Preschool Onset Depression, Parenting, and Brain Development

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Early Emotional Development Program
Current Funding/Conflicts:

- NIMH R01- Preschool MDD and School Age Outcomes
- NIMH Supp - Structural and Functional Imaging in MDD Preschoolers
- NIMH R34- Treatment of Preschool MDD
- NARSAD Independent Investigator Award
- CHADS Coalition for Mental Health
- Stanley Baer Foundation

No Conflicts of Interest
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Mental Disorders Arise in Early Childhood

- Scientific studies have validated that major mental disorders can arise as early as age 3.
- Refutes dogma that young children could not have serious disorders and "grow out of" behavioral problems.
- Earliest possible identification of disorders is critical for earlier and potentially more effective intervention.
Similar to studies of disorders such as diabetes, psychiatric disorders must be scientifically validated.

Compared to medical disorders, we understand relatively little about the pathophysiology of psychiatric disorders to date.

However, key features of validation are available for numerous disorders in the DSM system.
Validiation of Psychiatric Disorders: Key Principles

- The disorder runs in families. This may be genetic or psychosocial (or both).
- There is a biological marker of the disorder (ideally a blood test or a measurable physiological alteration).
- Longitudinal course: the disorder shows stability over time (not a necessary requirement).
Why is it important to identify mental disorder early in life?

- Earlier intervention is more effective in a number of conditions.
- There is a steep developmental trajectory early in life and this is associated with a period of greater brain “plasticity” or change-ability.
- Correcting problems early is important so that it doesn’t have a ripple effect across later phases of development.
Myths about Early Childhood Relevant to Mental Health:

- **Myth 1**: Infants/young children are not aware of their surroundings and cannot process psychological events.
- **Myth 2**: Young children are too immature to be vulnerable to disorders like depression or anxiety.
- **Myth 3**: Behavioral and emotional problems in early childhood will be transient and non-specific.
Focus on Early Childhood Depression:

- Scientific data shows children as young as age 3 (preschool age) can get clinical depression.
- Effects of exposure to depression have been detected even in infancy.
- Preschool onset depression appears to be an early onset of the same disorder known in older children and adolescents.
Data from two independent samples support the validity of preschool MDD (Luby et al., 2003, Luby et al., 2009).

Biological markers, familial transmission, and observational evidence provided (Luby et al., 2003, Luby et al., 2002, Luby et al., 2006)

Evidence of impairment in multiple settings (Luby et al., 2009)

Preschool MDD detected in at least three epidemiological samples (USA: Lavigne et al., 1996, Egger and Angold, 2006, Norway: Wichstrom et al., 2012)
Characteristics of Preschool Depression:

- Depressed preschoolers display “typical” symptoms and vegetative signs of MDD predominantly.
- Depressed preschoolers show high levels of guilt, anhedonia, extreme fatigue, sad/tearful and death thoughts/play.
- Depressed preschoolers are functionally and developmentally impaired (according to parents and daycare/preschool teachers).
<table>
<thead>
<tr>
<th>Variables entered into model</th>
<th>Wald $\chi^2$</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child’s Age (in months)</td>
<td>2.84</td>
<td>1.03</td>
<td>0.99 – 1.08</td>
<td>.092</td>
</tr>
<tr>
<td>Gender (M=1/ F = 0)</td>
<td>0.57</td>
<td>1.32</td>
<td>0.65 - 2.68</td>
<td>.451</td>
</tr>
<tr>
<td>Familial Income ($\leq$ $20k$)</td>
<td>4.82</td>
<td></td>
<td></td>
<td>.186</td>
</tr>
<tr>
<td>$20,001 - $40,000</td>
<td>0.93</td>
<td>0.56</td>
<td>0.17 - 1.82</td>
<td>.336</td>
</tr>
<tr>
<td>$40,001 - $60,000</td>
<td>4.64</td>
<td>0.26</td>
<td>0.07 - 0.89</td>
<td>.031</td>
</tr>
<tr>
<td>≥ $60,001</td>
<td>2.47</td>
<td>0.37</td>
<td>0.11 - 1.28</td>
<td>.116</td>
</tr>
<tr>
<td>Education: Some college education</td>
<td>0.92</td>
<td>1.79</td>
<td>0.54 - 5.90</td>
<td>.339</td>
</tr>
<tr>
<td>4 year college degree</td>
<td>0.41</td>
<td>1.61</td>
<td>0.37 - 7.01</td>
<td>.523</td>
</tr>
<tr>
<td>Graduate education and above</td>
<td>0.02</td>
<td>0.89</td>
<td>0.20 - 4.06</td>
<td>.879</td>
</tr>
<tr>
<td><strong>Co-morbidities and Other Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disruptive Disorder (Y/N)</td>
<td>7.44</td>
<td>3.04</td>
<td>1.37 – 6.77</td>
<td>.006</td>
</tr>
<tr>
<td>Anxiety Disorder (Y/N)</td>
<td>1.17</td>
<td>1.56</td>
<td>0.70 – 3.49</td>
<td>.280</td>
</tr>
<tr>
<td>Number of Stressful Life Events</td>
<td>1.18</td>
<td>1.09</td>
<td>0.94 - 1.26</td>
<td>.277</td>
</tr>
<tr>
<td>Maternal History of Affective Dis (Y/N)</td>
<td>0.12</td>
<td>0.87</td>
<td>0.40 - 1.92</td>
<td>.733</td>
</tr>
<tr>
<td>Family History of Affective Dis (%)</td>
<td>14.70</td>
<td>536.6</td>
<td>21.6 – 13344</td>
<td>.001</td>
</tr>
<tr>
<td>Depression at Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preschool MDD</td>
<td>10.78</td>
<td>3.64</td>
<td>1.68 - 7.88</td>
<td>.001</td>
</tr>
</tbody>
</table>

Preschool MDD does not spontaneously remit therefore requires clinical attention.

Preschool MDD is not a non specific precursor of later more general psychopathology therefore it requires specific intervention.

Preschool MDD has numerous features similar to the school age form—therefore appears to be the same disorder with earlier onset.
Alterations in Brain Structure and Function in Children with PO-MDD: Summary

- Increased activation in emotion regulatory regions in response to emotion stimuli based on depression under age 6
- Different patterns of connectivity suggestive of poor top down emotion regulatory control and enhanced internal/somatic focus (in children with depression <6 yrs.)
- Decrease hippocampal size related to PO-MDD support early stress related damage (consistent with elevated cortisol levels previously shown)
Neurocircuitry of Preschool Depression: Preliminary Results

- N = 11 Preschoolers
  - 4.5 ± 0.8 years
  - 6 males

- View emotion faces
  - Functional comparison: sad faces vs. fixation

- Significant positive correlation between activation and MDD severity in amygdala (x:22 y:-5 z:-13)
Depressed Preschoolers Show Changes in Brain Function Similar to Depressed Adults (Gaffrey et al., in preparation)

- fMRI conducted on children between ages of 4-7 (very new methodology)
- They show increased activation to negative emotion similar to pattern seen in depressed adults (and evident in children how had a past episode of PO-MDD)
- First data showing this as early as preschool age.
Can Preschoolers Be Depressed?

By PAMELA PAUL
Published: August 25, 2010

Kiran didn’t seem like the type of kid parents should worry about.
Early Environment and Brain Development:

- Early studies in animals demonstrate the robust impact of early environmental enhancement on brain development.
- It is now well accepted that brain development is determined both by genetic factors as well as environmental factors.
- There is much evidence that there are early sensitive and critical periods in brain development.
Living conditions in different experimental groups

a | A cage containing a running wheel for voluntary physical exercise  

b | A standard housing cage  

c | Cage for an enriched environment

Environmental Stimulation and Language Composite scores

Both enrichment (k,l) and voluntary exercise (h,i) enhance the survival of newborn neurons. Learning did not affect cell survival (e,f), similar to controls (b,c). Confocal images of sections triple labelled for BrdU (red), NeuN (green, neuronal phenotype) and s100β (blue, selective for glia), show that relatively more cells become neurons in the running and enriched groups.

Environment and Brain Development in Humans:

- A few studies have now provided data to inform this issue.
- Two studies have investigated young children in institutional settings vs. those adopted.
- Another study looked at babies in the NICU who received an intervention.
(a) Anatomical segmentation of the amygdala (in aqua) from neighboring structures. (b) Adjusted volumes by group. Children who had been adopted out of the orphanage at older ages (> 15 months old) had larger amygdala volumes than early-adopted children (< 15 months old) and comparison children, who did not differ from each other.

Bucharest Early Intervention Project (BEIP):

- An RCT of abandoned children reared in institutions vs. those moved to foster care.
- Cognitive development tracked through 54 months of age.
- Cognitive outcomes of institutionalized children were significantly below those moved to foster care.
- Improved cognitive outcomes most marked for children placed at younger ages.

n indicates effect size in multiples of the pooled standard deviation, and Y is younger than and O is older than age cutoff at entry to foster care.

### DQ and IQ of FCG by entry age group

#### Age cutoff

<table>
<thead>
<tr>
<th>Age cutoff</th>
<th>42 months (BSID-II)</th>
<th>54 months (WPSSI-R)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>20 months</td>
<td>93.5</td>
<td>82.6</td>
</tr>
<tr>
<td>22 months</td>
<td>90.4</td>
<td>83.0</td>
</tr>
<tr>
<td>24 months</td>
<td>91.5</td>
<td>80.0</td>
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<tr>
<td>26 months</td>
<td>90.9</td>
<td>79.1</td>
</tr>
<tr>
<td>28 months</td>
<td>89.8</td>
<td>78.8</td>
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</table>

### DQ and IQ of FCG by entry age group

#### Age at placement

<table>
<thead>
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<th>42 months (BSID-II)</th>
<th>54 months (WPSSI-R)</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>0–18 months</td>
<td>14</td>
<td>94.4</td>
</tr>
<tr>
<td>18–24 months</td>
<td>16</td>
<td>89.0</td>
</tr>
<tr>
<td>24–30 months</td>
<td>22</td>
<td>80.1</td>
</tr>
<tr>
<td>30+ months</td>
<td>9</td>
<td>79.7</td>
</tr>
</tbody>
</table>

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Results underscore negative sequelae of early institutionalization

Results suggest a possible sensitive period of cognitive development

Results underscore advantages of family placement in early childhood

Brain Development in Children Exposed to Maternal MDD:

- Children exposed to maternal depression since birth compared to those not exposed.
- Two brain regions (amygdala and hippocampus) were investigated.

Left and right hippocampal (Left) and amygdala (Right) volumes (cubic centimeters) in children exposed to MDS since birth and children not exposed to MDS since birth.

Error bars represent SEMs. **P < 0.01 for left and right amygdala volume.
Mechanisms of Effects of Nurturance on Brain Development:

- Work in animals has shown that maternal nurturance impacts gene expression which in turn impacts neuronal growth.
- Rat pups who experienced high maternal nurturance (licking) were better able to modulate stress and had larger hippocampus.
- High nurture pups show more nurture behavior with their own offspring.
Nurturance and Hippocampus in Humans:

- Data from a longitudinal study of preschool depression were used to investigate this issue.

- Preschoolers observed in interactive play with caregivers.

- At school age preschoolers participated in neuroimaging.
### Repeated measures mixed models of hippocampal volume

<table>
<thead>
<tr>
<th>Model</th>
<th>Estimate</th>
<th>F</th>
<th>df</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left brain hemisphere</td>
<td>-6.61</td>
<td>0.25</td>
<td>1, 75</td>
<td>0.620</td>
</tr>
<tr>
<td>Preschool depression severity</td>
<td>8.50</td>
<td>0.46</td>
<td>1, 87</td>
<td>0.500</td>
</tr>
<tr>
<td>Maternal support</td>
<td>13.60</td>
<td>18.40</td>
<td>1, 87</td>
<td>&lt;0.001</td>
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<tr>
<td>Preschool depression severity X Maternal support</td>
<td>-1.70</td>
<td>4.46</td>
<td>1, 87</td>
<td>0.038</td>
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<tr>
<td><strong>Model 2</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Left brain hemisphere</td>
<td>-6.23</td>
<td>0.13</td>
<td>1, 74</td>
<td>0.724</td>
</tr>
<tr>
<td>Preschool depression severity</td>
<td>8.51</td>
<td>0.46</td>
<td>1, 87</td>
<td>0.500</td>
</tr>
<tr>
<td>Maternal support</td>
<td>13.60</td>
<td>18.40</td>
<td>1, 87</td>
<td>&lt;0.001</td>
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<tr>
<td>Preschool depression severity X Maternal support</td>
<td>-1.69</td>
<td>4.46</td>
<td>1, 87</td>
<td>0.038</td>
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<tr>
<td>Preschool depression severity X Maternal support X Left brain hemisphere</td>
<td>-0.01</td>
<td>0.00</td>
<td>1, 74</td>
<td>0.975</td>
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<td><strong>Model 3</strong></td>
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<tr>
<td>Left brain hemisphere</td>
<td>-2.76</td>
<td>0.05</td>
<td>1, 74</td>
<td>0.830</td>
</tr>
<tr>
<td>Psychiatric medication use</td>
<td>-42.11</td>
<td>0.90</td>
<td>1, 80</td>
<td>0.345</td>
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<tr>
<td>Internalizing dimensional score</td>
<td>11.99</td>
<td>2.06</td>
<td>1, 80</td>
<td>0.155</td>
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<tr>
<td>Externalizing dimensional score</td>
<td>-4.22</td>
<td>1.51</td>
<td>1, 80</td>
<td>0.223</td>
</tr>
<tr>
<td>Number of traumatic life events</td>
<td>-18.10</td>
<td>2.29</td>
<td>1, 80</td>
<td>0.134</td>
</tr>
<tr>
<td>Maternal history of depression</td>
<td>43.69</td>
<td>1.33</td>
<td>1, 80</td>
<td>0.252</td>
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<tr>
<td>Preschool depression severity</td>
<td>14.31</td>
<td>0.68</td>
<td>1, 80</td>
<td>0.412</td>
</tr>
<tr>
<td>Maternal support</td>
<td>14.56</td>
<td>18.35</td>
<td>1, 80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preschool depression severity X Maternal support</td>
<td>-2.14</td>
<td>6.22</td>
<td>1, 80</td>
<td>0.015</td>
</tr>
</tbody>
</table>
Left Side Hippocampus Volume by Preschool MDD Severity and Maternal Support
Right Side Hippocampus Volume by Preschool MDD Severity and Maternal Support
Hippocampus Volume by Preschool MDD Severity and Maternal Support

- t=3.84, P<0.001
- t=4.21, P<0.001
- t=2.32, P=0.023
Mother and child image from http://todaysmama.com/2011/02/when-discipline-becomes-anger-creates-fear/
Global Conclusions:

- Early Identification
- Neuroplasticity
- Early (and potentially more effective) intervention