Early Experience and Brain Development: The Critical Role of Caregiving

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- NIMH
- CHADS Coalition for Mental Health
- Stanley Baer Foundation

- No Conflicts of Interest
Neuroimaging in Early Onset Mood Disorders: Longitudinal Assessment of Brain Changes (Luby, Barch and Botteron)

- Imaging assessment added to ongoing longitudinal study of preschoolers
- Subjects aged of 7-11 for baseline imaging
- Subsequent imaging assessments at 18 months and 36 months (3 waves of imaging data)
- This adds to >10 years of longitudinal developmental, psychosocial and mental health data
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 factor as well as environmental factors.
- There is much evidence that there are early sensitive and critical periods in brain development.
Effects of elements of enrichment, such as learning and exercise, on cell proliferation and neurogenesis (4 weeks post BrdU exposure) in the dentate gyrus.

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.

Experience Plays a Causal Role in Animal Brain Development:

- Influences brain structure:
  - Number of neurons and glial cells
  - Myelination
  - Blood Supply
  - Dendrites and synapses

- Influences on Brain Function:
  - Neurotransmitter and growth factor activity
  - Neurogenesis
  - Cell electrophysiology
  - Behavior
Environment and Brain Development in Humans:

- A few studies have provided data to inform this issue.
- Two studies have investigated young children in institutional settings vs. those adopted (Nelson et al., 2007, Tottenheim et al., 2010)
- Longitudinal study of children exposed to chronic maternal depression compared to controls with sMRI at school age (Lupien et al., 2011)
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 was sign below those moved to foster care
- Improved cognitive outcomes most marked for children placed at younger ages (<24 months)

Neural Evidence of “Catch-Up” from Early Intervention in BEIP:

- Cortical white matter and posterior corpus callosum smaller in institutionalized compared to never institutionalized but not different in those randomized to therapeutic foster care (TFC).
- Suggests that young children who received TFC showed “catch-up” of white matter growth

(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.

Brain Development in Children Exposed to Maternal Depression Since Birth:

- N=86 children from Quebec Longitudinal Study of Child Development continually exposed or never exposed to maternal depression since birth.
- N=38 participated in sMRI (17 high MDS, and 21 no MDS) and two brain regions (amygdala and hippocampus) were investigated.

Maternal CES-D Scores Across Child’s Development:


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 hippocamuses.
- High nurture pups show more nurture behavior with their own offspring.
Mothering and Methylation:

Whole Genome DNA Methylation in Institutionalized Children

Figure 2. A box plot of data on the methylation levels (AvgBeta) of 914 CpG sites that have shown differential methylation in genomes of children from the institutionalized and comparison groups.

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.
## Characteristics of the sample (N=91)

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F.E. = Fisher’s Exact Test
Hippocampus Volume by Preschool MDD Severity and Maternal Support:

Luby, J.L., Barch, D.M., et al., 2012 Maternal support in early childhood predicts larger hippocampal volumes at school age. Proceedings for the National Academy of Sciences
Implications of Findings:

- Early maternal support predicts larger hippocampal volumes at school age
- Association holds even when other key factors (trauma, maternal MDD etc.) are controlled
- An interaction between maternal support and depression severity evident only in non depressed preschoolers
- Suggests another process or additional factors at play in brain development of depressed preschoolers.
Nonsupportive Parenting as Partial Mediator of the Relationship Between Preschool-Onset Conduct Disorder and School-Age Depression:

- Preschool-Onset Conduct Disorder → School-Age Depression: $Z=3.35^{***}$
- Preschool-Onset Conduct Disorder → Maternal Non-Support: $t=3.75^{***}$
- Maternal Non-Support → School-Age Depression: $Z=2.40^*$
- Maternal Non-Support → School-Age Depression: $Z=2.69^{**}$

Covariates included baseline age, family income-to-needs ratio, traumatic life events frequency, maternal history of depression, and the interaction between preschool-onset depression and preschool-onset conduct disorder. The solid arrows indicate total effect; the dotted arrow indicates direct effect.

*p<0.05. **p<0.01. ***p<0.001.

Genetic Profile May Predict Sensitivity to Environment

- 5-HTTLPR and stressful life events predicting MDD onset (Caspi et al., 2003)

- Many have re-conceptualized 5-HTTLPR as “plasticity” gene (Belsky and Pluess, 2009)
How does this data inform child development and early intervention?

- Alterations in structure/function of brain emotion processing regions in children with early mental disorders or early deprivation
- Genetic and psychosocial factors known in the risk trajectory
- Psychosocial factors materially influence brain development
- Early psychosocial interventions targeting the parent child dyad and focused on emotion development important
Mother and child image from http://todaysmama.com/2011/02/when-discipline-becomes-anger-creates-fear/
Brain Plasticity

Ability to **alter brain function** in response to **experience**

Molecules adjust circuit connectivity through neural activity

“Brain cells fire in patterns”  – S Pinker

“Fire together, wire together”  – DO Hebb

“Out of sync, lose a link”  – G Stent
Review of Sensitive/Critical Periods:

- A window of opportunity when the effects of experience have a more robust effect on brain change/learning through enhanced plasticity.
- An experience at one point in development has a profoundly different impact on behavior than the same experience at another point.
- Age and timing a central variable—sensitive periods previously thought to permanent and irreversible.
The declining figure plots the payout per year per dollar invested in human capital programs at different stages of the life cycle. The opportunity cost of funds (r) is the payout per year if the dollar is invested in financial assets (e.g., passbook savings) instead.

Conclusions/Next Questions:

• Early parenting/psychosocial factors have a material impact on structural brain development in humans--

• Early interventions have robust effects sizes in several domains.

• Can we identify critical or sensitive periods in emotional/social development to target preventions/early interventions in this domain?
PCIT-ED: A Modification and Expansion of a Validated Tx for Preschoolers:

- Child Direction Interaction (CDI)
- Parent Directed Interaction (PDI)
- Emotion Development (ED)

- In vivo coaching through a “bug in the ear”
- Caregiver serves as “arm of the therapist”
- Emotionally evocative events in vivo
The Emotion Development (ED) Module of PCIT-ED:

- Focuses on enhancing emotion competence through in vivo coaching
- Teaches caregiver to serve as a more effective emotion coach, model and external emotion regulator for the child
- Builds on a emotion development model of early onset MDD (targets enhancing reward response, promotes adaptive guilt response, regulates loss/lack of reward response)
Emotional Competence: Definition

1. Awareness of one’s own emotional states.
2. Ability to identify the emotional states of others.
3. An ability to accurately verbally express one’s own emotional states.
4. Capacity for empathic involvement in the emotional states of others.
5. Ability to understand that inner experience may not correspond to outer expression of emotion.

6. Ability to label a substantial repertoire of emotions from facial expressions and gestures.

7. Awareness of cultural “display rules” of emotions.
8. Ability to understand and read individual differences in the expression of emotions.

9. Ability to understand how the expression of one’s own emotions will impact others.

10. Capacity for coping adaptively with aversive or distressing emotions (emotional regulation).

11. Capacity for “emotional self-efficacy”.
Modifying Emotion Dynamics:

- Optimal
- Irritable/Sustained
- Muted
- Long Latency
Penn Emotion Differentiation Test in PCIT-ED versus DEPI:

Percent Change from Baseline to Post 1

- ERC lability/negativity
- ERC emotion regulation
- My Child guilt feelings
- My Child guilt reparation

PCIT-ED vs. Waitlist
We are seeking N=250 children between 3.0-6.11 years for treatment.

Children must meet modified criteria for depression:

- increased guilt
- anhedonia or low pleasure
- sad/irritable

No evidence of Autistic Spectrum Disorders

Child not currently taking antidepressants
All Subjects Receive Active Treatment:

- 50-50 chance of enrollment into groups:
  - Immediate PCIT-ED treatment
  - 18 week waitlist with monitoring then PCIT-ED
- Active treatment completed over 18 weeks (20 sessions).

- Transportation and childcare can be provided.
- If 2 primary caregivers—both can participate together
1. **Initial Screener** (Preschool Feelings Checklist): paper, online link or phone

2. **Exclusion Screen** (10-15 min): by phone; rule-out ASD, severe medical conditions, cognitive delays, etc.

3. **Inclusion & Initial Diagnostic Screener** (30-45 min): by phone; assess modified MDD criteria

4. **Baseline Assessment** (3-5 hours): in-office; diagnostic assessment of parent ($50) & child ($10 gift card)

- Families who meet all eligibility criteria will complete additional assessments
  - Parents - $100 at midpoint, $150 at post; $25 at 4 short, online interval assessments
  - Children - $10 gift cards at baseline, midpoint & post
PCIT-ED Study Contact Information:

- CALL: (314) 286-1888
- EMAIL: pcited@psychiatry.wustl.edu
- WEBSITE: eedp.wustl.edu