IMAGING THE LONG-TERM EFFECTS OF DRUG EXPOSURE IN UTERO

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Drug Use During Pregnancy (% Women Reporting Use)

Epidemiology: Tobacco

- 27-33% of women of childbearing age
- 20-25% of expectant mothers continue use
- 27% were able to immediately quit use when told that they were pregnant
- An additional 12% were able to quit by the third trimester of pregnancy
MANY, DIFFERENT, DEVELOPMENTAL AND BEHAVIOR PROBLEMS ARE NOTED IN CHILDREN, ADOLESCENTS, AND ADULTS EXPOSED TO ALCOHOL AND DRUGS PRENATALY
The goal(s) of neuroimaging in the study of the effects of prenatal exposure...

- Identify specific teratogenic outcomes of drugs of abuse and of the abuse of specific drugs....
- Establish the brain basis for behavioral changes observed in affected individuals
- Facilitate diagnosis of the effects of prenatal exposure.
Many other factors that may affect outcomes............... 

- **Genetic differences** that characterize women who use drugs/alcohol during pregnancy
- **Social factors**, like nutrition, postnatal environment, social class, ethnic group...
- **Polydrug exposure** prenatally and postnatally
- **Experimental characteristics**-sample selection, research design, and so forth
Focus of Presentation

- Specific Drugs of Abuse
  - Alcohol
  - Stimulants (Cocaine/Methamphetamine)

- Methods - Status of knowledge
  - sMRI
  - DTI
  - fMRI
  - And, yes, there are lots of other methods....
Recent reviews of Imaging literature on Alcohol Exposure (Neuropsychology Review, 2011, 21 (2))

- **Coles CD; Li Z (2011)** *Functional neuroimaging in the examination of effects of prenatal alcohol exposure.*

- **Lebel C; Roussotte F; Sowell ER (2011)** *Imaging the impact of prenatal alcohol exposure on the structure of the developing human brain.*

- **Wozniak JR; Muetzel RL (2011)** *What does diffusion tensor imaging reveal about the brain and cognition in fetal alcohol spectrum disorders?*
Prenatal Alcohol Exposure and Brain Structure (see Lebel, et al, 2011)

- 20 years of research
- **Brain Volume** - Smaller in diagnosed cases and prenatal exposure
- With total BV controlled, *specific effects* noted in corpus callosum, caudate, hippocampus, cerebellum. Other areas also noted.
- Both *white and grey matter* affected but white more affected.
- Sowell and colleagues - cortical thickening
- Reductions found more often in frontal, parietal. Other areas less studied.
Structural effects of Prenatal Alcohol Exposure: an example

- Young adults identified prenatally and followed longitudinally. Matched for ethnicity and SES.
- 96 separate measurements of brain volume, ranging from total Intracranial volume to subcortical structures (e.g., hippocampus) using Free surfer
  - Examined:
    - Cortical regions
    - Subcortical
    - Corpus Callosum
- Compared:
  - Alcohol exposure vs Nonexposed Controls
  - Alcohol “affected” vs “non-affected” vs Controls
  - Male and female differences in alcohol effects
Cortical regions exhibiting PAE effects

Chen, et al., (2011) Understanding Specific Effects of Prenatal Alcohol Exposure on Brain Structure in Young Adults, Human Brain Mapping
Sub-cortical regions exhibiting PAE effects

Cbr: Cerebral Cortex
Cbe: Cerebellum
Cortex
Tha: Thalamus Proper
Hip: Hippocampus
Put: Putamen
Pal: Pallidum
Amy: Amygdala
Cau: Caudate
Acu: Accumbens
Area.
R: Right Hemisphere,
L: Left Hemisphere.
Segmentation of the corpus callosum (A), in which some portions (1, 4 and 5) exhibited the general PAE effect (B). 1: Anterior, 2: Mid-Anterior, 3: Central, 4: Mid-Posterior, 5: Posterior.

Cortex and Cerebellum volume in Alcohol Affected Adults and two control groups (N=78)

In Cerebral Cortex, Dysm<Controls, Left, p<.008; Right, p<.05, no other groups are significantly different.

Coles, Li, et al. 2008
White matter volume in alcohol-exposed adults and controls (N=78).

In Cerebral Cortex, both alcohol groups differ from both control groups and not from each other.

Coles, Li, et al. 2008
Prenatal Alcohol Exposure and DTI (see, Wozniak & Muetzel, 2011)

- 7 Studies, 2 with adults, 5 with older children and adolescents.
- Microstructural anomalies found in many regions studied, but particularly, Corpus Callosum
- Structural and functional deficits appear related
- DTI seems sensitive to teratogenic effects of alcohol; however, effects are not specific but similar to those in other disorders
- Lack of developmental norms makes interpretation difficult.
Using TBSS for DTI analysis, voxel-wise statistics on the skeletonized FA data reveal subregions of the **cingulum** with significantly lower FA values in both PAE groups versus control subjects.

Skeletonized FA difference between Control and Non-Dysmorphic PAE groups (green=skeleton, purple=anatomically defined ROI, pink=region of significant difference). Similar differences were seen between control and dysmorphic PAE groups.
TBSS results for bilateral cingulum. ROI shows significant differences between

(a) Control and Non Dysmorphic PAE groups
(b) Control and Dysmorphic PAE groups in FA.

Green indicates mean FA skeleton and red indicates regions of significant difference between groups, with thickened red-yellow for the bilateral cingulum ROI. Axial slices shown are $z=107$ to $z=112$. 
Prenatal Alcohol Exposure and Functional Imaging (see, Coles & Li, 2011)

- **Limited research** (ERP=5 studies; fMRI=9 studies)
- **Overall-global decrement in processing resources/neural efficiency**
- **Regional localization not best way to understand alcohol-related deficits?**
- **Experimental parameters affect activation** (e.g., subject characteristics, task difficulty)
- **Specific issues** (e.g., microcephaly, IQ, comorbidities)
fMRI results: Spatial Working Memory

Functional brain activation differences (bottom frame) between the PAE (top-left frame) and control (top-right frame) subjects in a spatial working memory task. The exposed group exhibited greater activation in extended brain regions.

This figure is adapted from Spadoni, et al, 2009 with permission.

Studied DMN in Alcohol Exposed young adults during Math Task

- Reduced DMN deactivations found in other clinical conditions, particularly those associated with attentional deficits
- Activities of this network can be used to examine functional synchrony (fMRI)
- Functional correlations in DMN can be correlated with evidence of Structural connectivity identified using DTI
Hypotheses regarding Effects of Alcohol

- DMN deactivation reduced in Alcohol-affected groups
- White matter integrity in DMN reduced
- Synchronization reduced between MPFC and PCC (fMRI activation)
- Correlation between FA (DTI) and fMRI results reduction associated with PAE
Regions of default mode deactivation during arithmetic task (using letter-matching task as baseline). MPFC and PCC clusters from these group average activation maps were used for subsequent resting-state analysis. Color bar indicates these regions are negatively activated.
Resting-state functional connectivity (correlation) group maps (a) with and (b) without global signal regression. At threshold p<0.001, only positive correlation (red-yellow) was noted with the seeding region regardless of regression method. Seeding was in the PCC region defined in Figure 1.
Resting State DMN correlations and Task Based DMN Deactivation

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>ARND</th>
<th>Dysm</th>
</tr>
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<tbody>
<tr>
<td>% Signal change in PCC</td>
<td>-0.585 (0.06)</td>
<td>-0.536 (0.05)</td>
<td>-0.425 (0.06)</td>
</tr>
<tr>
<td>Mean Corr. Coeff in MPFC</td>
<td>0.285 (0.03)</td>
<td>0.190* (0.03)</td>
<td>0.206* (0.03)</td>
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*Significantly different from Controls, p<.05
Results: Default Mode

- Task related deactivity in DMN affected by PAE
- Structural Connectivity lower (DTI)
- Functional Connectivity affected (fMRI)
- Implies that structural connectivity deficit affects functional network in system that modulates attention and cognition
Effects of Prenatal Stimulant Exposure: Reviews


Stimulant Studies

- Published studies of Cocaine very limited; Methamphetamine even fewer.
- Results are inconsistent
- In most studies reductions are noted in Brain Volume
- Polydrug use is very common; Often effects of stimulants do not persist when other drugs are controlled.
Cortical regions affected by Prenatal Cocaine Exposure

- **Left hemisphere**
  - A: Frontal Pole
  - B: Rostral Middle Frontal Gyrus
  - C: Precentral Gyrus
  - D: Inferior Parietal Lobule
  - E: Precuneus Cortex

- **Right hemisphere**
  - F: Caudal Middle Frontal Gyrus
  - G: Rostral Middle Frontal Gyrus
  - H: Pars Triangularis
  - I: Pars Opercularis
  - J: Medial Orbital Frontal Cortex
  - K: Caudal Anterior Cingulate Cortex
  - L: Precuneus Cortex

Bilateral amygdala area (brain images) comparing activation between Cocaine exposed and Controls (bar graphs). Activation level is the produce of mean regression coefficient (representing the fMRI signal amplitude) and number of activated voxels in the ROI (representing the activation volume). With “NEU0” value as the baseline (zero). The error bars represent standard error.

Cocaine exposed adolescents do not show the usual balance between cognitive and emotional arousal.

Summary

- The study of effects of prenatal exposure is in the early stages (Alcohol>Cocaine>other drugs)
- There is a great deal of similarity in outcomes (e.g., reduced brain volume, inefficient neural processing on fMRI) that suggest non-specific effects or polydrug effects.
- Sample sizes are not yet large enough to control for potentially confounding genetic and environmental factors.
- “developmental norms” are not yet available to allow interpretation of some findings.
- Current research findings based on group differences; Methods are not yet appropriate for diagnostic purposes.
Nevertheless...

- Neuroimaging, as experimental methods and imaging techniques continue to be refined, hold great promise both as a way of understanding the development and function of the prenatally exposed brain and as a method, eventually, for diagnosis of affected individuals.