, Vlassenko, Raichle et al. *Cell Metabolism* 2017
Hypothesis and a proposal

- The value of reperfusion extends beyond preventing infarct growth, as it might also be important to facilitate stroke recovery.
  - Heightened brain perfusion and metabolism are important for brain development.
  - Post-stroke recovery involves plasticity and likely recapitulation of several developmental processes, including synaptic growth, pruning, and myelination.
  - Therefore, post-stroke recovery might also depend upon increased brain perfusion and metabolism.
- Our lab has tools (metabolic PET and functional MRI) to measure this in stroke patients.
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