Mapping the Brain the Face and Neurocognitive Function in FASD (U01)

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Progress as of June 2008

U01 Specific Aims

Specific Aim 1: To evaluate cross-sectionally and longitudinally the effects of prenatal alcohol exposure on brain morphology and function. We will study differences in the patterns of results that occur across populations where drinking patterns may vary by making FASD/control comparisons within sites, and comparing the results across sites.

Specific Aim 2: To evaluate relationships between brain dysmorphology and facial dysmorphology both cross-sectionally and longitudinally to improve diagnostic criteria using facial morphology data from the dysmorphology core (cross-sectional data only) and the 3D camera project.

Specific Aim 3: To determine whether the anatomical "phenotype" relates to neurobehavioral profiles in children with fetal alcohol syndrome or FASDs.

Specific Aim 4: To investigate dysmorphology in the brains of human children based on findings in the mouse and sheep models conducted in the laboratories of Drs. Sulik, Zhou and Cudd.

Continued Progress from Previous Funding Period

Since our last progress report presented in June 2008, we have continued to analyze data collected by the brain imaging core from the initial funding period.

A new manuscript on the impact of prenatal alcohol exposure on brain activation during verbal working memory has is In Press at *Human Brain Mapping* (O'Hare et al., In Press).

We have applied new structural image analyses techniques, Tensor-based morphometry (TBM), which allows investigations of regional differences in the volumes of brain substructures throughout the entire volume of the brain.

Published Manuscripts:

Sowell E.R., Johnson A., Kan E., Lu, L.H., Van Horn, J.D.,Toga, A.W., O'Connor, M.J., and Bookheimer S.Y., (2008) Mapping White Matter Integrity and Neurobehavioral Correlates in Children with Fetal Alcohol Spectrum Disorders. *Journal of Neuroscience*, 28(6):1313-9.

In Press Manuscripts:

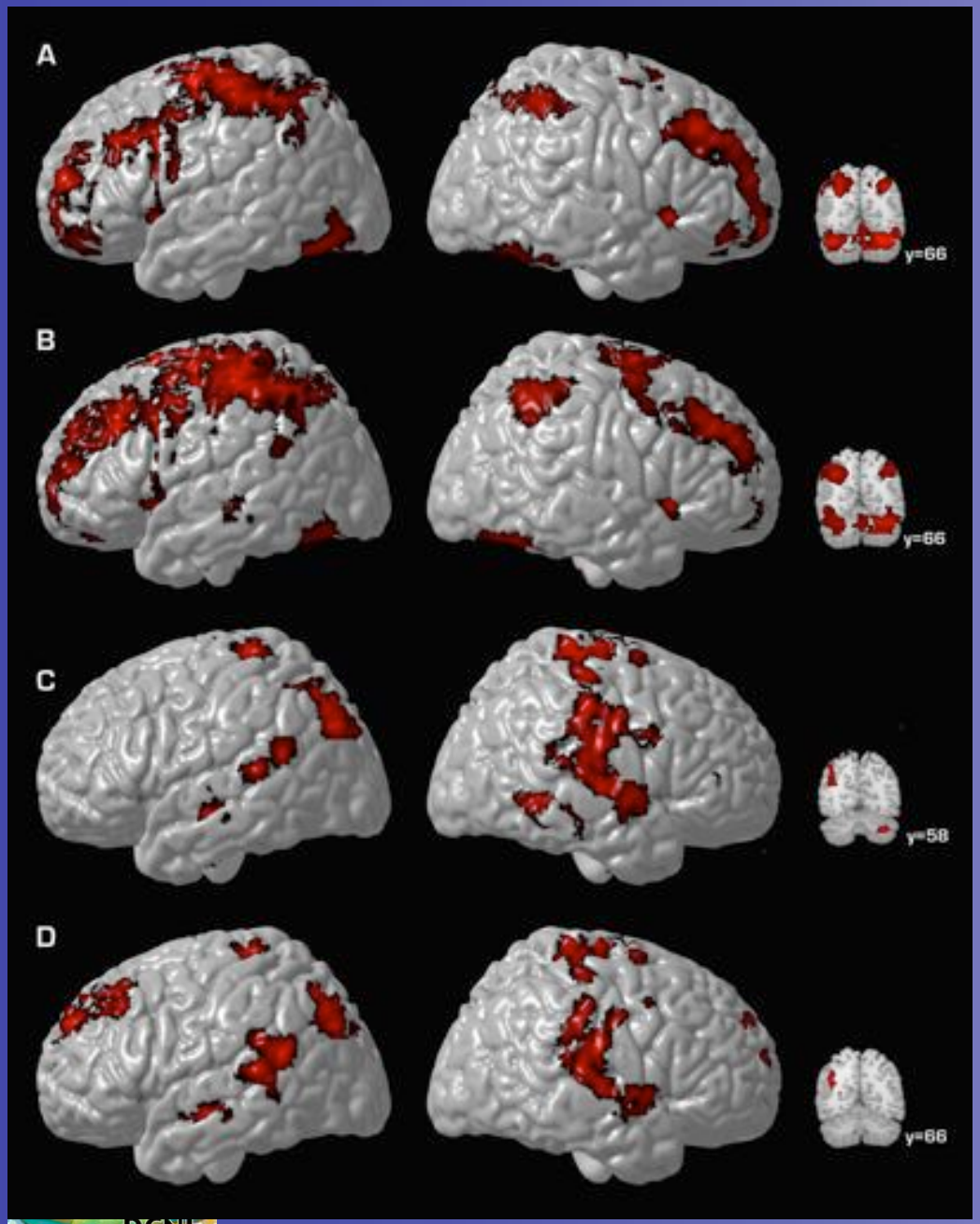
O'Hare E.D., Lu L.H., Houston S.M, Bookheimer S.Y., Mattson S.N., O'Connor M.J., and Sowell E.R. Altered frontal-parietal functioning during verbal working memory in children and adolescents with heavy prenatal alcohol exposure.

Abstracts:

Nuñez, C., Dapretto, M., Lu, L.H., Bookheimer, S.Y., O'Connor, M., **Sowell, E.R.** (2008). Increased frontal activation during language processing in children with Fetal Alcohol Spectrum Disorders. Poster session submitted to the 38th Annual Meeting of the Society for Neuroscience, Washington, D.C.

Altered frontal-parietal functioning during verbal working memory in children and adolescents with heavy prenatal alcohol exposure (O'Hare et al., Submitted).

This study evaluated the neural basis of verbal working memory (WM) function in a group of 20 children and adolescents with fetal alcohol spectrum disorders (FASDs) and 20 typically developing comparison participants using functional magnetic resonance imaging (fMRI).



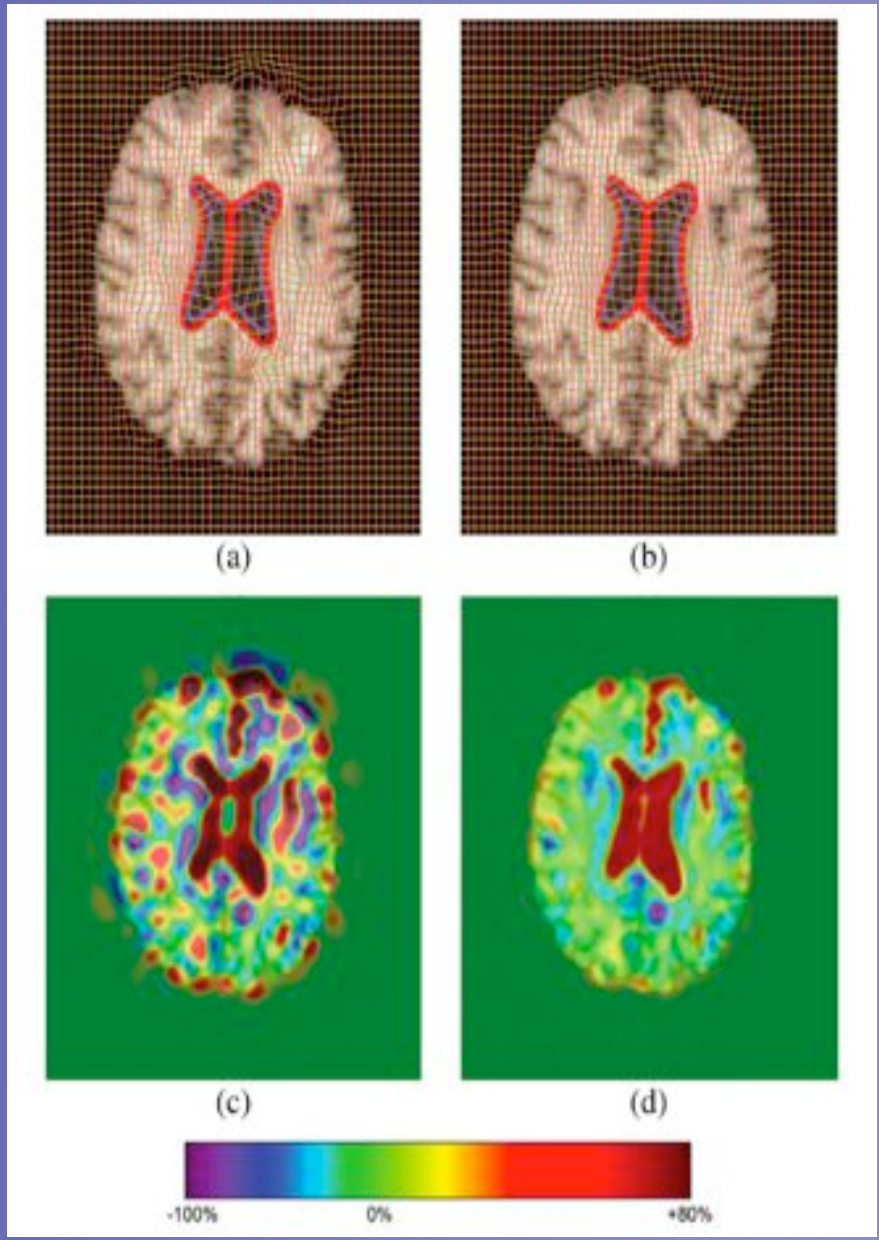
Surface renderings and coronal sections displaying group average activation for verbal working memory vs. rest in control participants (A), group average activation for alcohol-exposed participants (B), group differences in activation (C), and the difference between these groups when IQ differences are statistically controlled (D) for WM-related activation. Regions shown in panels C and D represent regions where alcohol-exposed subjects display greater activation relative to TD subjects.

This pattern of increased activation coupled with equivalent behavioral performance between groups suggests that individuals with FASD recruit a more extensive network of brain regions during verbal WM relative to typically developing individuals. These findings may suggest that frontal-parietal processing during verbal WM is less efficient in alcohol-exposed individuals.

Increased left dorsal frontal activation in individuals with FASDs relative to typically developing individuals is consistent with previous reports of altered functioning in this region during verbal learning in some of the same subjects studied here (Sowell et al., 2007), and response inhibition in an independent sample (Fryer et al., 2007).

Tensor Based Morphometry (TBM):

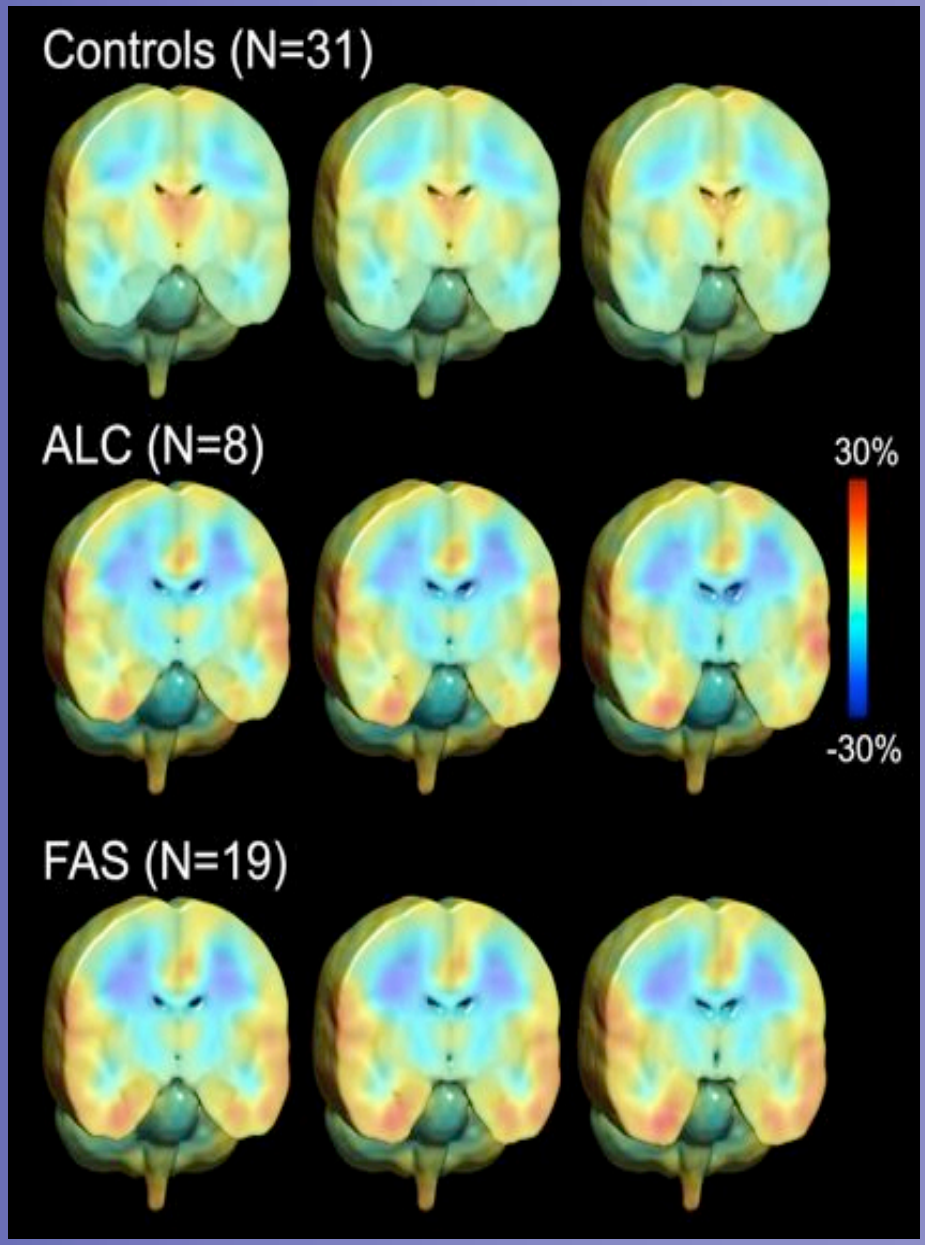
This method allows measurement of local tissue contraction or expansion using non-linear warping at each voxel in the brain.



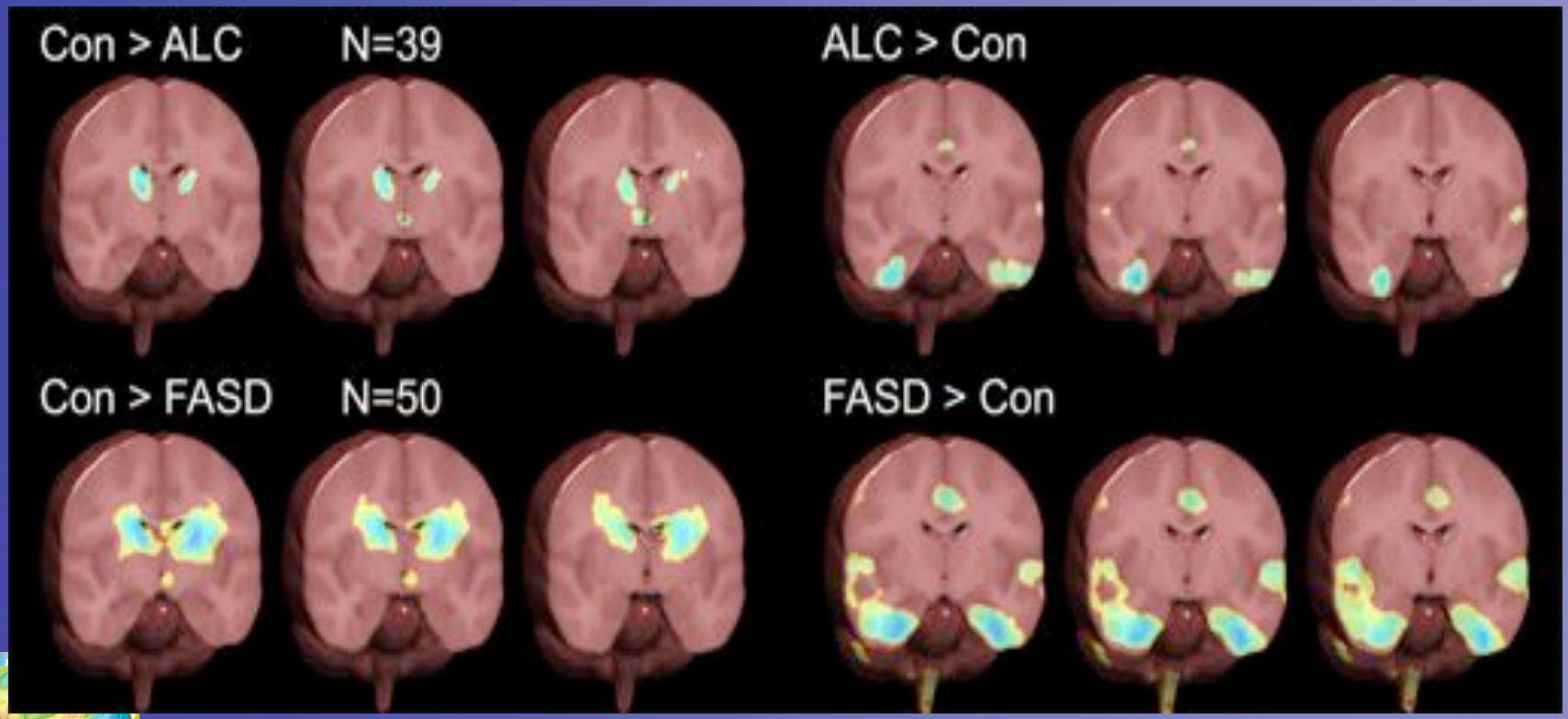
From Leow et al., *IEEE Transactions on Medical Imaging*, 2007

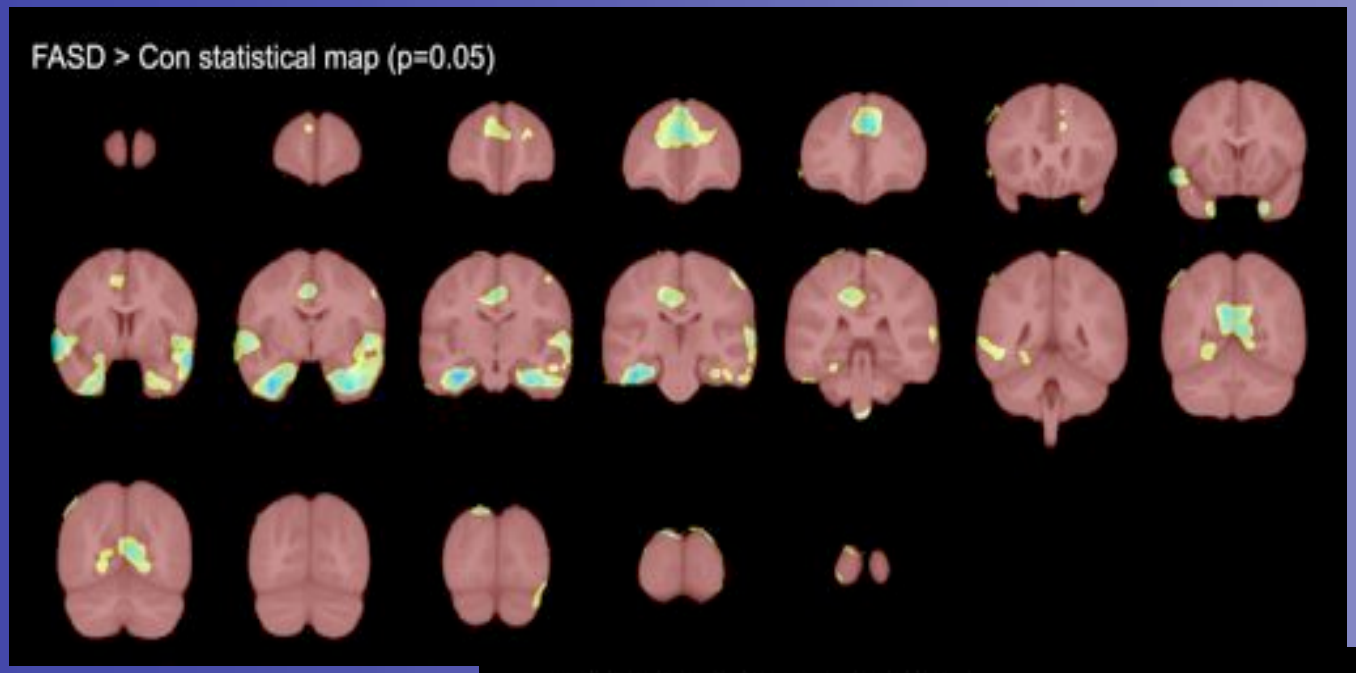
Tensor Based Morphometry (TBM) Results:

These maps show the percentage of deformation required to match those in each group to the average map of all individuals in the study.

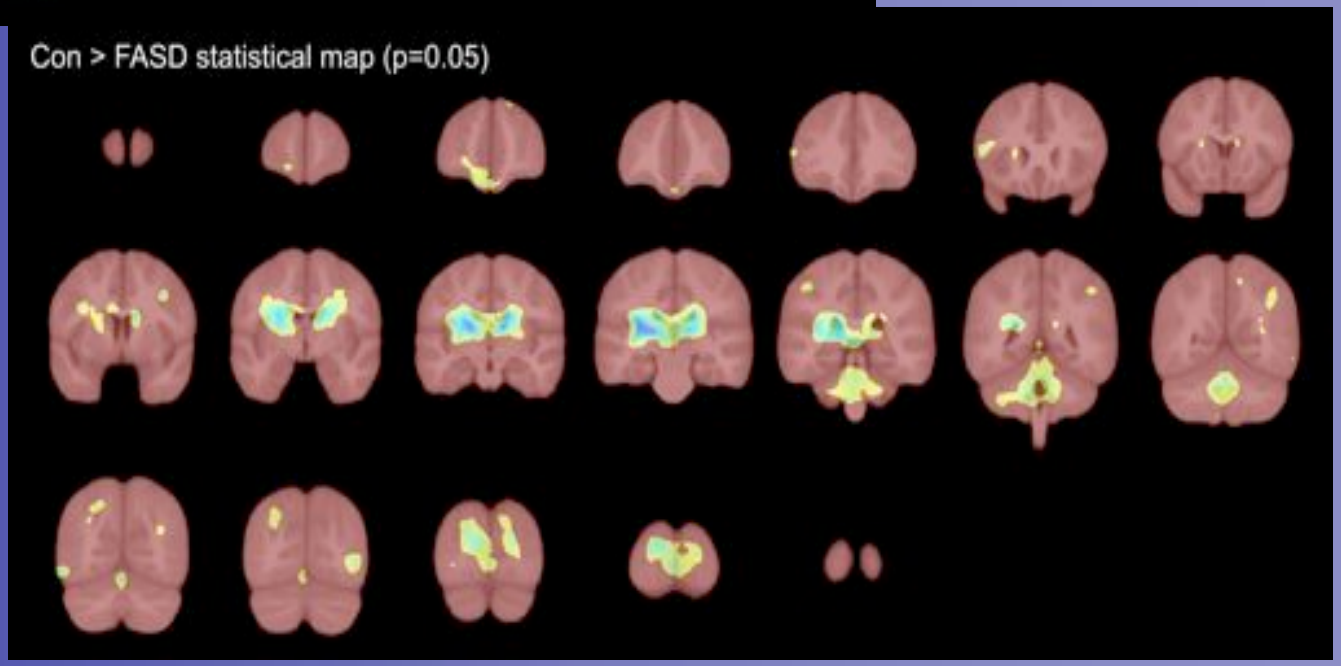


TBM statistical maps showing regions of expansion or contraction of brain tissue. Corrected for multiple comparisons using false discovery rate. Dysmorphology in basal ganglia, and medial and lateral temporal lobes bilaterally is present even in those children without the facial dysmorphology.





Regions of *increased* volume in children with FASDs relative to typical unexposed.



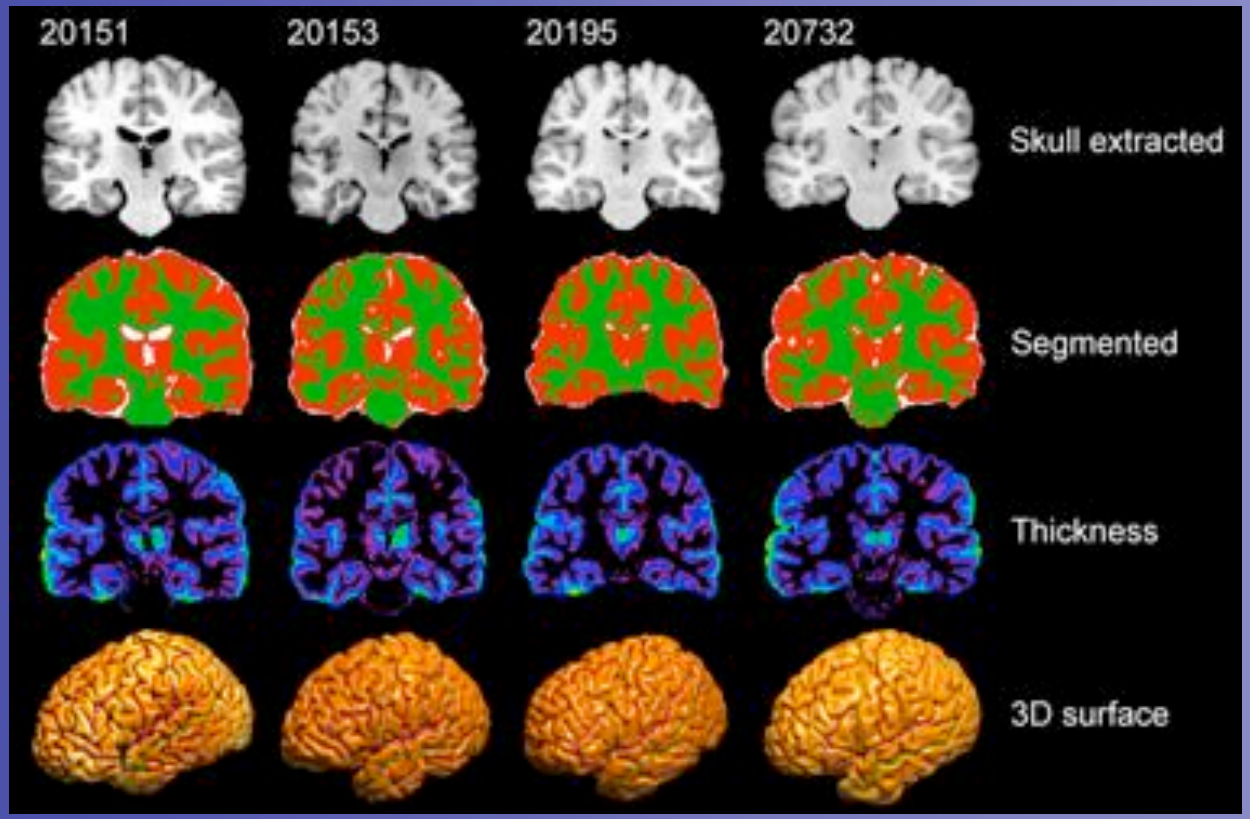
Regions of *decreased* volume in children with FASDs relative to typical unexposed.

DCNL

Progress since our last meeting in June 2008:

Brain Imaging:

UCLA: Structural MRI data has been collected for 13 CIFASD subjects. Three to four hi-resolution MPRAGE scans were acquired per subject. Of the structural imaging data collected, 95% of the total scans were of acceptable quality. fMRI for the N-back and PAL tasks were collected for the same subjects.



Progress since our last meeting in June 2008:

Brain Imaging:

SDSU: We have IRB approval for this component, have piloted the procedures and are currently screening subjects for eligibility. Of the 13 children tested using the neurobehavioral test battery, 1 has been scheduled for the mock scanning session and will be scheduled for scanning upon successful completion of that session.

Progress since our last meeting in June 2008:

Brain Imaging:

South Africa: Imaging protocols were tested and refined on the Siemens 3T Allegra system housed at the Tygerberg Academic Hospital, Stellenbosch University, Cape Town, South Africa in coordination with Dr. Colleen Adnams (Subcontract PI) and colleagues and Dr. Katherine Narr (co-investigator, Brain Imaging) in February, 2008. The translation of functional imaging stimuli from English to Afrikaans and of supporting experimental materials were subsequently completed during the current budget period. Data collection is scheduled to begin in March 2009.

To facilitate the collection of test subject data for the Brain Imaging project in FY2, Dr. Narr will visit the Cape Town site in February 2009. Goals for this visit will include (1) the review of imaging protocols with Dr. Adnams and Dr. Meintjies (imaging project collaborator), technical staff and post-doctoral students, (2) testing of the translated functional imaging stimuli in the scanner environment, (3) the collection of human phantom data that is planned to occur at all three CIFASD imaging sites within each budget period, (3) the collection of pilot data from 2-3 healthy control children demographically similar to the FASD group, and (5) the resolution of any other remaining issues relating to the CIFASD imaging experiments.

Neurobehavioral Data Collection:

UCLA staff trained in administration of neuropsychological and parent measures at SDSU in December 2007 and January 2008, and the primary research assistant met reliability standards established by SDSU in May 2008. Subjects began participating in May 2008, and since then six exposed children (mean age=12.7, 6 males) and eight unexposed children (mean age=11.0, 3 males) have participated in the study, including completion of the neuropsychological battery and parent interviews/behavioral measures. In addition, five exposed children and six controls are currently scheduled to participate through February 2009.

Facial Imaging and Genetic (saliva) Data Collection:

Dr. Ken Jones is scheduled to conduct dysmorphology exams on 19 alcohol-exposed and control subjects on January 15 and 16, 2009. Dr. Elizabeth Moore will also travel to UCLA in January and will take 3-D photographs at that time.

Finally, IRB approval has been obtained for collection of saliva samples, and we will begin collecting genetic data for our next subjects scheduled in January 2009.

Plans for the next funding period:

1) Data collection will commence or continue at all 3 sites. With subjects scheduled through February 2009 and continued recruitment efforts in place, it is expected that UCLA will be at or close to its February 1, 2009 goal of 19-24 subjects.
2) Human phantom data will be analyzed for normalization of data across scanners and we will begin combined data analysis from the multiple data collection centers.
3) Analyses of data collected in the earlier CIFASD will continue.