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MRI Biomarkers for Pediatric Brain Assessment

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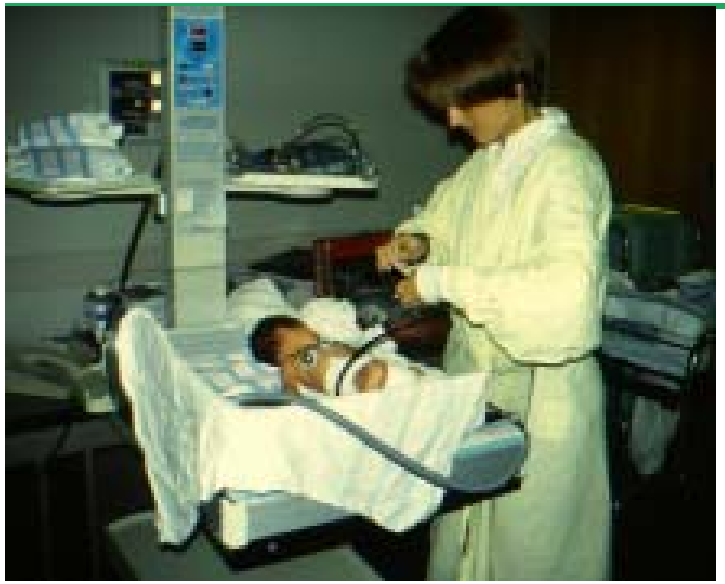
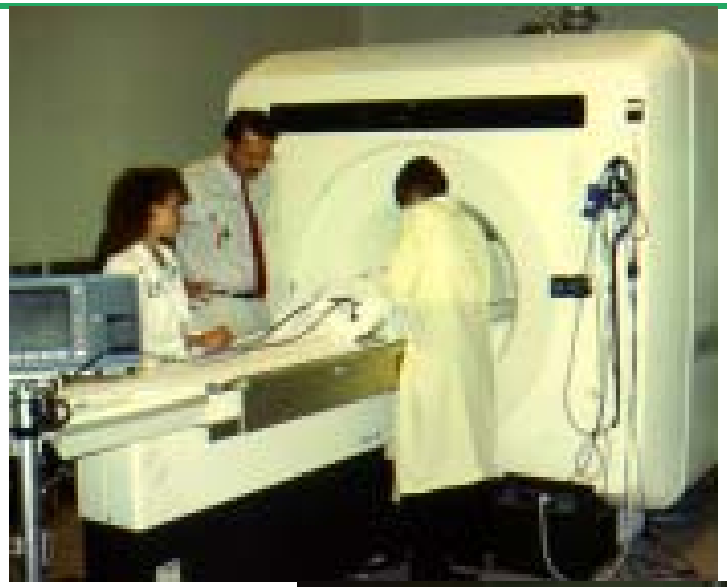
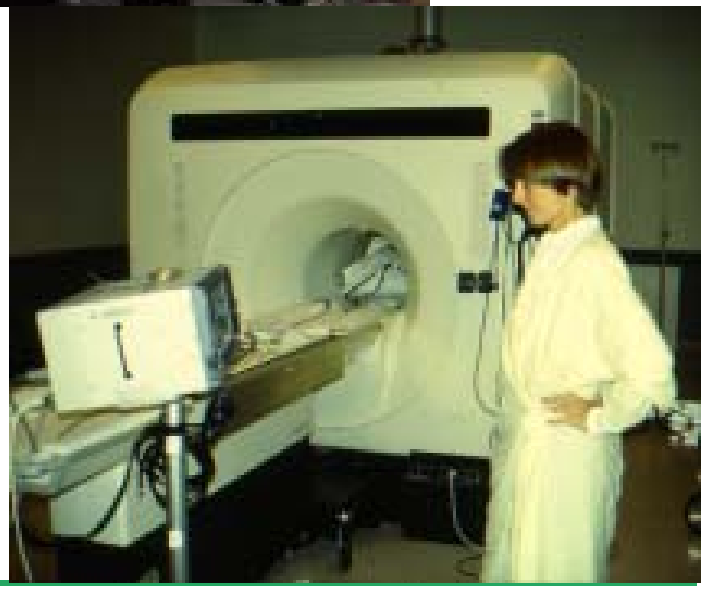
MRI of Premature Newborns







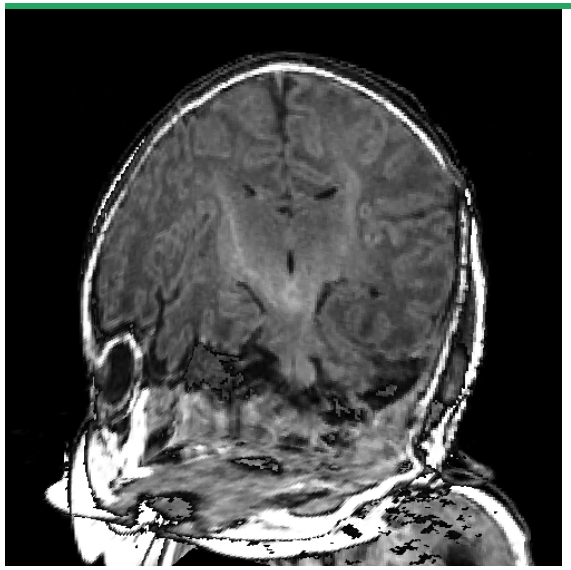
1994 - collaboration initiated with Petra Huppi to investigate structural brain changes in premature infants.

Imaging of Newborn Infants

Motivation

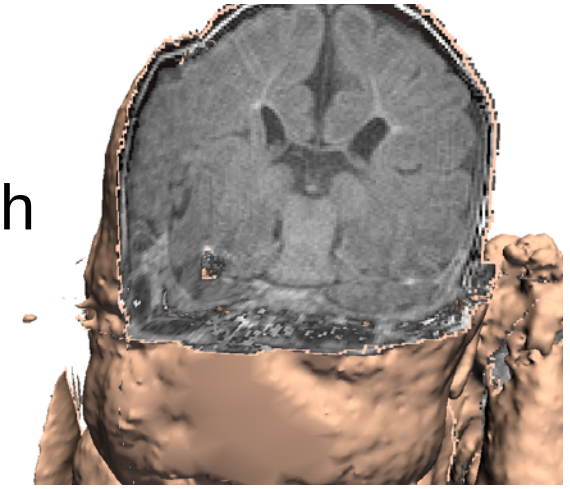
- Increasing prevalence of surviving very low birth weight premature infants
- Very low birth weight infants have high rates of adverse neurodevelopmental outcomes:
  - 10-15% develop cerebral palsy
  - 50% develop significant neurobehavioral problems including
    - Lowered IQ
    - ADHD
    - Anxiety disorders
    - Learning difficulties
- Considerable educational burden with significant economic and social implications.

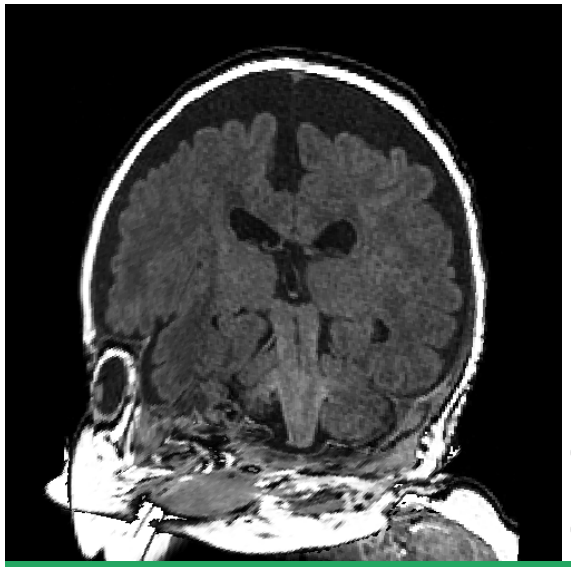
Newborn Brain: Structural MRI



Healthy fullterm infant.

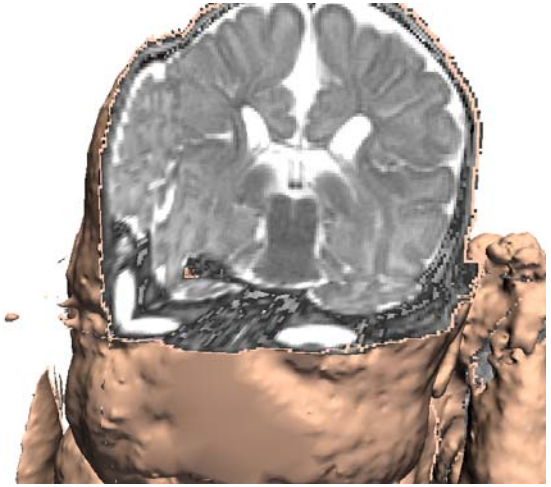
SPGR (T1w) of infant with PVL.





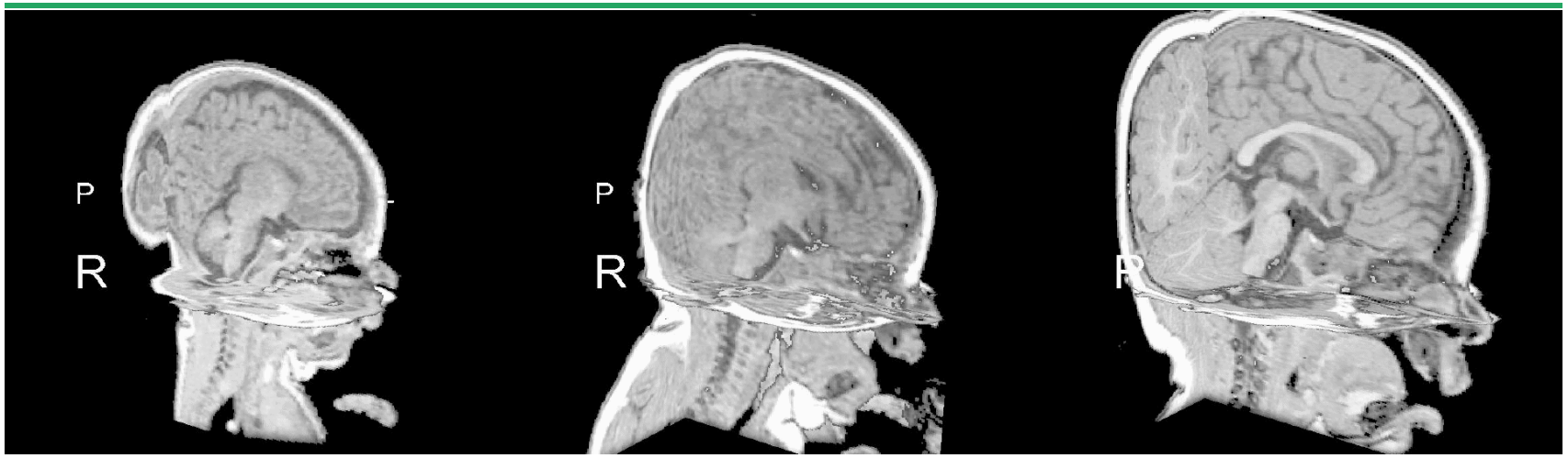
Fullterm infant with delayed development.

CSE (T2w) of infant with PVL.



Skin shown in pink.

Studying Brain Development



10 weeks premature

Term equivalent age

9 months

A sequence of MRI of the same infant: shortly after premature birth, at term equivalent age, and at nine months. The sequence of growth of the brain and development of myelination in the white matter can be best followed by quantitative 3D assessment.

Motivation

- VLBW infants are at risk of altered neurodevelopment and adverse outcomes from brain injury.
  - What are the patterns of brain injury that explain the adverse outcomes ?
  - What are the perinatal risk factors ?
  - What are the causes and mechanisms of brain injury ?
- Can we develop imaging and image analysis procedures to :
  - characterize these patterns of injury and assess potential interventions ?
  - Establish timing of injury or developmental periods of vulnerability ?

MRI can predict later outcomes

- Qualitative assessments at term age MRI predict motor and cognitive outcome at term age (Woodward et al. NEJM 2006).
  - White matter abnormalities at term are predictive at two years of age of:
    - cognitive delay (OR: 3.6),
    - Motor delay (OR: 10.3),
    - Cerebral palsy (OR: 9.6)
  - Gray matter abnormalities at term predictive of cognitive delay, motor delay, cerebral palsy.

MRI can predict later outcomes

- Quantitative MRI at term equivalent age has been shown to predict:
  - Impaired visual function in VLBW infants at age 2 (Shah et al. 2006)
  - Object working memory deficits at age 2 (Woodward et al. 2005)
  - PDI and MDI at age 2 (Thompson et al. 2008)
  - Cognitive and motor outcomes at 1.5 and 2 years (Peterson et al. 2003)

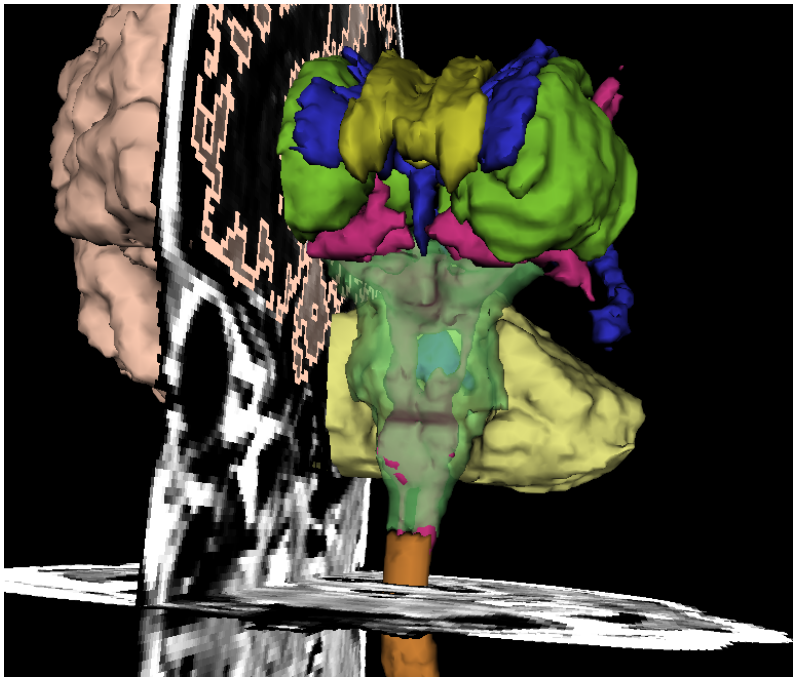
Biomarkers

- We aimed to develop a set of MRI measures that can
  - 1. characterize the patterns of brain injury in premature infants, and
  - 2. can predict motor and cognitive outcomes in those children.

Structural MRI Analysis

- MR parameters
- Image analysis: Segmentation is key
  - battery of measures
  - Individual subjects:
    - Volume measures
    - Thickness measures e.g. cortical thickness
    - Shape measures (spherical harmonic representation, deformable models)
  - Groups of subjects (registration is key)
    - Statistical atlases.
    - Correspondence field morphometry.

3D Segmentation of Newborn Brain



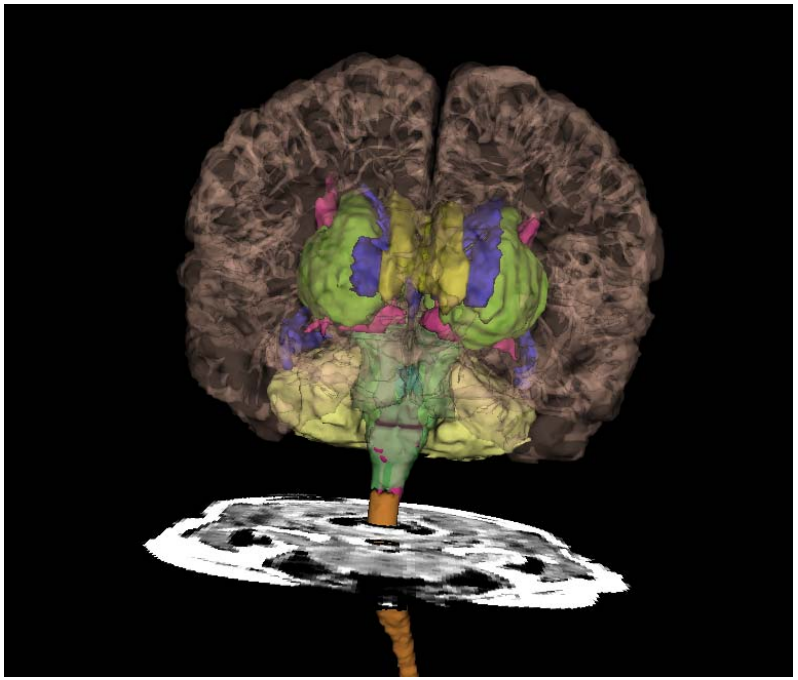
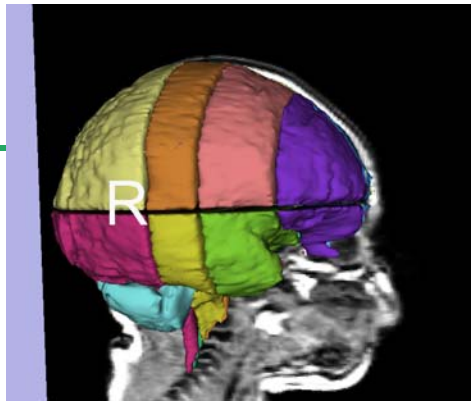


Image Segmentation



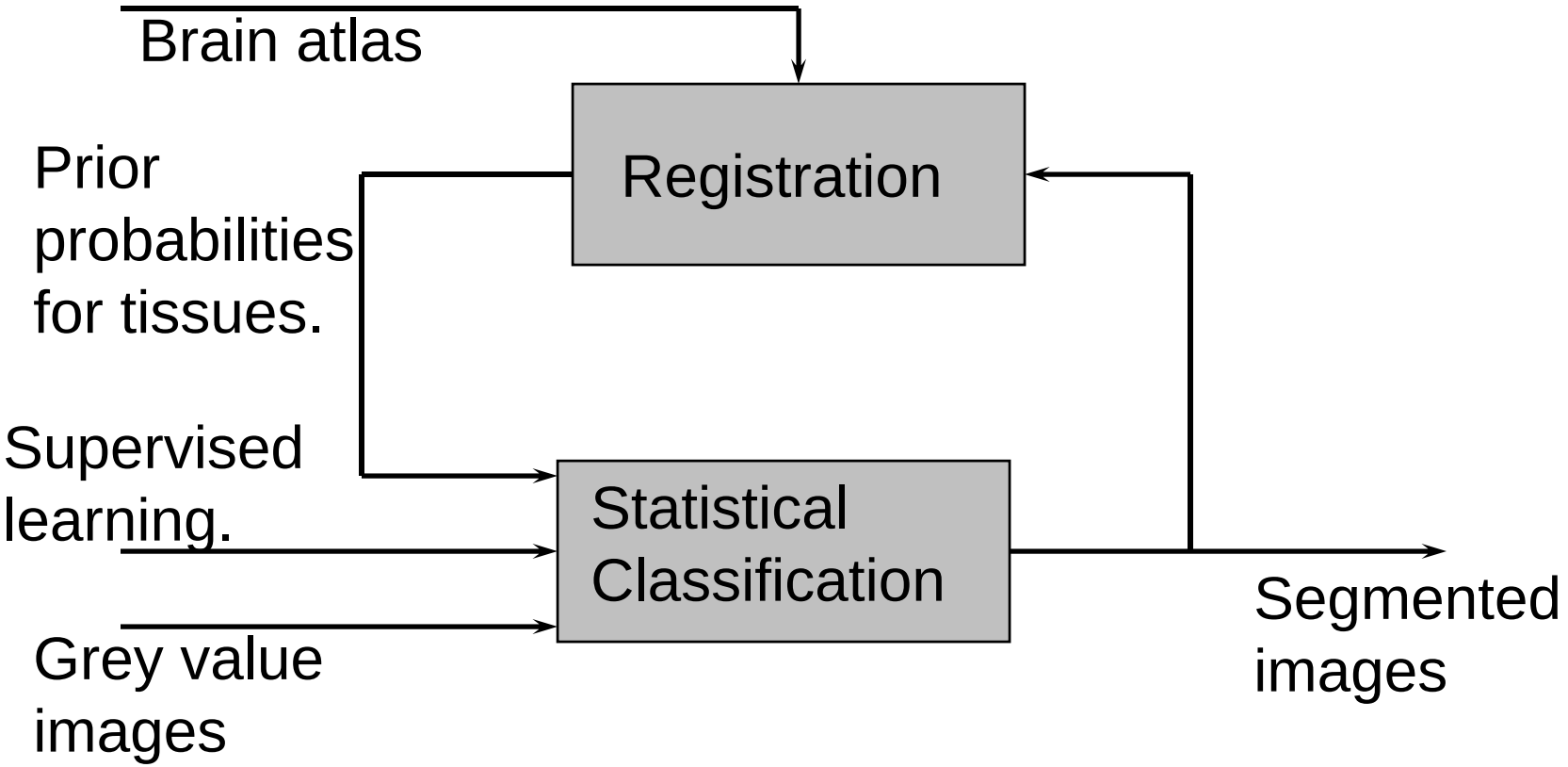
- Segmentation issues:
  - Interactive segmentation:
    - time consuming.
    - significant intra-rater and inter-rater variability (Kikinis et al., 1992, Warfield et al. 1995).
  - Automatic segmentation:
    - Challenges.
      - Imaging artifacts.
      - Normal and pathological variability.
    - Prospects:
      - Objective assessment of imaging data.

Validation of Image Segmentation

- Segmentation critical to further measures such as thickness, gyrification.
- STAPLE (Simultaneous Truth and Performance Level Estimation):
  - An algorithm for estimating performance and ground truth from a collection of independent segmentations.
    - Warfield, Zou, Wells MICCAI 2002.
    - Warfield, Zou, Wells, IEEE TMI 2004.
    - Warfield, Zou, Wells, PTRSA 2008.

Segmentation

Combine statistical classification and registration of a digital anatomical atlas (Warfield et al. 2000)



Estimation of Class Distributions

$$P = \int_R p(\mathbf{x}')d\mathbf{x}'$$

$$\approx p(\mathbf{x})V$$

Select n samples:

$$P_k = {}^nC_k P^k (1-P)^{n-k}$$

$$E[k] = nP$$

Consider a region enclosing a volume V around **x**, which encloses k samples, k_i of which are labelled class w_i.

An estimator for the joint probability is then (Duda,Hart 1973):

$$p(w_i, \mathbf{x}) = \frac{k_i / n}{V}$$

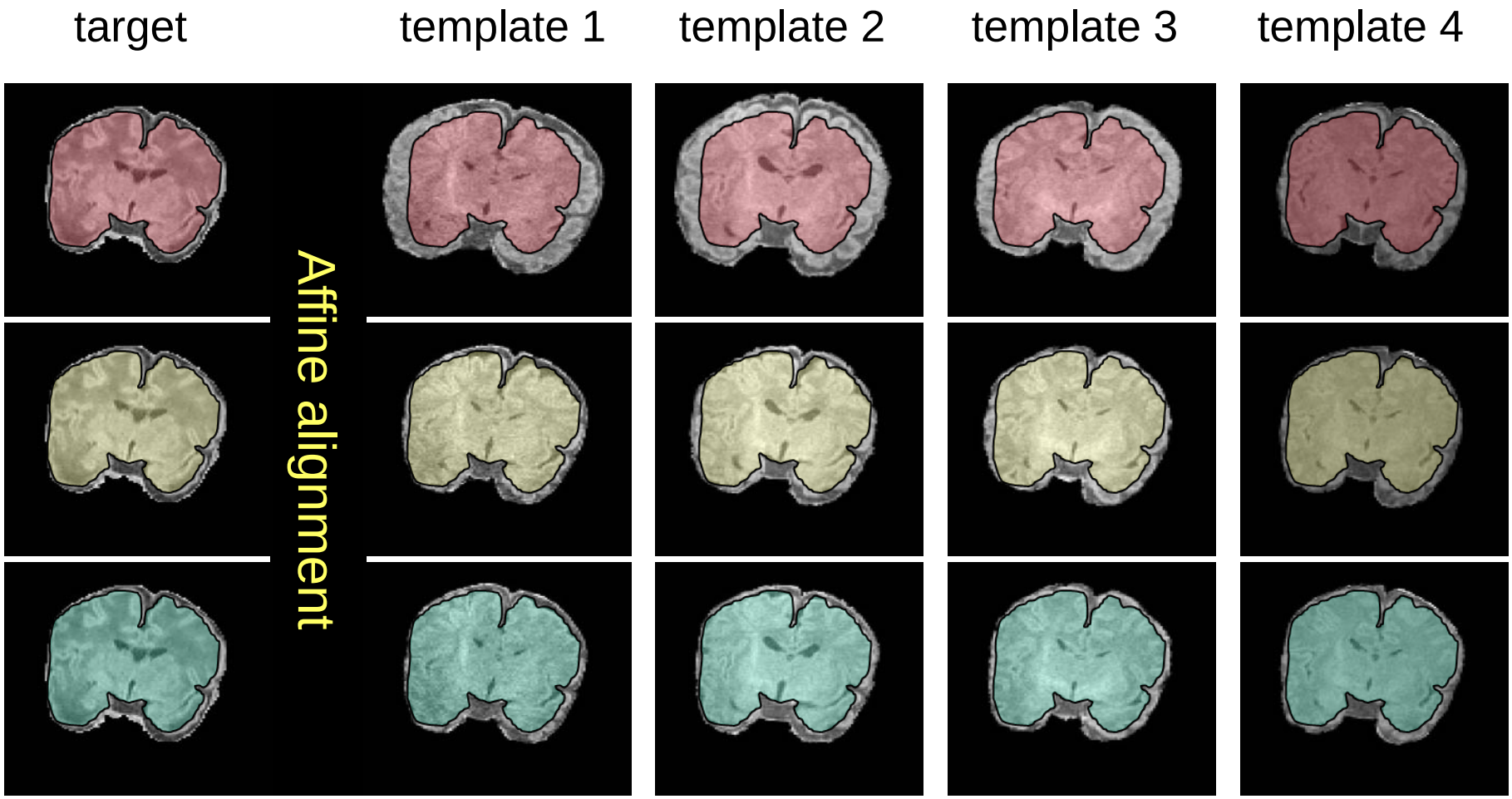
and so the tissue class probability is:

$$\Pr_n(w_i \mid \mathbf{x}) = \frac{p_n(w_i, \mathbf{x})}{\sum_j p_n(w_j, \mathbf{x})} = \frac{k_i}{k}$$

Tissue Class Prototypes

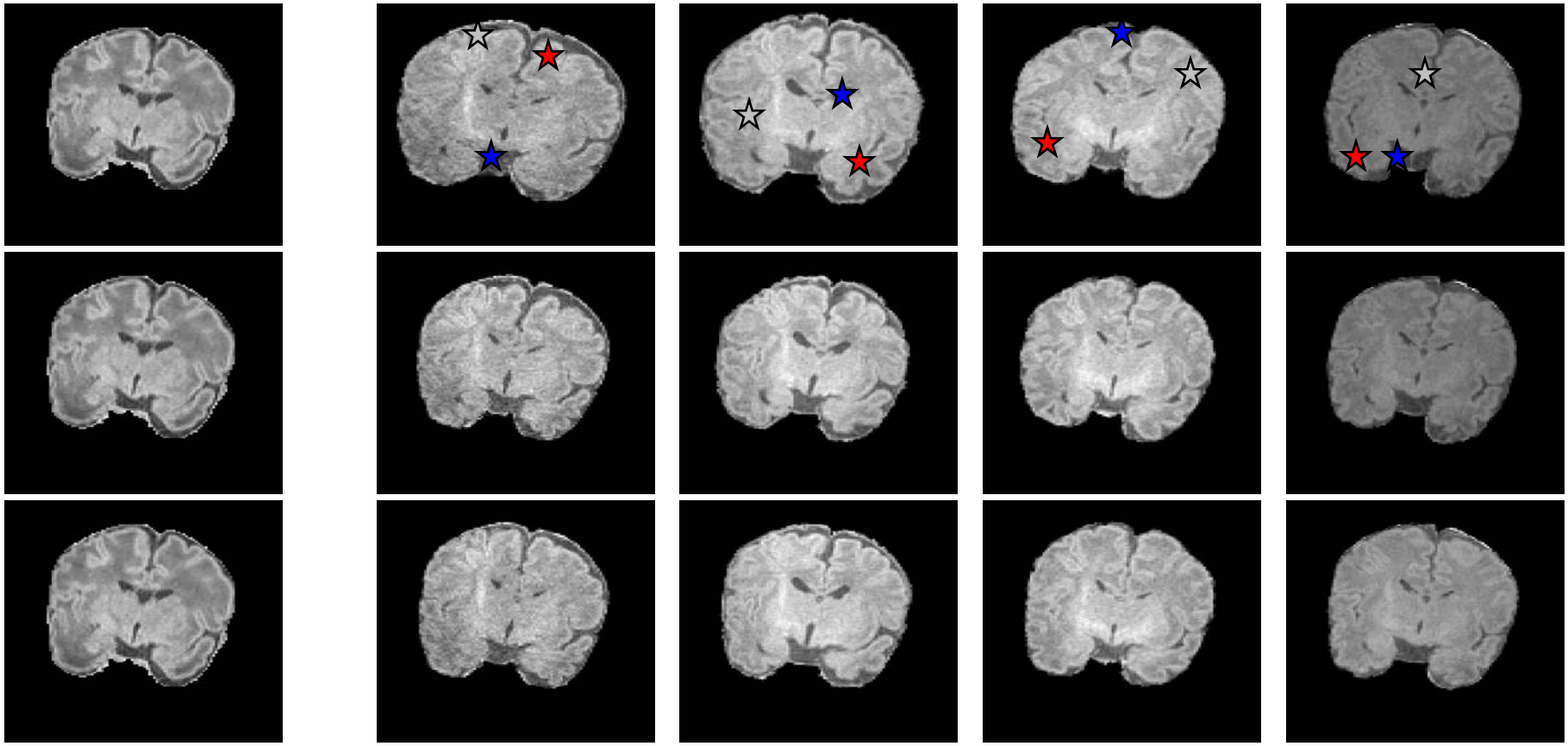
- Our previous work has utilized interactive selection of per-subject training data:
  - Time consuming,
  - Subject to intra-rater and inter-rater variability,
  - Enabled identification of subtle contrast between different tissue types.
- Seek an algorithm that avoids per-subject interaction, while maintaining excellent performance.

Template to Target Registration



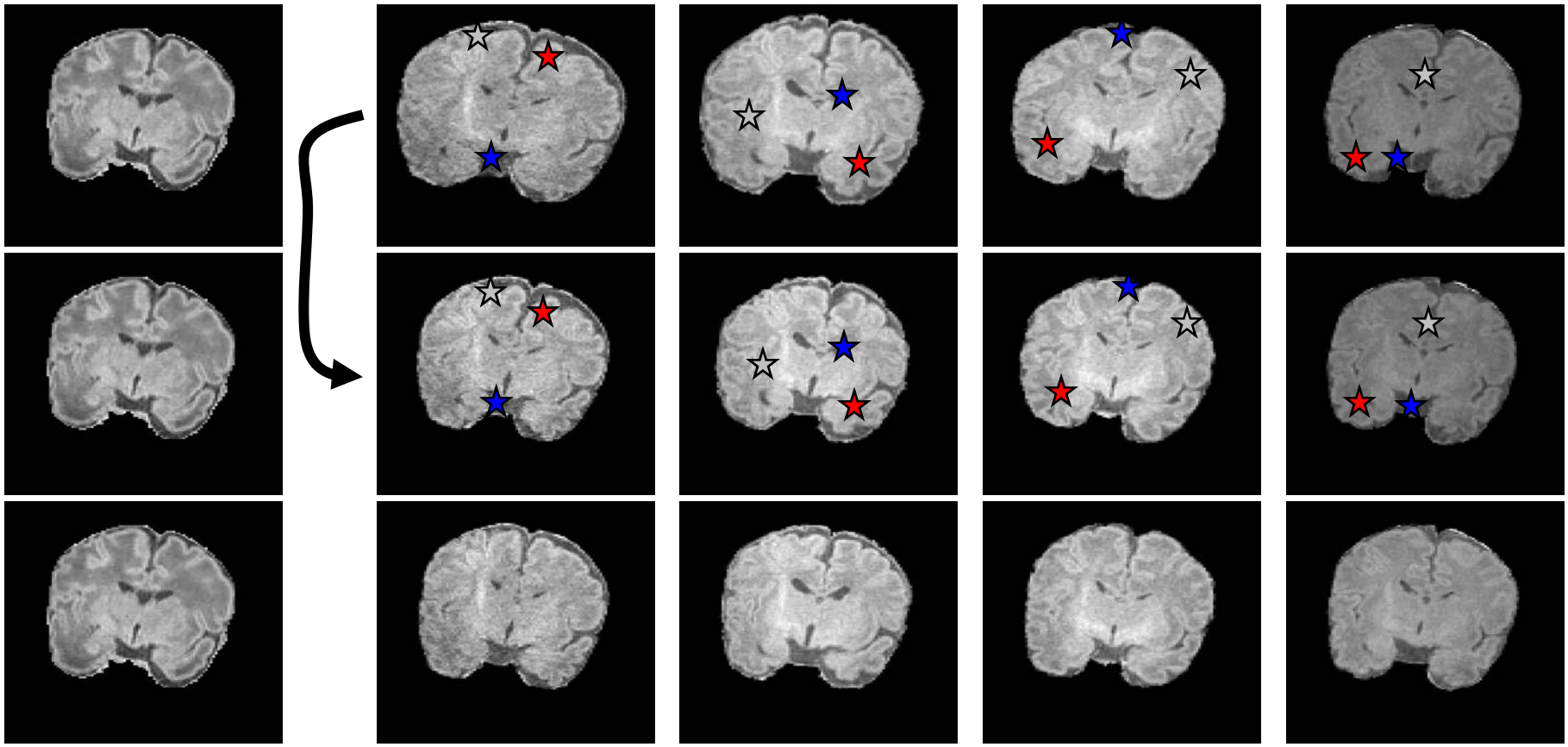
Tissue prototypes manually identified

target | template 1 | template 2 | template 3 | template 4



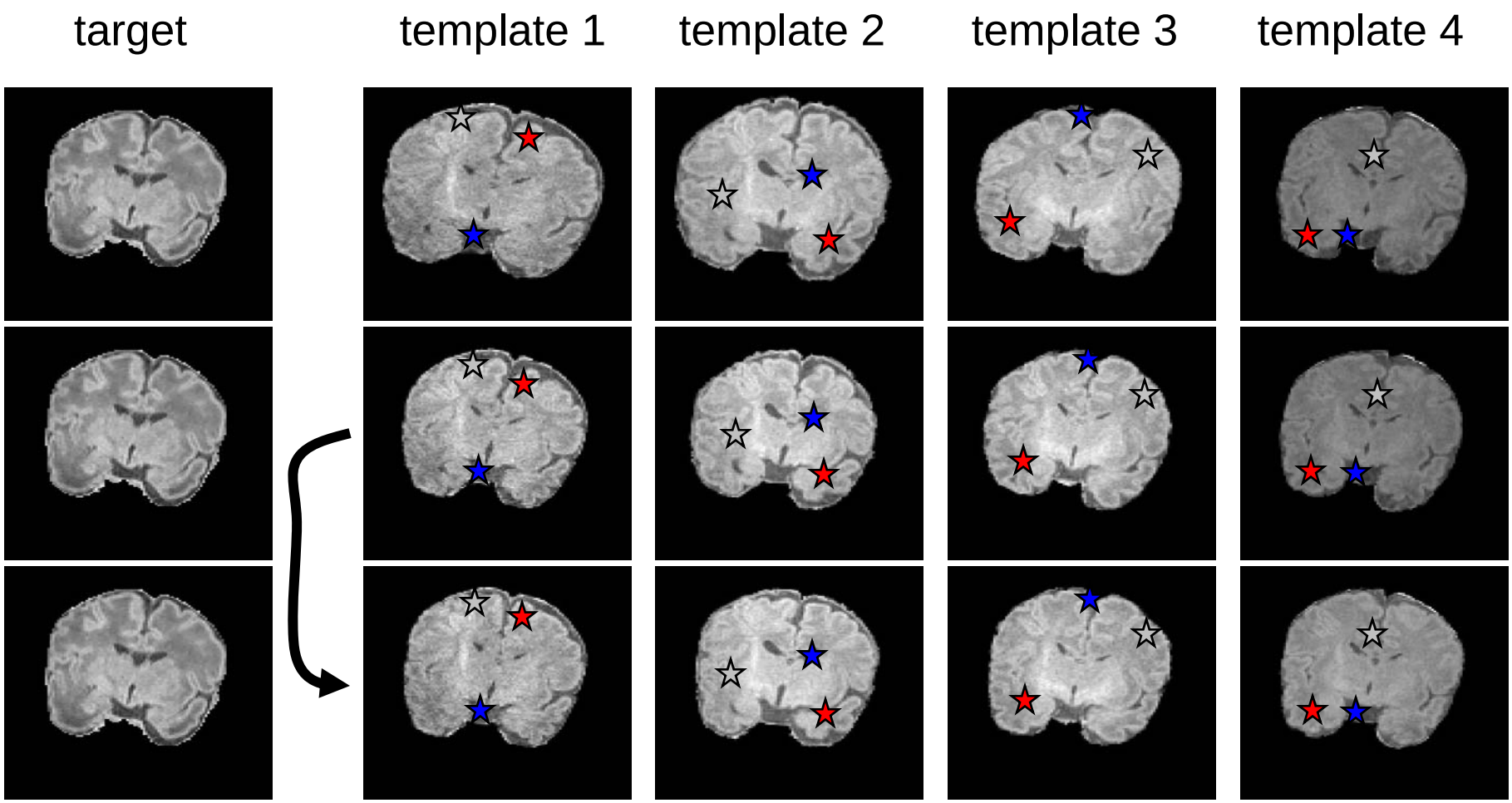
tissue class samples selected once on the original template images.

Tissue prototypes transferred



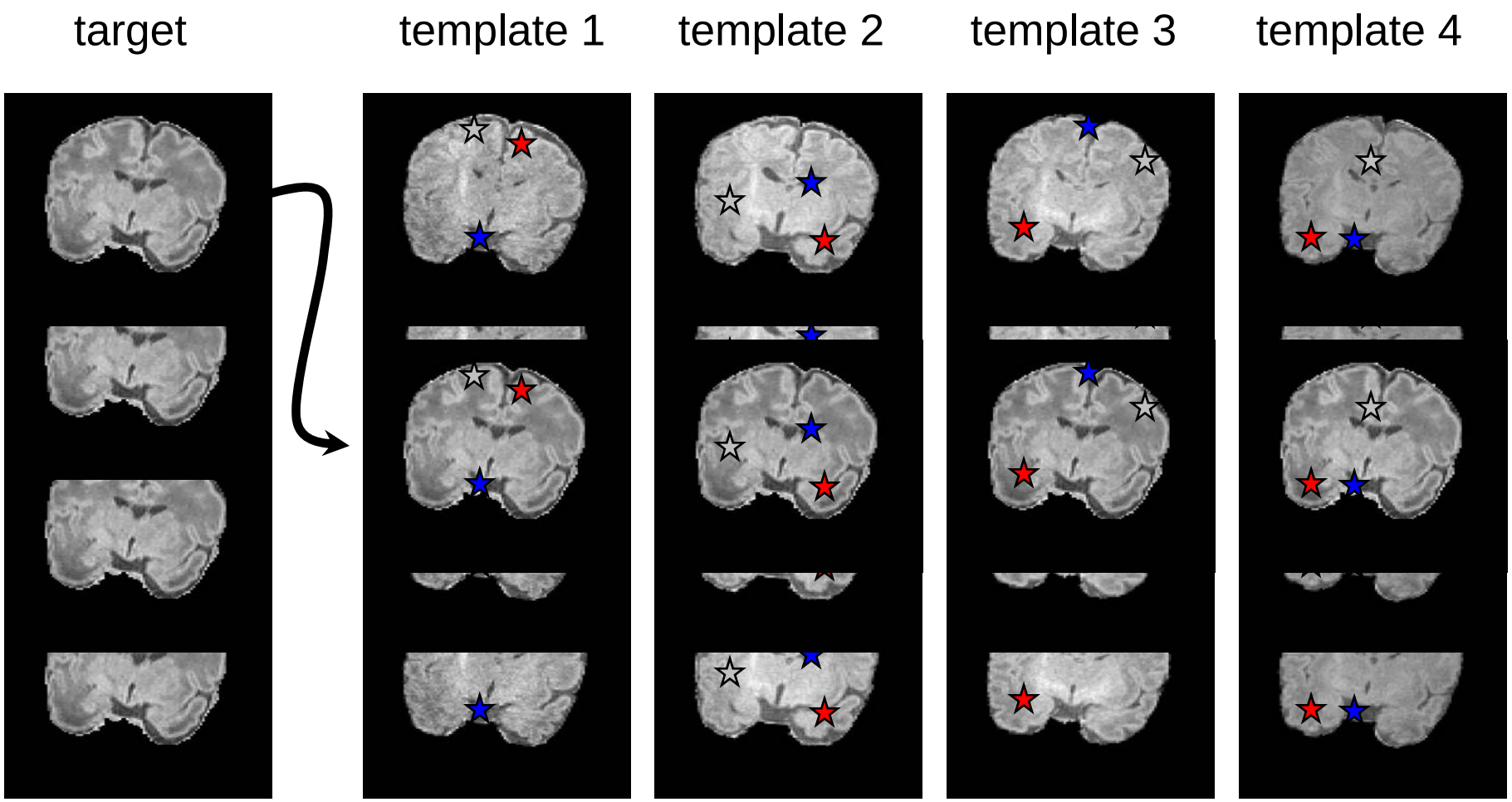
and then projected through the affine transform…

Tissue prototypes transferred



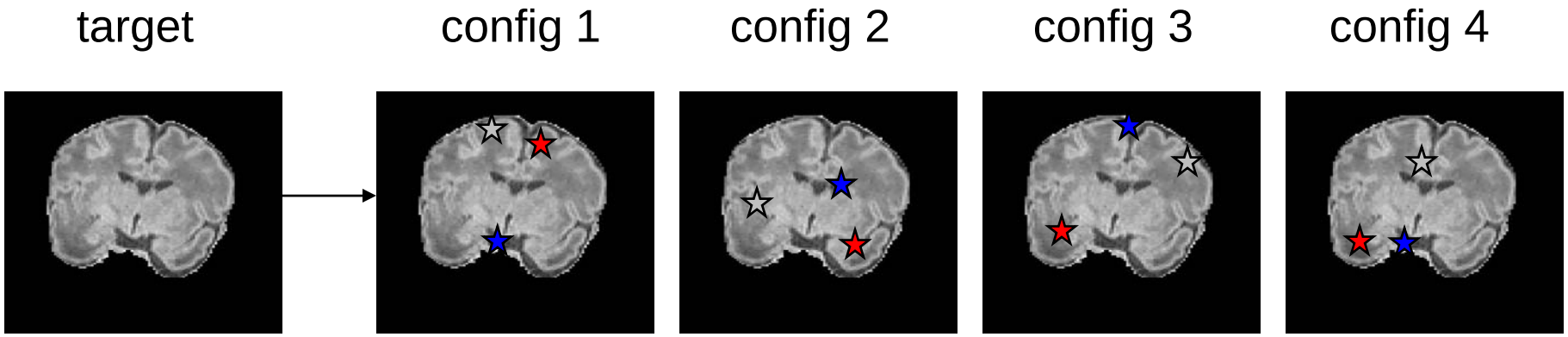
and then projected through the b-spline *non-linear* transform…

Tissue prototypes transferred



Different prototype configurations are projected onto the target subject

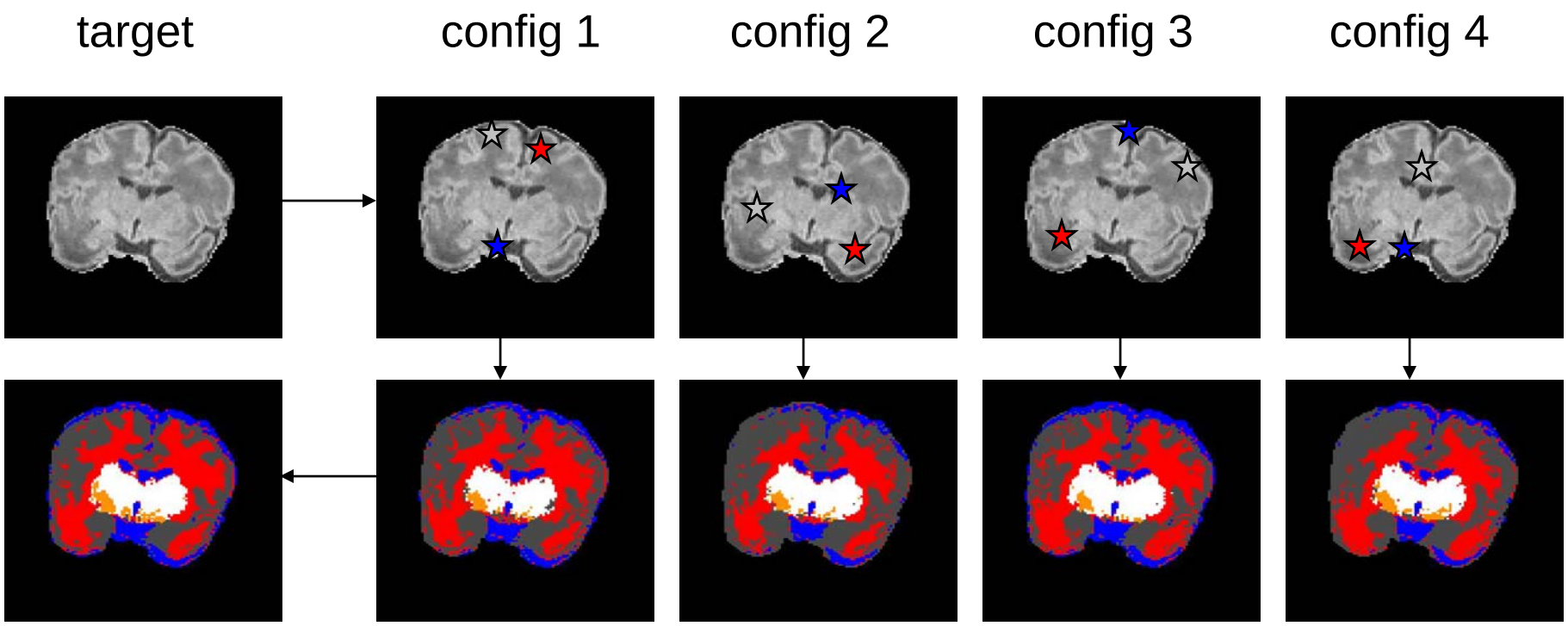
Multiple Configurations on the Target



The different prototype configurations represent the physical variation among the template subjects. By adding template subjects, and choosing prototypes by hand *only once*, a wider range of physical variation can be accommodated. Once a template subject is added, it is re-used without further human intervention.

The image *intensity* data used is *only* from the individual under study (the target).

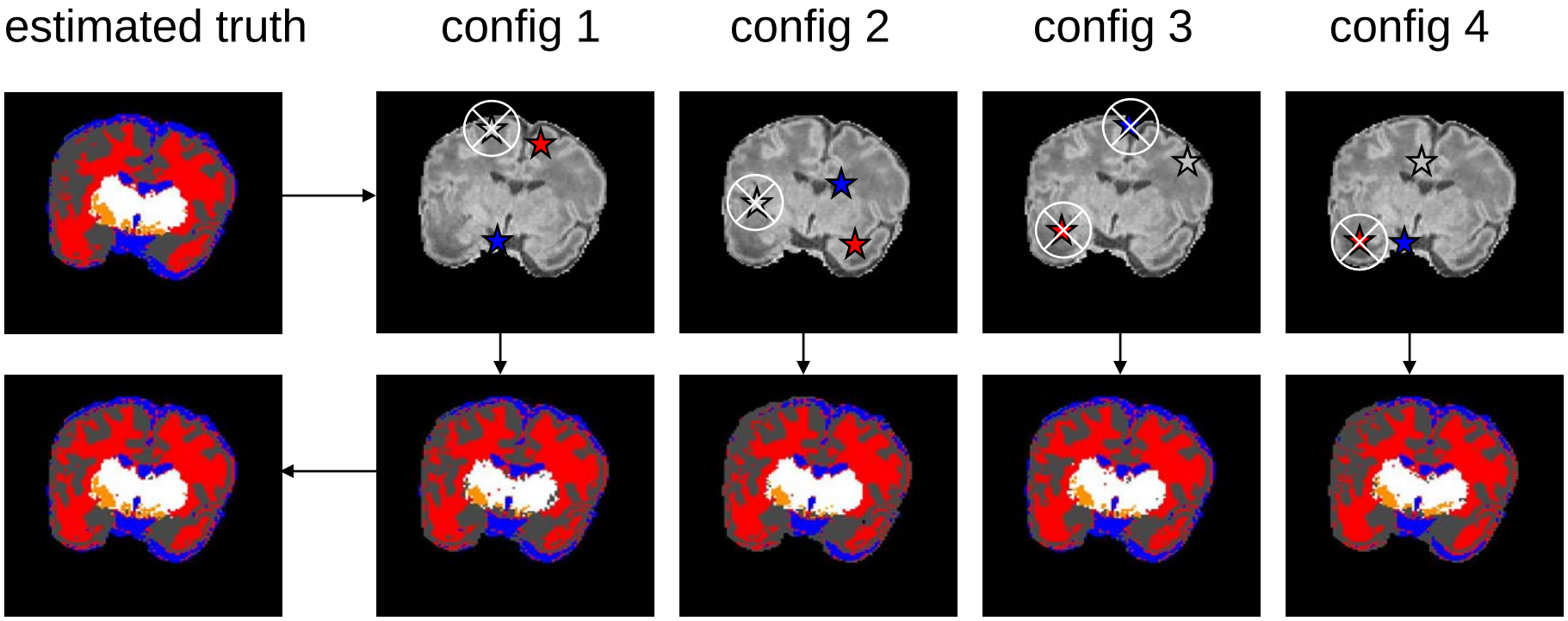
Multiple Configurations on the Target



Each configuration of sample coordinates leads to a different candidate segmentation of the target subject.

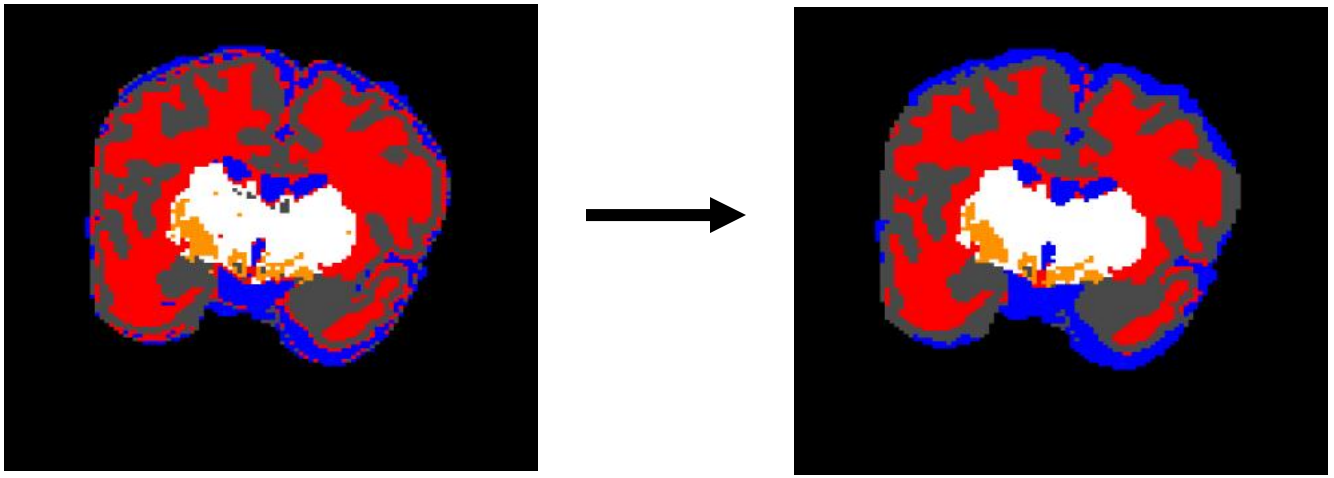
STAPLE is used to combined candidate segmentations.

Configurations are Edited



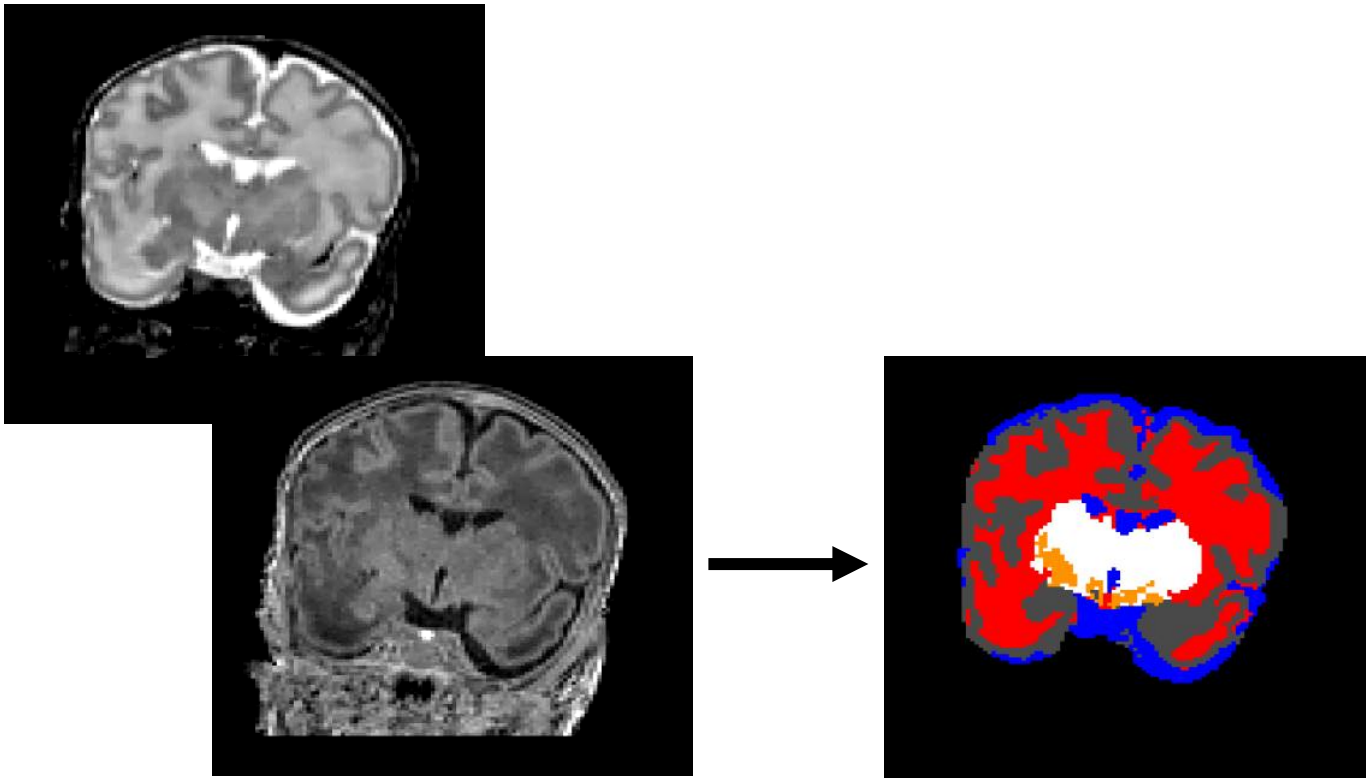
The previous iteration's STAPLE output (top left) is used to weed out prototypes which are inconsistent with the data.

Spectral-Spatial Segmentation



After several iterations, a spectral-spatial (watershed) segmentation (Grau et al. IEEE TMI 2004) is used to eliminate partial volume effects and generate the final result.

Final Result



The final result is a fully automatic labeling of myelin (orange), unmyelinated white matter (red), cortical gray matter (gray), subcortical gray matter (white), and cerebrospinal fluid (blue).

Prenatal Methadone Exposure

- Mothers in methadone maintenance program recruited in Christchurch, NZ
- Structural MRI of 27 control infants and 48 infants prenatally exposed to methadone.
- Automatic tissue segmentation utilized.

- Presented at PAS 2008 by Warfield, Weisenfeld, Woodward.

Prenatal Methadone Exposure

- Comparison of group means for each type of brain tissue found that prenatal exposure to methadone is associated with a reduction in brain tissue volume:

tissue	TBV	CGM	SCG	UWM	MWM	CSF
p-value	0.001	0.087	<.001	0.039	0.017	0.033

- Total Brain Volume, Cortical Gray Matter, Subcortical gray matter, Unmyelinated white matter, Myelinated White Matter, and Cerebrospinal fluid.

Quantitative Volumetric MR Techniques

- Provided baseline data and identified several risk factors in premature infants.
- Enabled description of patterns of brain injury in premature infants.

- **Limitations:**
  - Limited by the signal contrast and resolution of the imaging acquired.
  - Structural measure – implications for function and underlying connectivity require further probes.

Acknowledgements

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