

# Vascular Visualization

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Why look at blood vessels in the brain?

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- Anomalous blood flow is associated with abnormal cognitive and psycho-social function

Alzheimer's

Parkinson's

Vascular Dementia

Congenital vascular anomalies

Autism

# Vascular Visualization

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Autism is a  
developmental disorder

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- Core Features
  - Delayed Communication
  - Lack of Social Reciprocity
  - Repetitive Behaviors
  - Circumscribed Interests
- Early Onset (1-3 Years)
- Prevalence 30/1000)
- Broad Spectrum

# Vascular Visualization

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## Unclear etiology of Autism

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- Genetic
  - Heritable
  - Unclear linkage studies
- Environmental
  - Thimerosal controversy

# Vascular Visualization

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Autism exhibits  
anomalous (variable)  
blood flow patterns

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- decreased blood flow in the bilateral insula, superior temporal gyri, and **prefrontal cortex** (Ohnishi et. al. Brain 2000)
- decreased blood flow in the **prefrontal cortex** and progressive decrease in left temporal lobe (Wilcox et. al. Neuropsychobiology 2002)
- When looking at facial expressions, less blood flow to cortical 'face area', left **amygdala**, and left cerebellum (Critchley et. al. Brain 2000).

# Vascular Visualization

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High blood flow to the brain is redundant and consistent

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- The brain comprises less than 2% of the body weight and receives 12% of the cardiac output.
- There is redundancy of carotid and vertebro-basilar blood supplies via the Circle of Willis
- Young hypothermic mammals maintain blood flow to the brain at expense of other organs

# Vascular Visualization

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What is vascular development in mouse models with autistic-like traits?

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- We use gene-targeted mice with developmental disorders to understand the role of vascular development in social behavior.



# Vascular Visualization

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## Mouse Models with autistic-like traits

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### Oxytocin and vasopressin receptor nulls

impaired social recognition  
less pup vocalizations

### FosB null

impaired nurturing

### Dvl1 null

fewer social interactions (whisker trimming)  
association with wnt2 signaling

### Nr-1 hypomorph

fewer social interactions and repetitive behaviors

# Vascular Visualization

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How do we see  
blood vessels in  
the mouse brain?

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Access aortic arch with pulled glass pipette



Close descending aorta



Incise Right Atrium



Set perfusion flow rate according to age, cardiac index and body mass



Stain with 4% FITC-conjugated *L. esculentum* lectin



Fix with 10% neutral buffered formalin



# Vascular Visualization

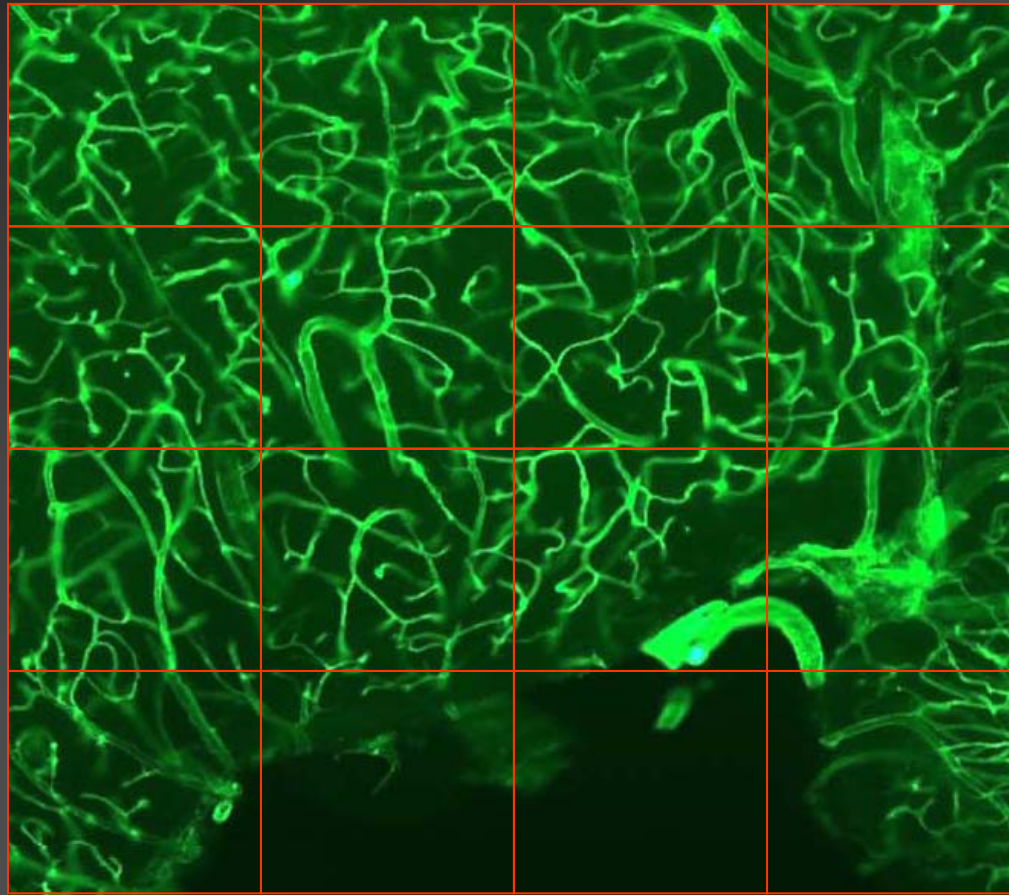
section with vibrating  
microtome



montage photography

## Montage photography

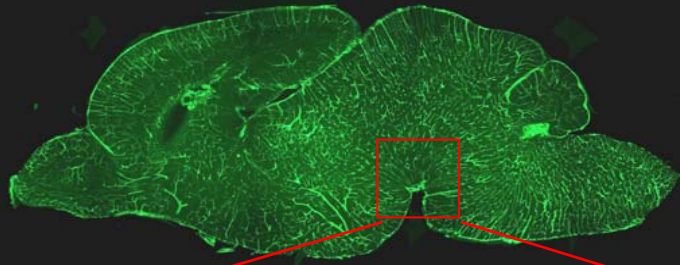
Single  
image



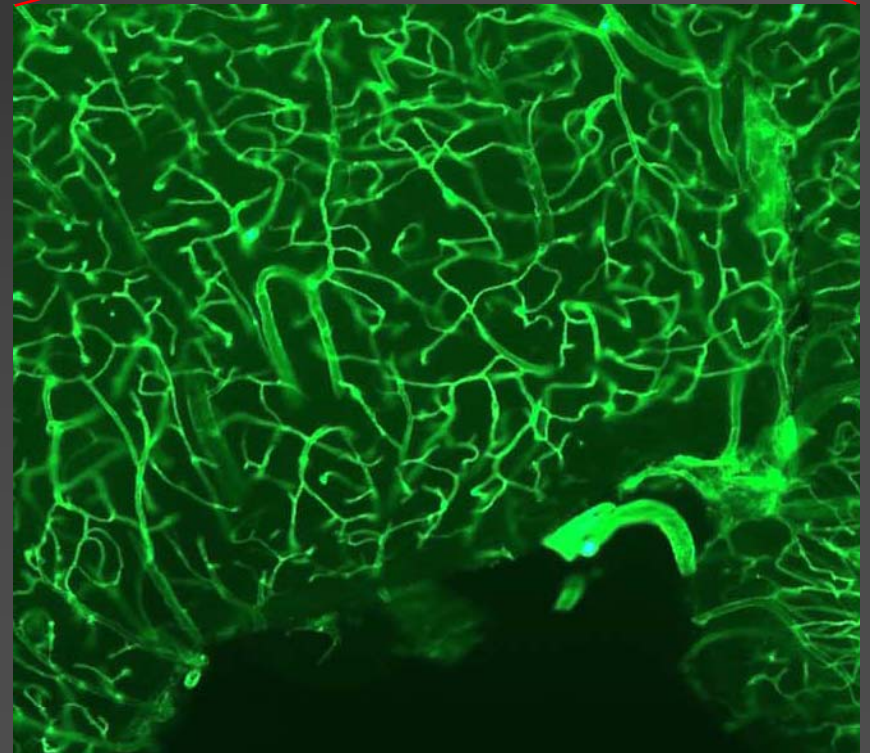
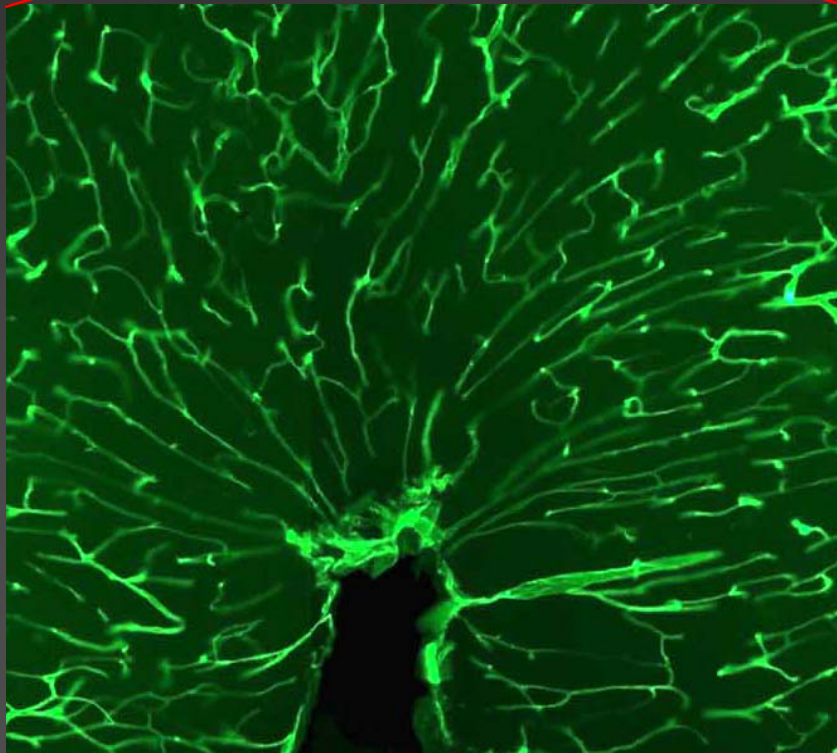
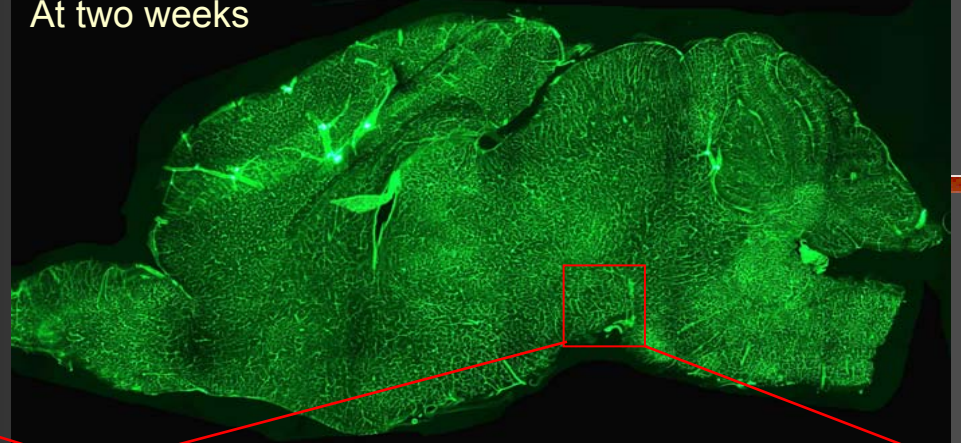
# Vascular Visualization

## Vessels in the newborn brain

Newborn



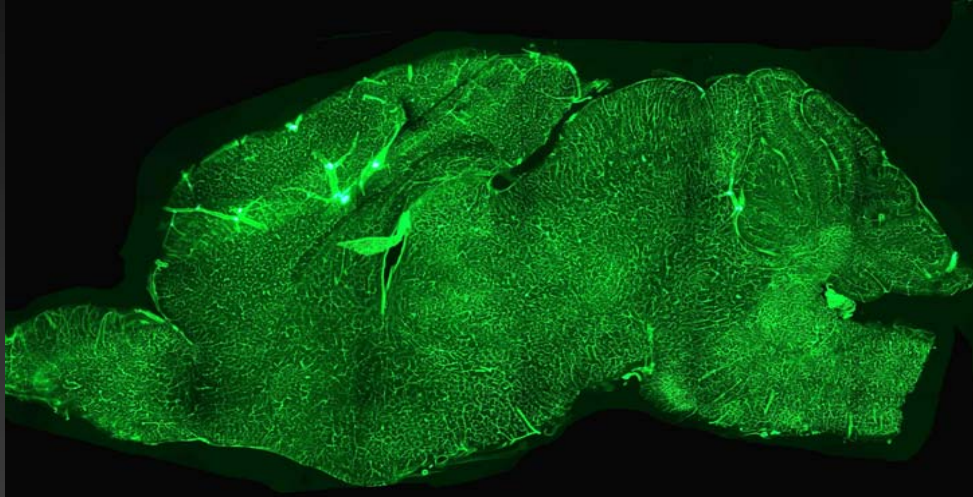
At two weeks





# Vascular Visualization

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## Developmental Anatomy

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- Where and when do vessel patterns emerge during development?
- What is the functional significance of these patterns?
- Do these patterns differ between normal and socially abnormal mice?

# Vascular Visualization

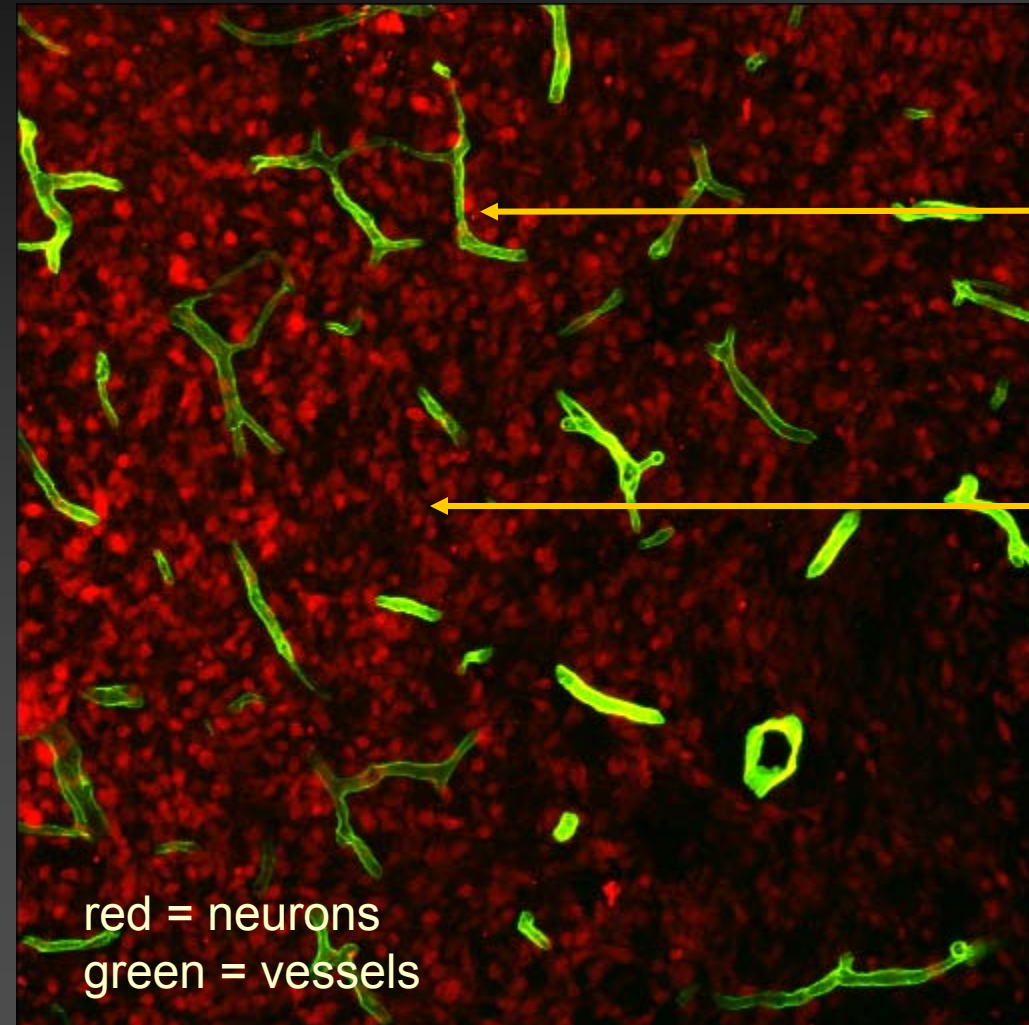
What is the relationship between angiogenesis and neuronal function?

neurogenesis?

neuron death?

red = neurons  
green = vessels

35 micron section



# Vascular Visualization

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## Vessels and social behavior

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- Are changes in behavior associated with anomalous vessel patterns?
  - Vessel patterns could reflect neuron activity
  - Neuron activity/growth may be affected by anomalous vascular patterns
  - Blood flow/brain function association is the basis of functional MRI imaging

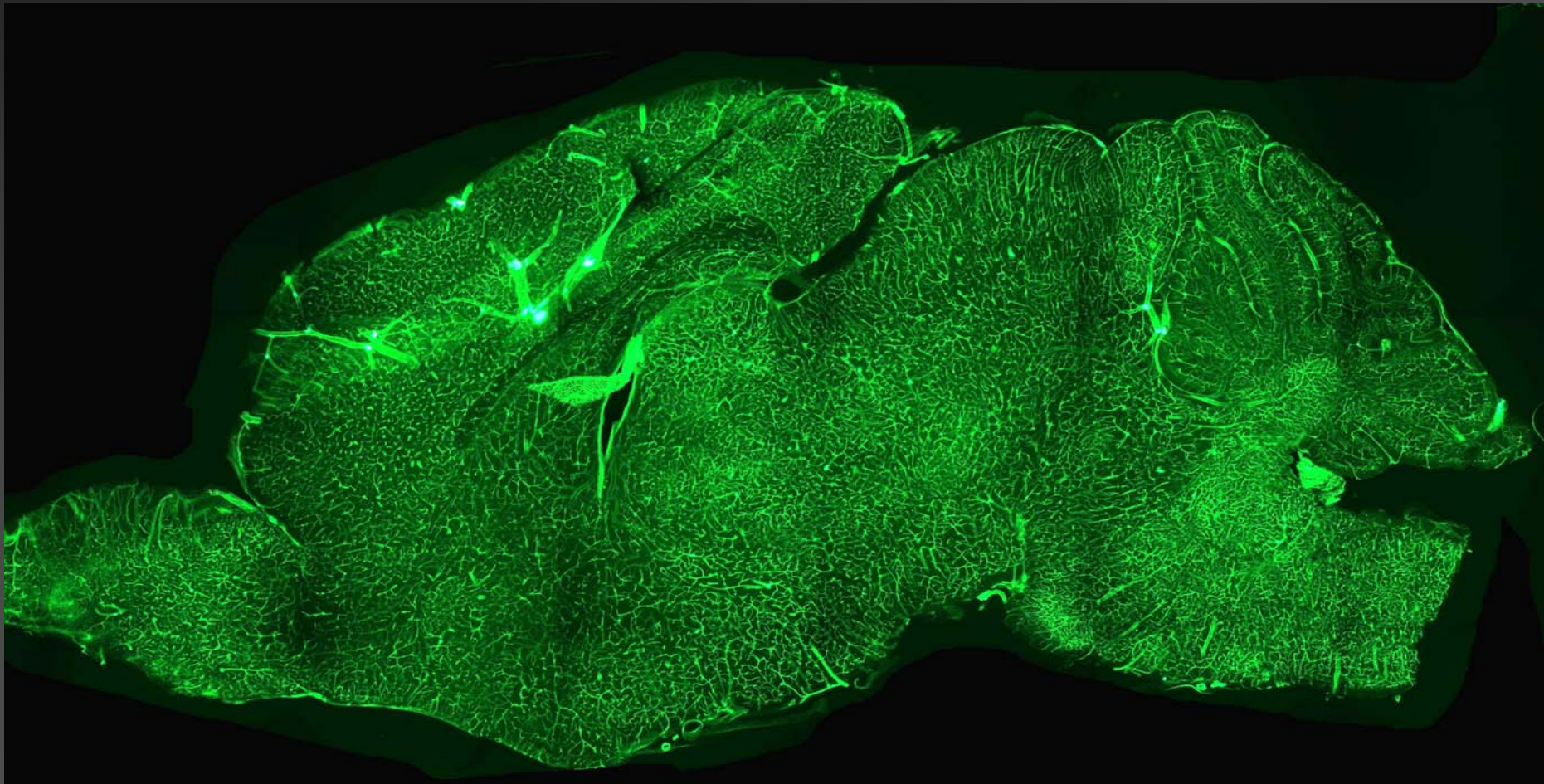


# Vascular Visualization

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How does the  
architecture change?

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# Vascular Visualization

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Density

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How do **vessel densities** change with age?

**vessel orientations**

**vessel anastomoses**

**vessel tortuosities**



# Vascular Visualization

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## Orientation

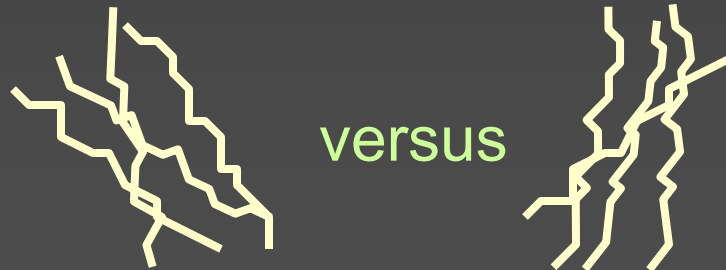
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vessel densities

How do vessel orientations change with age?

vessel anastomoses

vessel tortuosities





# Vascular Visualization

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## Anastomosis

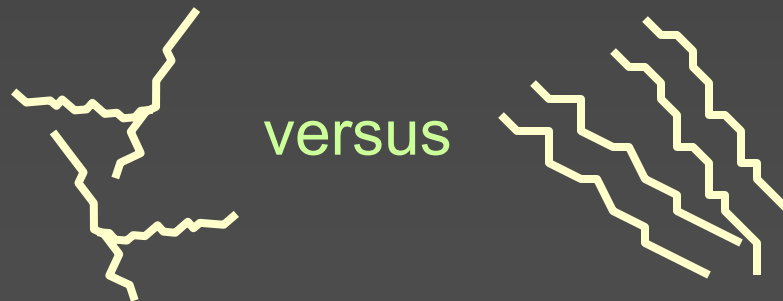
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vessel densities

vessel orientations

How do vessel anastomoses change with age?

vessel tortuosities



# Vascular Visualization

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## Tortuosity

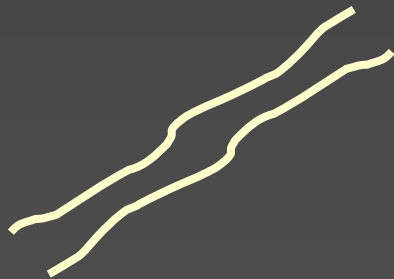
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vessel densities

vessel orientations

vessel anastomoses

How do **vessel tortuosities** change with age?



versus



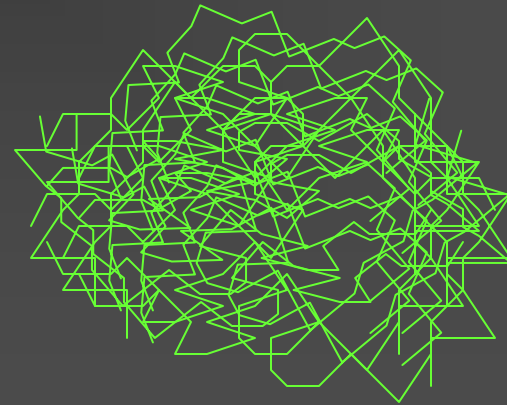
# Vascular Visualization

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When we think about reconstructing the brain from serial sections

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- We'd like to see these relationships in their full 3-D context, but can't see the vessels inside.....



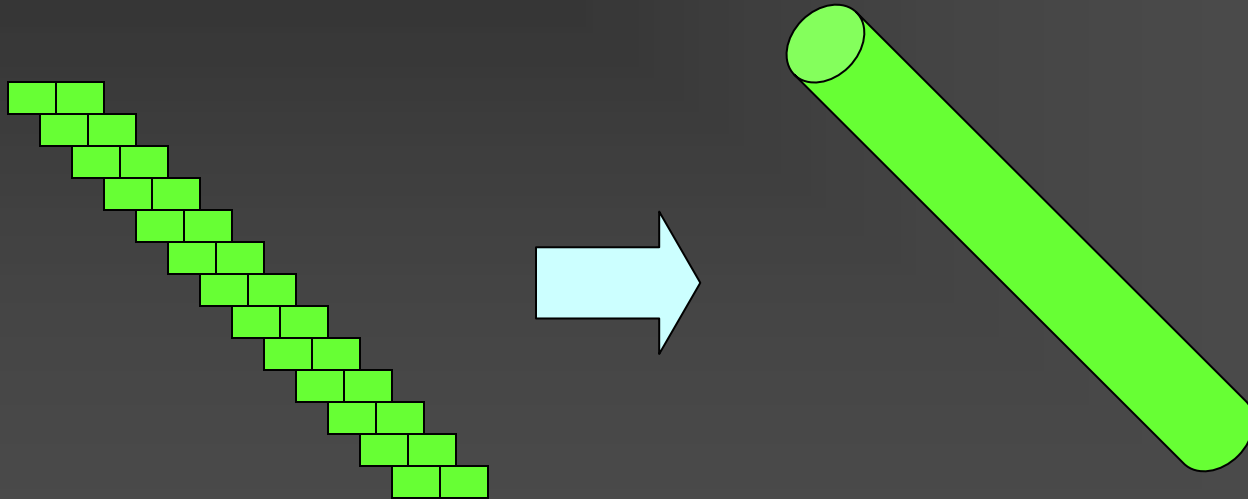
# Vascular Visualization

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## A Solution

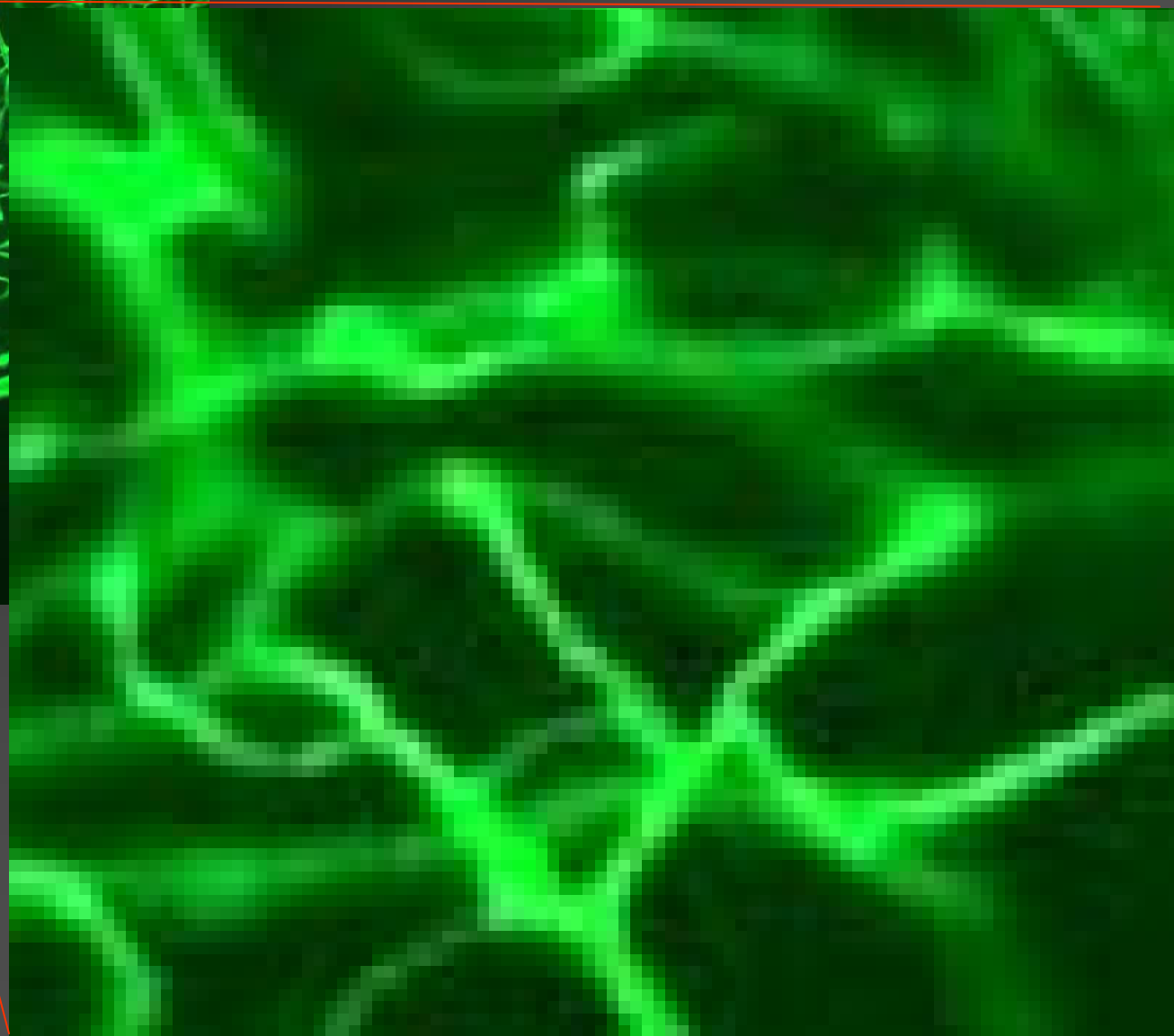
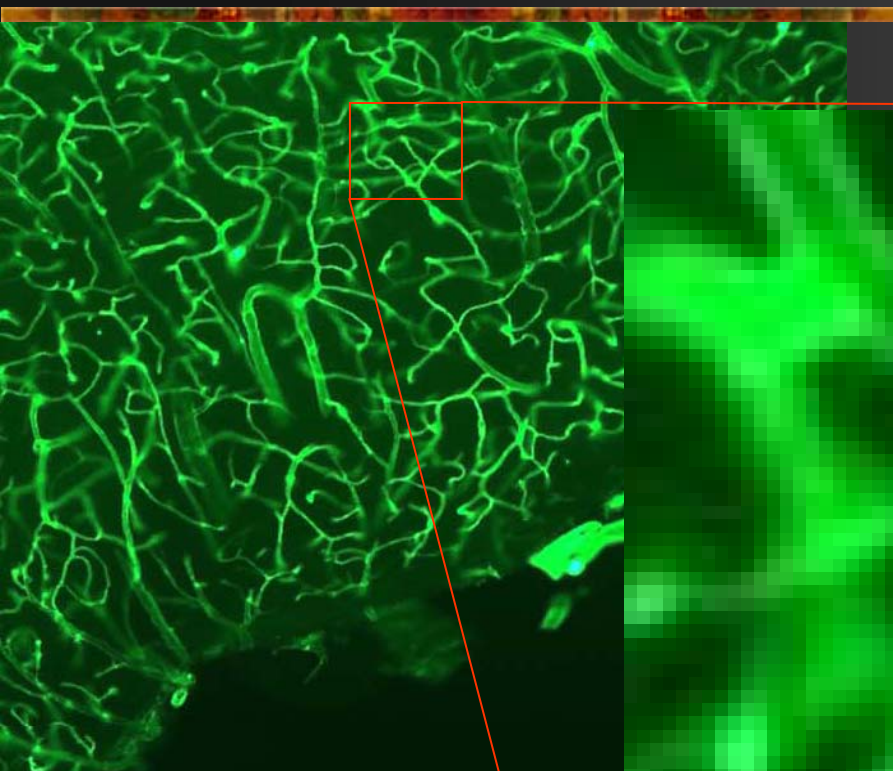
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- Describe vessels with geometry, not pixels



# Vascular Visualization

# Another Problem



Pixel-based image  
is too much data  
and  
I can't quantify this

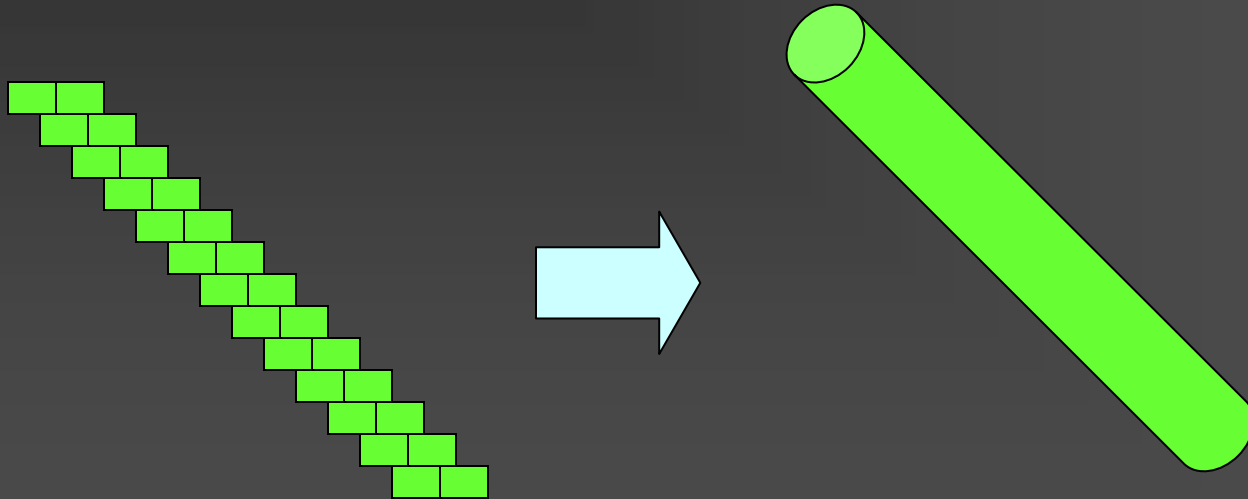
# Vascular Visualization

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Same Solution

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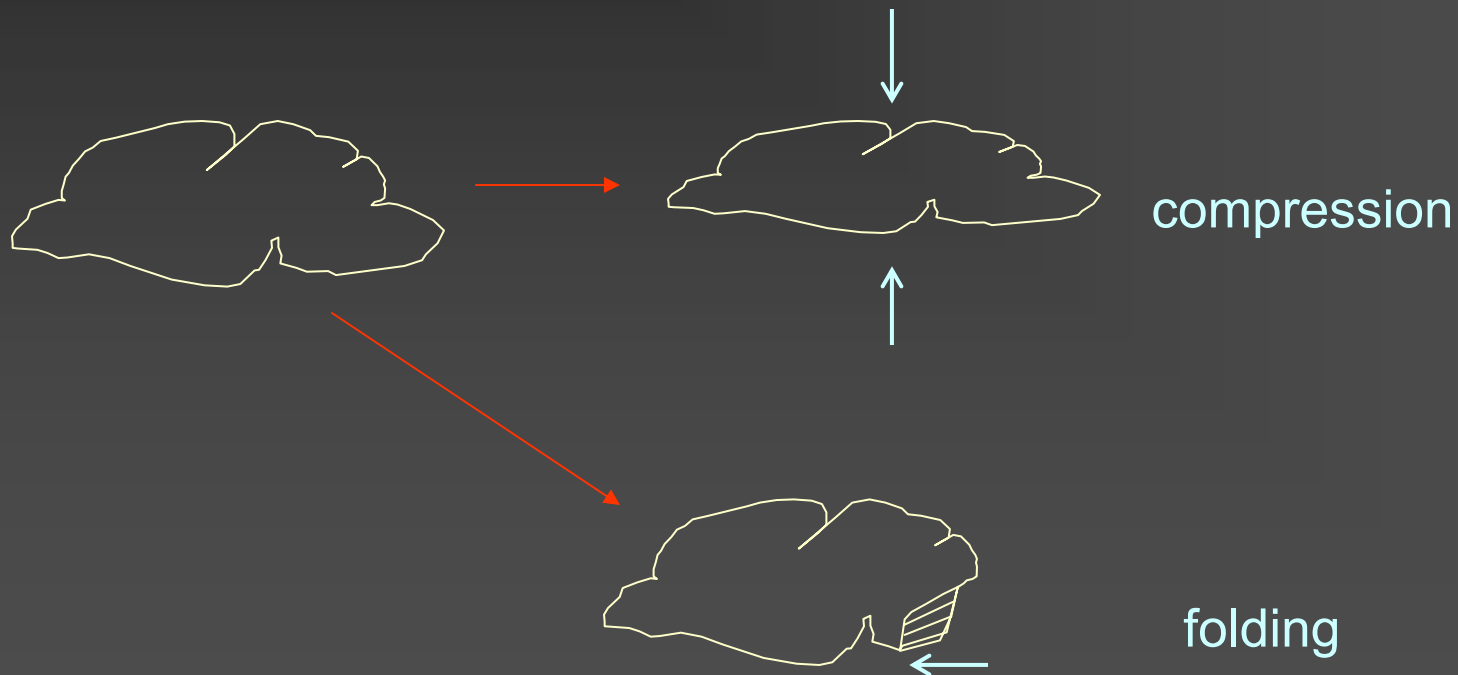
- Describe vessels with geometry, not pixels



# Vascular Visualization

Deformation affects morphology

- We need to remove deformations in histology processing



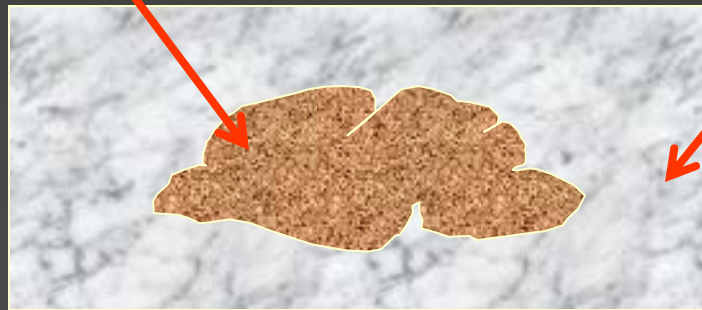
# Vascular Visualization

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## Evolving solutions

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- Perfuse agarose into brain vessels
  - Embed brain in gelatin





# Vascular Visualization

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## Our focus

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- To understand the role of vascular development in social behavior.



# Vascular Visualization

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## Other applications

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- Understand relationship between vascular architecture and function in other organs
- Develop scaffolding for molecular imaging