

Development: A Clinical View of Exceptions to Typical Brain Developmental **Trajectories**

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CHILDREN ARE OUR AGENTS OF CHANGE





- 1600 to 1900 major shifts in societal views on children's value and importance
- By the 1900s specialized health care, mental health care, and compulsory school
- · And NO VIDEO GAMES!



We cannot stop...

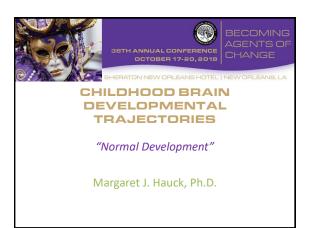
- · Early childhood is full of change
- The very young are vulnerable...but resilient.
- We are still learning about the most vulnerable who do not have a voice of their own

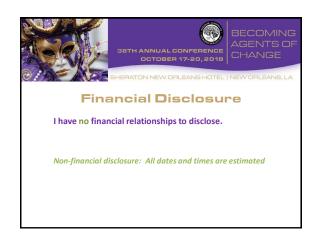


Today

- · Development in Early Childhood
 - Typical
 - Faced with adversity
 - Atypical development
- · Differences, but similarities too









- Building the brain
- Development of areas and abilities



- Begins 18-22 days post-fertilization, with the neural plate that then folds into the neural tube. One end will become the brain...
- Vesicles form and tissue around them becomes:
 - Cerebral hemispheres, thalamus, hypothalamus, basal ganglia
 - Midbrain
 - Medulla oblongata, pons, cerebellum



Building the brain

- By 3 months post-fertilization, cerebral hemispheres are forming
- By the end of the second trimester, gyri and sulci are nearly complete



Building the brain In broad terms...

- Neurons are born.
- Migrate to ultimate locations
- Differentiate, Connect
- Prune



Migration

- Cells migrate to inner areas first, to outer areas later
- Migrate to different places at different times
- 25 weeks after conception, 6 layers of cortex



Connecting

- Axons
- Dendrites
- Synapses (overproduce)
- Pruning (cut back synapses)



Myelination

- Speeds communication
- Starts in the second trimester ... and ...
- Persists for 2 decades



Cortical Development

- · Cortex both thickens and thins
- Different regions follow different patterns
- Asymmetry appears early on
- In the third trimester, the cortex is starting to learn...

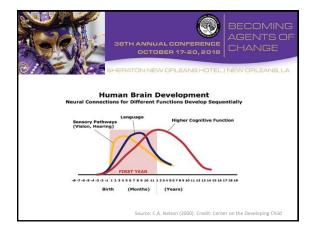


- The newborn brain is prepared to experience
- And is prepared by experience
- · And, has greatest plasticity in early years



Abilities and Brain Areas involved

- Motor and sensory
- Language
- Memory
- Attention
- · Executive functioning
- Social/Emotional







18 months

2 - 3 years

tool use

draws

walking

running





Neuroanatomy of motor development

- · Brain stem: tone, balance
- Cerebellar: spinal-control, cortex-initiation & planning
- Basal ganglia: facilitates movement, chooses, inhibits
- Motor cortex: plans, prepares, executes



Motor

 Motor is movement, but also planning, memory, consequences. Motor development is important for development of other systems ... and motor behaviors need other systems



Sensory

- Visual
- Auditory



Visual

- (this is a good place to remember that, since the brain is developing, the perception/experience/skill of an infant/child is different than that of an adult)
- So, in vision, the development of neurological areas that adults use happens over time ... So the vision of an infant is actually different than the vision of an adult



Visual

- First to mature: primary sensory information processing areas
- Next, parietal association cortices (spatial attention)
- Then, higher order association areas, such as prefrontal cortex
- So, the infant, without mature parietal or prefrontal areas, is seeing differently



Visual

- Can see 8-12 inches at first
- At 2 months, can focus to discriminate
- By 3 months, can focus and follow
- Depth perception at 5 months
- Occipital lobe is rapidly growing up through 8 months
- By 9 months, vision is nearly as good as adults



Auditory

- · Sounds start with the cochlea.
- · Auditory nerves process aspects of sound
 - Frequency by 3-6 months
 - Intensity gets better with age, 5-7 months need much more difference in sounds than adults
- Auditory cortex is involved in tasks such as localizing sound
- As for making sense of sound ...



Language

- Temporal lobe (Left, in right handers at least, except prosody)
- Superior temporal gyrus, including Heschl's gyrus, superior temporal sulcus, temporal pole



Language

- Babbling at 2 months, with vowels
- Consonants at 5 7 months
- Parsing output (e.g. finding the phrases) at 8 months
- Sounds and meanings around 12 months
- Understanding (Weirnicke's) comes earlier than Using (Broca's)
- By 2 $\frac{1}{2}$ much of the adult language brain is up and running



Written Language

- Motor skills ... 2 & ½ can draw letter shapes
- Visual skills ... left visual cortex
- Language skills ... to tie the sounds and symbols together



Memory

- Implicit or Procedural memory
 - Striatum, cerebellum, brain stem
 - Very early to mature
 - Visual-expectation, operant conditioning, and classical conditioning are shown in very young infants



Memory

- Declarative memory develops later ... as structures it needs develops
- Hippocampal development:
 - Cell formulation continues through gestation (e.g. 28 weeks) and migration for a year postnatally.
 - Recognition memory (dependent on hippocampus) improves significantly around 3 months of age
- Medial temporal lobe memory system:
 - Slower than hippocampal system, with development through 2 years



Memory

 Declarative memory – encoding, retention, retrieval, develops through infancy and early childhood.



Encoding

- Older infants can encode faster than younger
- Myelination speeds up processing, making encoding more efficient



Retention

- See increased length of retention up through early childhood
- Dentate gyrus also matures over the course of early childhood (as late as mid-elementary)



Retrieval

- In infants, need exact retrieval cues need the same props, environment ... Infants do not generalize
- By 24 months, toddlers can learn on one and perform on another prop, learn in one environment and perform in another



Retrieval

 This mirrors the development of the hippocampus – need the dentate gyrus and inhibitory interneurons to make flexible memories



Retrieval

Also environmental exposures are in play.
Younger but crawling infants can make more
flexible memories. If a connection is made
between two props the 6 month old can learn
with one and show the learned knowledge
with the other



Episodic and Autobiographical Memory

 Improvement in the ability to connect items together is shown between 4 and 6, improvement in story memory continues well out of early childhood ... hippocampus and medial temporal lobe are maturing and building maturing connections with the prefrontal lobe.



Attention

- Birth to two years sees the development of alertness and vigilance sustained attention
- Areas of the thalamus and several neurochemicals (noradrenergic, cholinergic, serotonin, and dopaminergic) are involved in general attention
- System-specific areas also come into play for in the functioning of those systems



Attention

- Working memory
 - Dorsolateral PFC functioning
 - Myelination
 - Shown as early as 3-5 years



Joint attention

- Gaze following (to benefit from JA); temporal areas, especially superior temporal sulcus
- Gaze shifting, head turning, vocalizations (to use JA); frontal areas, especial medial frontal
- See as early as 3 -6 months and response to JA at 6 months predicts language development later



Executive functions

- What are EF? Planning, starting-persistingstopping, inhibiting, self-judging ... So, in people who are 0 to 6 ... Well, they're still working on this development.
- (EF mature well in to 20s)



Executive functions

- On the other hand, the prefrontal cortex is developing and impacting function by the first year.
- · Myelination is occurring
- Corpus Callosum connections are happening in frontal lobes (3-6 years)
- $\bullet \;\;$ Gray matter is increasing, and then, in later childhood, decreasing
- Synaptic density peaks around 3 years of age (200 times the density of adults



Executive functioning

 Prefrontal cortex is becoming more active in areas needed for EF and especially the anterior PRC is taking on the job it does in adulthood



Executive functioning

 Inhibition improves with development of orbitofrontal cortex (3 year olds are worse than 4/5 year olds)



Executive functioning

- Anterior Cingulate Cortex: performance monitoring realizing an approach is not working and needs to be changed
- As early as 2, child can see errors (what is wrong) but most 3 year olds cannot correct ... even when they realize they are making errors
- Also, once the brain can spot the errors, needs PFC to problem solve, and this ability continues to develop



Social/Emotion

- Processing of emotion in voice (in R hem) emerges in first days post birth
- Smiling at 6 weeks (motor and visual)
- Focusing on faces (seeing immediately, improved vision at 2 months)
- Laughing at 3 4 months old



Social/Emotion

 Temper tantrums ... 2-3 year old can be more independent ... meaning more likely to be frustrated ... and the limbic system is not yet regulated by the frontal lobes



Areas involved in emotions/social

- Amygdala
- Orbitofrontal cortex
- Anterior Cingulate cortex
- Fusiform face area (middle lateral fusiform gyrus)
- Mirror neurons



Areas involved in emotions/social

- · Limbic system development
 - Emotion
 - Turn taking around 4 years of age



Emotion

- Amygdala development
 - Maturing prenatally
 - Functional at birth
 - Continues to change and mature across development ...
 - With differing activation in child and adult



Attachment

- HPA axis (Hypothalamic-Pituitary-Adrenal) and Cortisol levels regulated by Oxytocin and social interaction
- Hippocampal development needed for memory
- Reward system: Ventral-striatal (novelty seeking) and Dorsal-striatal (comfort seeking)
- Amygdala for discrimination (caregiver vs other)



So, to summarize

Just like the humans who carry them, brains are made by a multitude, traveling far and wide, building, keeping, and ending connections in response to the environments that keep us.



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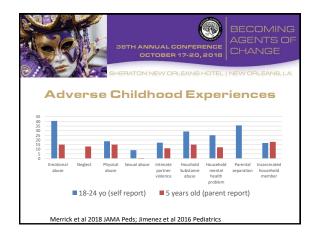


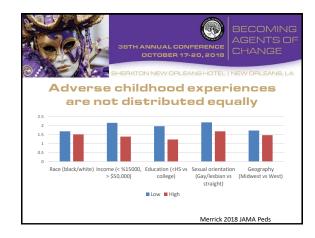
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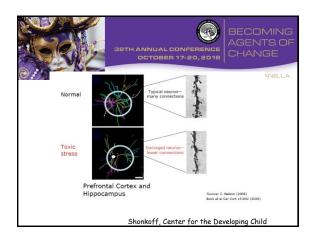


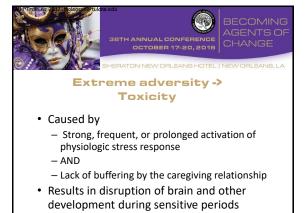
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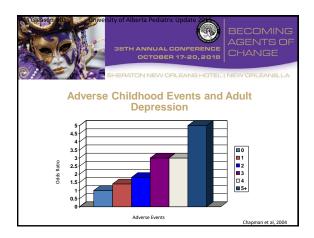


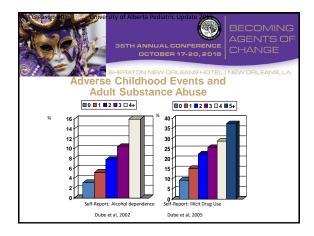


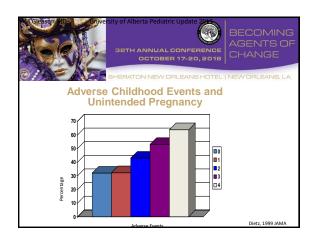


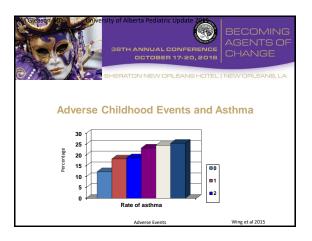


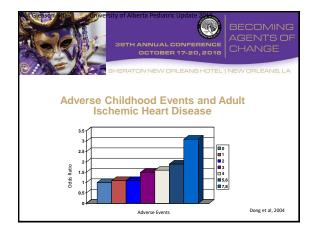


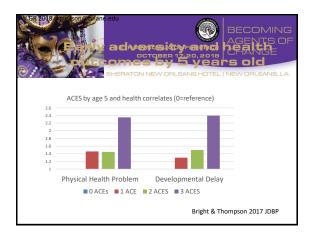


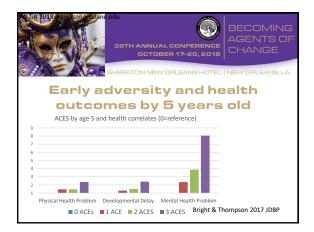




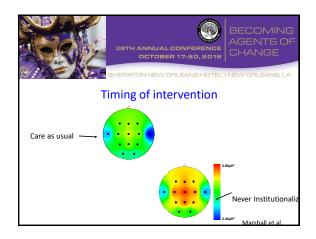


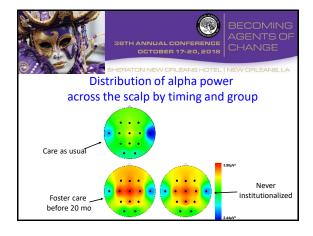


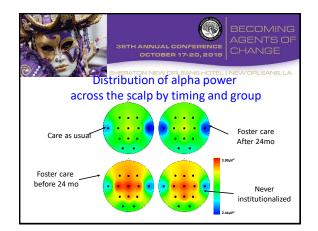




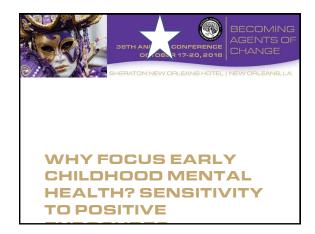


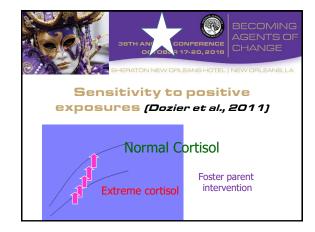


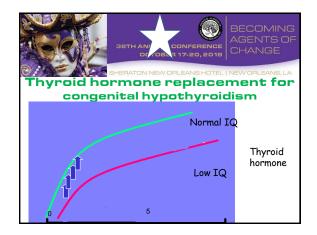


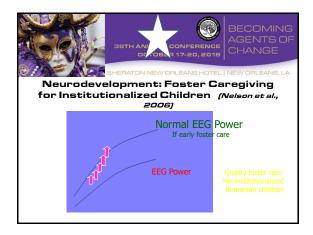




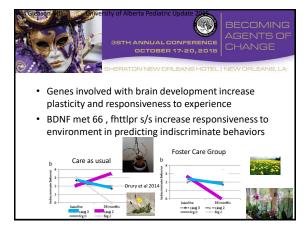


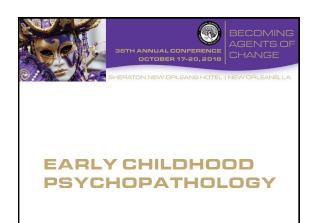




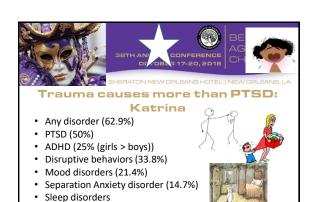












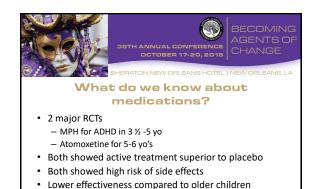
Scheeringa & Zeanah 2008

• No new disorder without some PTSS

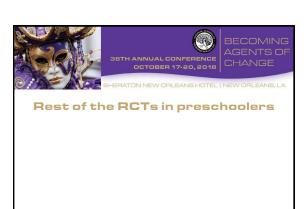


• 14 year old who was 4 during Katrina





Greenhill 2006; Kratchovil 2011











and Early Brain Development

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Objectives

- · Review diagnostic criteria of ASD
- · Review basic neurobiological basis of ASD
- · Dissect specific symptoms of language impairment, social impairment, and RRBs and how the brain contributes to the deficits



Disorders

"Neurodevelopmental disorders...typically manifest early in development...and are characterized by developmental deficits that produce impairments of personal, social, academic, or occupational functioning...frequently co-occur."



Autism Spectrum Disorder

- 1 in 59 children at 8 years of age across 11 sites in the US
- · Impairments in social interaction and communication
- · Presence of Restricted Interests and Repetitive Behaviors



Limitations

- ASD is a spectrum and no homogeneous
- Heterogeneous causes
- · Heterogeneous presentations
- · Variability in severity



Social Communication

- Deficits in social-emotional reciprocity
 - Abnormalities in social approach, conversation, sharing of interests, sharing affect, sharing emotions, initiating/responding to social interactions



Social Communication

- Deficits in nonverbal communicative behaviors
 - Difficulty with integrating verbal and nonverbal communication, eye contact, body language, gestures, facial expressions, and nonverbal communication



Social Communication

- Deficits in developing, maintaining, and understanding relationships
 - Problems adjusting behavior to suit a variety of social contexts, poor imaginative play, problems making friends, little-to-no interest in peers



Restricted/Repetitive Behaviors

- Stereotyped or repetitive motor movements, use of objects or speech
 - Motor stereotypies, lining up toys, flipping objects, echolalia, idiosyncratic



Restricted/Repetitive Behaviors

- Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior
 - Extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day



Restricted/Repetitive Behaviors

- Highly restricted, fixated interests that are abnormal in intensity or focus
 - Strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests



Restricted/Repetitive Behaviors

- Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment
 - Apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement



Associated Features

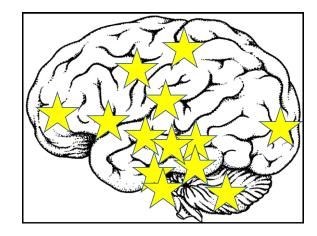
- · Intellectual disability
- Language impairment
- Uneven profile of abilities (IQ vs Adaptive)
- Motor deficits (odd gait, clumsiness, toe-walk)
- Self-injury, disruptive/challenging behaviors
- · Anxiety/depression
- Catatonia (mutism, posturing, grimacing, and waxy flexibility)



Early Signs of ASD

- · Atypical eye contact
- Poor visual tracking
- Disengagement of visual attention
- Stereotyped play
- Self-stimulatory play
- · Increasing irritability
- · Lack of orienting to name
- · Poor imitation
- · Reduced social smiling
- Reactivity, to sensory input
- · Reduced social interest
- Visual fixation to non-social aspects of environment

Zwaigenbaum et al, 2005





Theories of ASD Neurobiology

- Excitatory/Inhibitory Dysregulation
 - GABA & glutamate
- Impeded Plasticity
 - Structural (HC, volume, surface area)
 - Connectivity
- · Inflammatory Response



What we know about ASD and the Brain

- · Brain dysfunction begins prenatally
- There are structural differences, but...
 - Function?
- · These difference are influenced by genes
- · Which are activated by environmental factors



LANGUAGE & COMMUNICATION **DEFICITS**



Language in ASD

- · A consistent linguistic profile has not been established
 - Phonology, semantics, and syntax
- Impaired prosody and pragmatics have remained hallmarks of ASD
 - Intonation & stress; context-based appropriate responses



Observable Language Problems

- · Overall level of language
 - Nonverbal, single words, phrase, fluent/complex
 - 25-30% speak few to no words
- · Quality of the speech
 - Rate, rhythm, volume, tone
- Echolalia



- Stereotyped Language
 - Delayed echolalia, jargon, repetitive phrases, misuse of pronouns
- · Use of other
 - Body as a tool
- Pointing
 - Visually directing, requesting, sharing attention,



- Gestures
 - Descriptive, conventional, instrumental, or emotional
- Offering and asking for information
 - Thoughts, feelings, experiences
- · Reporting on novel events
- · Conversation skills



Neuroscience of Language & **Communication Deficits**

- · Difficulty conducting studies with young children for multiple reasons
- · Basic hypotheses:
 - Difficulties attending to speech
 - Brain volume differences affect language



Lateralization

- Abnormalities in frontal and temporal cortical organization in spoken and written language
 - Increased responsiveness in the right hemisphere and decreased responsiveness in the left hemisphere
 - Less functional lateralization or at least an asymmetry toward the right side.
 - Use of right side for language could be nudging out room for social communication abilities

Kleinhans et al 2008; Knaus et al 2008; Just et al 2004; Mody et al 2013; Friederici et al 2004; Sandson et al 1994; Manoach et al 1995



Disrupted Language Network

- · Anatomical differences:
 - Reduced white matter in the superior longitudinal fasciculus
 - Increased ventral temporal white matter
 - Increased activation in lateral occipito-temporal sulcus
- · Results: heightened reliance on visual input
- Autism preference for visual over language is supported with these findings

Sahvoun et al 2010: Manialy et al 2007: Silk et al 2006



Reduced Activation

- Inferior frontal gyrus shows reduced activation between semantic and perceptual processing
- Decreased inferior frontal gyrus activation in sentence comprehension

Just et al 2004; Harris et al 2006



Receptive Language

 Positive correlation between superior temporal gyrus volume and receptive language scores on the CELF-3 in control subjects but not ASD

Bigler et al 200



Childhood Apraxia of Speech

- Most children with CAS have normal structure on MRI
 - May be too subtle to be detected
- Connectivity across specific brain regions involved in speech/language is supported

Fiori et al 2016



Echolalia

- Audio-visual mirror neuron system is responsible
 - located in ventrolateral prefrontal cortex, superior temporal gyrus, and inferior parietal lobule overlapping with the dorsal speech-processing stream; these areas are linked by the arcuate fasciculus

Berthier et al 2017



Understanding Irony

- Hyper-activation in the right inferior frontal gyrus and bilateral temporal regions
- Increased activation due to impairment in interpreting communicative intentions

Wang et al 200



SOCIAL INTERACTIONS



- Eye contact
 - Appropriate or poor for initiating, maintaining, and terminating social interactions
- Facial expressions
- Linking language and nonverbal communication



- Sharing enjoyment
 - Indicating enjoyment in the interaction not toy
- · Social smile
- · Responding to name
- Requesting
- Giving
 - Sharing or for help/routine based



- Showing
- Joint Attention
 - Initiating & responding to bids for joint attention
- · Social overtures and social responses
- · Commenting on emotions/feelings
- Showing insight into relationships/social situations





Facial Processing

- Use object processing areas, not specialized face processing areas
- · ASD have less difficulty identifying upside down faces
 - At 6 months, NTs have trouble (facial inversion effect)



Facial Processing

 Babies with ASD and older high-functioning individuals with ASD look at mouths and upper face in intense social interactions





Reading Emotions

- Lower activation of R amygdala, R STS, and R IFG when looking at fear face
- Low activation of L insular cortex when looking at happy face
- · Conclusion: deficits in social cognition from impairment of visual analysis of facial expressions



Social Reinforcement Deficits

- · Children with ASD are less reinforced by positive social reward (such as smiling)
- · Impaired social reward learning leads to social communication impairment

Choi et al 2015



Sensory Distraction

- · ASD participants unable to process social information when simultaneously stimulated by sensory input (tactile)
- Increased activation in multiple brain regions (frontal)
- · However, when given specific instructions, activation fell to levels similar to no sensory distraction

Green et al 2018



RESTRICTED **INTERESTS &** REPETITIVE **BEHAVIORS**



Observable RRBs

- Sensory interests
 - Sensory seeking and sensory aversions
- · Hand and finger mannerisms
- · Full-body, complex mannerisms
 - Rocking, arms, legs



- Excessive interests in topics, objects, behaviors
- · Unusual, odd, esoteric topics
- · Not well integrated, non-sequiturs
- Refer to object in a highly specific manner
- · Move body in highly specific manner



- · Difficulty with transitions
- · Maintaining routines and rituals
- Compulsions
- Significant resistance and distress when transitioning or moving/removing objects



Neuroscience of RRBs

- · Linked to differences in the striatum
- Theory: failure to adjust behavioral strategies after response monitoring
 - Increased activities in anterior medial prefrontal cortex and L superior temporal gyrus
 - Attention turned toward emotional state of making mistake

Thakkar et al 2008;Goldberg et al 2011



Repetitive Behaviors

- Reduced frontoparietal/limbic and motor/limbic circuit ratios for high RB compared to low RBs in the right hemisphere
- There is an association between repetitive behaviors and an imbalance of connectivity
 - Higher in limbic and lower in frontoparietal and motor circuits

Abbott et al 2018



Repetitive Behaviors in Mice

- Cortico-basal ganglia-thalamic circuit and brain regions associated with social AND repetitive behaviors
- Brain regions involved in social behaviors are also involved in RRBs



Early Sensory Seeking

- Sensory seeking at 18 months was related to early social engagement and later social difficulties
- At 24 months, sensory seeking early predicted later social difficulties

Damiano-Goodwin et al 2017; Baranek et al 2017



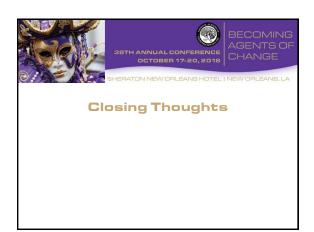
Summary

- Autism Spectrum Disorders
 - Social communication delays
 - Restricted repetitive behaviors
- Deficits in ASD are due to size, connections, activation, structures, and lack thereof
- Difficulty studying young children using imaging techniques that require stillness and following directions
- · New information is forthcoming weekly



- Translational component is lacking
- Increasing clinically relevant information or application is necessary for next steps in many of these studies









"WE SEE HOW EARLY
CHILDHOOD EXPERIENCES
ARE SO IMPORTANT TO
LIFELONG OUTCOMES,
HOW THE EARLY
ENVIRONMENT LITERALLY
BECOMES EMBEDDED IN
THE BRAIN AND CHANGES
ITS ARCHITECTURE."
-- Andrew S. Garner

