



# mTOR Inhibitors as Therapy for Tuberous Sclerosis

An alternative and accessible version of this presentation is available at 11:25 am in the [Videocast of Day One](#)

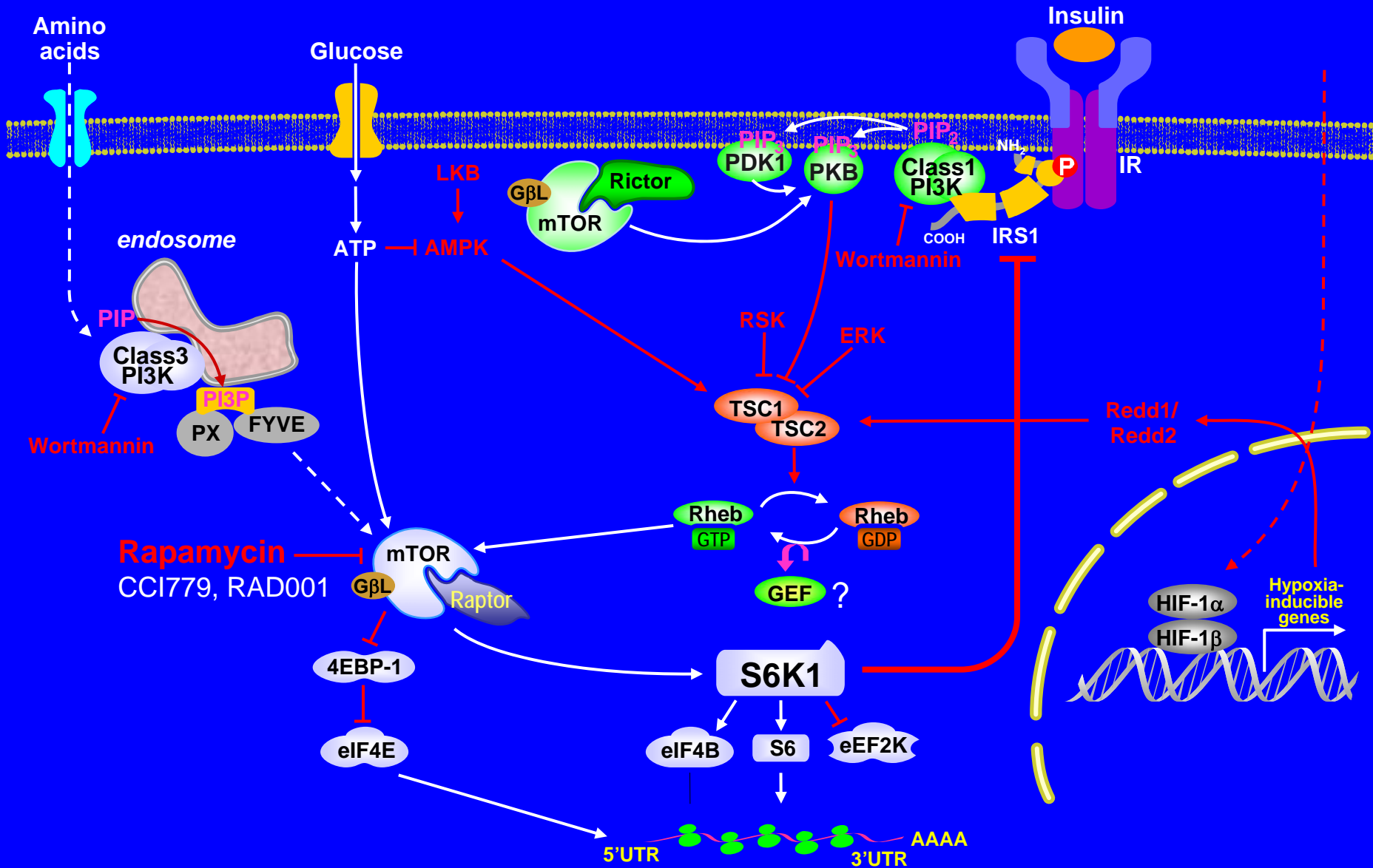
David Neal Franz, MD

Professor of Pediatrics and Neurology

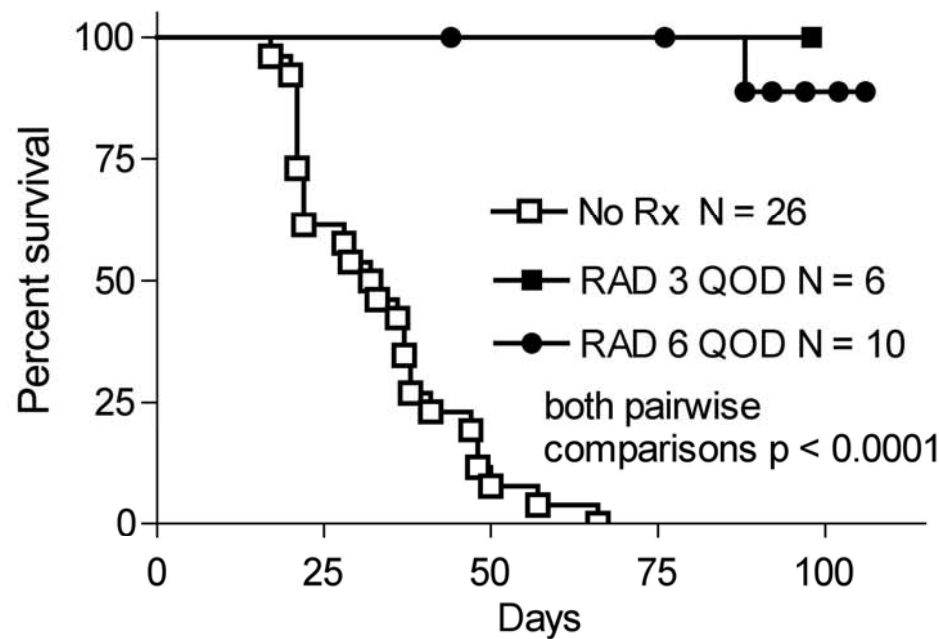
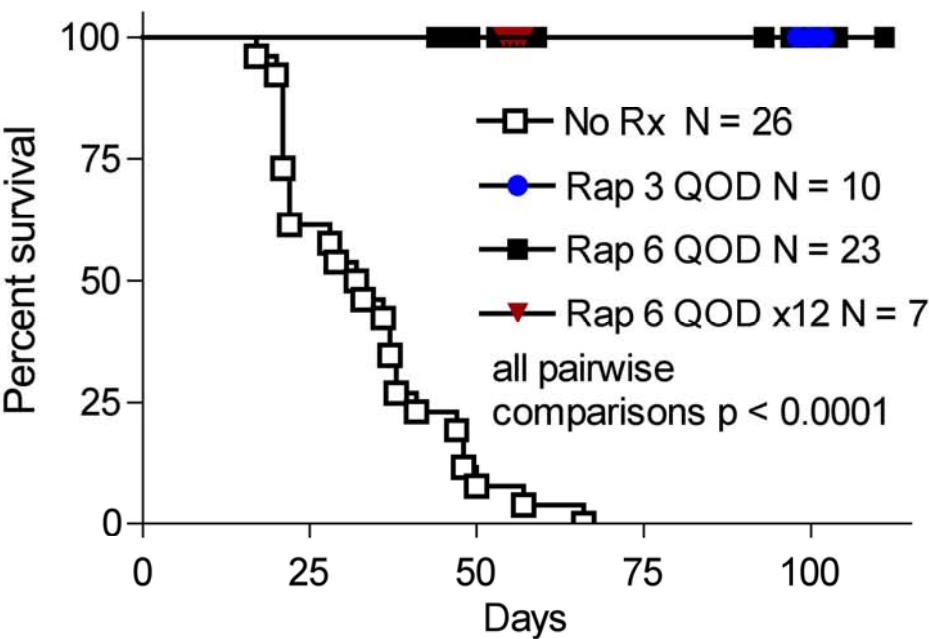
Director, Tuberous Sclerosis Clinic

Children's Hospital Medical Center, University of Cincinnati

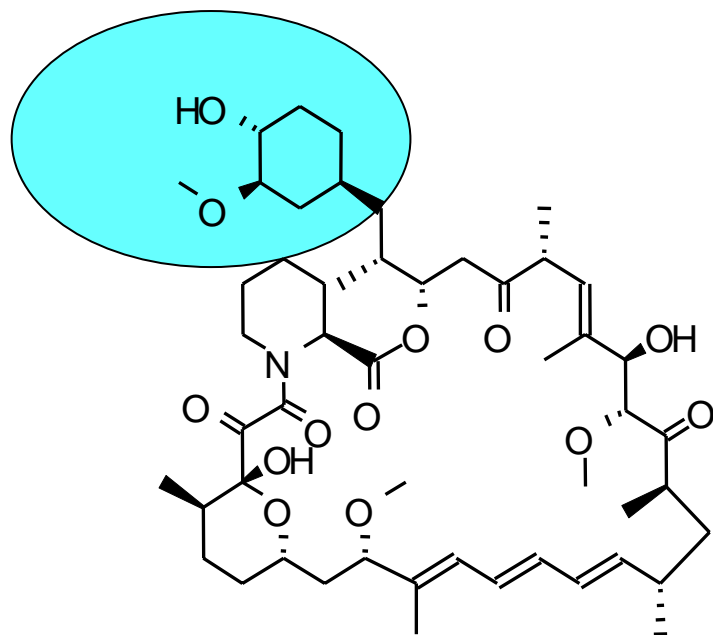
# mTOR/S6K1 Signaling



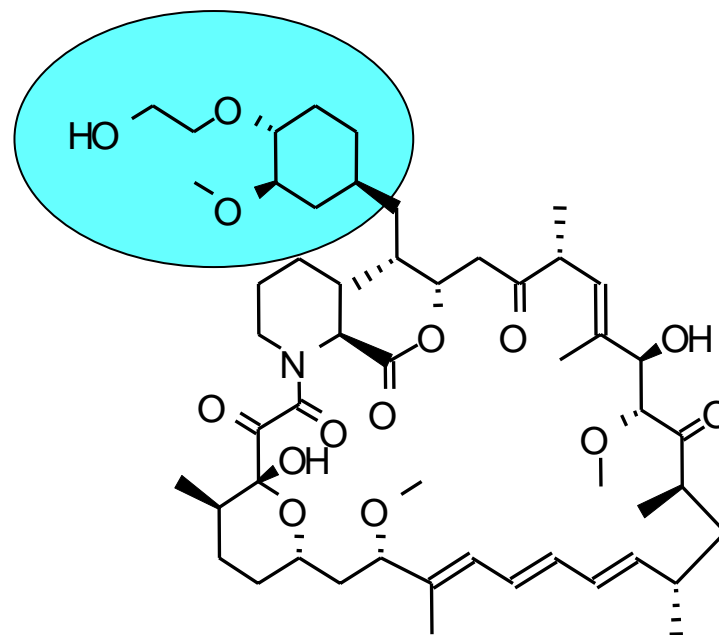
# Rapamycin/RAD001 in *Tsc1<sup>c</sup>-Syn/Cre<sup>+</sup>* mice



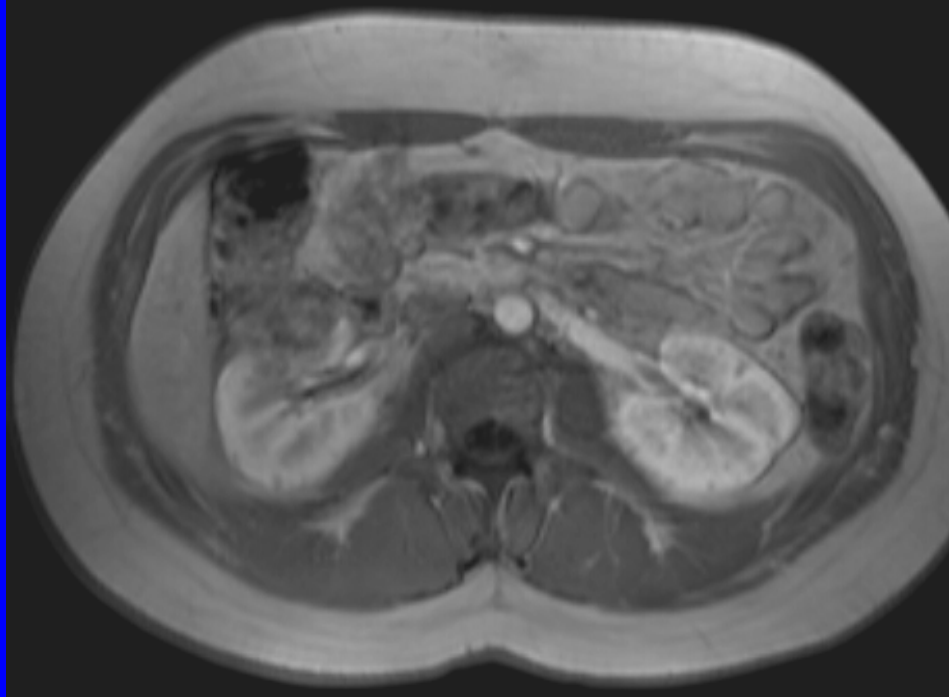
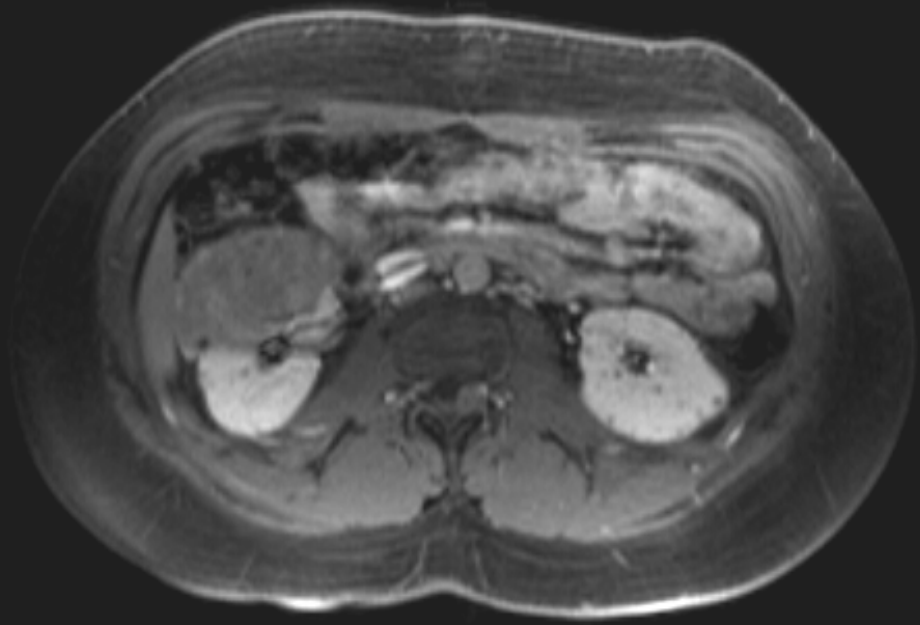
# Chemical structure of Rapamycin and RAD001



**Rapamycin**

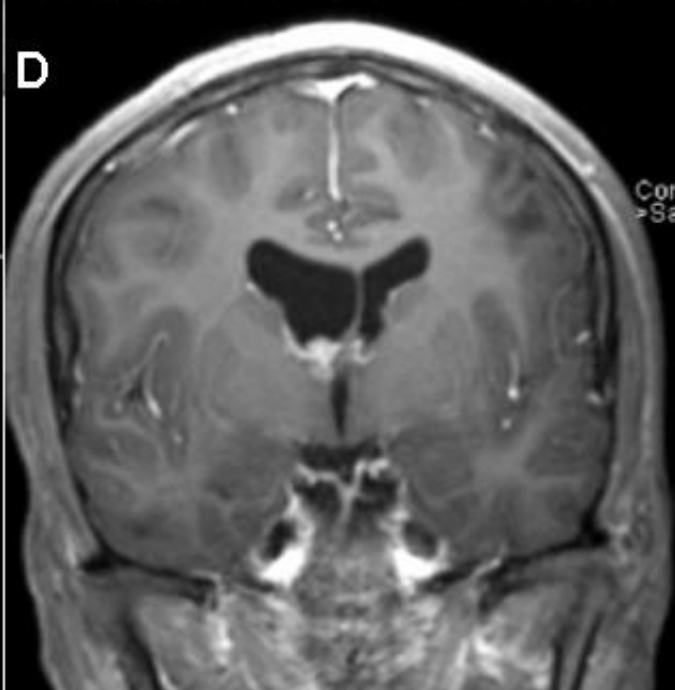
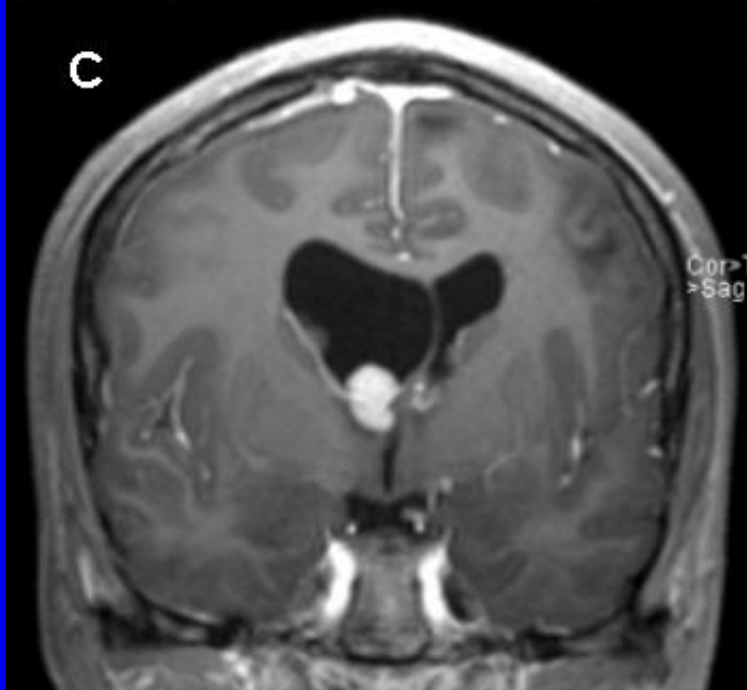
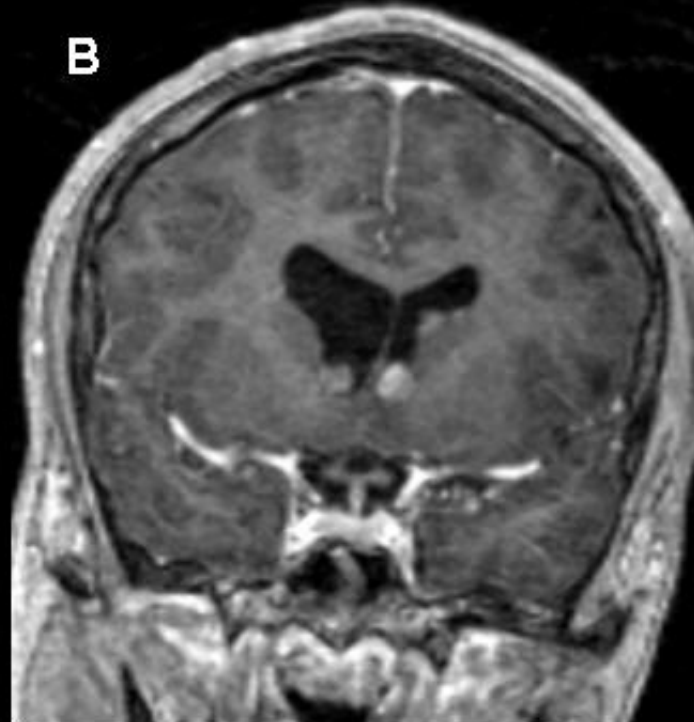
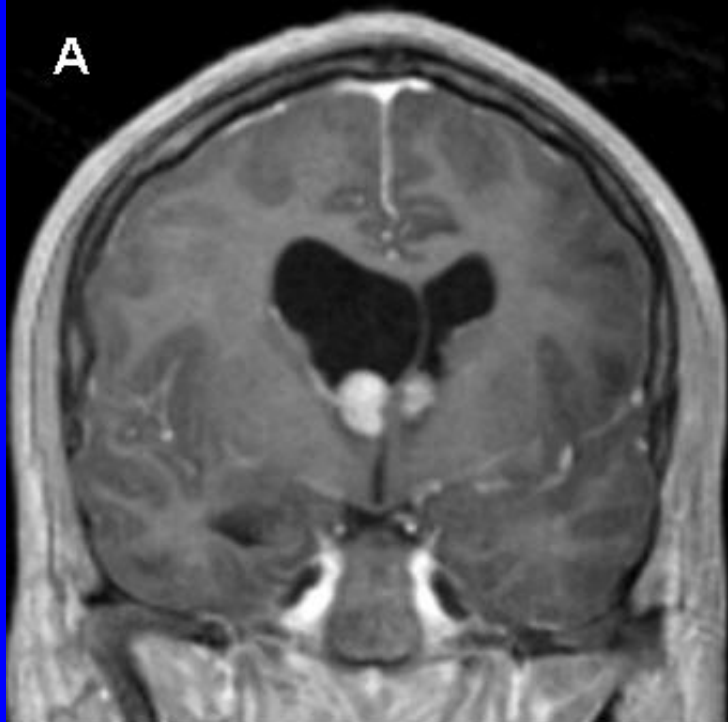


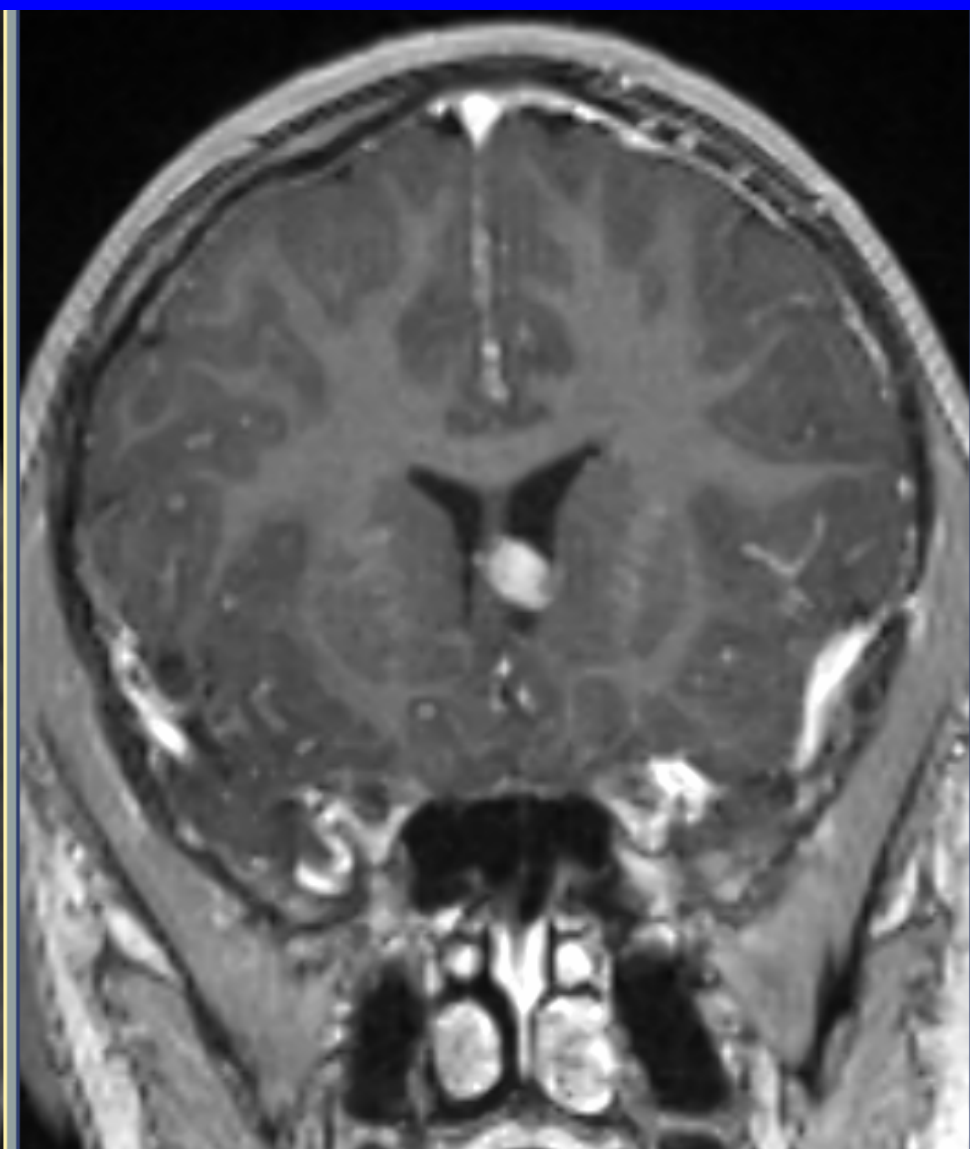
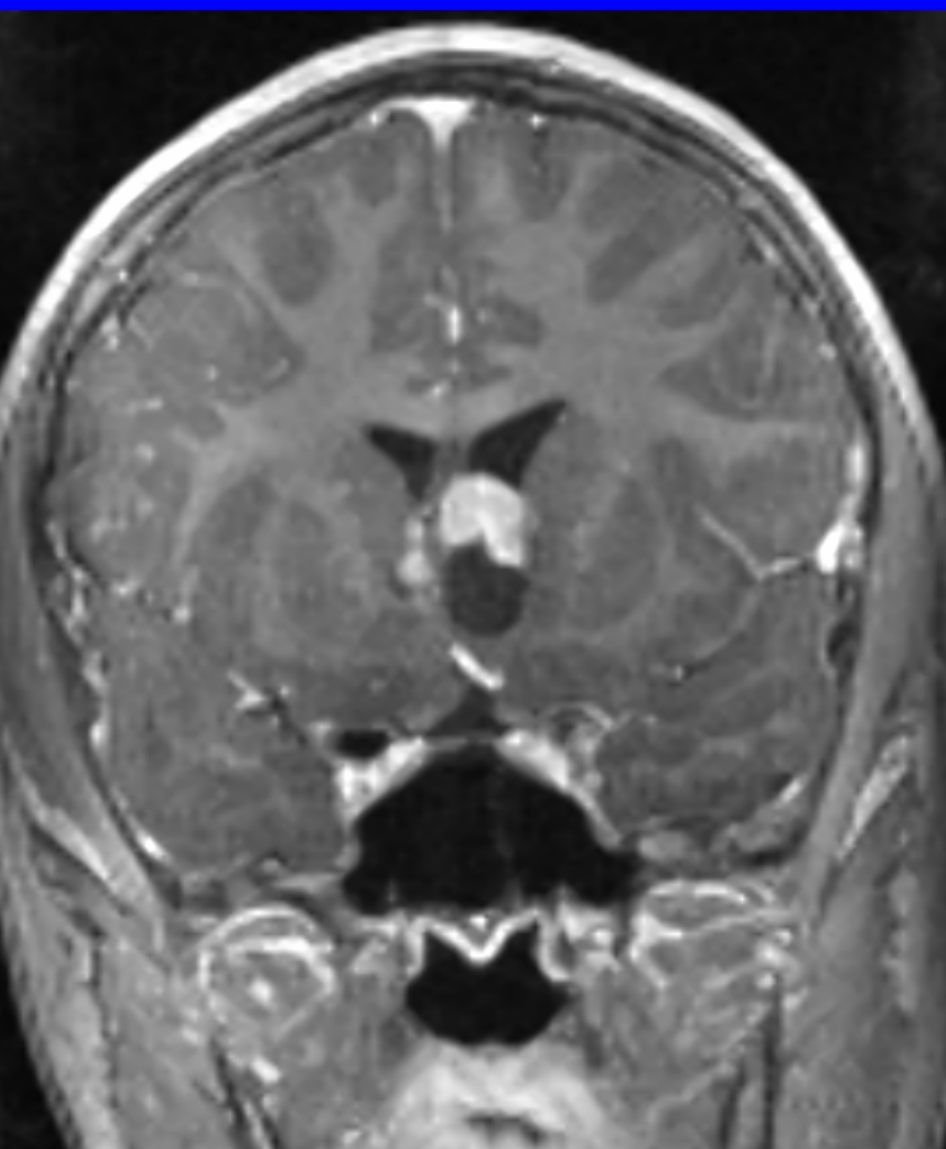
**RAD001**



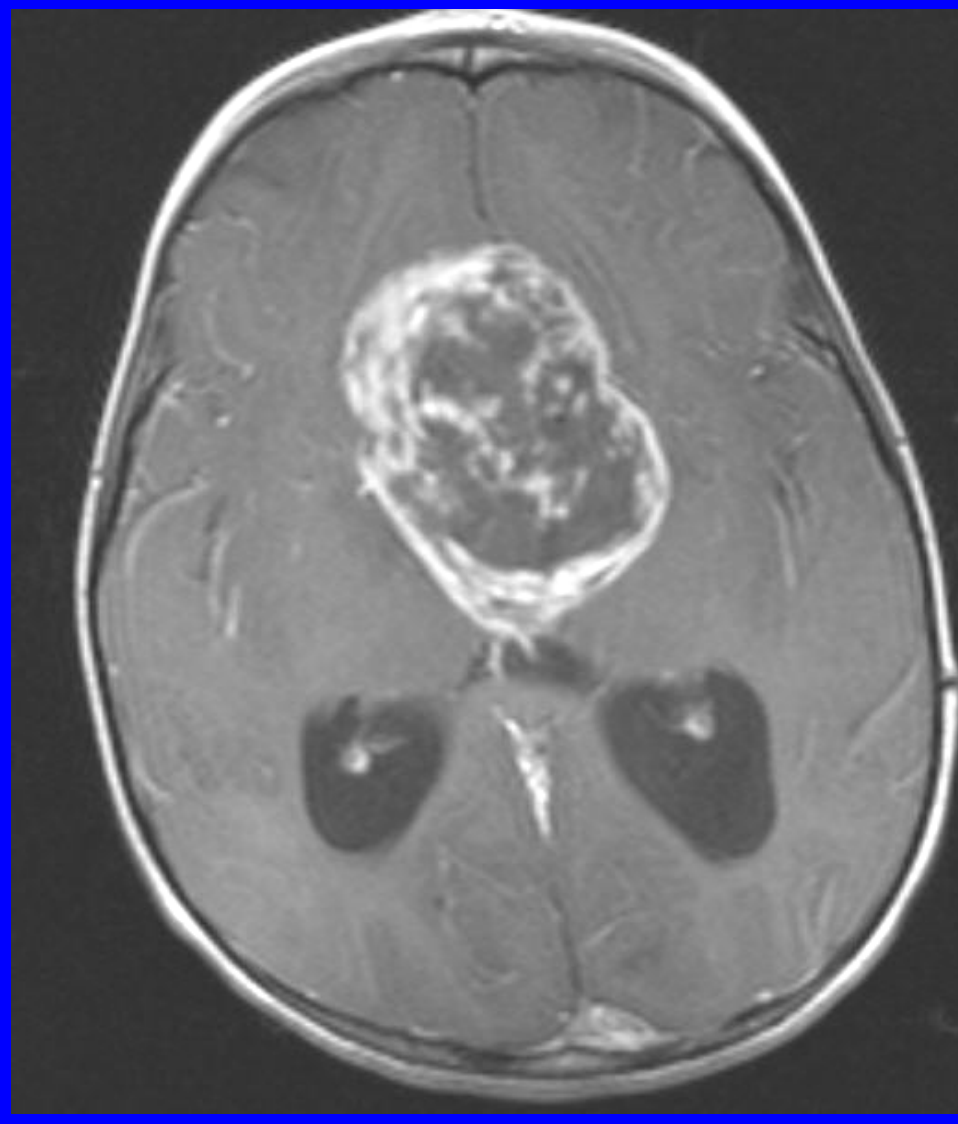
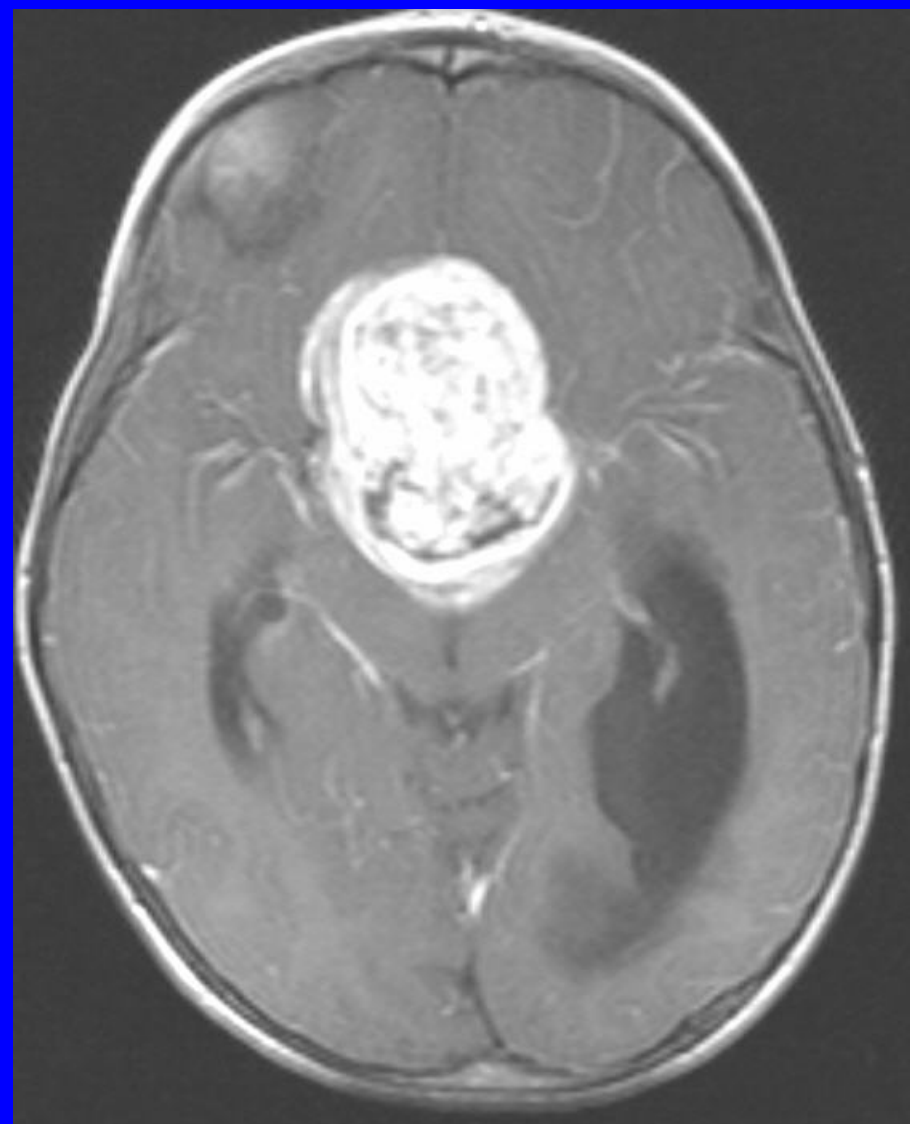
# Patient Characteristics

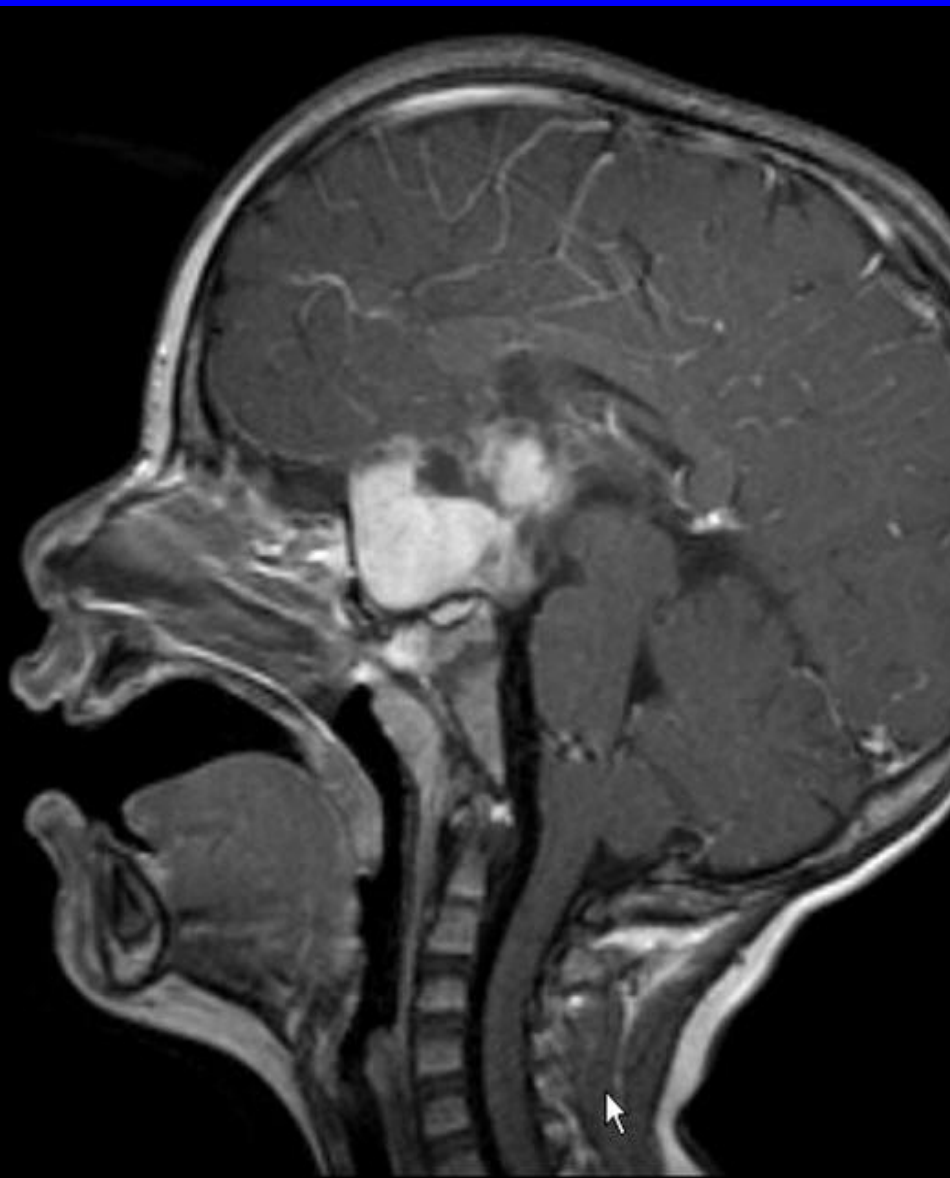
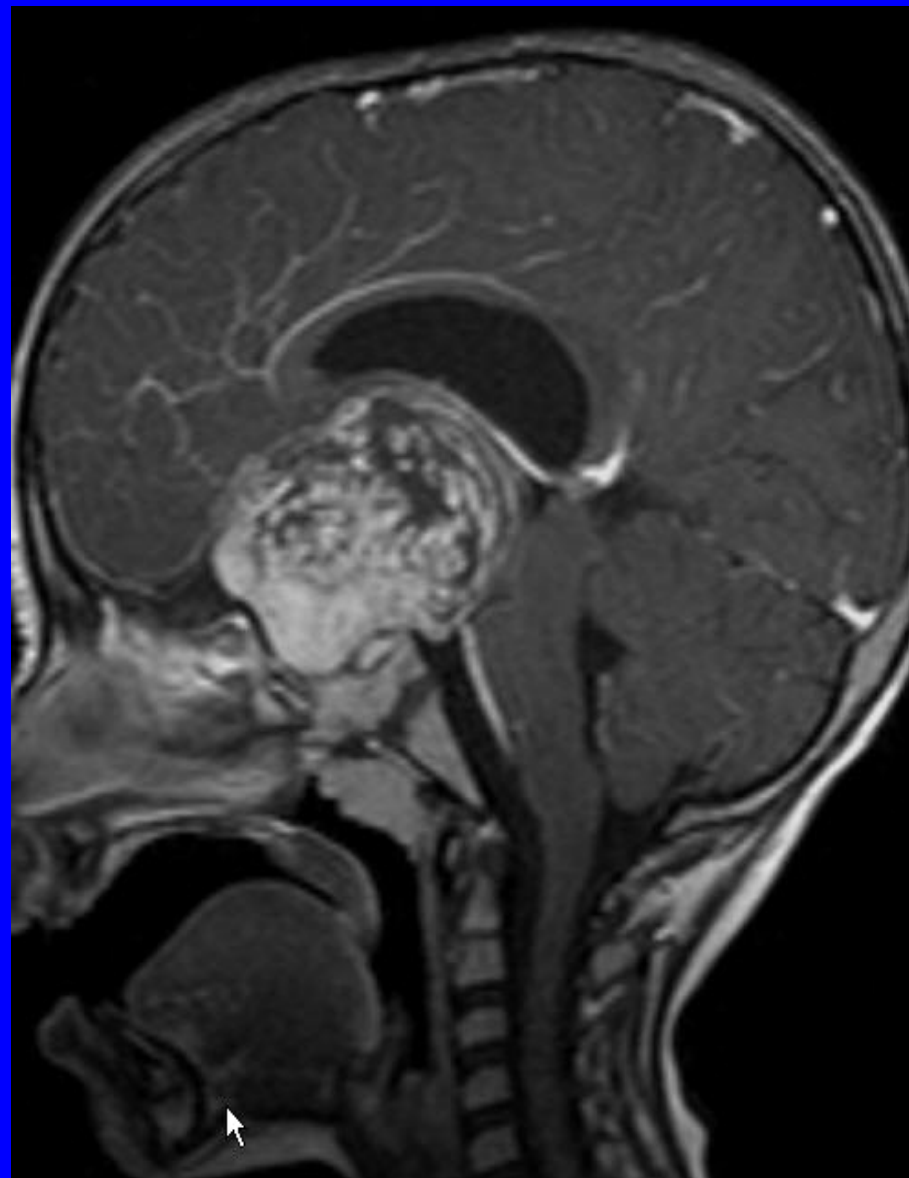
- 6 males, 5 females
- Age 3 – 41 years (mean 14.8)
- Rapamycin dose 4 – 7 mg/day
- Trough serum level 10 – 15 ng/ml
- Adverse effects
  - Hyperlipidemia – 4, aphthous ulcers – 2, acneiform rash – 2, ankle edema – 1
  - Pulmonary embolism – 1 (pt. with Factor V Leiden deficiency)
  - Pseudomonas brain abscess – 1 (chronic dexamethasone, multiple neurosurgical procedures)





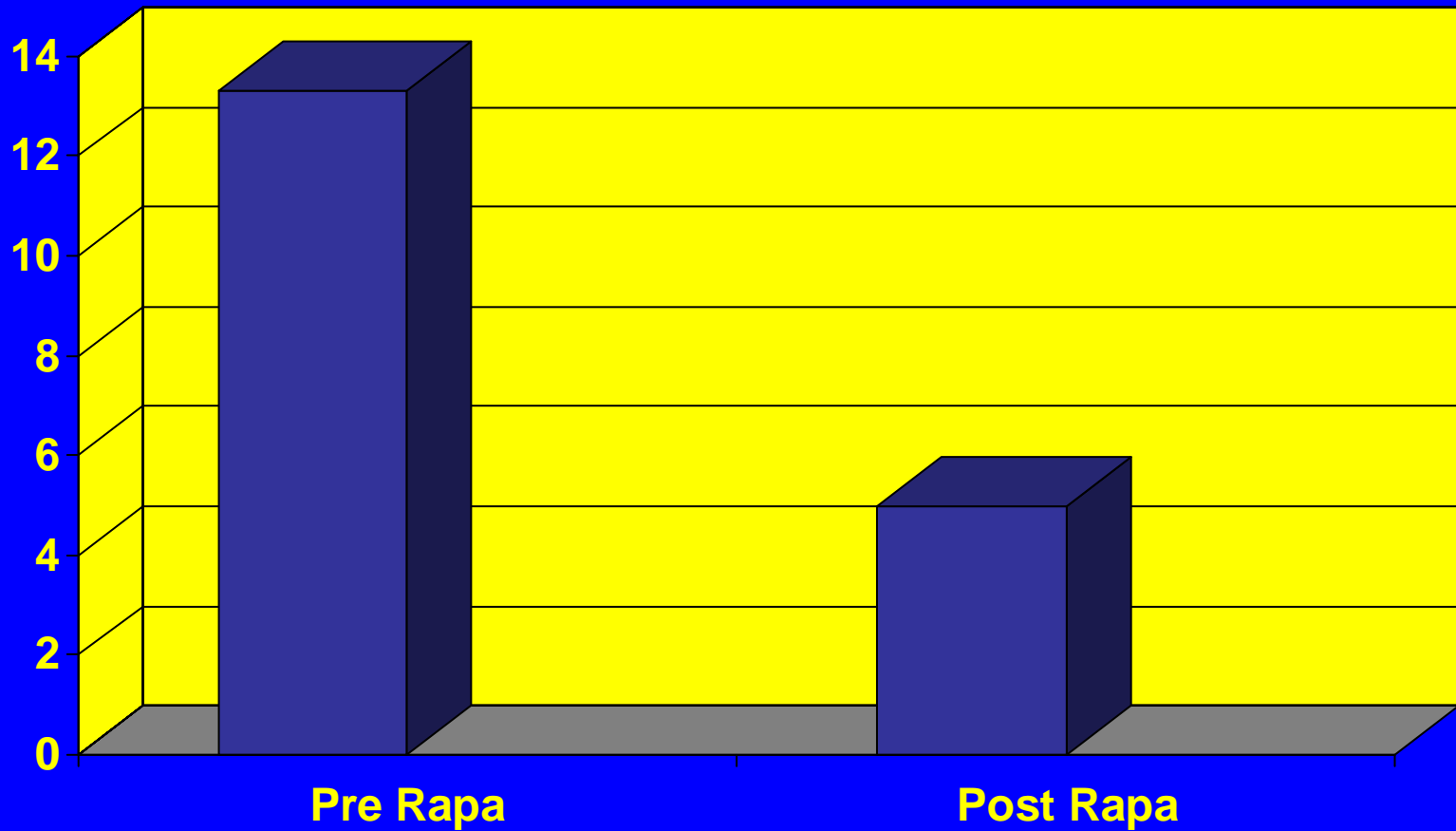




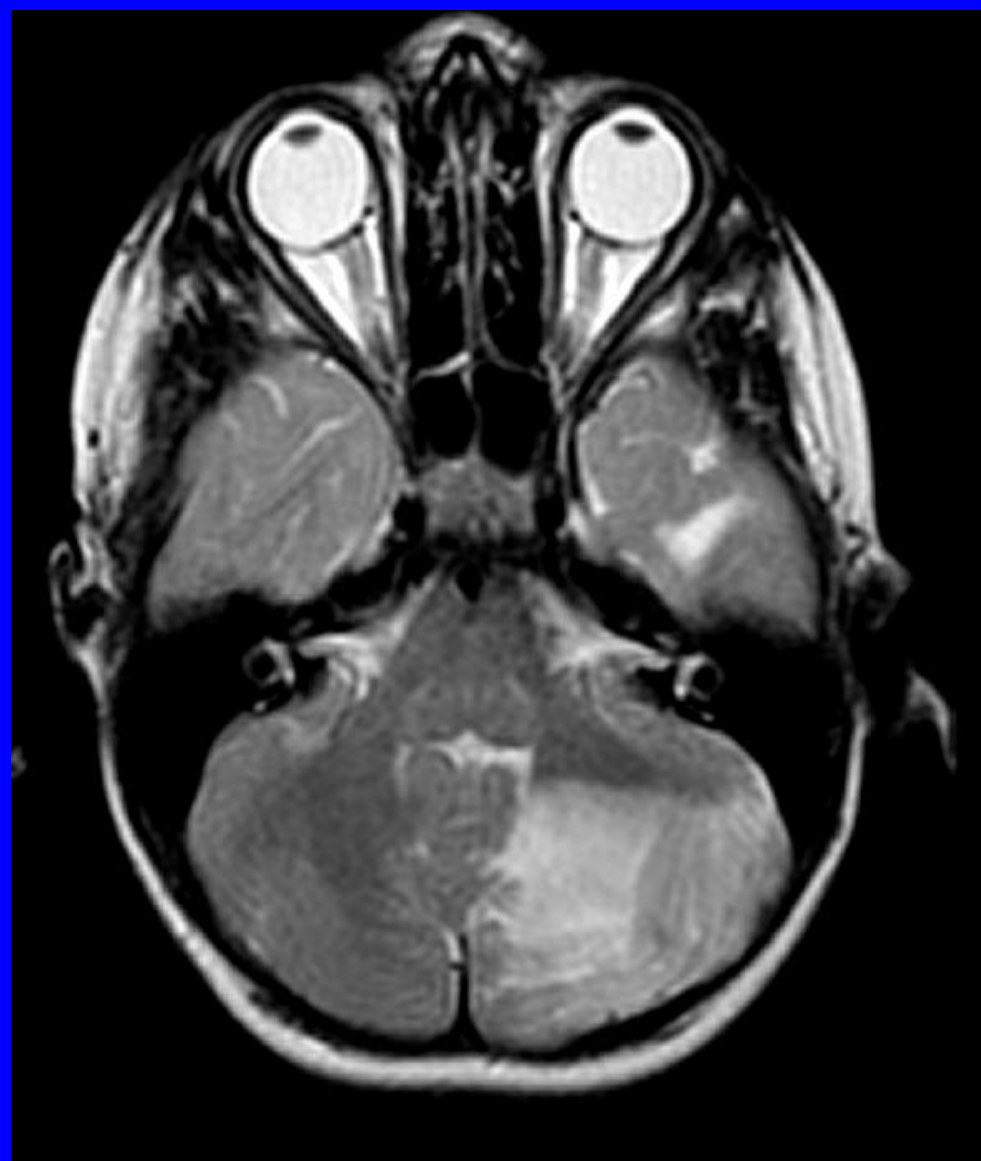
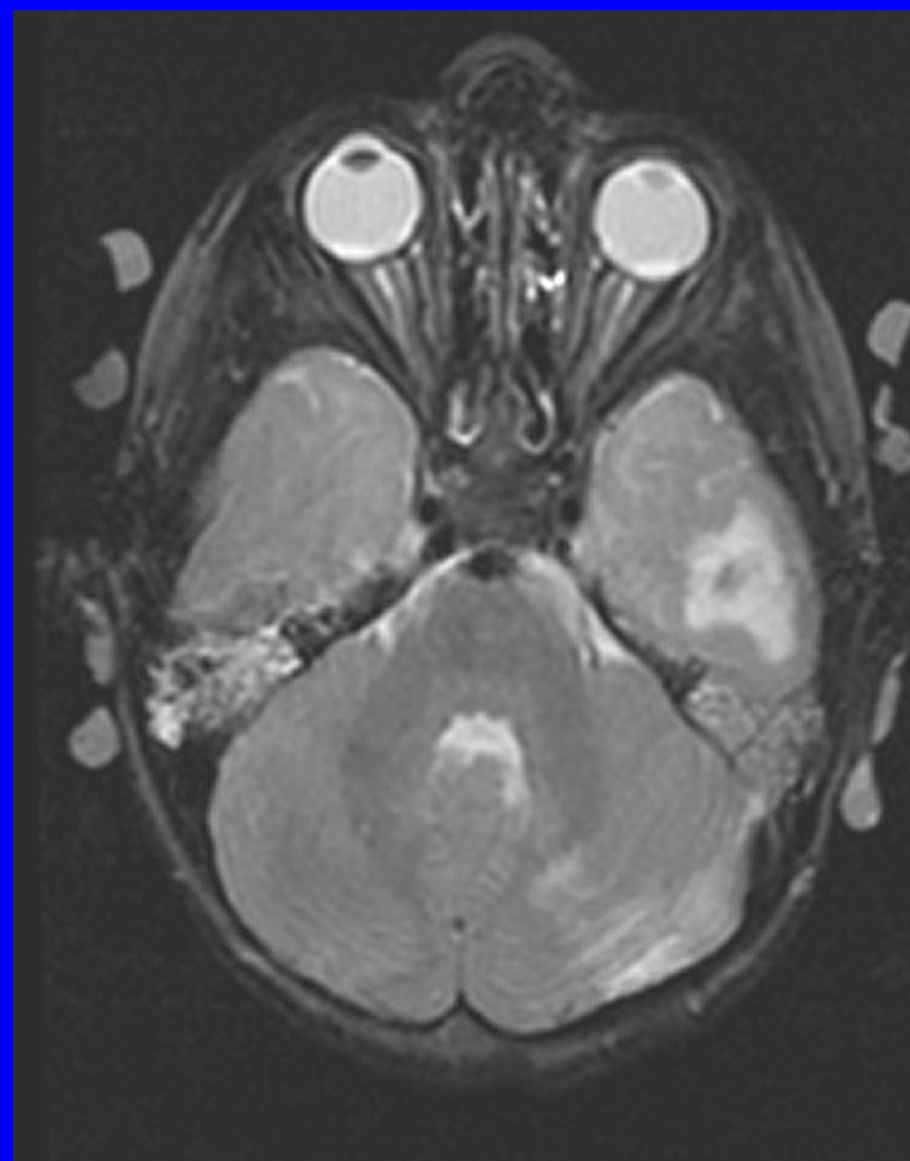


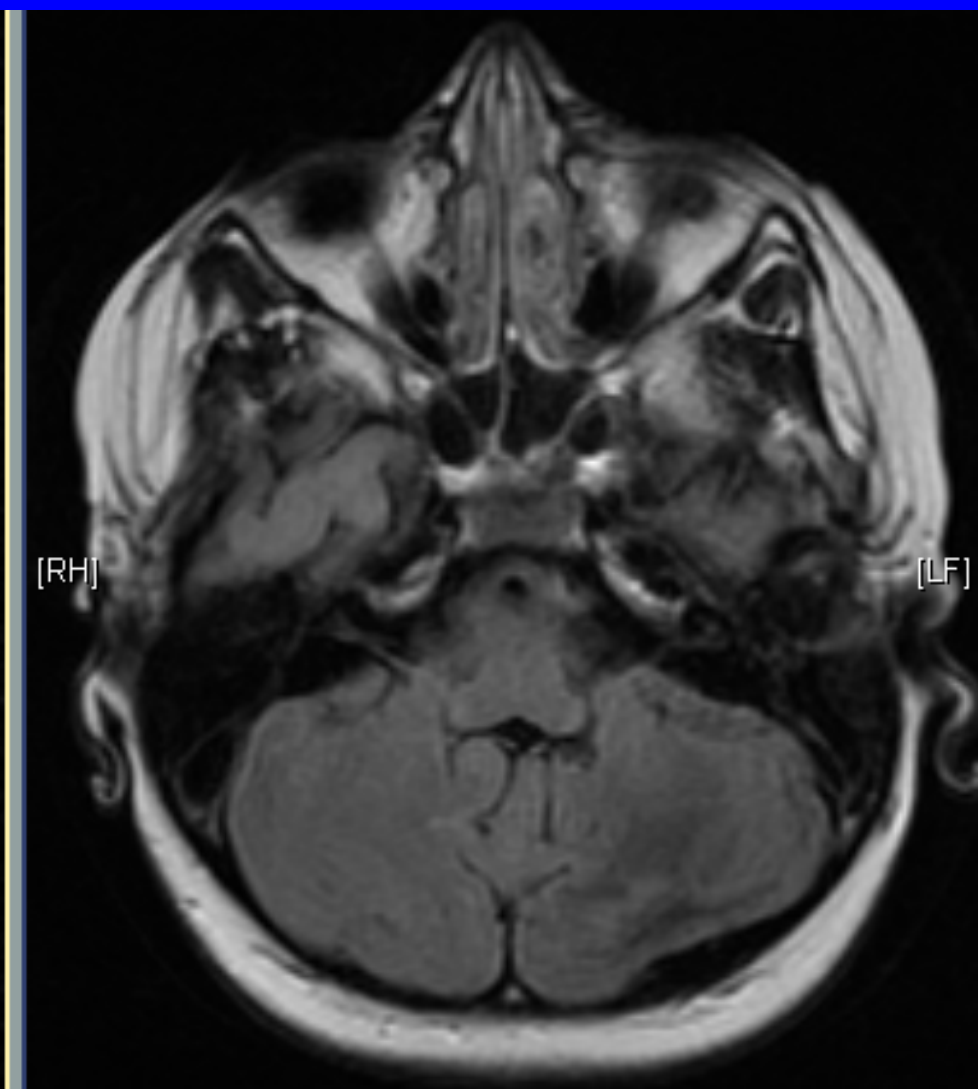
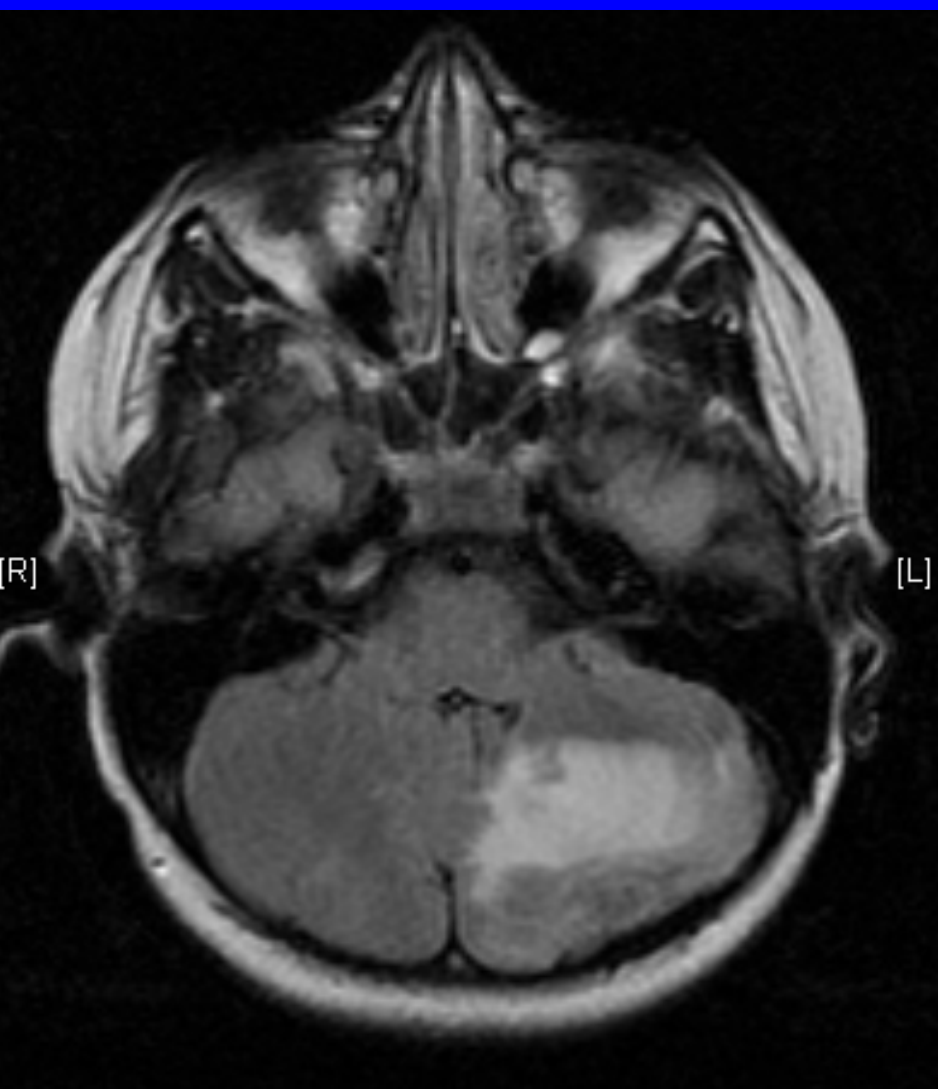


# Total Change Astrocyte Volume (cc)

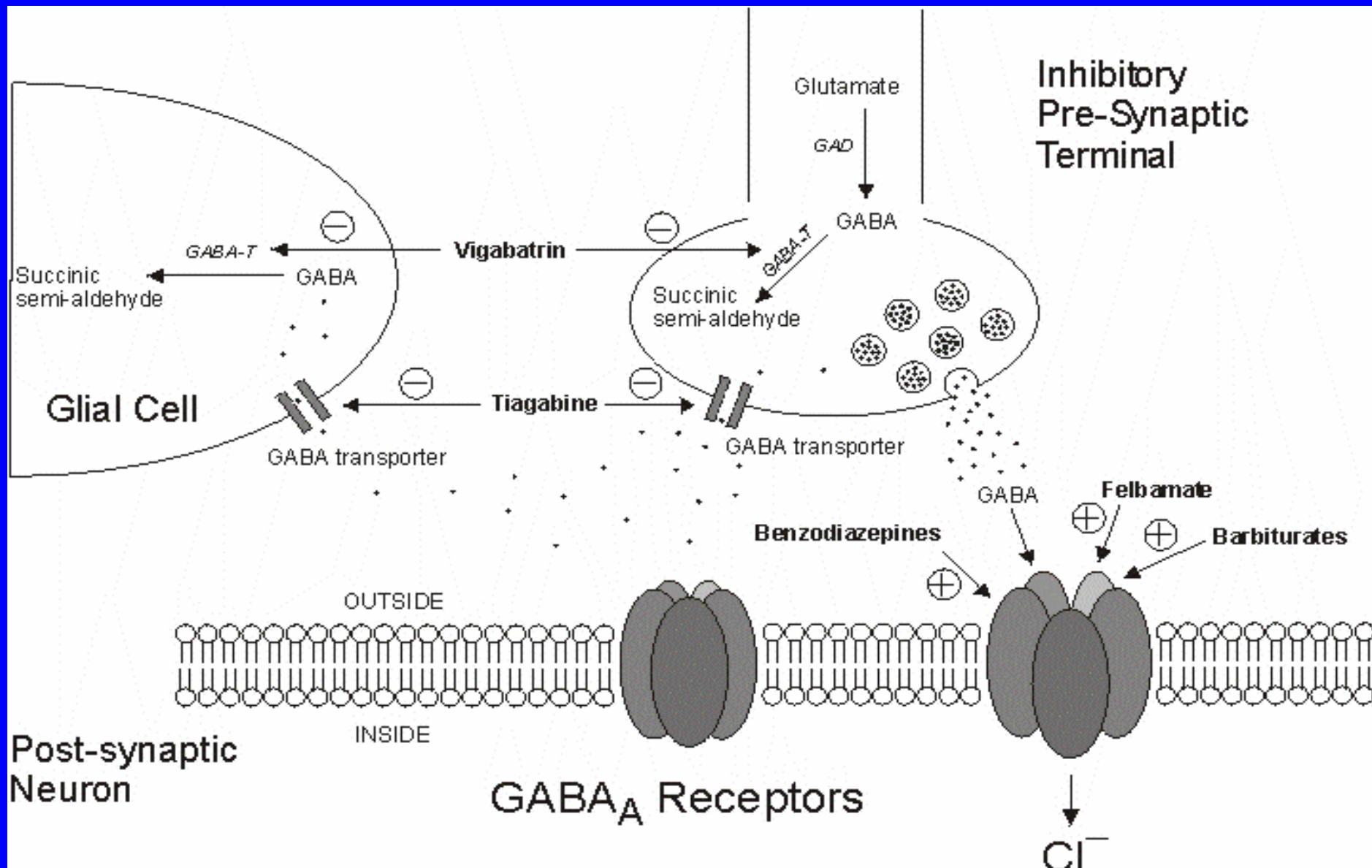


**Overall 62% Volume Reduction**

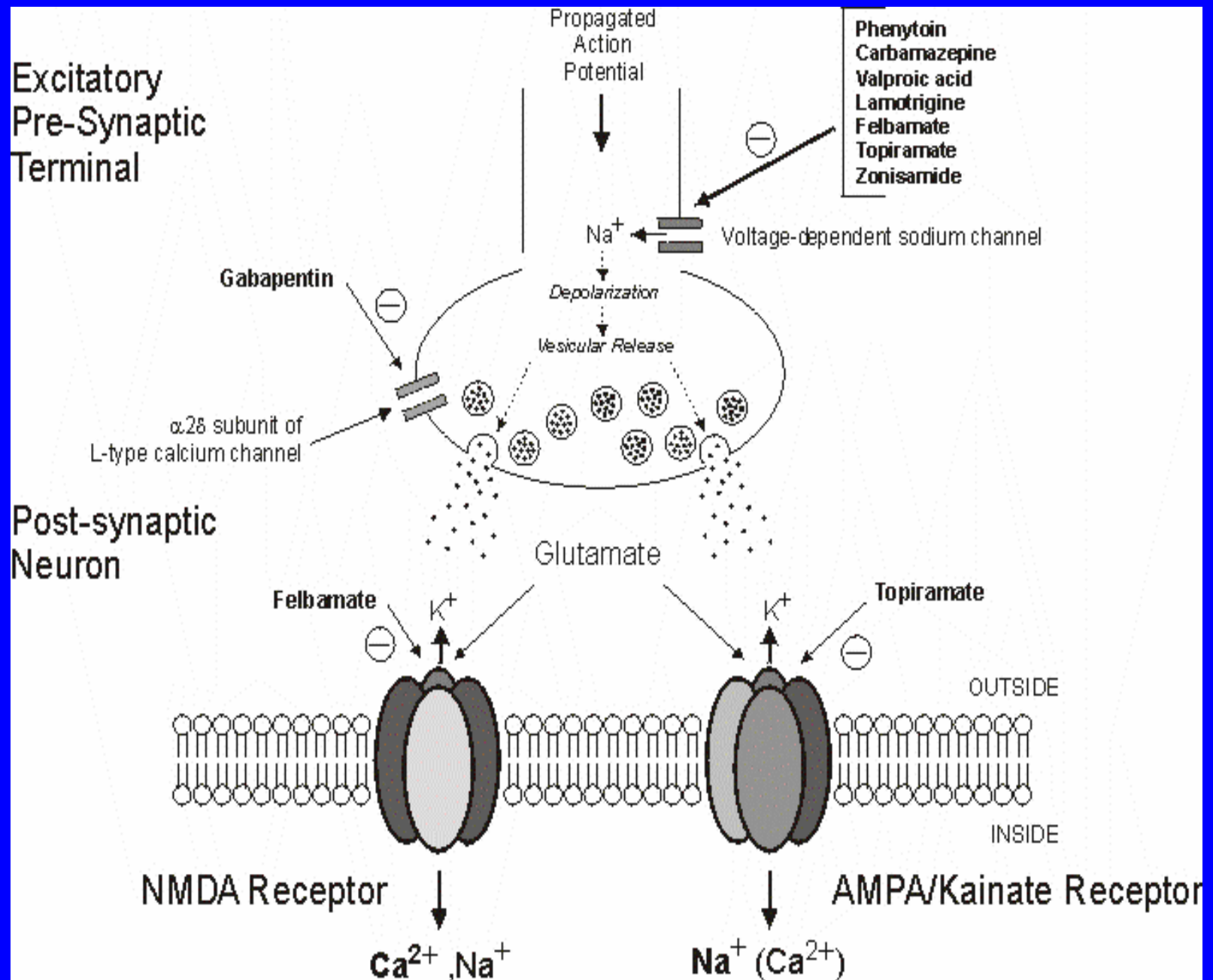




# AED Effects: GABAergic mechanisms

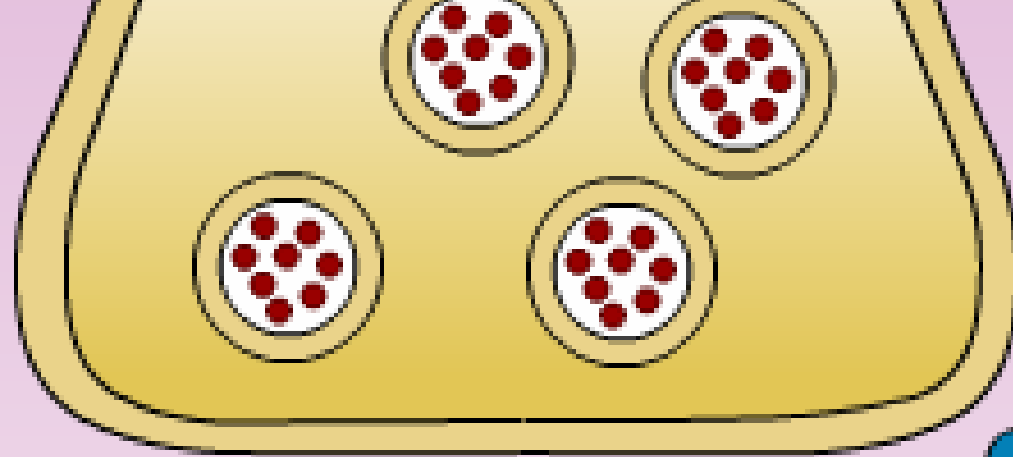


# AED Effects: Glutamatergic Mechanisms

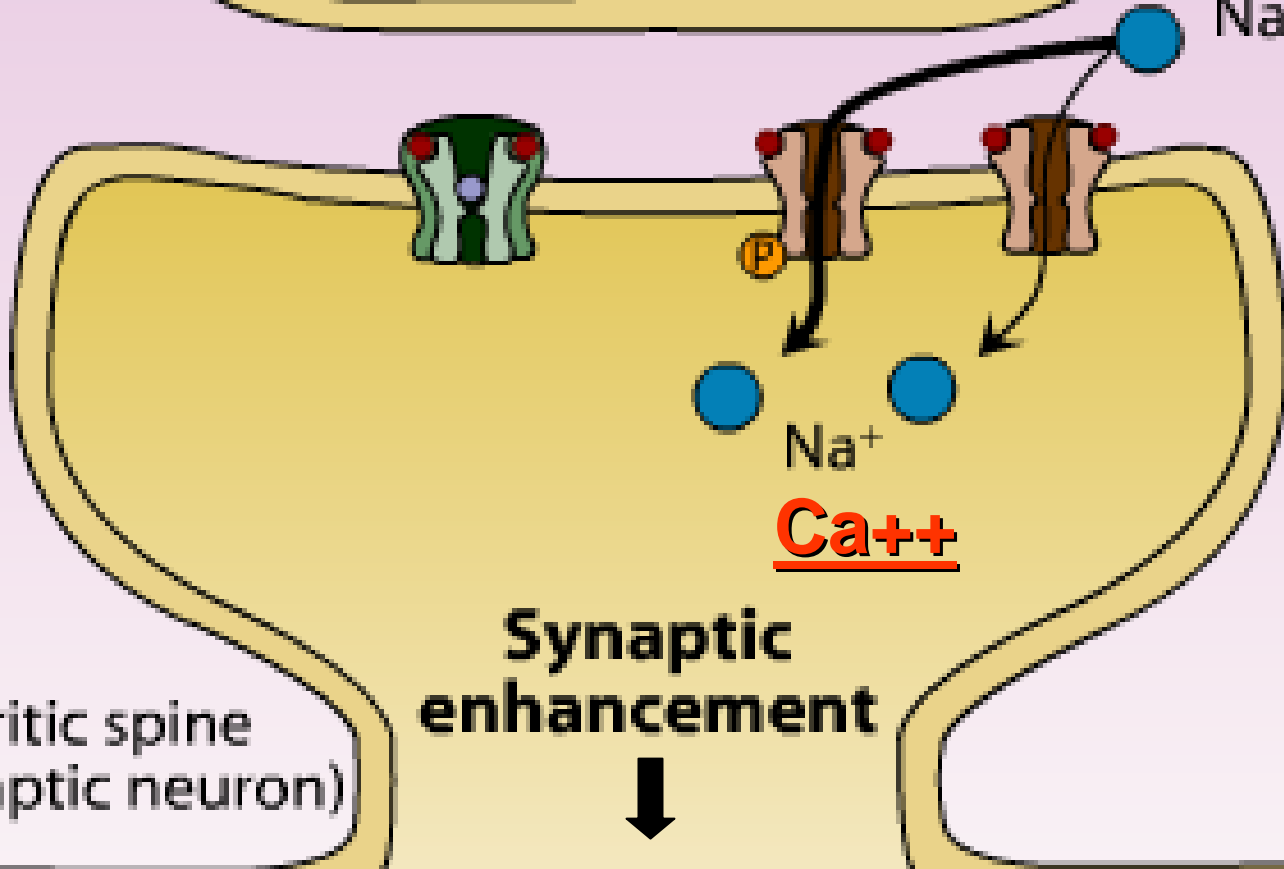




Axon terminal



Na<sup>+</sup>

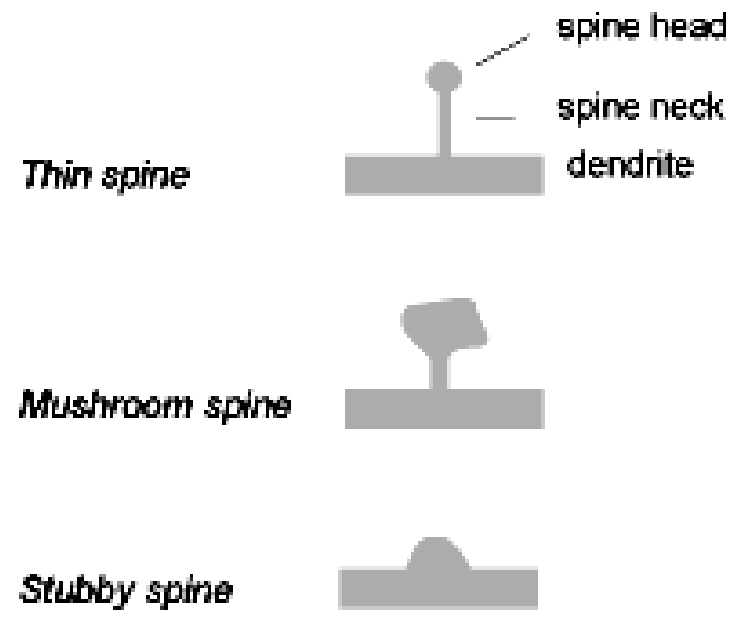
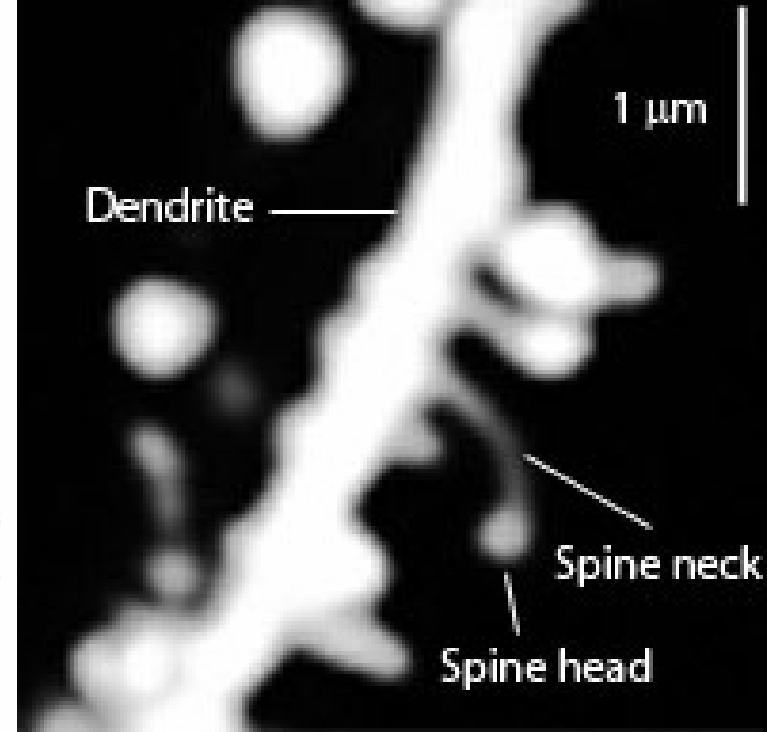
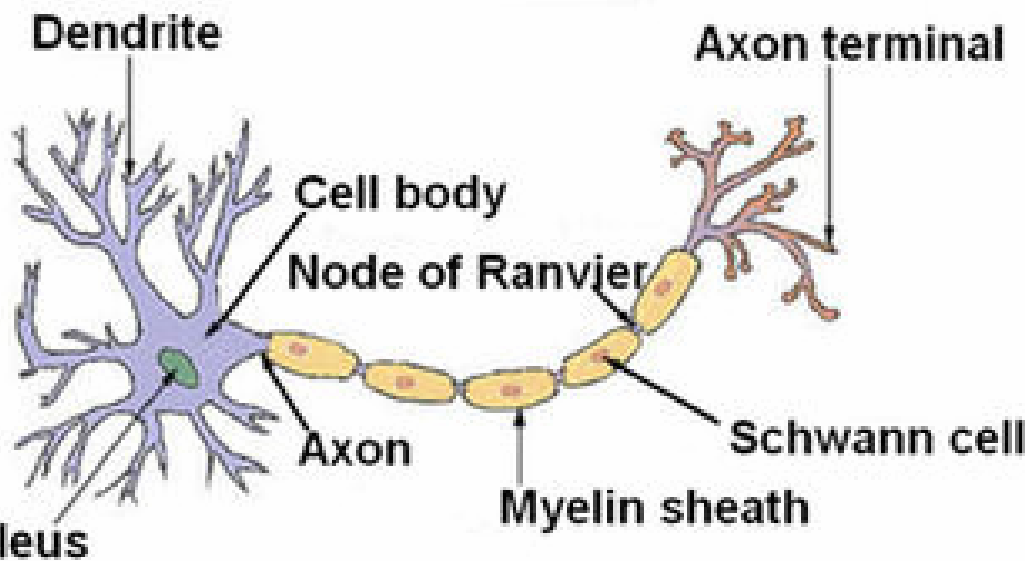


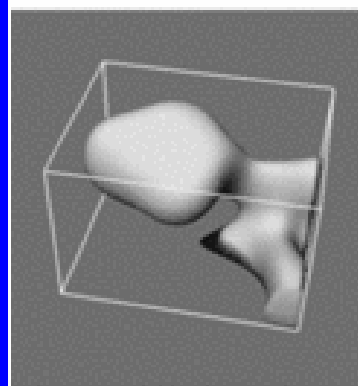
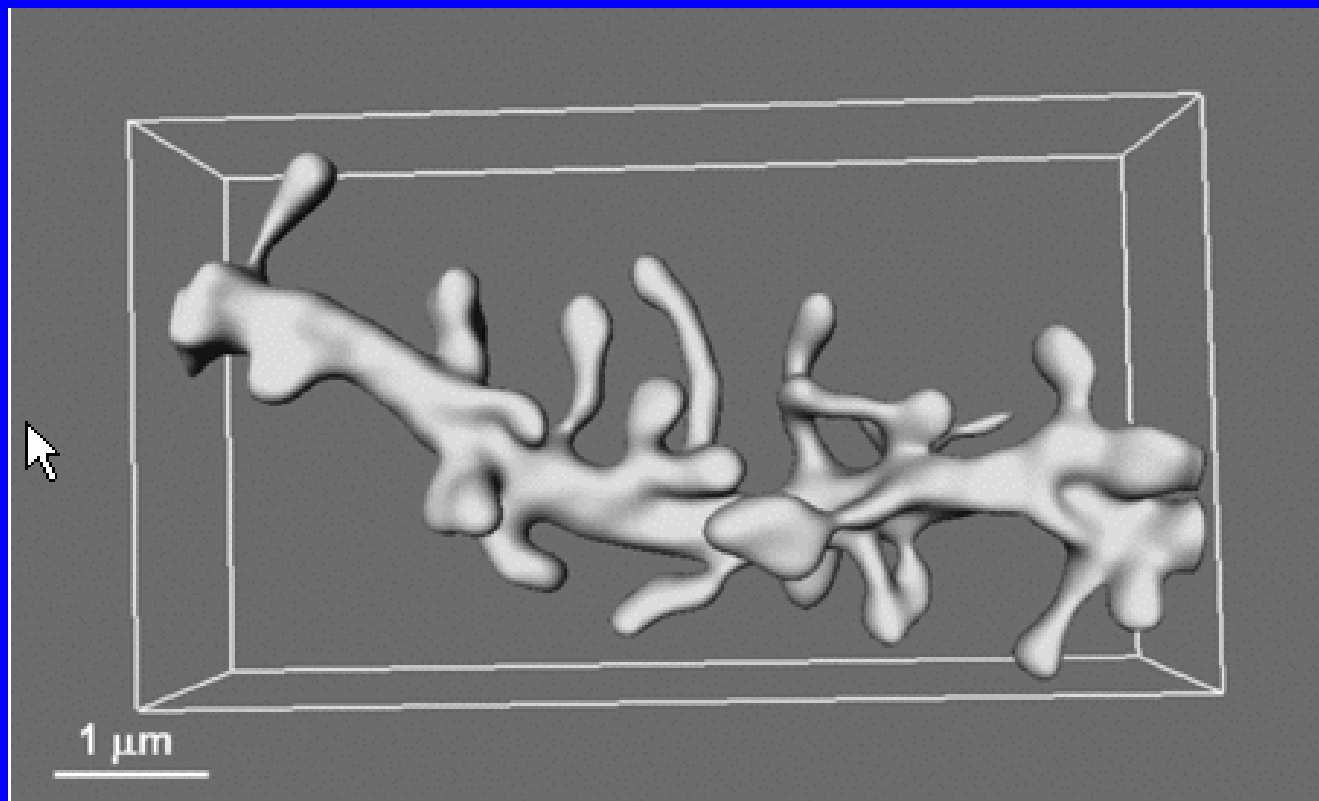
Dendritic spine (postsynaptic neuron)

Synaptic enhancement

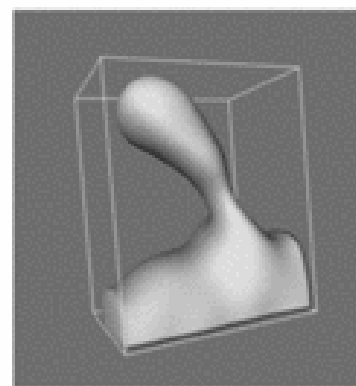


mTOR/S6kinase activation-  
protein synthesis, apoptosis

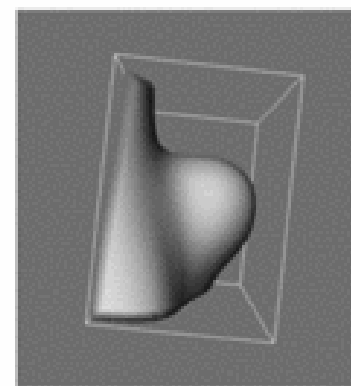




**Mushroom**



**Thin**



**Short stubby**

# Rationale

- mTOR/Rapamycin alters morphology of dendritic spines in TSC and non-TSC neurons
  - Basis of long term potentiation, memory formation, learning, epileptogenesis
- mTOR regulates synthesis and density of glutamate receptors and other proteins in dendritic spines

# Rationale

- Metabotropic Glutamate receptors activate mTOR/S6 kinase in neurons
- Excessive mTOR activation should produce chronic excitatory changes
  - Dendritic spines
  - Receptor density
  - Impairment of long term potentiation
- Epileptogenesis/Encephalopathy

# Rationale

- Rapamycin/mTOR inhibition mimics effects of starvation/ketogenic diet
  - Similar genomic profiles
  - Immunosuppression
  - Lipid elevation
  - Induction of autophagy, catabolism
  - Cognitive impairments (Non-epileptic state)

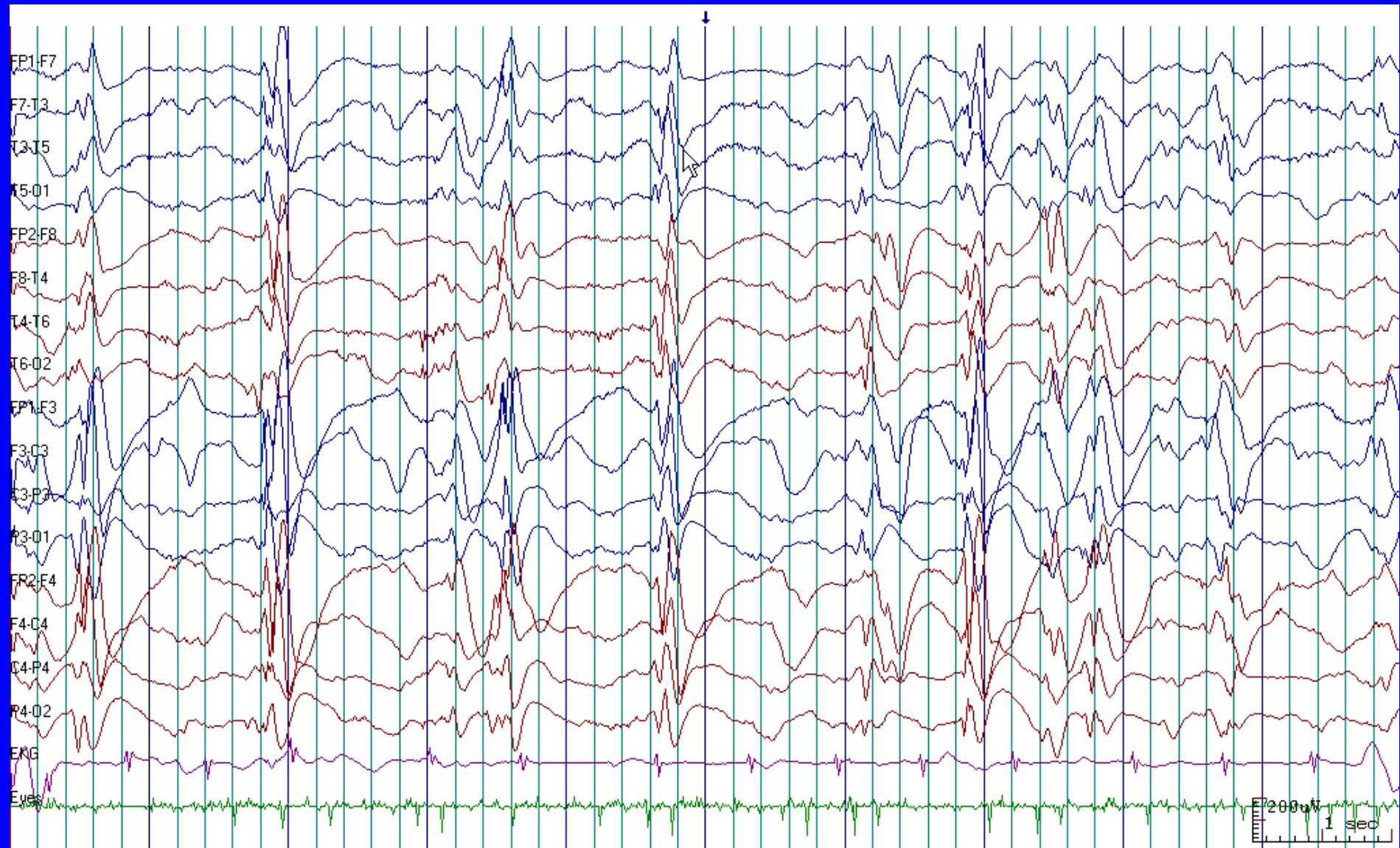
# Rapamycin, TSC, and Intractable Epilepsy

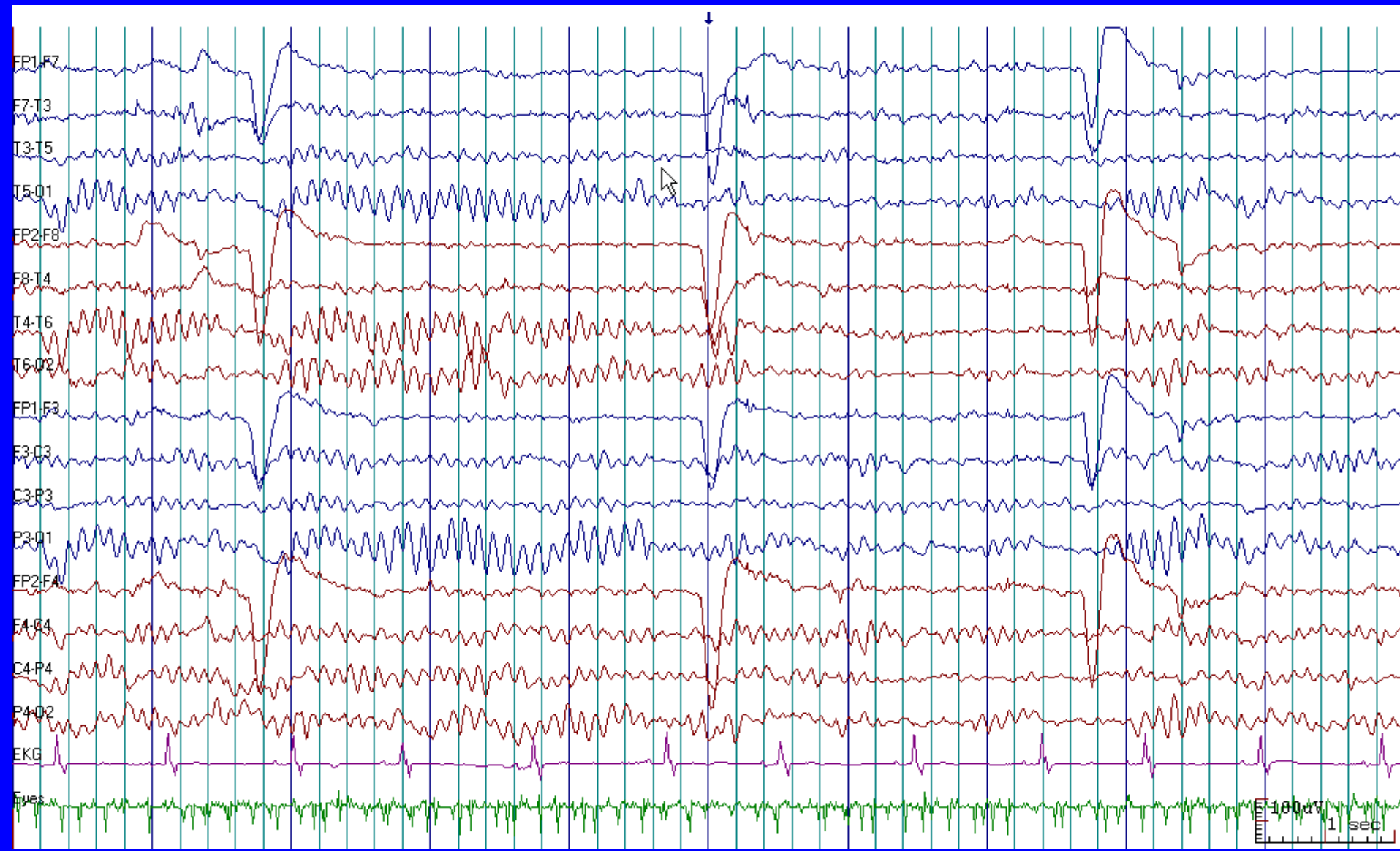
- N = 14 with multiple daily partial seizures
  - 8 males, 6 females
- Ages 3 – 26 years (mean 13 yrs)
- All failed minimum > 9 AED's
- 13/14 with Hx infantile spasms
- 8 failed vagus nerve stimulation (VNS)
- 3 failed VNS + epilepsy surgery

# TSC & Intractable Epilepsy Results

- Rapamycin added to AED regimen, trough 10-15 ng/ml
- 3 (21%) > 90% reduction
  - All with subjective cognitive improvement
- 7 (50%) > 50% reduction
  - 3 pt's lost efficacy over 3-6 mo
  - 2 persistent improvement on drug
  - 2 persistent improvement off drug
  - 5 subjective cognitive improvement
- 4 Non-responders
- Duration of Rx 1 - 40 mo, mean 14 mo
- Max dose 10 mg/d







# Adverse Effects

- Aphthous ulcers 9/14 (64%)
- Otitis media/URI 8/14 (57%)
- Lethargy 3/14 (21%)
- Insomnia, acneiform rash each 2/14 (14%)
- Pneumonia 2/14 (14%)
- AGE/dehydration 1/14 (7%)
- Agitation 1/14 (7%)
- 2 patients hospitalized for AE

# Die gar traurige Geschichte

## mit dem Feuerzeug



Paulinchen war allein zu Haus,  
Die Eltern waren beide aus.  
Als sie nun durch das Zimmer sprang  
Mit leichtem Mut und Sing und Sang.

Da sah sie plötzlich vor sich stehn  
Ein Feuerzeug, nett anzusehn.  
„Ei,“ sprach sie, „ei, wie schön und fein!  
Das muß ein trefflich Spielzeug sein.  
Ich zünde mir ein Hölzchen an,  
Wie's oft die Mutter hat getan.“

Und Minz und Maunz, die Katzen,  
Erheben ihre Tatzen.  
Sie drohen mit den Pfoten:  
„Der Vater hat's verboten!  
Miau! Mio! Miau! Mio!  
Laß stehn! Sonst brennst du lichterloh!“



Paulinchen hört die Katzen nicht!  
Das Hölzchen brennt gar hell und licht,  
Das flackert lustig, knistert laut,  
Grad wie ihr's auf dem Bilde schaut.  
Paulinchen aber freut sich sehr  
Und sprang im Zimmer hin und her.

Doch Minz und Maunz, die Katzen,  
Erheben ihre Tatzen.  
Sie drohen mit den Pfoten:  
„Die Mutter hat's verboten!  
Miau! Mio! Miau! Mio!  
Wirf's weg! Sonst brennst du lichterloh!“