NEURAL DEVELOPMENT

H-126: Typical and Atypical Neurodevelopment

30 August 2017

OUTLINE

- Background to development
- Background to brain assembly
  - Conception and prenatal development
- Putting the pieces together
- Role of experience in brain development
  - Neural plasticity
  - Critical periods

DEVELOPMENTAL MILESTONES ACROSS THE LIFE SPAN

At age 4 success is . . . not peeing in your pants.
At age 12 success is . . . having friends.
At age 16 success is . . . having a driver's license.
At age 20 success is . . . having sex.
At age 35 success is . . . having money.
At age 50 success is . . . having money.
At age 60 success is . . . having sex.
At age 70 success is . . . having a driver's license
At age 75 success is . . . having friends.
At age 80 success is . . . not peeing in your pants.

Introduction to Brain Development

- There are general principles of brain development that apply to (nearly) all members of the species.....
  - Genetics supplies basic blueprint for brain development.
  - Experience adjusts the blueprint and shapes the architecture of its neural circuits, according to the needs and distinctive environment of the individual.

CHANGE IS PARTICULARLY DRAMATIC BEFORE BIRTH

BRAIN DEVELOPMENT

http://medstat.med.utah.edu

PRENATAL DEVELOPMENT

- Development begins with *fertilization*, whereby male gamete (sperm) and female gamete (oocyte) unite to give rise to zygote
- Humans have ~20,000 genes on 46 chromosomes (23 pairs)
  - 1 pair = sex chromosome (X,Y)
  - 22 pairs = autosomes

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RAPID CELL DIVISION FOLLOWS CONCEPTION

- 1 week after conception cluster of cells (blastocyst) forms
- Inner layer of blastocyst gives rise to embryo
- Embryo divides into 3 layers (endo-, meso- and ectoderm)
- Ectodermal germ layer gives rise to:
  - Central Nervous System
  - Peripheral Nervous System
  - Sensory epithelium of ear, nose, and eye
  - Skin (including hair and nails)
  - Pituitary, mammary and sweat glands
  - Enamel of teeth

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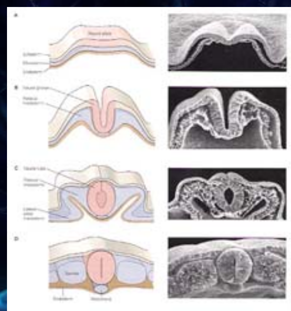
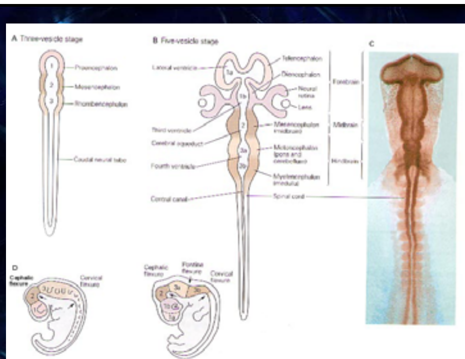
STAGE I: NEURULATION

- Days 18-24:
  - Dorsal (rear) region of ectoderm thickens and forms neural plate
  - Neural plate forms a groove
  - Neural tube forms
  - Tube closes at rostral (top), then caudal (bottom) ends
  - Cells trapped inside tube form CNS, those outside tube form ANS

NEURAL TUBE FORMATION



Source: From "The Induction and Patterning of the Nervous System," by T. M. Jessell and J. R. Sanes, 2000, in E. R. Kandel, J. H. Schwartz, and T.M. Jessell (Eds.), Principles of neuroscience (4th ed., p. 1020, fig. 52-1), New York: McGraw Hill.



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ERRORS IN NEURULATION (2 EXAMPLES OF MANY)

- *Anencephaly* (anterior portion of tube fails to close) (**see next slide**)
- *Myelomeningocele* (posterior portion of tube fails to close; also known as "open spine")

Spina bifida

Drawing of anencephaly

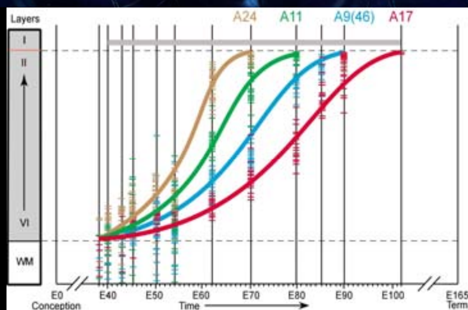
STAGE II: NEUROGENESIS (BIRTH OF BRAIN CELLS)

- Precursors to neurons and supportive tissue (glia) form; this continues postnatally.
- Was previously believed most neurogenesis was complete at birth.
- We now know that there is postnatal neurogenesis through at least middle age in olfactory bulb and dentate gyrus (part of the hippocampus).

LASTLY....

- Is orderly progression of neurons and
- All neuronal types start at approximately the same point in time (next slides)

TIMING OF NEURON ORIGIN IN RHESUS MONKEY CORTEX



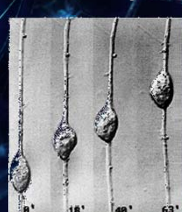
Rakic, Nature Review Neuroscience, 2002, Clinical Neuroscience, 2002

ERRORS OF NEUROGENEIS

- *Microcephaly* (probably occurs prenatal weeks 6-18)
  - Cause could be genetic or environmental (e.g., Zika, which is a result of *fetal brain disruption*)
- *Macrocephaly*
  - Cause generally genetic

STAGE III: CELL MIGRATION (BUILDING THE CEREBRAL CORTEX)

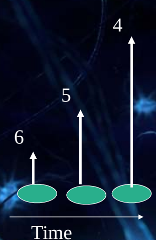
- Following neural tube closure, there is proliferation of a single layer of epithelial cells that line the tube.
- Cells are connected to each other and in some cases, to radial glial fibers.
- Expansion occurs between layers
- Neuroblasts climb onto fibers and migrate radially or tangentially.



Source:www.rockefeller.edu/pubinfo/astrotactin.nr.html (photo: Mary E. Hatten, Ph.D.)

CELL MIGRATION IN FERRET BRAIN

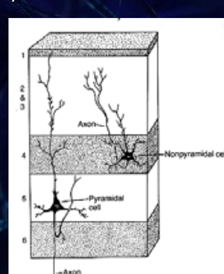
CELL MIGRATION (CON'T.)



- Cerebral cortex (which has 6 layers) forms in inside-out pattern

CELL MIGRATION (CON'T)

- Neurons in each layer have a distinct function. Examples:
  - Layer II neurons involved in short cortico-cortical connections
  - Layer III neurons involved in longer, cortico-cortical connections, including inter-hemispheric connections.
  - Layer IV neurons serve as targets from thalamic neurons
  - Layer V neurons serve as origin of projections to subcortical structures
  - Layer VI neurons project from cortex back to thalamus.
- Most cell migration complete by 24-25 weeks gestation (age of viability)

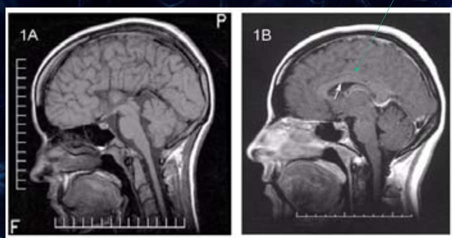


Source: From "The Neural Basis of Perception and Movement," by J. P. Kelly, 1991, in E. R. Kandel, J. H. Schwartz, and T.M. Jessell (Eds.), Principles of neuroscience (3rd ed., p. 292, fig. 20-10), New York: Elsevier Science Publishing Co., Inc.

ERRORS IN CELL MIGRATION

- *Agenesis of Corpus Callosum**

Corpus callosum



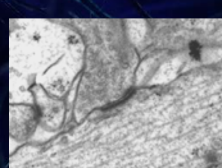
* One of the most common malformations in Zika exposure

Errors in Cell Migration (Con't)

- Schizophrenia (?)
- Prematurity may be example of interrupted cell migration

STAGE IV: DIFFERENTIATION

- Differentiation refers to
  - Outgrowth of axons and dendrites from the cell body
  - Formation of synapses and
  - Synthesis of neurotransmitters.
- Growth of axons towards their targets is controlled by signaling molecules that act to attract or repel growing axon
- Not all cells differentiate; there is massive programmed cell death (apoptosis), during which 40 - 60% of cells pass away.



Source: http://technology.open.ac.uk/emsuite/img23.html

DEVELOPMENT OF AXONS

- Growth cone plays key role in guiding axon to target – tend to use cues from extracellular matrix surrounding neuron (e.g., aminin, tenascin, collagen, fibronectin, slit), coupled with local gene expression
  - Within growth cones, *lamellipodia* and *filopodia* play a role in axon guidance. Former are fan-shaped structures, whereas latter are long, thin spikes that radiate forward
- There are also molecular cues that sit on surface of established axon and acts as guides (e.g., Cell Adhesion Molecules)

DEVELOPMENT OF DENDTRITES

- Dendtritic spouting begins around prenatal week 15 (about same time axons reach the cortical plate)
- Between prenatal weeks 25 and 27, dendtritic spines appear on both pyramidal and non-pyramidal neurons.
- **Both axons and dendrites continue to develop into second postnatal year; thus, is an initial overproduction of axons and dendrites followed by retraction**

DISORDERS OF AXON AND DENDRITE DEVELOPMENT

- Oxygen deprivation *(anoxia*), toxins, malnutrition associated with such disorders.
- Genetic disorders such as Angelman Syndrome, Fragile X, autism and muscular dystrophy all show possible errors in development of dendrites.

Stage V: Synaptogenesis (making connections)

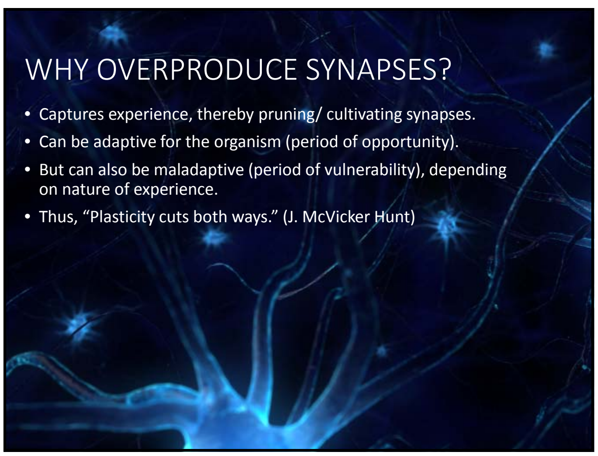
- As with axons and dendrites, is an initial overproduction of synapses, such that newborn brain has many more synapses than adult brain.
- First synapses observed about 23rd prenatal week, with rapid proliferation that follows and continues postnatally.
- This is followed by retraction to adult levels.
- In human, rate of retraction varies from brain area to brain area.

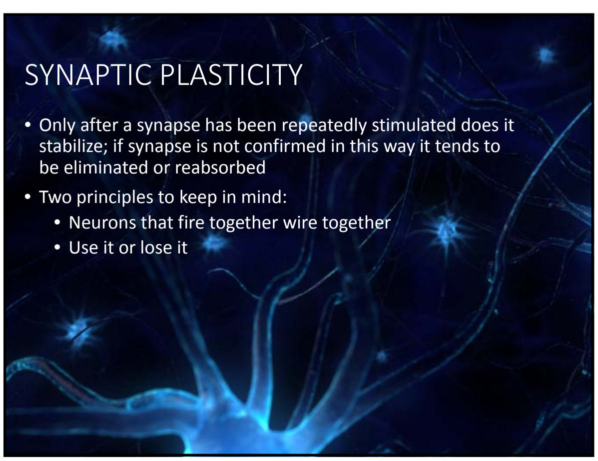
BUILDING A WIRING DIAGRAM

OVERPRODUCTION OF SYNAPSES

- In the visual cortex, a burst of synapses occurs at 3 – 4 postnatal months, with the peak occurring at 4 months.
- The primary auditory cortex (Heschl's gyrus) follows similar timetable.
- There are slightly fewer synapse at 3-4 months than in the primary auditory cortex in
  - The area involved in receptive language (angular gyrus)
  - The area involved in language production (Broca's area)
  - i.e., these areas lag slightly behind basic auditory areas.
- In middle frontal gyrus, the maximum density is not reached until 12 months.


RETRACTION OF SYNAPSES
• In visual and auditory cortices, adult levels of synapses are obtained in early childhood (2 - 6 years).
• In the middle frontal gyrus, adult levels are not reached until mid- to late adolescence.


WHY OVERPRODUCE SYNAPSES?
• Captures experience, thereby pruning/ cultivating synapses.
• Can be adaptive for the organism (period of opportunity).
• But can also be maladaptive (period of vulnerability), depending on nature of experience.
• Thus, “Plasticity cuts both ways.” (J. McVicker Hunt)


SYNAPTIC PLASTICITY
• Only after a synapse has been repeatedly stimulated does it stabilize; if synapse is not confirmed in this way it tends to be eliminated or reabsorbed
• Two principles to keep in mind:
• Neurons that fire together wire together
• Use it or lose it

ERRORS IN DIFFERENTIATION AND SYNAPTOGENESIS

- Likely linked to most causes of mental retardation
  - Angelman Syndrome
  - Fragile X
  - Down Syndrome (trisomy 21)
  - Tuberous Sclerosis Complex?
- Autism?
- Malnutrition?
- Toxin exposures (Especially in utero drug exposure)

STAGE VI: MYELINATION (IMPROVING EFFICIENCY)

- Myelin is lipid/protein substance
  - Oligodendroglia produce myelin in CNS
  - Schwann cells produce myelin in ANS
- Myelin wraps itself around axon as form of insulation.
- Myelin speeds conduction velocity
- Myelination has implications for both serial and parallel processing

MYELINATION (CON'T)

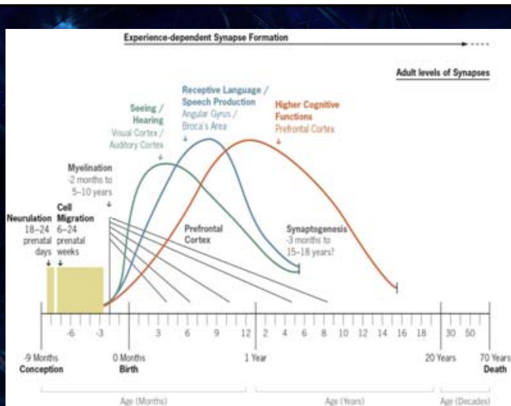
- Myelination occurs in "waves" beginning prenatally and ending in young adulthood (and in some regions, as "late" as middle age).
- Historically, researchers stained for myelin in postmortem tissue.
- We now use
  - Magnetic Resonance Imaging (MRI) (see next slides; see lecture 2) to distinguish white from gray matter
  - Diffusion Tensor Imaging (DTI) to identify fiber tracts)

MYELINATION DURING PRENATAL AND EARLY POSTNATAL PERIOD

- Prenatal:
  - Myelination of peripheral nervous system
  - Motor roots
  - Sensory roots
  - Somesthetic (touch) cortex
  - Primary visual (seeing)
  - Primary auditory (hearing) cortex
- First Postnatal Year:
  - Regions of brain stem, cerebellum and splenium of corpus callosum all begin
  - By 1 year myelination of all regions of the corpus callosum underway

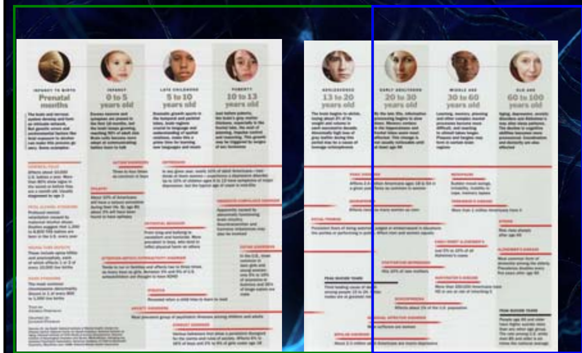
Errors of Myelination

- Genetics
  - Congenital hypomyelination syndromes
  - Inborn errors of metabolism
- Environment
  - Nutritional deficiencies (e.g., iron deficiency)
  - Hypoxic Ischemic Injury (i.e., anoxia)



Source: Thompson and Nelson (2001). Figure provided by Heckman (2013).

TIMING OF BRAIN DISORDERS



Time Magazine "YOUR BRAIN", 2009

II NEURAL PLASTICITY AND CRITICAL PERIODS IN HUMAN DEVELOPMENT: SETTING THE STAGE

OUTLINE

- What do we mean by "neural plasticity"?
- General mechanisms of neural plasticity
- Modeling the role of experience in development
- Sensitive vs. critical periods – what's the difference?
- Examples of sensitive periods in human development:
    - Sensory processes
        - Vision
        - Audition
    - Social-Emotional Processes
- Adult Plasticity
- Conclusions

THE TERM "PLASTICITY"....

...has generally been used 2 ways:

- ***RECOVERY OF FUNCTION,*** whereby some function is returned following injury.
  - A related concept is **SPARING** (or lack of loss in performance following brain damage)
  - Both are often categorized as ***FUNCTIONAL PLASTICITY***.
- ***NEURONAL PLASTICITY*** is hypothesized to underlie functional plasticity

MECHANISMS OF NEURONAL PLASTICITY

- Anatomical: e.g., ability of existing synapses to modify their activity by spouting new axons or by an expansion of dendritic surfaces (e.g., new dendritic spines).
- Neurochemical: e.g., ability of existing synapses to modify their activity by, for example, increasing neurotransmitter synthesis and release
- Metabolic: e.g., fluctuations in cortical and subcortical metabolic activity (e.g., glucose utilization; increases blood supply via new capillary growth)

SUMMARY

- So, *functional* plasticity reflects the malleability of behavior (e.g., to be protected following damage or to recover from damage), whereas *neural* plasticity reflects the mechanism the underpins functional plasticity.
  - Example: efficacy of cognitive behavior therapy for treatment of depression or anxiety based on changing thought patterns (functional plasticity); such changes must be mediated by changes in brain (e.g., neural networks)

THERE ARE 4 WAYS ENVIRONMENTAL INPUT AND GENETIC CONSTRAINTS INTERACT DURING DEVELOPMENT:

- 1) **Maturation** - behaviors that occur without any necessary experiential influence (e.g., reflexes)
  - (*experience-independent*)
- 2) **Maintenance** - a fully established behavior whose continued expression depends on adequate and appropriate experience
  - (e.g., human infants produce and comprehend wide range of phonemes in early babbling, but only exposure to restricted set of phonemes will maintain those phonemes in language)

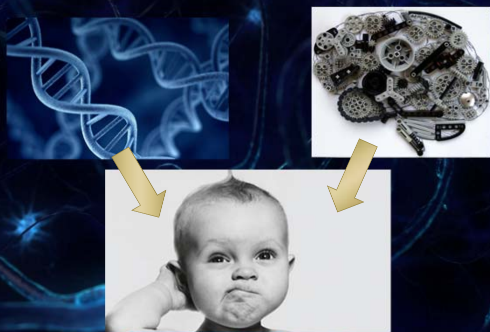
CON'T

- 3) **Facilitation** - behavior that can develop fully without appropriate environmental input, but which matures more rapidly with appropriate experience
  - (e.g., the onset of walking may appear sooner among infants receiving practice in walking….although the timing of practice is important).
- 4) **Induction** - behavioral components that will never fully emerge without appropriate experience
  - (e.g., children will not learn elements of native language lexicon without hearing native language spoken).

INDIVIDUALITY IS THE PRODUCT OF BOTH PERSONAL EXPERIENCE AND BIOLOGICAL INHERITANCE

- Genetics specifies the properties of neurons and neural connections to different degrees in different pathways and at different levels of processing.
- But, because many aspects of an individual's world are not predictable, the circuitry of the brain relies on experience to customize connections to serve the needs of the individual. Experience shapes these neural connections and interactions but always within the constraints imposed by genetics.

INDIVIDUALITY IS THE PRODUCT OF BOTH PERSONAL EXPERIENCE AND BIOLOGICAL INHERITANCE



EXPERIENCE IS THE PRODUCT OF AN ONGOING, RECIPROCAL INTERACTION BETWEEN THE ENVIRONMENT AND THE BRAIN

- Any given experience can vary enormously under identical environmental conditions, depending on the history, maturation, and state of the individual's brain
- The relative maturity of the brain has an enormous impact on experience. Different areas of the nervous system mature at different rates, and lower level processing areas mature earlier than those at a higher level. A less mature brain is affected largely by more fundamental features of the environment, such as patterned light or the speech train.
- As the brain matures and changes with experience, more detailed aspects of the environment influence it. Thus, as an individual's brain changes, particularly during the early developmental periods, the same physical environment can result in very different experiences.

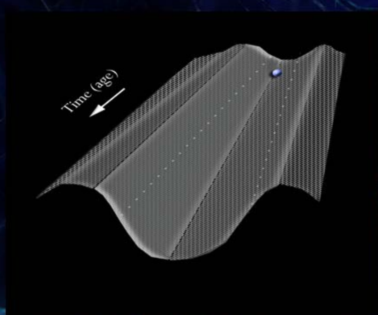
SENSITIVE VS. CRITICAL PERIOD?

- "Sensitive" periods are defined as a time in development during which the brain is particularly responsive to experiences in the form of patterns of activity
- This time point may be termed a "critical" period if the presence or absence of an experience results in *irreversible* change

INDIVIDUAL DIFFERENCES

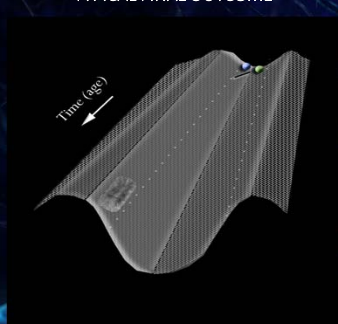
- Trajectories of development can be impacted by “pushes” and “pulls” that occur at different times of development
- In theory, genes interact with these pushes and pulls to influence individual trajectories – see next slides

TYPICAL TRAJECTORY – A FEW “SPEED BUMPS” BUT BASICALLY DEVELOPMENT STAYS ON COURSE



Courtesy of William Greenough, modified by Eric Knudsen, “borrowed” by Charles A. Nelson III

EFFECTS OF EARLY (BLUE BALL) VS. LATE (GREEN BALL) “NEGATIVE” EXPERIENCE ON BRAIN DEVELOPMENT, BOTH LEADING TO NON-TYPICAL FINAL OUTCOME



Courtesy of William Greenough, modified by Eric Knudsen, “borrowed” by Charles A. Nelson III

HOW DOES EXPERIENCE INFLUENCE THE DEVELOPING BRAIN? (BORROWING FROM BILL GREENOUGH)

- **Experience-Independent**
  - **Pretty much like it sounds; experience isn’t necessary.**
  - **This is often what psychologists often mean when they refer to something as “innate” (even this sentiment is often misguided)**
- **Experience-expectant**
  - Development based on the expectation that appropriate environments will provide information needed to select appropriate subsets of synaptic connections. Common to all members of the species
- **Experience-dependent**
  - Unique to each individual - most likely involves active formation of new synaptic connections throughout the life span based on each person’s interaction with his/her environment.

EXPERIENCE-INDEPENDENT

LORENZ’S DUCKLINGS(EXPERIENCE INDEPENDENT?)

DEVELOPMENTAL PLASTICITY: THE REMAINDER OF THIS LECTURE

- Sensory/Perceptual Development
  - Vision
  - Hearing
- Language Development
- Cognitive Development
- Emotional development

DEVELOPMENTAL PLASTICITY

- Visual Development
  - ***Stereoscopic depth perception*** (binocular vision) is dependent on activity-dependent elaboration of ocular dominance columns (driven by visual experience); columns themselves experience-independent but their elaboration and function highly experience-dependent.
    - If proper eye alignment does not occur by end of sensitive period, binocular vision will be permanently compromised.

VISUAL DEVELOPMENT

- ***Visual Acuity***: Under normal conditions, visual acuity develops rapidly across the first years of life; e.g., newborn vision 40x worse than adults; 6 months only 8x worse; by 4-6 years is adult-like
  - In Snellen notation, newborn vision about 20/400 (compared to 20/20 for "normal" adult vision)

  - A great deal of work has now been done following children born with cataracts and then have their vision surgically restored

SENSORY DEVELOPMENT - VISION

- Lewis, T. L., & Maurer, D. (2009) report….
  - At least for low-level vision, aspects of vision that develop the earliest are the least likely to be adversely affected by abnormal visual input whereas those that develop later are affected more severely.
  - Early visual input is necessary to preserve the neural infrastructure for later visual learning, even for visual capabilities that will not appear until later in development.
  - The later cataracts are removed, the greater the consequences for visual development
  - There are multiple sensitive periods during which experience can influence different aspects of visual development (shall return to this point later).

SENSORY DEVELOPMENT - AUDITION

- Studies by deCasper and Fifer 30+ years ago established that infants' ability to recognize mother's voice due to exposure to that voice last weeks of pregnancy; thus, full term infants at birth
  - Recognize and prefer mother's voice vs. stranger's voice
  - Distinguish between mother reading familiar nursery rhyme (one heard prenatally) and unfamiliar
  - Do not recognize father's voice ☹

HEARING, CON'T - CASE STUDY

Nicholas, J. G., & Geers, A. E. (2007). ***Journal of Speech, Language, and Hearing Research***

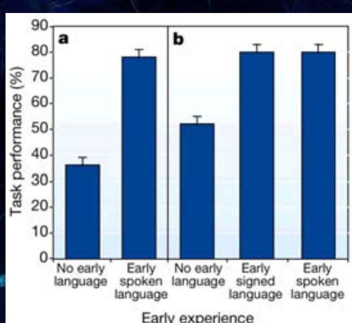
- Focused on language development among deaf children receiving cochlear implant
- Studied 3.5 and 4.5 year old children who had received implant by 3rd birthday
- Language scores increased with younger age at implant, even when controlling for duration of implant use.
- Children who received the implant at the youngest ages obtained language scores comparable to those of hearing age-mates by 4.5 years, but those children implanted after 24 months of age did not catch up with hearing peers.
- **Conclusion**: Children who received a cochlear implant before a substantial delay in spoken language developed (i.e., between 12 and 16 months) were more likely to achieve age-appropriate spoken language.

COMPENSATION: DO DEAF INDIVIDUALS SEE BETTER?

In some domains, yes:

- **Visual orienting and reorienting** (Paranis and Samar, 1985; Bosworth and Dobkins, 2002)
- **Visual motion processing** (Neville and Lawson, 1987; Bavalier and Neville, 2002)
- **Visual stimulus onset direction** (Loke and Song, 1991)

HEARING, CON'T



Mayberry, R. I., Lock, E., & Kazmi, H. (2002). *Nature*

Language abilities of adults who learned English and/or American Sign Language (ASL) at different ages

Study 1 (a) Groups:

) Born deaf, no experience with language until learning ASL at school (age 9-15)

2) Born hearing, English from infancy, learned ASL after becoming deaf at age 9-15

Study 2 (b) Groups:

1) Born deaf, no experience with ASL until school (age 4-13)

2) Born deaf, ASL in infancy

3) Born hearing, non-English language in infancy, learned English at school age

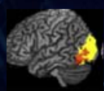
Conclusion: Language development compromised without early language exposure; Timing of early language influences later language learning capacity

HEARING, CON'T

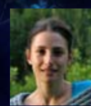
Some evidence suggests that even relatively brief auditory disruption during early language development may influence later language abilities

- Children who experienced multiple episodes of otitis media (ear infections) during their first years, resulting in periods of hearing loss, have shown subtle speech perception deficits into late childhood (e.g., Mody, Schwartz, Gravel, & Ruben, 1999)
- May be at risk for long-lasting central auditory impairments (Whitton & Polley, 2011)
- However effects are subtle and may depend on factors such as SES (e.g., Paradise et al., 1988), or the aspect of language that is measured (e.g., phonemic judgments vs expressive language)

A SENSITIVE PERIOD FOR LANGUAGE IN THE VISUAL CORTEX: DISTINCT PATTERNS OF PLASTICITY IN CONGENITALLY VERSUS LATE BLIND ADULTS



People blind from birth "hear" language in their visual cortex

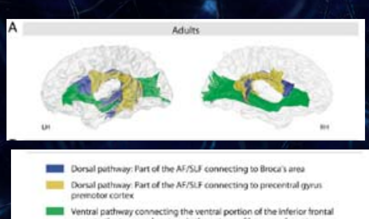


Marina Bedny

SPEECH AND LANGUAGE

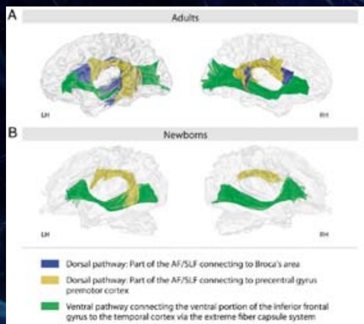
- We don't recognize speech and we don't acquire language without hearing speech or language
- But as with vision, the brain likely comes pre-wired with the ability to benefit from experience
- With experience comes specialization

ADULT BRAIN: DTI RENDITION OF CONNECTIVITY



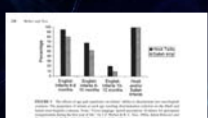
Perani et al., *PNAS*, 2011

NEONATE BRAIN: FOUNDATION IN PLACE



Perani et al., *PNAS*, 2011

MAJOR POINT: THE TIMING AND NATURE OF EXPERIENCE WITH LANGUAGE AFFECTS PERCEPTION OF DIFFERENT LANGUAGES



Effects of experience on perception of language (Werker & Tees, 2005)

Before 9-10 months of age, infants can discriminate the sounds of all languages. By the end of the first year of life, they are only able to discriminate the language(s) they hear in their environment

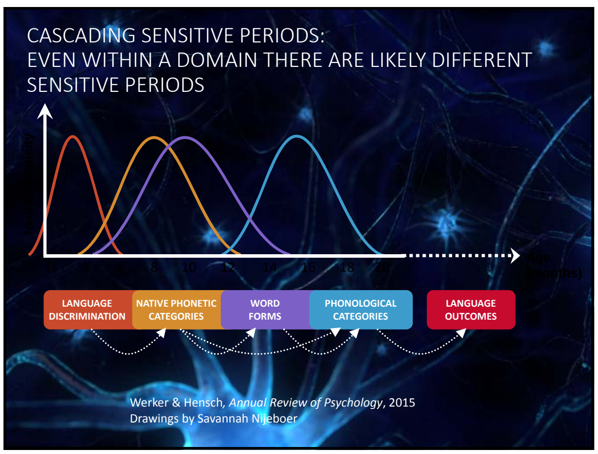
Janet Werker

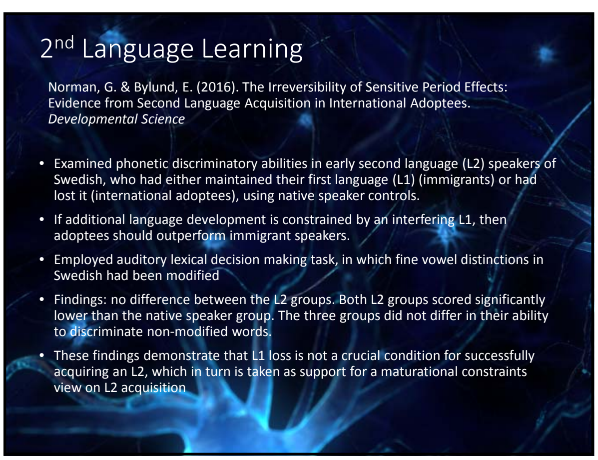
INFLUENCE OF EXPERIENCE: SPEECH AND LANGUAGE DEVELOPMENT

- …but, if you give 9 month olds ~5 hours of exposure to non-native language (by live "tutor"), can recapture ability; if exposure occurs via audio or video tape, no effects *

*Kuhl, Tsao & Liu (2003) PNAS, 100, 9096-9101


SO, WE HAVE ORGANIZATION AND REORGANIZATION
Japanese Spanish **English** German Tagalog Swahili Czech Cherokee Mandarin Monkey Calls
Japanese Spanish **English** German Tagalog Swahili Czech Cherokee Mandarin
Japanese Spanish **English** German Tagalog Swahili Czech Cherokee Mandarin
Dalia – newborn
Dalia – 5 months
Dalia – 1 year


CASCADING SENSITIVE PERIODS:
EVEN WITHIN A DOMAIN THERE ARE LIKELY DIFFERENT SENSITIVE PERIODS
LANGUAGE DISCRIMINATION
NATIVE PHONETIC CATEGORIES
WORD FORMS
PHONOLOGICAL CATEGORIES
LANGUAGE OUTCOMES
Werker & Hensch, *Annual Review of Psychology*, 2015
Drawings by Savannah Nijeboer


2nd Language Learning
Norman, G. & Bylund, E. (2016). The Irreversibility of Sensitive Period Effects: Evidence from Second Language Acquisition in International Adoptees. *Developmental Science*
• Examined phonetic discriminatory abilities in early second language (L2) speakers of Swedish, who had either maintained their first language (L1) (immigrants) or had lost it (international adoptees), using native speaker controls.
• If additional language development is constrained by an interfering L1, then adoptees should outperform immigrant speakers.
• Employed auditory lexical decision making task, in which fine vowel distinctions in Swedish had been modified
• Findings: no difference between the L2 groups. Both L2 groups scored significantly lower than the native speaker group. The three groups did not differ in their ability to discriminate non-modified words.
• These findings demonstrate that L1 loss is not a crucial condition for successfully acquiring an L2, which in turn is taken as support for a maturational constraints view on L2 acquisition

SUMMARY

- Organization is in place by birth for learning language
- The perceptual systems provide the first entry
- Babies open to different aspects of language at different points in development
- Critical or Sensitive periods for both heard and seen speech
- But targeted experiences and exposures can change timing
- Changes in timing may have implications for language acquisition, language use, and later literacy

EMOTIONAL DEVELOPMENT

MODERN VERSION OF HARLOW'S STUDIES

- Judy Cameron separated infants from mothers by leaving infant in pen with other monkeys but removing mother
- Mother removed at 1 week or 4 weeks of age, or 3 or 6 months of age.
- Studies behavior and brain of separated animals
- Also conducted intervention study ("super mom")

FINDINGS

- Animals separated at 3 or 6 months normal (this would be the normal age at which separation would occur in the wild)
- But, big difference in 1 week vs. 4 week separated animals:
  - 1 week: animals have no interest in other monkeys and if approached by other monkeys animals appear autistic (generally have a variety of autistic traits)
  - 1 month separated animals have intense need to be physically attached to other animals and are anxious if are unable to be with other monkeys

“SUPERMOM” STUDY

- Cross fostered the 1 week or 1 month separated animals with so-called “supermoms” (female monkeys with history of being good mothers).
- Bottom line: if fostered early enough, most animals showed complete recovery; if fostered late, did not

CONCLUSIONS

- Is differential sensitive period for negative sequelae of early maternal separation
  - If separated at age at which separation would normally occur in the wild (3-6 months), no ill effects
  - If separated at 1 week or 1 month, bad outcome, but different outcome
    - 1 week: many autistic traits
    - 1 month: many elements of anxiety

THE HUMAN ANALOGUE TO HARLOW'S STUDIES

SUMMARY

- Many elements of sensory and perceptual development are constrained by sensitive periods….and these sensitive periods even vary within a domain
- Less is known about sensitive periods in cognitive or social emotional development
- My bias is that temporal constraints on human development are mostly of the sensitive periods persuasion vs. critical period…mostly based on recent evidence of some recovery later in life, long after a sensitive period has closed

PAUSE

- adult plasticity?

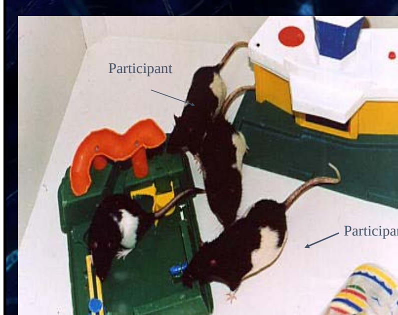
ADULT PLASTICITY

- Is great interest in adult plasticity (for obvious reasons)
- Unclear if the neurobiological mechanisms that underlie adult plasticity are same as or different from developmental plasticity…as will hear from Takao later in this workshop, at a molecular level they may be the same.
- but conceptually, would appear to be a difference in building a circuit from scratch vs. reorganizing an existing circuit

LEARNING AND MEMORY

- When I was an undergraduate at McGill we heard stories about Donald Hebb bringing his rats home, only to discover that when tested in the lab they were "smarter" than cage-reared rats
- Of course, Marian Diamond and colleagues followed this up in the 1960s and later; Bill (William) Greenough then unpacked this with his usual precision and methodological rigor, leading to the following observation:
  - rats raised in complex laboratory environments cognitively superior to isolated rats in complex, appetitively motivated learning tasks; for example, they make fewer errors.

COMPLEX ENVIRONMENT (COURTESY OF WILLIAM GREENOUGH)



BRAIN CHANGES INDUCED BY EXPERIENCE

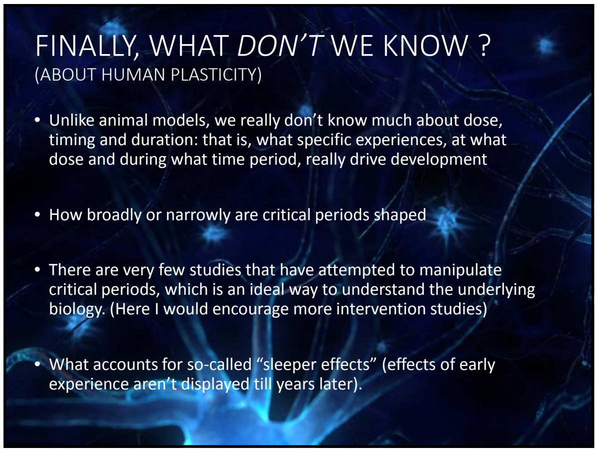
- In brief, are many data, mostly with rats, that changes occur at cellular level with experience-dependent stimulation.
  - a) rats in complex ("enriched?") environments have several regions of dorsal neocortex (e.g., occipital) that are heavier and thicker and have more synapses per neuron;
  - b) synaptic connections improve; dendritic spines and branching patterns increase in number and length; amount of glia increases;
  - c) find increased capillary branching. (acrobatic rats of Greenough) **note that these effects will also occur in the mature brain, not just juvenile.**

MOTOR, SOMATOSENSORY, AND PERCEPTUAL SYSTEMS

- Effects of amputations on human:
  - Areas in the brain representing amputated limb show reorganization by neighboring area (e.g. forearm & face)
  -
- Effects of skilled motor learning:
  - stringed instrument players (e.g., violinists) show reorganization of somatosensory cortex after years of practice (e.g., area of right hemisphere representing fingers of left hand larger in musicians than non-musicians).
- Congenitally blind, Braille-reading adults show activation of visual cortex when reading Braille.

GENERAL CONCLUSIONS ABOUT PLASTICITY

- Many neural systems formed early, during sensitive period; beyond this window of time, difficult or impossible to alter structure of brain
  - Example: visual, auditory development; language development? Some aspects of emotional development (attachment)?
- *However*, higher-level systems may retain some plasticity, which may provide work-around (compensation) to structural damage (e.g., recovery from stroke)
- Finally, some systems (e.g., learning and memory) retain plasticity throughout the lifespan


FINALLY, WHAT *DON'T* WE KNOW ?
(ABOUT HUMAN PLASTICITY)
• Unlike animal models, we really don't know much about dose, timing and duration: that is, what specific experiences, at what dose and during what time period, really drive development
• How broadly or narrowly are critical periods shaped
• There are very few studies that have attempted to manipulate critical periods, which is an ideal way to understand the underlying biology. (Here I would encourage more intervention studies)
• What accounts for so-called "sleeper effects" (effects of early experience aren't displayed till years later).


THE END