A Psychobiological Model of **Parental Dysfunction: The Role of Early Adversity** and Chronic Stress Linda C. Mayes, M.D. Yale Child Study Center New Haven. CT Anna Freud Centre/ University College London London, UK

Subtext/Research Model:

### How Addiction Compromises Parenting



# **Orienting Points -- 1**

- Increasing appreciation for relationship between prenatal and early childhood adverse events/exposures and chronic health conditions in adulthood:
  - Cardiovascular disease
  - Cancer
  - Depression/Mood disorders
  - Drug abuse/addictive disorders



- Broad "mechanisms" include:
  - Exposure during biologically sensitive periods with change in developmental trajectory of brain systems
  - Accumulating damage over time (e.g., one adversity increases risks for others)
  - Gene by experience interactions

## **Orienting Points -- 2**

- Parallel evidence for intergenerational "clustering" of adverse health outcomes
  - Cardiovascular disease
  - Drug Abuse/additive disorders
  - Anxiety and depression



- "Broad" mechanisms may include:
  - Clustering of "risk" genes with increased expression under adverse/stressful conditions
  - Accumulated chronic stress in families perpetuate chronic adversity in offsprings' early experience
  - Compromised parenting secondary to parents' own early adverse experiences

### **Proposition One**

- Adaptive parental function involves key capacities and neural circuits involved in reward seeking and stress regulation:
  - Self-control versus impulsivity
  - Emotional regulation or distress tolerance
  - Decision making/Consequence appraisal
  - Capacity to maintain specific executive control functions under heightened arousal
- Parental <u>dysfunction</u> is a long-term, latent consequence of early adversity and the impact of acute and chronic stress on key biological systems (reward and stress modulatory systems)

### **Proposition Two**

- Effects of toxic and/or chronic stress at key sensitive periods is a common etiologic mechanism for range of later disorders including addiction and parental dysfunction
- Common pathway (equifinality) for abuse/neglect across different psychopathologies associated with parental dysfunction
  - Substance abuse/addictive processes
  - Severe parental depression
  - Personality disorders

Child Abuse and Neglect

NATIONAL SCIENTIFIC COUNCIL ON THE DEVELOPING CHILD

#### **Three Levels of Stress**

#### Positive

Brief increases in heart rate, mild elevations in stress hormone levels.

#### **Tolerable**

Serious, temporary stress responses, buffered by supportive relationships.

#### Toxic

Prolonged activation of stress response systems in the absence of protective relationships.

#### **Sources of Toxic Stress in Young Children**



Maltreatment

Parental Substance Abuse

Postpartum Depression

Source: Finkelhor et al. (2005)

Source: SAMHSA (2002)

Source: O-Hara & Swain (1996)

# **KEY MESSAGE**



- Early chronic, toxic stress compromises not only children's cognitive and emotional development but also specific capacities in these children as adults that are key to caring for the next generation
- Important implications for interventions for children and their parents and also for working with addicted adults who are parents
- ALSO SUGGESTS ANOTHER LINE OF CONSORTIUM RESEARCH ON STRESS AND PARENTAL FUNCTION

### Outline

- Parenting and neural circuitry of attachment
  - Imaging and electrophysiology studies of adult processing infant visual and auditory cues
  - Parental emotion regulation
  - Parental decision making
  - Parental distress tolerance
- Parenting and stress regulation in children
- Addiction and parenting
- A model for parenting, stress, and relapse
- Intervention implications

### **Basic Science of Parental Care &**

### Attachment



Decades of work on impact of parental care on child health and development, but.....



How does becoming a parent impact adults' psychological, neuropsychological, and neural systems development?

 Presence of a new infant activates specific neural circuitry involved in balance between reward seeking and stress modulation

•Enhancement in neural circuits with increasing time with infant





### **RETHINKING "PARENTING"**









What's "beneath" or required for parental "sensitivity" and "contingent responding"?

#### Neurobiology of Parental Behavior

- Extensive data from rodents regarding "affiliative" circuits:
  - Reward circuits (accumbens, striatum)
  - Associated approach/avoidance pathways (amygdala)
  - Modulation by oxytocin, estrogen, prolactin, dopamine
  - At least 10 genes identified (fosB, prolactin & estrogen receptors, oxytocin, dopamine) as involved in



Rutherford, Williams, Moy, Mayes, & Johns, 2011, under review Motivational Systems and the Neural Circuitry of Maternal Behavior in the Rat

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Human studies using brain imaging converge with animal model findings

### Lines of Work: Parenting Research Program

- Parental response to infant affect (MRI/EEG)
  - Non-Parents
  - Non-drug-using parents
  - Drug-using parents
- Parental Emotional Regulation
- Parental Decision Making
- Parental Distress
  Tolerance

- Olfactory system, gene regulation and parenting (H. Treolar)
- Touch (K. Pelphrey)
- Perception of caring motion (P. Fearon)
- Parental Mindfulness (Luyten)
- Parenting interventions
  - Mothering Inside Out (Suchman)
  - Minding the Baby (Sadler, Slade)
  - MomsConnect (M.Smith)

### Collaborators and Support for Parenting Studies

- Mayes Lab: Helena Rutherford, Michael Crowley, Kara Holcomb, Max Gregor-Moser, Jia Wu, Sarah Nicholls, Marion Mayes, Rebecca Hommer, Emily Simpson, Laura Noll. Amanda Ng, Ann Thomasson, Kara Holcomb, Scott McCreary, Julia Blood, Kathy Armstrong, Patricia Miller, Eliza Sholtz
- Yale collaborators: Marc Potenza, Rajita Sinha, Nancy Suchman, David Reiss, Megan Smith, Lois Sadler, Arietta Slade, Nancy Close, Nicole Landi, Einar Mencl, Hedy Kober, Jessica Montoya, Patrick D. Worhunsky, James Leckman, Tara Chaplin, Kevin Pelphrey, James McPartland
- London Collaborators: Eamon McCrory, Pasco Fearon, Peter Fonagy, Mary Target, Essi Viding, Tessa Baradon
- UNC Collaborators: Joey Johns, Sandy Zeskind, Karen Grewin, Guido Gerig
- Baylor: Lane Strathearn and Thomas Kosten
- U. Illinois: David Bridgett
- U. Maryland: Carl Lejuez
- Belgium: Patrick Luyten
- Oregon Health and Science: Suzanne Mitchell
- University of Milano-Bicocca: Alice Proverbio, Ph.D.

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### **Human Studies of Neural**

# **Circuitry of Parental Care**

- Multimodal (Imaging, EEG, MEG)
- Comparing responses to salient infant cues (e.g., visual, auditory)
- Linking neural activation to individual differences in behavior
- Longitudinal to examine changes with experience/exposure

- Comparing first time to experienced parents (e.g., sensitization or amount of child exposure)
- Limitations to date include
  - Primarily normative samples
  - Primarily maternal
  - Primarily passive response paradigms





#### CORE TECHNIQUE IN DEVELOPMENTAL ELECTROPHYSIOLOGY LABORATORY





• Electrical Geodesics 128 or 256electrode dense array.

Three data collection systems plus eye tracking and photogrammetry available

• Enhanced spatial as well as time resolution

### **INFANT FACES**



### ERP studies – Infant Faces

 Early and later visual ERPs are sensitive to parental status when viewing infant faces and to differences in facial affect (Proverbio et al., 2006; Grasso, et al., 2008)



#### **Own Baby Images Activate Orbitofrontal Cortex**

### OFC appraisal of positive/

negative emotions

#### Nitschke, 2004, Neuroimage

-0.2

Infant 1 Infant 2

Scan Run

Adult 1 Adult 2



Infant 1 Infant 2

Scan Run

Adult 1 Adult 2

Infant 1 Infant 2

Scan Run

Adult 1 Adult 2

#### OWN BABY VISUAL CUES ACTIVATE DOPAMINE REGULATED REWARD CIRCUITS



Happy, but not neutral or sad own-infant faces, activated nigrostriatal brain regions.

STRATHEARN, et al., 2008



Own > Unknown Contrast (affect groups combined) Own-Happy > Unknown-Happy Contrast

Own vs Other: VTA/SN,striatum, mPFC, ACC, insula



### **Oxytocin and Attachment Security**

# Predicts Striatal Response (Strathearn, et al, 2010)



### Differential Response to Infant Affect by

Attachment Profile (Strathearn, et al, 2010)

a





Gray Matter Change With Experience and Parental Investment (Kim,Leckman,Mayes, Feldman, Wang, & Swain, 2011, in press)



 Grey matter increase from 2-4 weeks to 3-4 months postpartum (n = 19, p<.05, (FDR corrected) > 100 voxels

 Grey matter increase from 2-4 weeks to 3-4 months postpartum predicted by mothers' positive perception of own baby at 2-4 weeks postpartum



### Relation to Maternal Depression (Noll,

Rutherford, Mayes, 2011, in preparation)



Moms (17) and Non-moms (12); Viewed happy, sad, and neutral infant faces – no modulation of the N170 amplitude by emotion.



### Interim Summary – Infant Faces

- Consistent differences with parents vs non parents
- Activate components of reward circuitry
- Own infant especially salient
- May be changes in circuitry over time with exposure to infant
- Relation to individual differences in mothers (e.g., mood, attachment) and differential response to positive or negative infant cues depending on maternal characteristics

#### CRY AS SALIENT SIGNAL FOR ACTIVATING ATTACHMENT/REWARD SYSTEMS IN HUMANS





### Infant vocalizations of affect

 Auditory N100 ERP component heightened in mothers for both infant cries and control sounds compared to nonmothers (Purhonen et al., 2001; 2008)



### Infant vocalizations of affect

 Across limbic regions, parents show stronger response to cries than laughter with converse true for non-parents(Seifritz et al. 2003)



### Parents and Non-Parents fMRI Response to

Low and High-Distress Cries (Montoya, et al, in preparation)

- In both mothers and non-mothers, Low-Distress and High-Distress Cries activated auditory cortex, with low-distress generating relatively greater activation
  - Low-Distress cries may require greater utilization of auditory circuitry to discern aspects of cries
- In Hi vs Lo Distress Cry Contrast, mothers show greater activation of post-central gyrus, Implicated in motoric responses, and less PCC activation implicated in stress responsiveness
  - Mothers may be primed to initiate motoric responses and less of a stress response to high-distress cries

#### Hi vs Lo Non-Moms



Hi vs Lo Moms



Hi vs Lo Moms Vs Non-Moms



 $p_{voxel}$ <0.01  $p_{cluster}$ <0.05

### **Maternal Response to Infant Cries Change over Time**



Point 1: Both novice and experienced mothers active superior temporal regions

Point 2: By 3-4 months, for both, increased R medial temporal lobe activation

Point 3: For novices, increase in R hippocampal activation by 3 mos; for veterans present at 2 weeks already & no change by 3 mos

### MATERNAL CIRCUITS ENHANCED WITH

Functional relation between R hippocampus (memory) and regions related to reward and stress regulation

Increasing connectivity for novice mothers between 2 wks -3 mos

**EXPERIENCE** 

More modest increase for veteran mothers

Experience based learning



Analyses conducted by Leslie Jacobsen; Data from Swain, Leckman, Mayes, 2008

#### **Breastfeeding and Response to Infant Cries** (Kim, Feldman, Leckman, Mayes, and Swain, 2011, in press (JCPP)



 Breastfeeding mothers show greater activations in superior frontal gyrus, insula, precuneus, striatum, and amygdala while listening to their own baby cry as compared to formula-feeding mothers.

### Predicting Maternal Sensitivity at 3-4 months with neural response to infant cries

(Kim, Feldman, Leckman, Mayes, and Swain, 2011, in press (JCPP)

Pulamon R Globus Pallidus/Armyodala Breastfeeding Formula-feeding Superior frontal gyrus (2) Breastfeeding ormula-feeding

= 62 p< 01

Maternal sensitivity at 3-4 months postpartum positively correlated with activations in right superior frontal gyrus (r=.62, *p*<.01), and right lateral globus pallidus/amygdala (r=.53, p<.05) at 2-4 weeks postpartum to own versus other cries.

### Interim Summary –Infant Cries

- Differences between parents and nonparents
- Cries especially salient to parents
- Change in circuitry over time
- Related to individual differences among mothers

### A conceptual framework



Slide/schematic from Helena Rutherford
## Lines of Work

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Do mothers regulate their emotions differently compared to non-mothers?

Helena Rutherford's Work in Progress

## Late Positive Potential: ERP component generated in response to emotional pictures that can be manipulated by regulation instructions



Emotion regulation with IAPS pictures: Arrow A, the effect of enhance: enhancing the emotion generates larger amplitude around 300 ms (P3). Arrow B, the effect of suppress: suppressing the emotion decreased the amplitude during 400 to 900 ms slow wave. Sample: 30 male and female undergraduates (Rutherford & Crowley).

## Regulating to Negative Expressions





Moms of children < 4 years N=12

Non-Moms N=7

(Electrode Pz but observed in parietal region)



LPP responses to infant faces in non-moms are comparable to existing literature employing emotional images
No LPP modulation by regulation instructions suggests that mothers are in a heightened regulation state

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## Parental Decision Making (Helena Rutherford's work)

- Do mothers change trait-like decision making behaviors when asked to think about a child as compared to non-mothers?
- Delay discounting experiment with changing who is recipient of the money (e.g., playing for self or for child)



### Parenting Status Shifts

## **Discounting Behavior**

- Non-Moms (n = 11): No difference between self and child condition
- Mothers (n = 13): Significant difference between self and child condition



Mothers discount more when thinking for self versus child

Suggests that mothers become more future-focused when thinking about the needs of a child

Rutherford, et al., 2011, under review

## Lines of Work

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## Parental Distress Tolerance

#### (Helena Rutherford's work)

- A challenge for a new parent is regulating stress when caring for new infant
- Can we assess this capacity in an experimental but ecologically valid way?

Simulated Baby



Designed to be 4-6 mos old
Computer controlled to generate cries
Certain behaviors (e.g., feeding, rocking, diaper changing) can soothe the simulator

Gustafson & Harris (1990)

## Early Findings – Is the Simulator

## a Reliable Stressor?

- Collecting data with parents and nonparents
- Among parents, substance using and non-substance using
- Validating against PASAT, ERQ, Adult Temperament
- Coding soothing behavior with simulator

- Adults treat simulator as "real" and persist for varying lengths of time
- For non-parents (college students), more looks away from simulator associated with lower effortful control
- More smiles toward simulator, higher reappraisal score on emotional regulation questionnaire

## Early Findings – Is the Simulator a Reliable Stressor?

- For non-parents, reliable changes in HR and B/P
  - Heart rate pre- and post-simulator task: Significant increase, 67 vs 74 bpm, p<.05</li>
  - Blood pressure pre- and post-simulator task: Mean BP 116/86 vs 125/88
  - Significant increase for systolic BP, *p*<.05
- Similar physiologic changes for parents
  - Heart rate increases 67 to 74, p=.039
  - Systolic BP increases 116 to 125, p=.011
  - Greater reported frustration, greater systolic BP (r=.67, p=.02) and diastolic BP(r=.78, p=.007)
  - Greater reported frustration = greater overall stress (r=.80, p=.003)

## Interim Summary

- Salient infant cues activate circuits involved with reward, motivation, stress response, and emotional appraisal
- Adaptive parenting requires constellation of behaviors/capacities reflective of effective stress regulation, self-control, and effective decision making
- Adult transition to parenthood brings with it adaptations in decision making/self-control and stress regulation

## Early Life Experiences Are Built Into Our Bodies (For Better or For Worse)



#### Early Parenting Experience and Adult Stress Response Systems

Offspring of, or those cross-fostered to "low care" mothers show, as adults, increased response to acute stress, decreased exploration in novel environments, enhanced startle, decreased hippocampal glucocorticoid receptor mRNA expression

• Among cross-fostered offspring, individual differences in maternal behavior related to rearing, rather than biological, mother.



#### Intergenerational Transfer of Parenting Behaviors

Offspring from high levels of maternal care cross-fostered to "low care" mothers and vice-versa (low to high)



Francis et al., 1999

## Individual Differences in Maternal Care



Hane and Fox, 2006

#### Low Maternal Care in Humans Associated with Greater Striatal Dopamine Response<sup>\*</sup> to Stressor as Adult



\*\* reduction in [11C]raclopride binding potential

## **Interim Summary**

 Individual differences in parenting behavior convey individual differences in stress-reward systems in offspring enduring into adulthood

#### PARENTING AMONG SUBSTANCE ABUSING ADULTS

## BALANCE BETWEEN SELF-CONTROL AND STRESS SENSITIVITY



• With early adversity/chronic, toxic stress, switch point moved "earlier" so more likely to decrease prefrontal function under stress

- Impulsivity
- Poor decision making
- Lowered distress tolerance

Animal Models of Parenting and Drug Addiction

 Suckling increases activation in dopaminergic reward system but cocaine diminishes this activation (Ferris, et al., 2005; Febo and Ferris, 2007)



#### Animal models of Parenting and Drug Addiction

- In prenatal, chronic exposure model (Johns and colleagues):
  - Diminished attention to pups and to pup environment (e.g., nest building, gathering pups)
  - Heightened aggression to intruders but not to protect pups
  - Decreased attention to pup vocalizations



Parenting Behavior Among Substance Abusing Adults

- In human mothers:
  - Withdraw in face of infant distress
  - Less attentive to infant bids for attention
  - Less contingent responding or increased noncontingent behaviors
  - Higher rates of negative affect in interactions and heightened physical provocation and intrusiveness
- ? Each as markers of heightened stress in response to infant

Truman and Mayes, 2005

#### OWN BABY VISUAL CUES ACTIVATE DOPAMINE REGULATED REWARD CIRCUITS



VTAJ Substantia

nigra region

Amygdala

n=28, p<0.001(uncorr.)

Preliminary findings in cocaineabusing mothers: Relative decrease in activation in ventral striatum in response to infant positive affect

#### Substance Using versus Non-Using Mothers Differential Neural Responses to Faces



Substance using mothers show less activity than healthy controls in response to happy faces in the right parahippocampal area, associated with memory formation and recall; and also the orbitofrontal gyrus, associated with cognitive processing of emotion.

#### Reduced Sensitivity to Infant Faces in Substance Using Mothers (Rutherford, et al., in preparation)



Slower N170 Latency



#### Substance Using Versus Non-Using Mothers Differential Neural Responses to Cries



Substance using mothers show less activity then healthy controls in response to highdistress cries in core speech/vocal processing regions, including the right middle/superior temporal gyrus.

#### Cocaine-Using Mothers Show Diminished Oxytocin Response and Greater Perceived Stress in Response to Infant Cries



### Interim Summary

- Addictive processes reflect dysregulation of stress reactivity and reward sensitivity
- Early adversity increases risk for addiction
- Profile linked to long-term effects of early adversity parallels the neural circuitry and behavioral pattern of addiction
- Addicted adults experience infant cues as insufficiently rewarding (and ? more stressful) secondary to dysregulation of stress/reward system in addiction

#### How Early Adversity/Addiction Impacts Parenting

- Consider caring for a crying infant
  - Cry is stressful, eliciting a range of adaptive, decision making, prefrontally regulated processes –or top down interpretive processes
  - "Reward" of responding to cry is in the future capacity to be mindful of consequences of actions.
  - Mindfulness, consequence appraisal modulates stress of caring for crying infant
- But in addicted adult with increased stress sensitivity, salient infant cues are increasingly stressful and capacity to anticipate actions is diminished.

#### HOW INFANT CUES INCREASE STRESS AND CRAVING IN ADDICTED ADULTS

- Infant signals that are stressful, difficult to interpret, increase parental stress with withdrawal from infant
- Stress in turn increases craving for habitual behavior that downregulates acute stress
- Individual turns to drugs or other habitual behavior rather than infant (neglect...) or....
  - Needs to quieten infant to decrease own stress (poor distress tolerance) (abuse....)

# Model for Parenting Stress and Addiction



### Intervention Implications

- Mechanism for clinical observation of increased drug use/relapse in adults after birth of infant
- Changes or amplifies intervention focus
  - Decrease drug use-----improve parenting or.....
  - Improve parenting----decrease drug use
- Improve parenting improve self-control, distress tolerance, decision making
- Nancy Suchman and Team: "Mothering from the Inside Out" for substance abusing mothers
  - Focus on Changing Parenting and response to parenting stress

Mothering from the Inside Out (Suchman and colleagues) Mother's responsiveness to her child during the teaching session d > .50



#### Mothering from the Inside Out (Suchman and colleagues) Mother's substance use


## Intervention Approach

- Focus on adult as parent
- Focus changes from "what baby needs" to how demands of caring for infant are stressful and impact understanding infant's needs
- Focus on increasing adults' distress tolerance/capacity to maintain decision making in face of stress/ remain mindful of own emotional states



# SUMMARY

- Early adversity and impact on stress-reward systems may be a common mechanism across a range of adult disorders associated with poor parenting
- Addiction and impact on parenting is a specific model of a broader mechanism for how dysregulated stress/ reward systems compromise parenting
- With chronic parental dysfunction, poorer stress regulation in infant/child further increasing stress for parent
- May serve as a mechanism for understanding child abuse/neglect
- Interventions for at-risk children must also target parents



# **Research Directions**

- Expanding sample of substance abusing mothers
- Moving to dynamic paradigms
- Adding sensory modalities including work on olfaction, motion perception, and touch
- Adding challenge/stress sessions to "probe" model with/without oxytocin administration
- Focus on functional endophenotypes among parents (e.g., distress tolerance, impulsivity, decision making, etc.) and characterize individual neural differences by function
- Need for more translational collaborations

#### Collaborators and Support for Parenting Studies

- Mayes Lab: Helena Rutherford, Michael Crowley, Kara Holcomb, Max Gregor-Moser, Jia Wu, Sarah Nicholls, Marion Mayes, Rebecca Hommer, Emily Simpson, Laura Noll. Amanda Ng, Ann Thomasson, Kara Holcomb, Scott McCreary, Julia Blood, Kathy Armstrong, Patricia Miller, Eliza Sholtz
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