Typical and Atypical Memory Development

H-126

23 October 2017

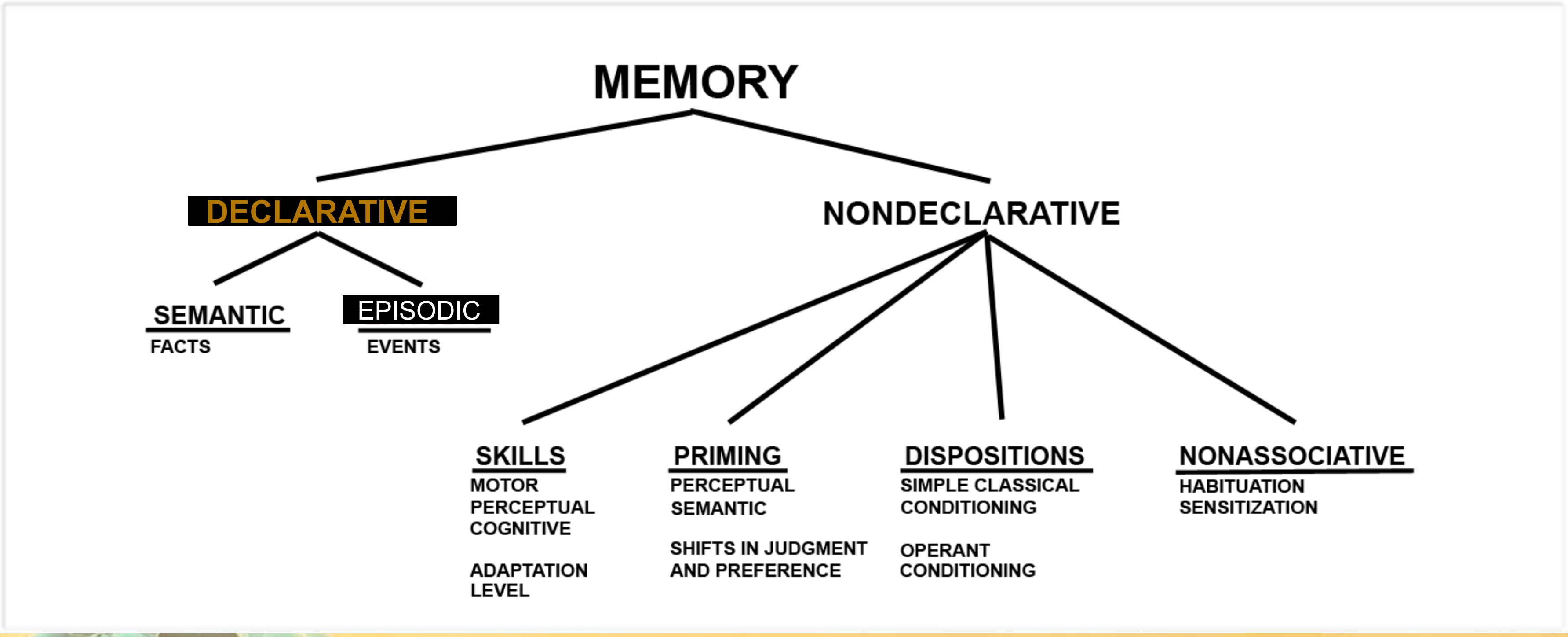
Outline

- What is known about memory in adults
  - Two memory systems
    - Declarative
    - Non-declarative (procedural)
- Differential postnatal maturation of the brain regions subserving declarative memory
- Emergence of specific declarative memory functions
- How to link the emergence of memory and brain development?
- Atypical memory
  - Hypoxic-ischemic injury
  - Infants born to diabetic mothers
  - (Effects of stress on memory – if time permits)

Outline of lecture

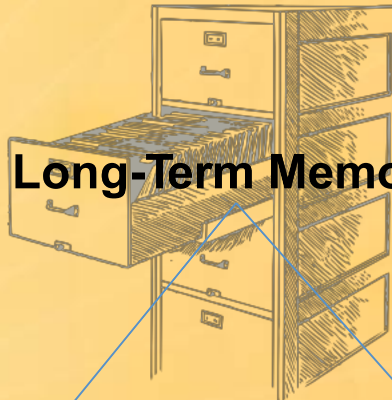
- What is known about memory in adults
- Differential postnatal maturation of the brain regions subserving declarative memory
- Differential emergence of specific declarative memory functions
- How to link the emergence of memory and brain development?
- Application to atypical populations

Part I: What is known about memory in the adult



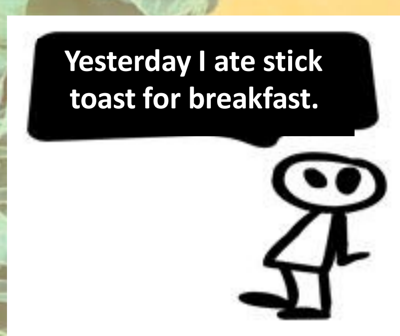
Adapted from Squire, 1992

Memory Systems



Long-Term Memory

Declarative (Explicit)



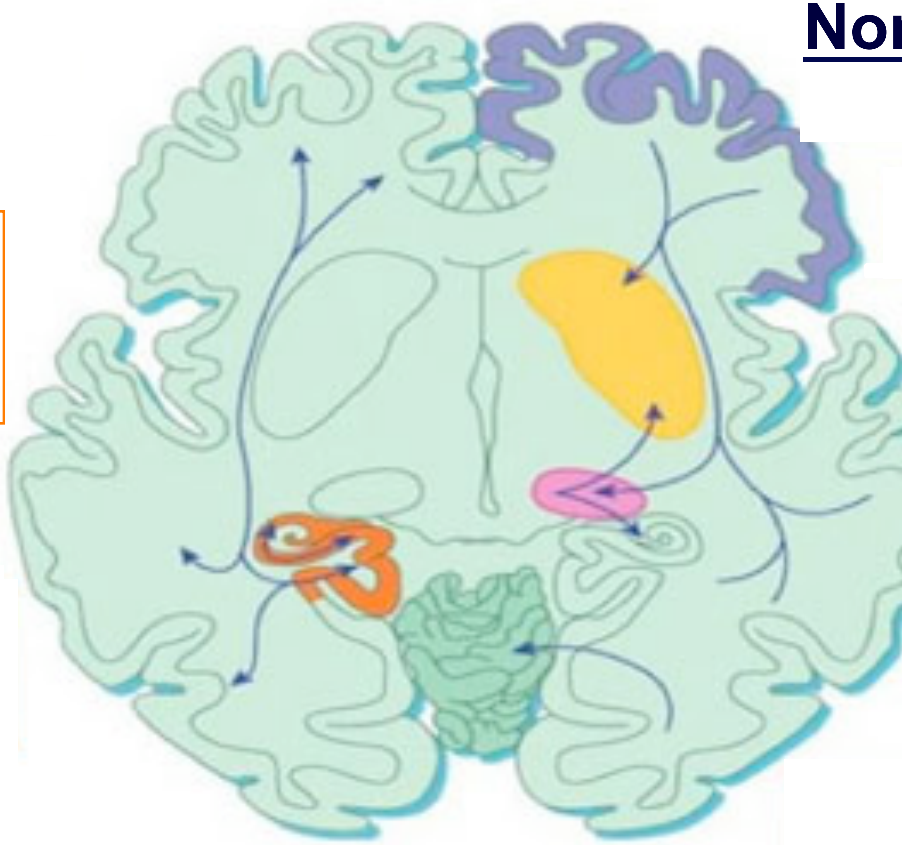
Nondeclarative (Implicit)

What is known about memory in the adult

Declarative

Episodic memory
Semantic memory

Medial Temporal Lobe
Diencephalon

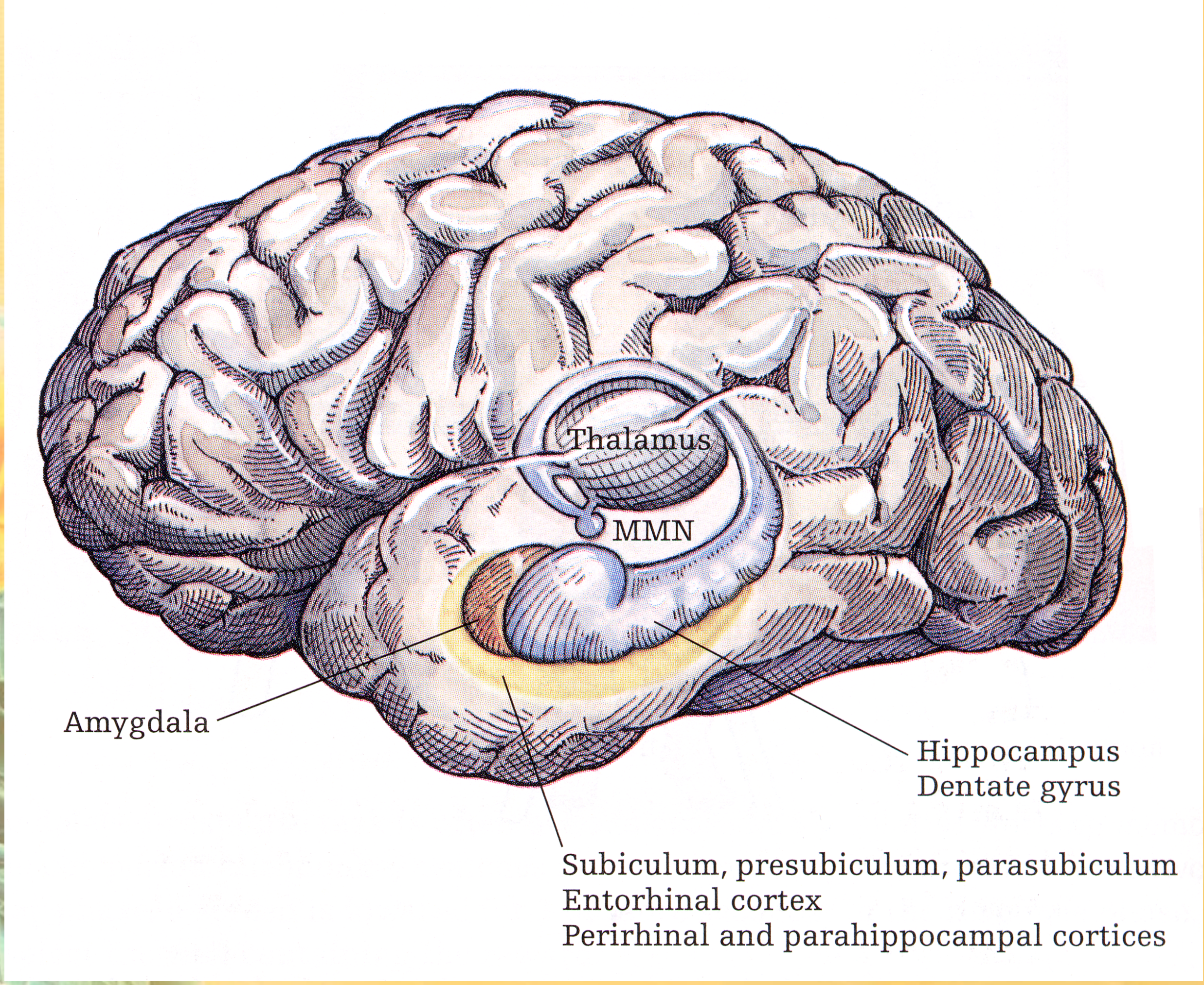


Non Declarative

Priming Cerebral Cortex
Skills Basal Ganglia Cerebellum
Classical conditioning Cerebellum
Non associative learning Reflex pathways

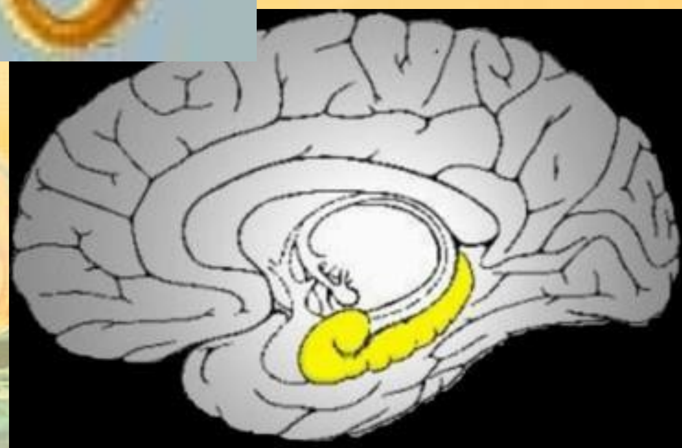
Adapted from Huynh, 2008

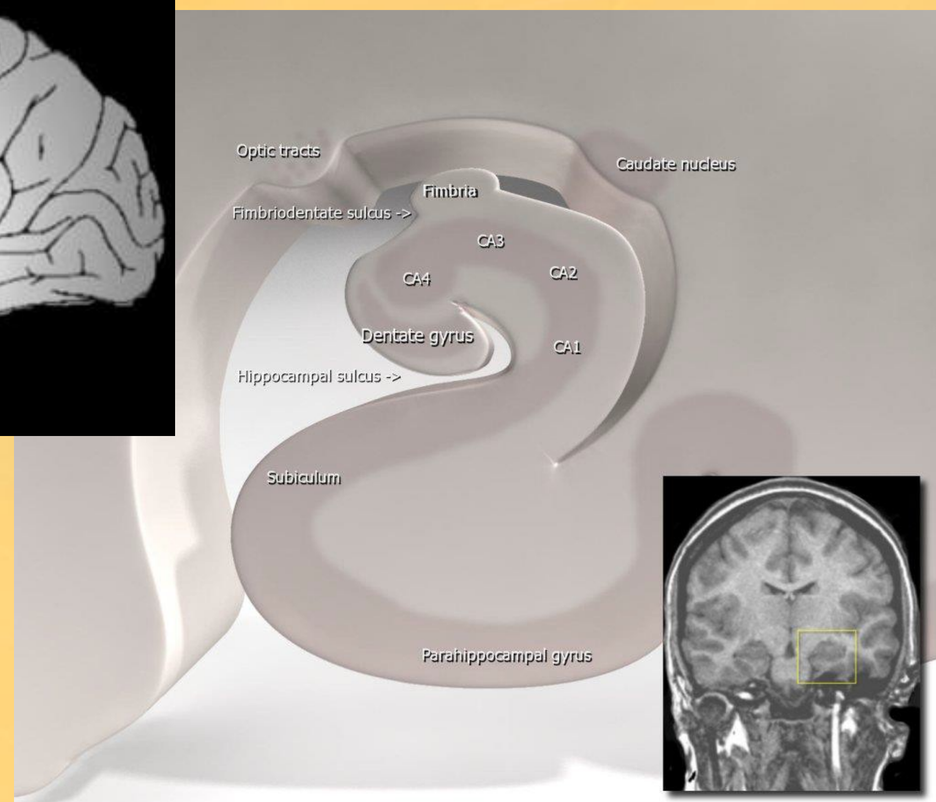
Neural structures involved in declarative memory



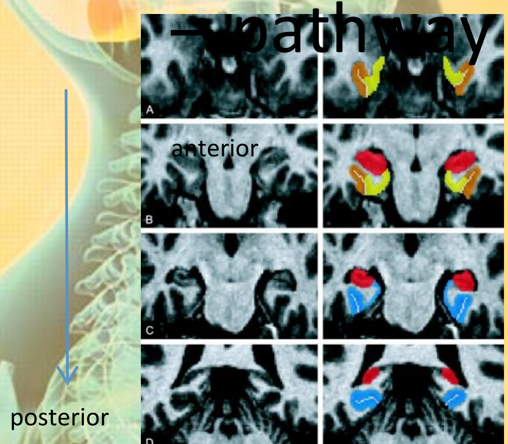
Bloom, Nelson & Lazerson, 2001

Hippocampus

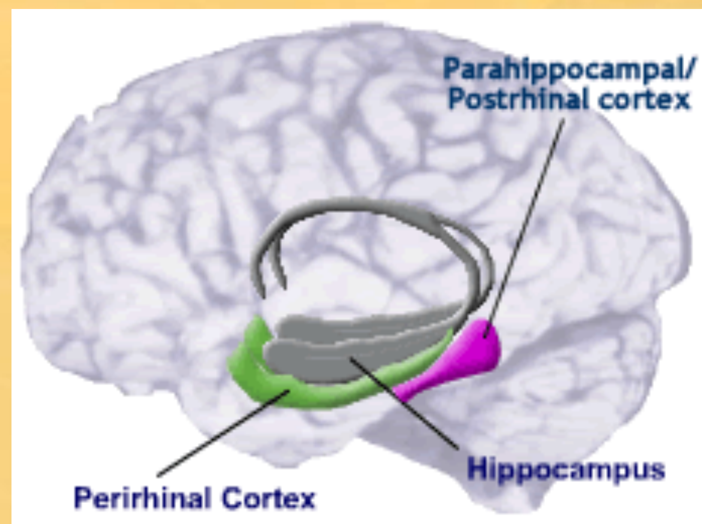




- <u>Parahippocampal</u> and <u>perirhinal</u> cortex
  - combine inputs across senses
  - send this highly integrated polysensory information to the <u>hippocampus</u>
- <u>Entorhinal</u> cortex
  - interface between the hippocampus and cortex
- <u>Subiculum</u>
  - pathway for output



Entorhinal
Perirhinal
Hippocampus
Parahippocampal



Anterior v. Posterior Hippocampus

- Anterior more involved in
  - responding to novelty
  - flexible memory encoding and retrieval

- Posterior more involved in
  - responding to repeated events
  - rigid, perceptually fixed memory encoding and retrieval

Part II: Ontogeny of memory

Limitations in infants that present challenges

- No language before 2 years of age
- Short attention span
- No motor response

Behavioral tasks used to study infant memory during the years of life

- Conjugate reinforcement: The mobile task
- Visual Paired Comparison task
- Deferred imitation task

The mobile task

Infants are in a crib, with a mobile suspended above them.

Measure of kicking without reinforcement.

A ribbon connects the mobile to the infant's leg. Increase of leg kicking in relation to the baseline.

After a retention interval a test phase is done immediately or after some delay.

Infants are simply presented with the non-moving mobile

Nonreinforcement - retrieval

If they remember they will kick more than the baseline

The mobile task

https://www.youtube.com/watch?v=kGo-oy-ojQ0

Specificity in the mobile task

- Long term memory (days, weeks), starting as early as 3 months of age
- But, memory fails if:
  - Crib liner color changes
  - Ambient odor changes
  - Ambient noise changes
  - Change in >1 mobile object
- Hence, memory is very specific to the original cue and context (i.e., memory is fragile)

Rubin et al., 1998; Butler & Rovee-Collier, 1989; Rovee-Collier et al., 1985; Fagen et al., 1997

What does the task measure ?

- Procedural learning?
- May not display representational flexibility because memory results from reactivation of previous motor pathways
- Seems unlikely to be a type of memory dependent on the medial temporal lobe

Visual Paired Comparison

- The key measure is the length of time spent fixating each of the two stimuli.

- Longer duration of looking to the novel stimulus indicates recognition memory.
- Caution: *lack* of visual preference difficult to interpret (null case)

- Visual Paired Comparison (VPC) Task: Present pair of identical images for x period of time (enough to become familiar) and then present familiar and novel images side by side; longer looking to novel permits inference about discrimination and memory

Familiarization (25s)

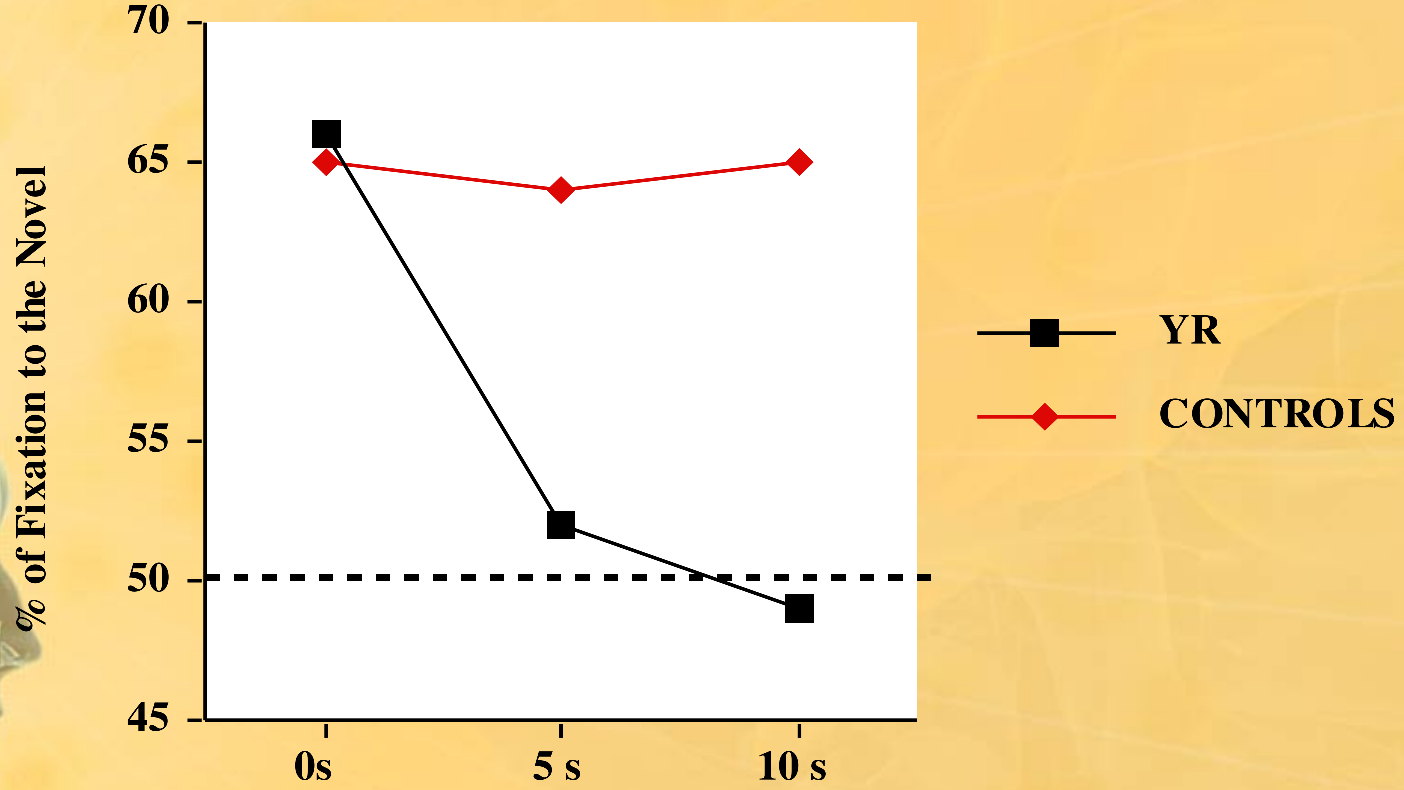
Test Pair with Familiar face on right side (10s)

Test Pair with Familiar face on left side (10s)

Recognition memory assessed by VPC in human

- Novelty preference in Adults (Pascalis and Bachevalier, 1998)
- Novelty preference at 3 days of age after a 2-min retention interval (Pascalis & de Schonen, 1994)
- Novelty preference at 3 months of age after a 24-hr retention interval (Pascalis et al. , 1998)
- Novelty preference at 6 months of age after 15 days (Fagan, 1974)

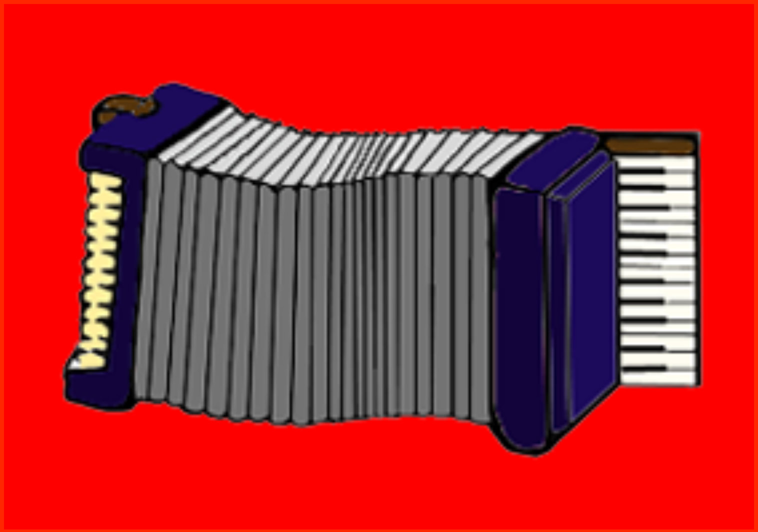
Recognition after a delay in an Amnesic patient (hippocampal damage)

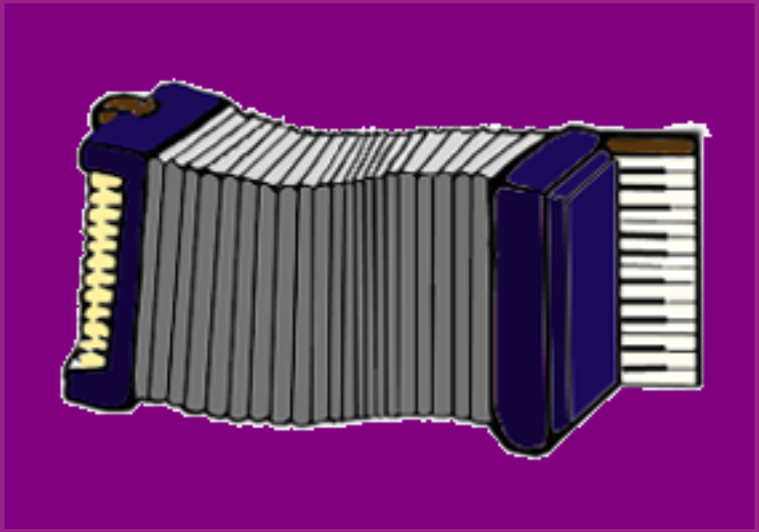


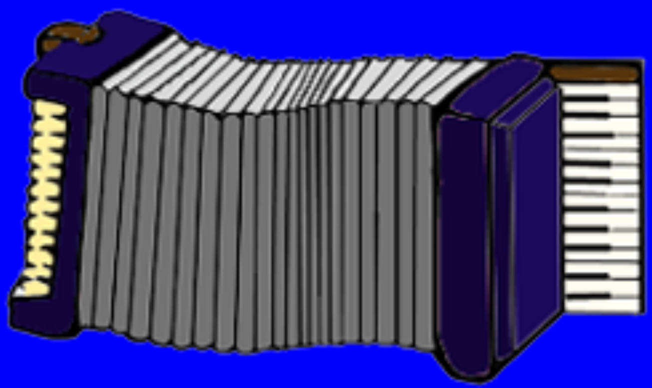
(Pascalis et al, 2004)

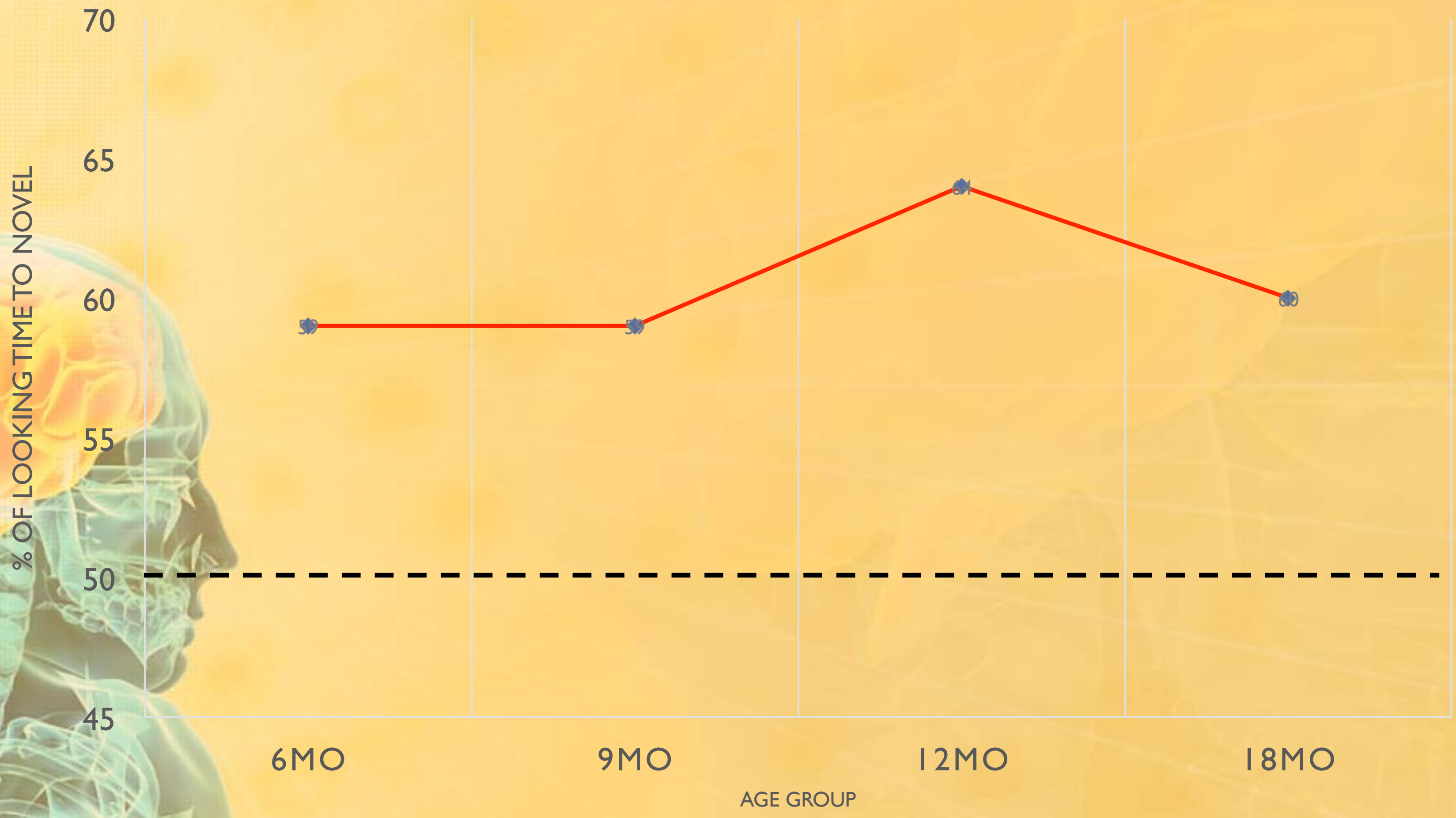
Big shift in performance seen later in first year, when memory becomes more flexible

- See next slides







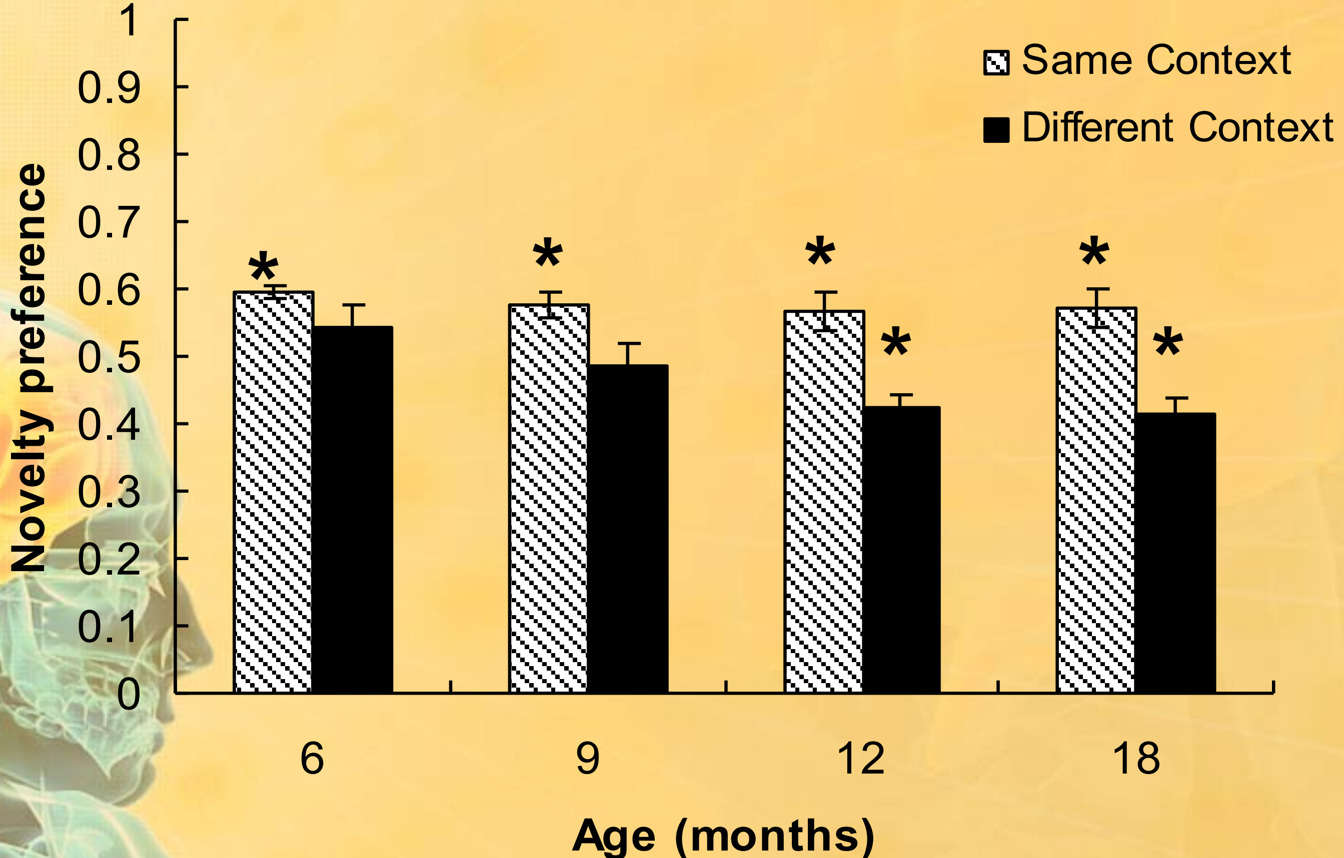


70
65
60
55
50
45
% OF LOOKING TIME TO NOVEL
6MO
9MO
12MO
18MO
AGE GROUP

What about wider context?

- The context can be close: background
- The context can be further away: the room
- The context can be multimodal (e.g., recognize an object visually that previously experienced only haptically)

Changing room



Only 12- and 18-month-old infants show evidence of recognition memory in the Different Context condition

Summary

- The visual recognition memory as measured with the VPC task is dependent on the integrity of the hippocampal formation.
- Long term recognition has been found with this task during the first year of life.
- It is independent from the context from 18 months of age

Imitation tasks

- Imitation over a delay relies on memory for a specific past experience, involving novel stimuli and actions
- Deferred imitation tasks are failed by patients with temporal lobe or developmental amnesia (amnesia filter) (McDonough et al., 1995;)

Between 12 and 18 months, infants learn one to two novel behaviours a day through imitation (Barr & Hayne 2003)

Deferred Imitation

- An experimenter demonstrates a series of novel actions and the infant’s ability to reproduce those actions is assessed either immediately or after a delay.
- The performance of infants in these experimental conditions is compared to the performance of infants who have not seen the target actions prior to the test.


A
Picture 1
Picture 2
Picture 3
Picture 4
Picture 5
Picture 6
B
Picture 1
Picture 2
Picture 3
Picture 4
Picture 5
Picture 6

Deferred Imitation – the puppet task

Specificity in the puppet task

- 6 months 24 hr (Barr et al.,1996)
- 9 months 24 hr (Meltzoff,1988)
- 12 months 7 days (Hayne & Campbell, 1997)

Changes in the object 24 hr after the training disrupted the performance of 6- and 12-month-olds but had no effect on the performance of 18-month-olds. Changes in the context (the room) disrupted the performance of 6-month-olds but had no effect on the performance of 18-month-olds.

Conclusion on imitation task

- It is present as early as 6 months of age.

- It is independent from the context from 18 months of age
- As infants move into 2nd year, memory span increases from days to months

Outline of lecture

- What is known about memory in adults
- Differential postnatal maturation of the brain regions subserving declarative memory
- Differential emergence of specific declarative memory functions
- How to link the emergence of memory and brain development?
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Differential maturation of distinct declarative memory functions

Relational memory

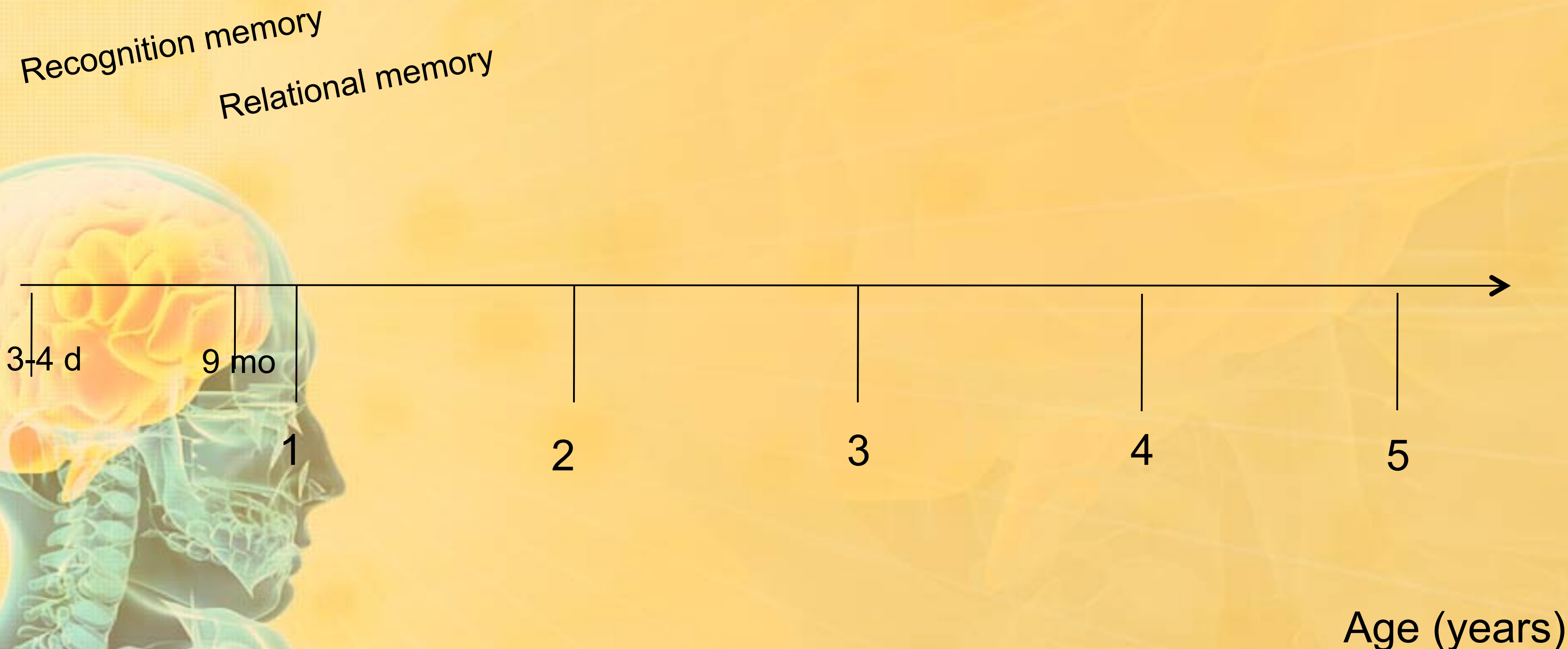
- Relational memory: Memory for relations among the constituent elements of experience, providing the ability to remember a name with a face, the location of objects, or the order in which different events occurred (Konkel & Cohen, 2009).

- Can be contrasted to item memory: the memory of the individual elements themselves

- Relational memory has been shown to emerge between 6- and 12 months of age as assessed by a deferred imitation task.

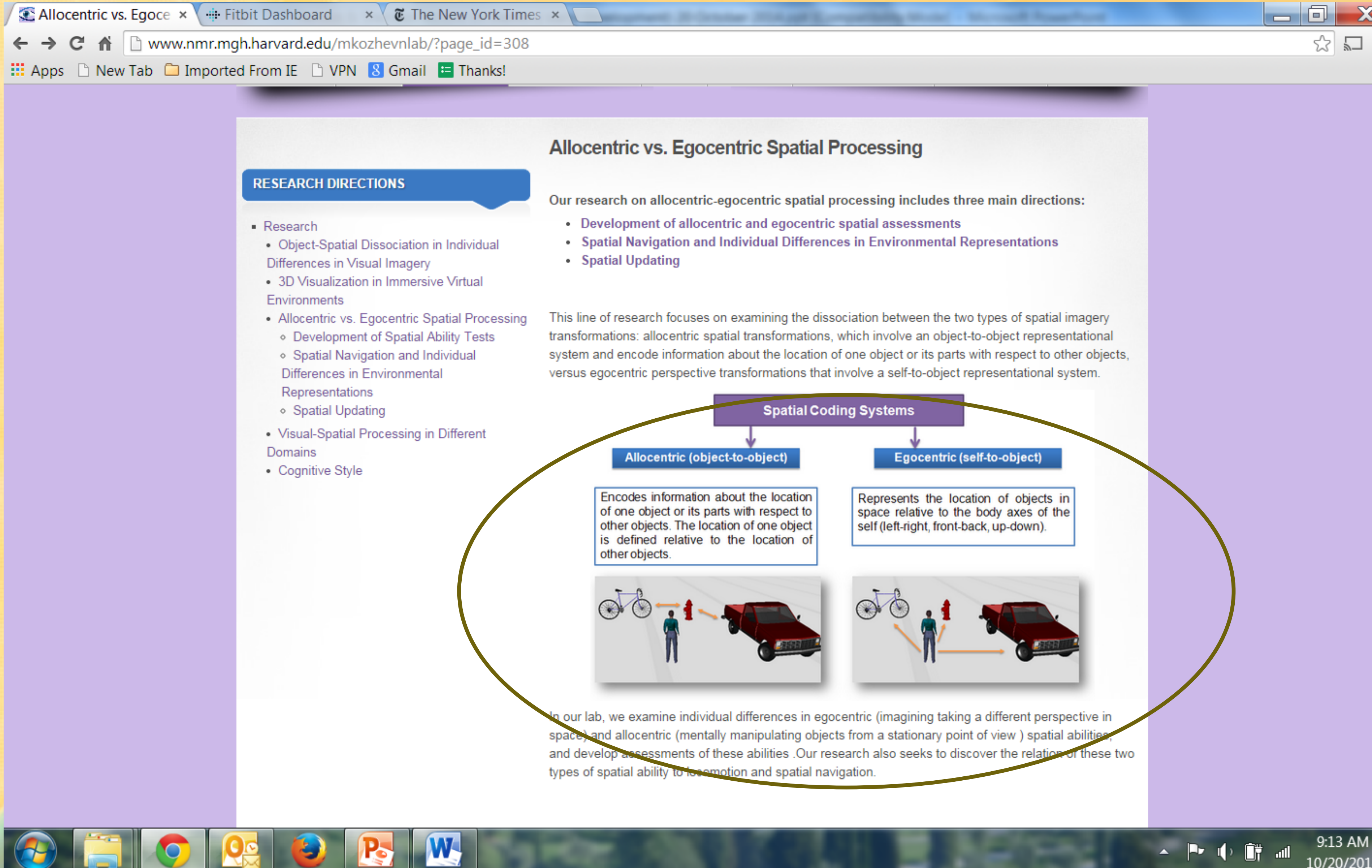
- Impacted by hippocampal lesions in adults (Hannula et al., 2007)

Differential maturation of distinct declarative memory functions



From Richmond and Nelson, 2009

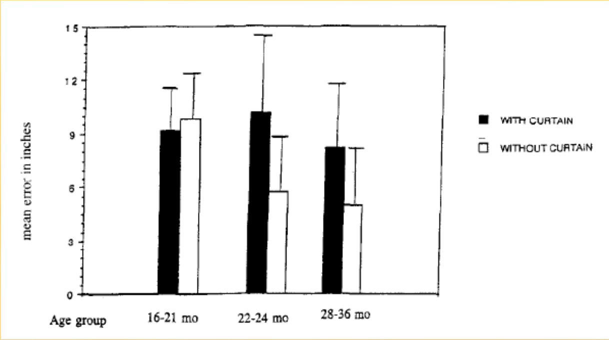
Allocentric vs. Egocentric spatial memory



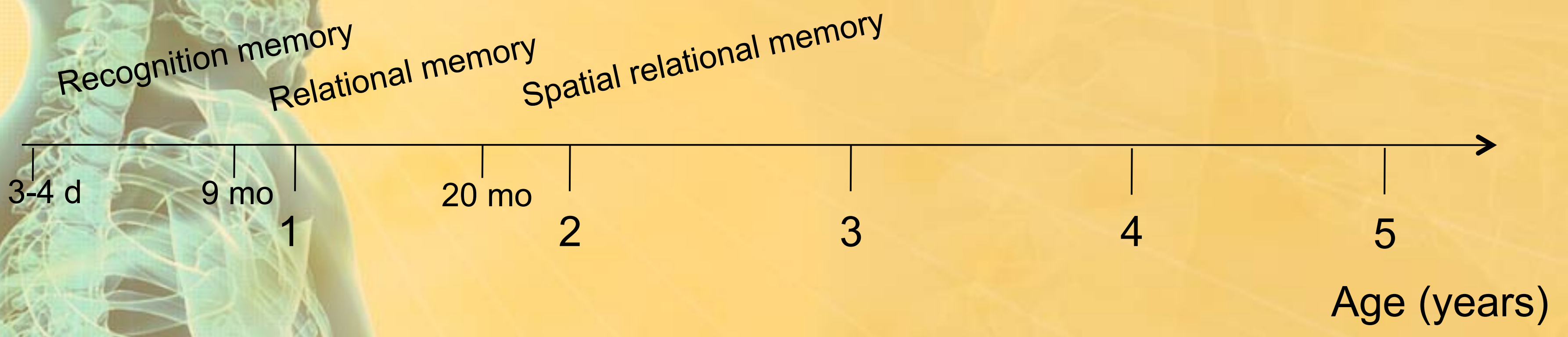
Differential maturation of distinct declarative memory functions

Spatial relational memory

→ allocentric spatial memory has been shown to be sensitive to hippocampal lesion in adult individuals (Banta Lavenex, Amaral, & Lavenex, 2006; Morris et al., 1982; O'Keefe & Nadel, 1978)



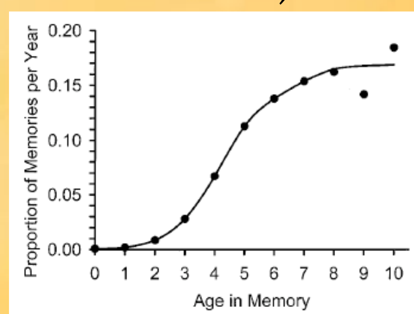
Newcombe et al., 1998



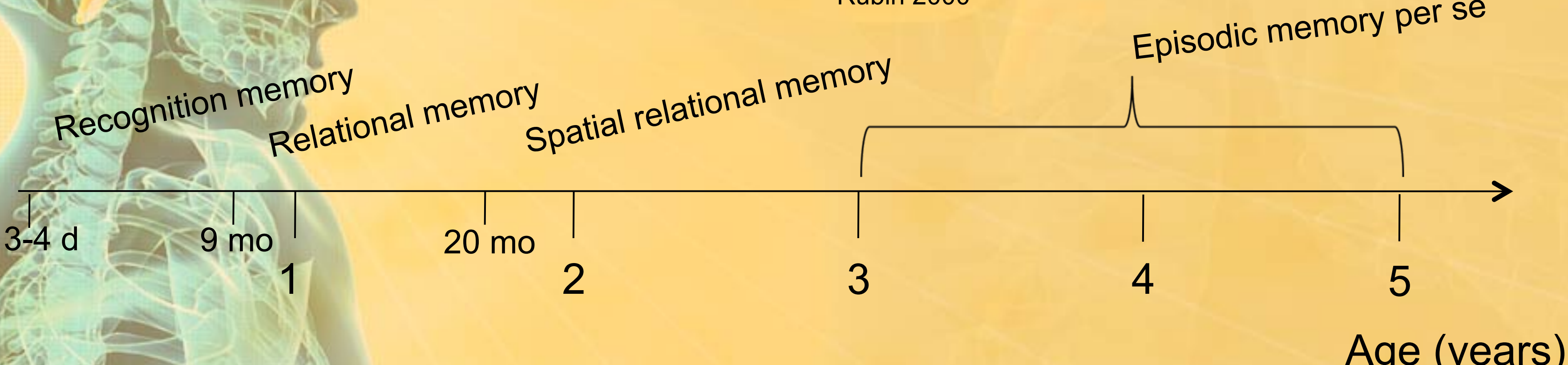
Differential maturation of distinct declarative memory functions

Episodic memory per se

➔ Dependent on the integrity of the hippocampal formation (Bright et al., 2006; Rempel-Clower et al., 1996; Squire and Zola, 1996; Zola-Morgan et al., 1986).



Rubin 2000



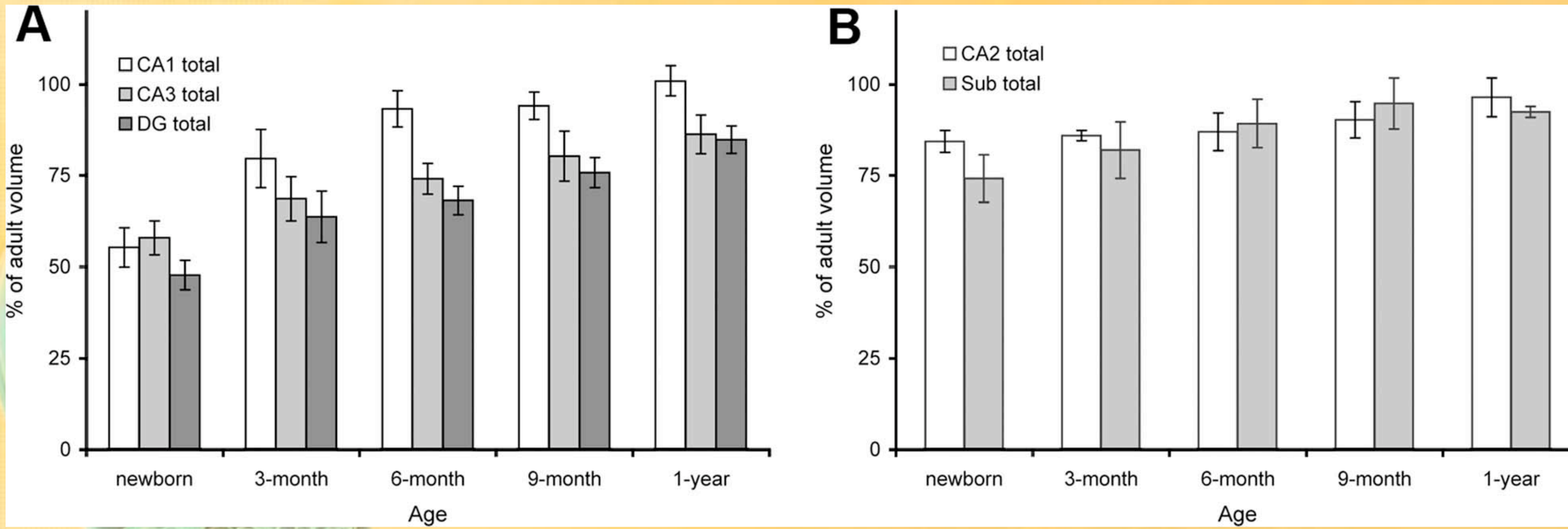
If episodic memory doesn't come on line until after 1st or 2nd birthday, how do we refer to memory in the first year?
Pre-episodic memory

- Inferred from novelty preferences over a delay; cross modal recognition memory
- May appear in first months of life
- May depend on hippocampus proper
- May serve as a building block for formal episodic memory (Nelson, 1995; Jabes & Nelson, 2015)

Differential maturation of distinct MTL regions?

- Whereas some MTL structures seems to be fairly mature at birth or shortly after (perirhinal cortex?; Berger & Alvarez, 1994)…
- … some might exhibit a protracted development (hippocampal formation, postnatal neurogenesis.)

Differential maturation of distinct MTL regions?



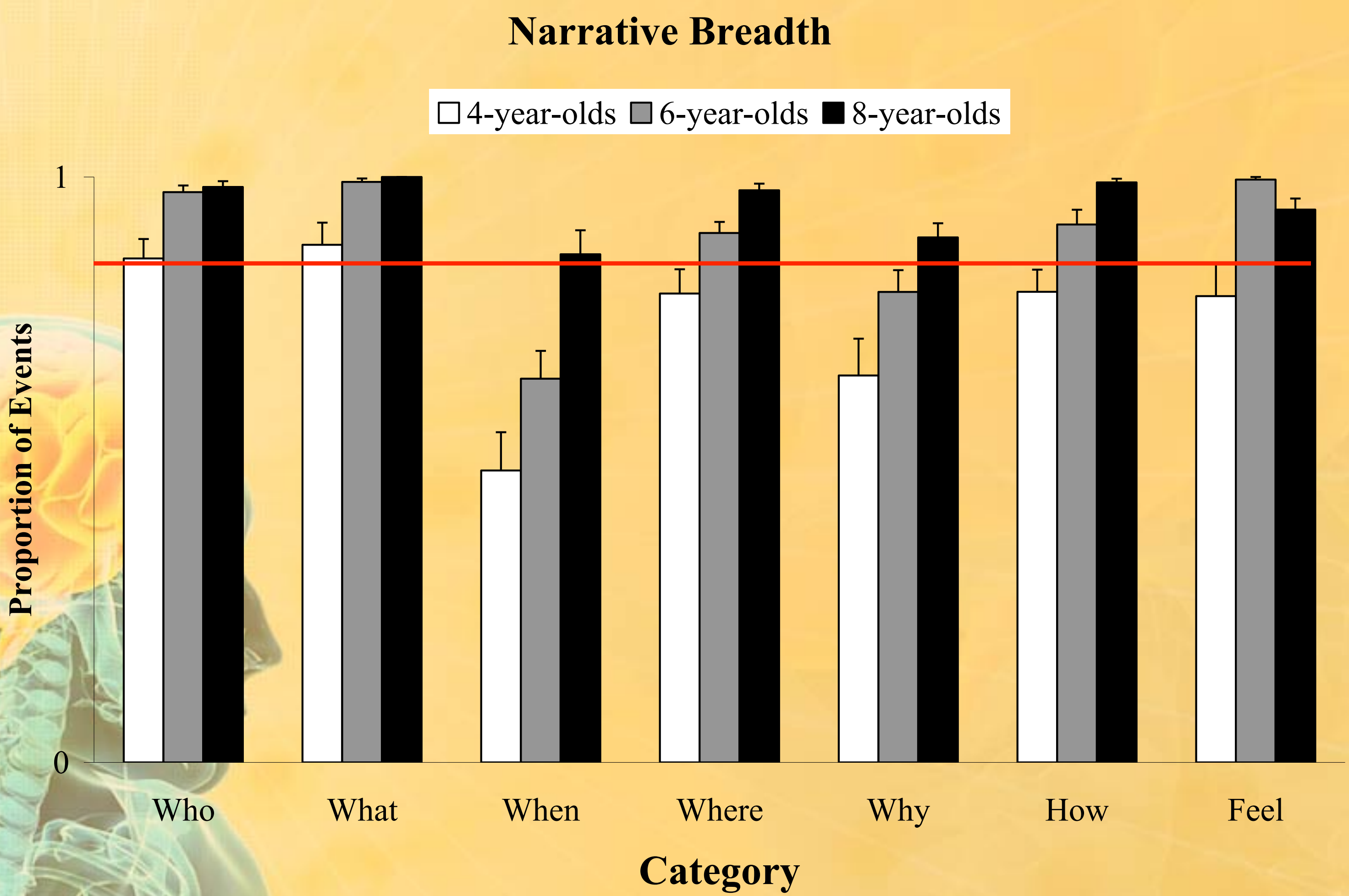
➔ Differential maturation of distinct hippocampal regions
(notice gradual increase in volume over first year)

Jabès et al., 2011

Memory in early childhood

- Autobiographical Memory – inserting yourself into your memories

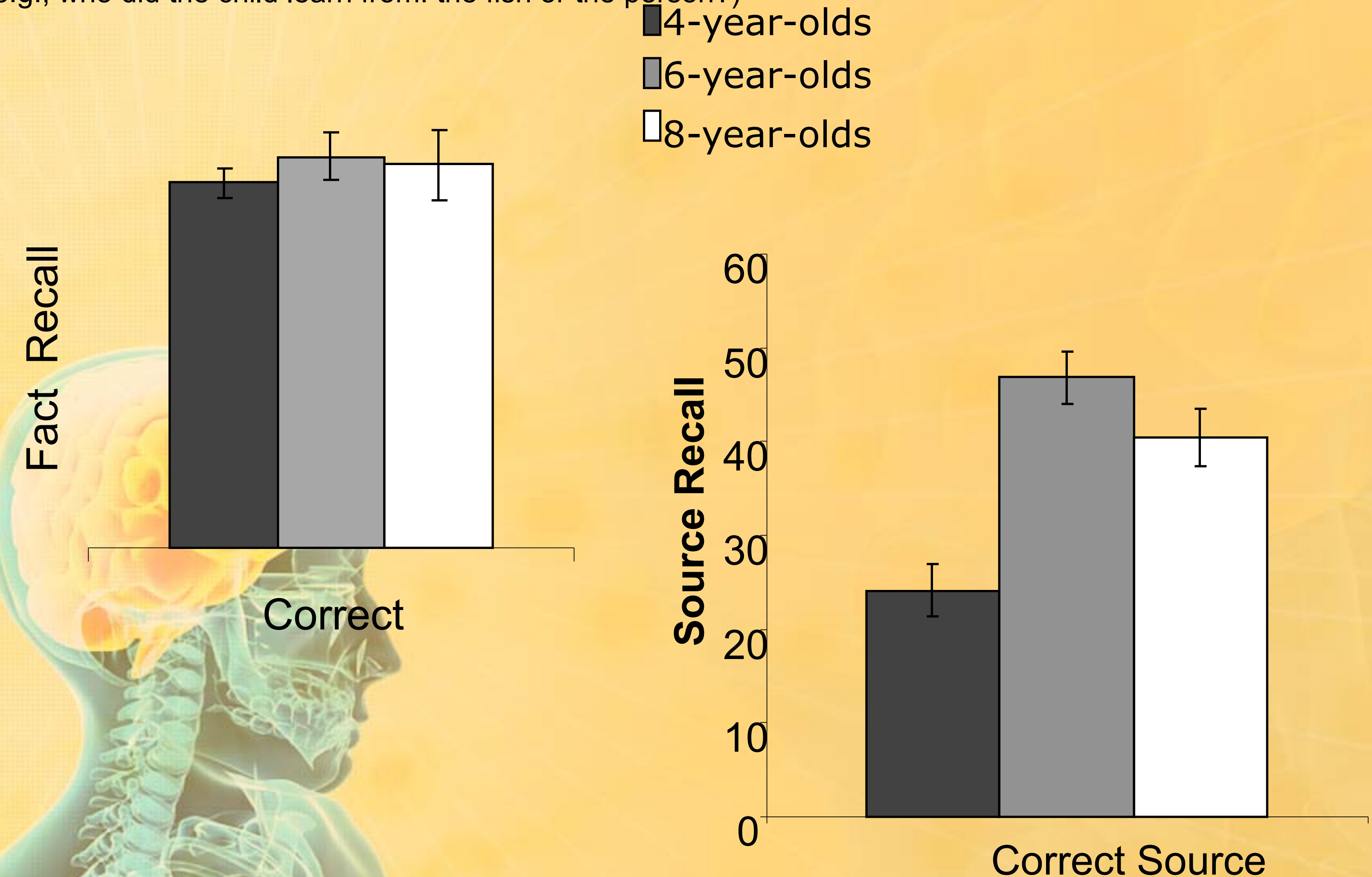
Retrieval of contextual details shows dramatic improvement…



DeBoer (2005)

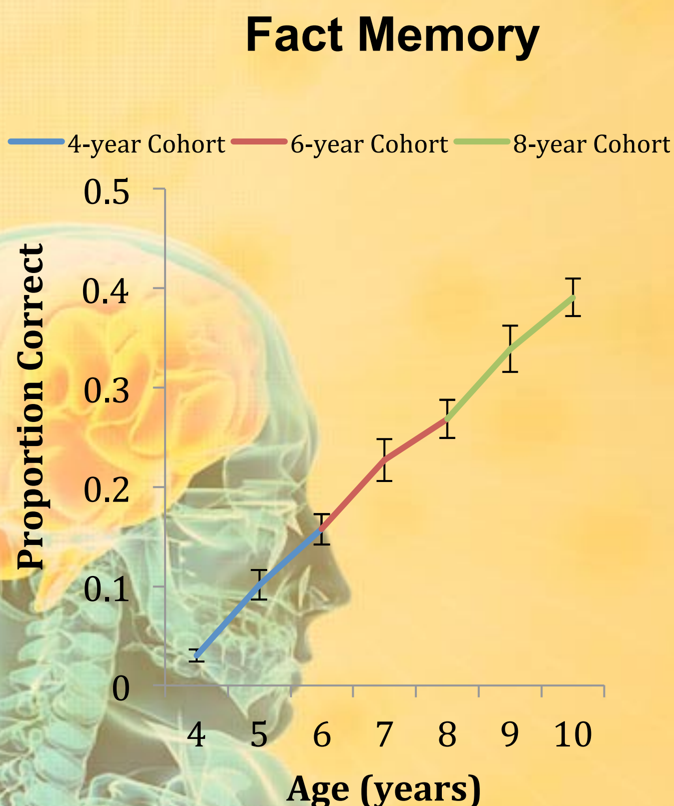
Lab studies examining memory for contextual details: Memory for Source

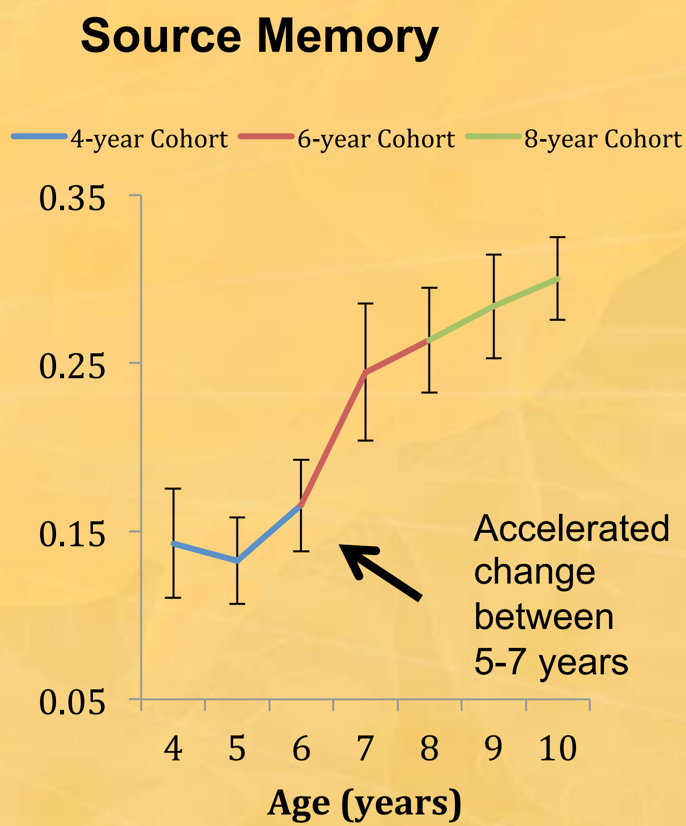
(e.g., who did the child learn from: the fish or the person?)



Drummey & Newcombe (2002)

Longitudinal study of memory for source





Colors represent different longitudinal cohorts; data points between transition years are averaged.

Riggins, 2014, *Dev Psych*

Summary

- Although the foundations for most aspects of declarative memory are laid down in infancy, there are dramatic improvements in most domains until ~age 10 years
  Note: Little is known about early development of non-declarative memory.
  Reason: often embedded in motor activity, which is immature early in life.

What accounts for improvements during childhood?

- Memory improvements during middle childhood are mainly due to emergence of strategies (mnemonics) for remembering things
  - Cognitive control via frontal-parietal networks that undergo protracted maturation
- Medial temporal lobe (inc. hippcampus) develops early and contributes little to change during this period
  - Binding processes that mature early

Nelson & Richmond, 2007; Newcombe, Lloyd, & Ratliff, 2007; Shing et al 2010

Long-Term Memory

1. **Encoding**: how you 'put' things in to memory.

2. **Consolidation:** Rehearsal (usually not conscious)

3. **Retrieval:** getting things 'out' of memory

Long-Term Memory: Encoding

1. **Encoding**: The 'deeper' and more elaborative the processing, the stronger the encoding
    - What color is this word? Pretty (shallow encoding)
    - Does this word describe you? Pretty (deep encoding)

- Mnemonic strategies capitalize on this:
    - **E**very **G**ood **B**oy **D**eserves **F**un
    - Remembering random objects: Imagine yourself in a room you know, put those objects in the room.

- Good mnemonic strategies encourage *relational* encoding:
    - binding together a stimulus with other cues (how you feel about yourself; words; spatial or room contextual cues)

Why does recollection get better across middle childhood?

Significant improvement in encoding strategy use:

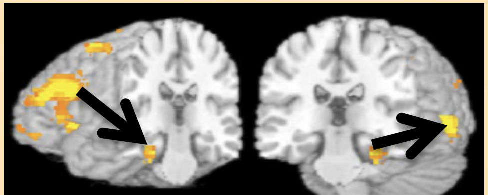
"Remember these pictures"

-Life experience may help with this

- If you have more knowledge, activation can spread more readily & more connections can be made: encoding can be deeper (big jump after children start school, which teaches children that things can be forgotten and the need to develop strategies to help you remember)

-More mature prefrontal cortex may help with this

- If you are better at holding things in mind, you can associate concepts with each other more readily
- Children (and older adults) are better at *incidental encoding*



Why does recollection get better across middle childhood?

Significant improvement in retrieval strategy use:

"Did you see this before?"

-Older children are better at flexibly using memory cues

-Older children are better able to 'know when they know,' to know things can be forgotten and thus, to use strategies to help them remember (meta cognition)

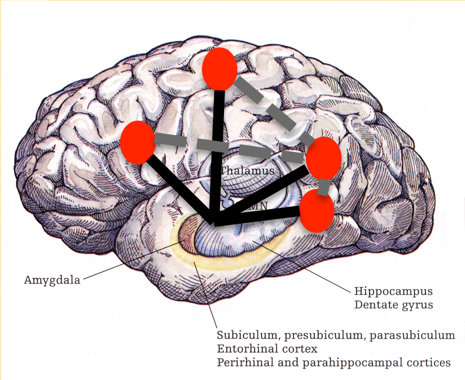
•Prefrontal cortex activation during encoding increases across age (known changes in PFC structure & connectivity across middle childhood)

•Activation of the prefrontal cortex predicts more accurate memory

Consolidation

- After you've encoded, unbeknownst to you, your brain 'practices' memories
- Sleep is integral (necessary?) for this process.
- When running a maze, rodents activate the hippocampus in an ordered fashion. During sleep, they activate the same way & this predicts memory
- Sleeping (even a nap) makes long term memory more robust.

So… SLEEP! (but not in class)



Conclusions

- Basic circuitry for memory laid down in infancy
- Elaboration of this circuitry over the preschool and early childhood period leads to dramatic improvements in memory, such that by age 10 or so memory is quite adult like

Conclusions, con’t

- However, as move through adolescent period, further development/refinement of the PFC, which is intimately connected with memory circuits, allows for additional improvements in memory
- This facilitates:
  - Development “meta” skills (use of strategies in helping us remember)
  - Better retrieval from long term memory
  - “tagging” of memories; sweet spot for adult memories tends to be late teens to early 20s (“it feels like just yesterday that I….”

INFANTILE AMNESIA

- We established that infants are capable of remarkable feats of memory; indeed, between the 1st and 2nd year of life, infants can remember some things for months.
- And we know that early experience plays a crucial role in development; for example,
- Maintaining and retrieving knowledge about previous experiences is crucial to making sense of the present.
- Yet, as adults we never remember things much before 3-5 years of age
- What’s going on?

- Do you remember your second birthday? Your third? Your fourth?
- Unlikely, unless someone told you about it or if you often looked at a picture of the event.

The early memory system

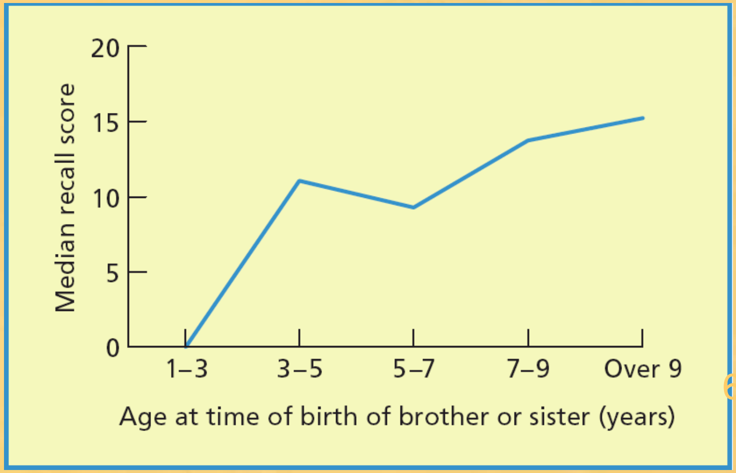
- When directly questioned :“what is your earliest memory” or using cued “tell me about the birth of you sister”, most adults report very few memories from before 2- or 3-years of age

- The inability to recall early childhood memories was named “childhood amnesia” by Freud.

Infantile Amnesia

- Sheingold and Tenney (1982):
  - *Participants*:
    - College students and children (ages 4–12)
  - *Task*:
    - Answer specific questions about a sibling's birth from when they were 3–11 years old
      - e.g. "Who took care of you while your mother was in the hospital?"
    - Mothers were asked the same questions

- *Results*:
  - If the birth occurred after 3 years old, very little forgetting occurred
    - Even if it occurred many years ago
  - If birth occurred before 3 years, virtually nothing was remembered



Newcombe and colleagues

- Presented 10 year olds with pictures of their preschool classmates whom they had not seen since age 5
- Recorded skin conductance *and* looked at memory ("do you recognize…")
- Results: recognition performance was at chance; but, skin conductance suggested that there was some recognition of preschool classmates, although not at a conscious level.

Causes of childhood amnesia.

- Freud originally proposed a repression theory that has largely been discredited.

- The offset of childhood amnesia is marked by the onset of autobiographical memory, ability to recognise themselves as an individual (Howe & Courage, 1997).

Causes of childhood amnesia.

- The development of language: inability to recall early memories that were encoded in the absence of language.

Causes of childhood amnesia.

- **Brain Development:** during infancy, the brain is still going through intensive changes that may account for differences in memory observed between different age groups.
- The infant's brain may not be mature enough to encode or remember early events.
- And, it may not be mature enough to retrieve memories

Supposition?

- Structures/circuits that underpin formation of new memories intact early in life; however, structures/circuits that *store* these memories (association cortex), and that permit *retrieval* of these memories (prefrontal cortex) are immature; thus, early memories are not actually laid down in such a way as to be retrievable – they may even be non-existent (i.e., physically erased)

But remember…..

- Just because we cannot explicitly recall the events of our lives < 3 years doesn't mean these early experiences are not important (see final lecture on early adversity)
- Rather, it is just that these events are not retrievable using declarative/explicit memory (think of challenges in child protection cases of abuse when children are <3 years)

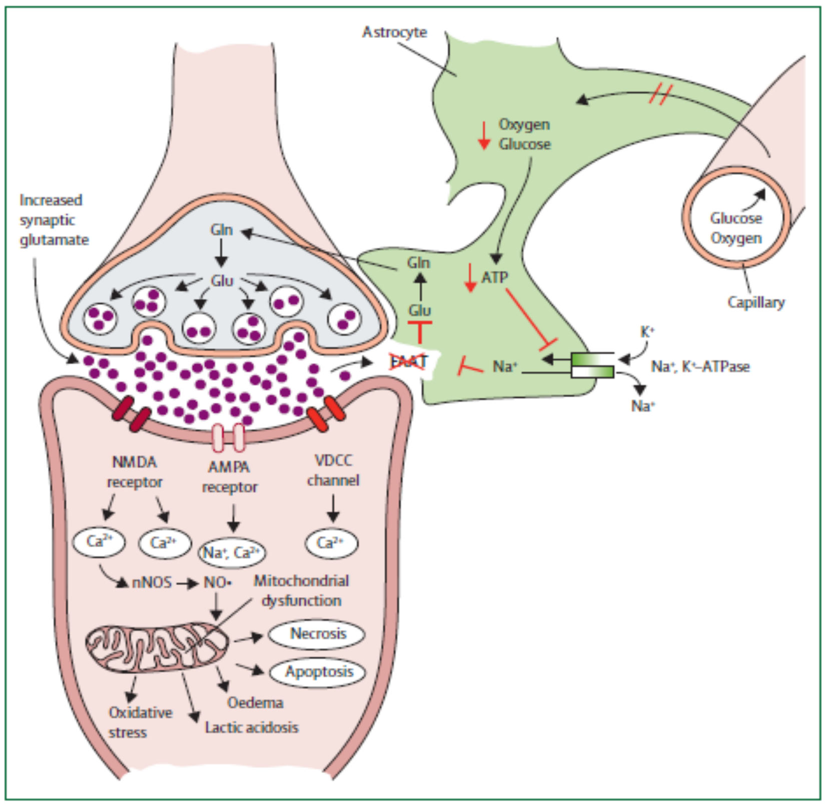
Part III: Disorders of memory

- Infants deprived of oxygen at birth (hypoxic ischemic injury or “anoxia”)
- Infants born to diabetic mothers

Hypoxic Ischemic Injury (HII)

- Cause:

  Lack of oxygen and/or blood flow to an area of tissue resulting in cell death



Johnston et. al., 2011.

Hypoxic Ischemic Injury (HII)

- Cause:

  Lack of oxygen and/or blood flow to an area of tissue resulting in cell death

- Risk Factors:

  Obstetric: placental abruption, umbilical prolapse, prolonged labor, difficult delivery

  Maternal: gestational diabetes, drug addiction, infectious disease

  Neonatal: premature, RDS, cardiovascular, sepsis

- Prognosis varies as function of:

  Gestational age

  Duration and severity of insult

  Other clinical risk factors (i.e. seizures)

Hypoxic-Ischemic Injury (HII)

- Affected brain regions:

  → Basal Ganglia, thalamus, cerebral cortex

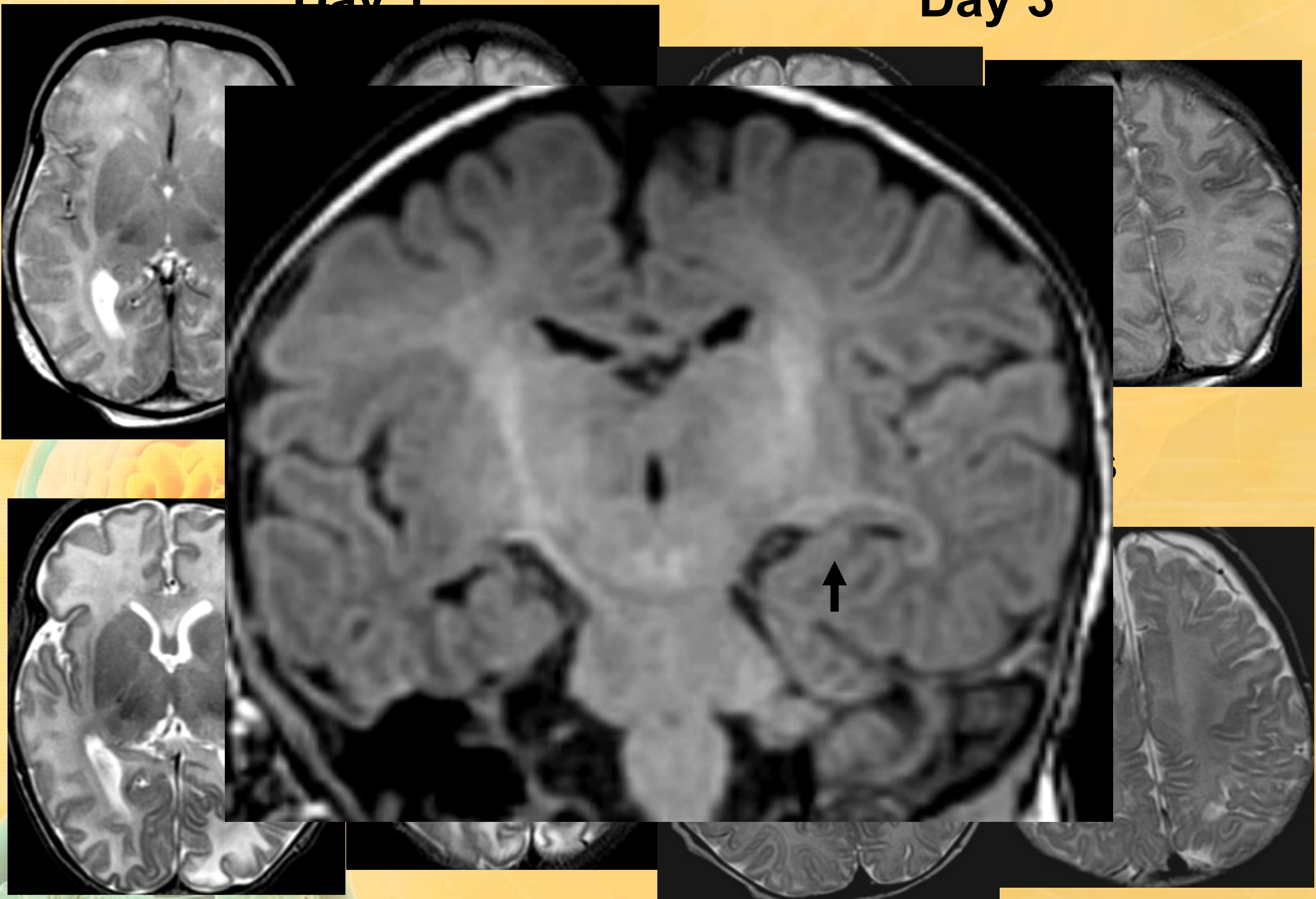
  → Hippocampus:

    Susceptible to excitotoxic cell death (high concentration of NMDA receptors)

(see next slides)

Day 1

Day 3



Hypoxic Ischemic Injury (HII)

- Long-term Neurodevelopmental disability

  ➔ Adolescents and/or young adults show impairments in:

  - delayed visual and verbal memory, perceptual-motor speed, attention and executive function

  (Maneru et al. 2001)

  - Developmental amnesia (discuss examples)

  (Gadian et al 2000; Baddeley et al., 2001; Isaacs et al., 2003; Vargha-Khadem et al., 2003; King et al., 2004; Adlam et al., 2005)

- Prevalence:

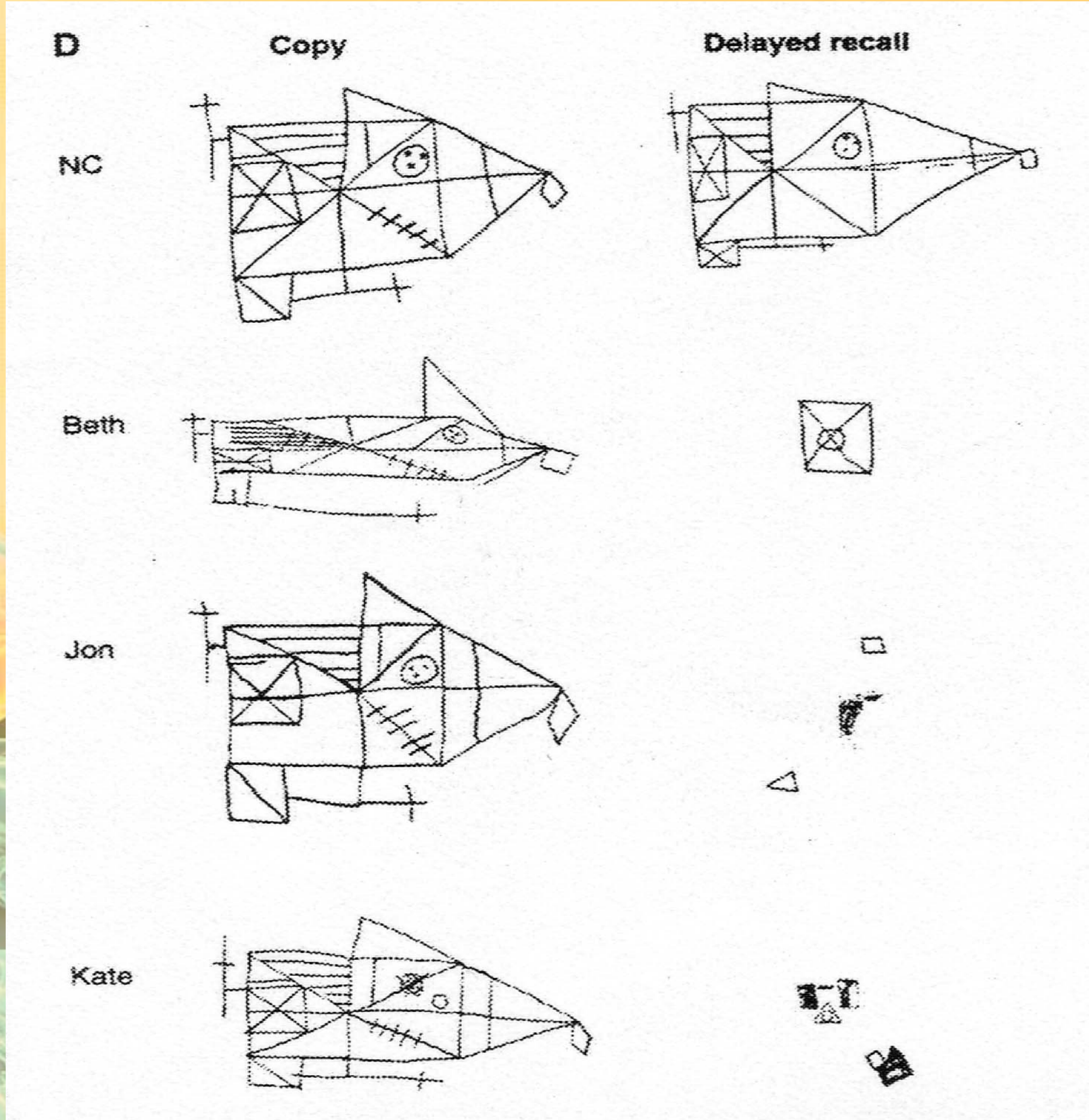
  0.3-0.5% live births
  0.05-0.1% defined as moderate or severe
  10-60% infants worldwide die

Amnesic children

- What Is happening if the memory system is destroyed during childhood?
- Will any learning be possible?
- Few patients around: Three patients with **bilateral hippocampal injury** that occurred at birth, by age 4 and at 9 years of age (Vargha Khadem et al., 1997)

Amnesic children

- Spatial: can not find their way or remember where are objects
- Temporal: problem in date and time
- Episodic: no reliable account of day’s activities


D
Copy
Delayed recall
NC
Beth
Jon
Kate

Cognitive development in amnesic children?

- Reading and writing is almost normal in these children
- Semantic memory (knowledge base) is intact

- How is it possible to explain this paradox?

Conclusions

- Vargha-Khadem et al. (1997) proposed that cortices adjacent to the hippocampus can support the formation of context-free semantic memory but not of context-rich episodic memory.

- These children can learn how to read but won't remember when they did it.

Thought Question:

- Might mild H-I injury be responsible for some idiopathic learning disabilities?

  (don't know)

Public Health Issue: think of the large number of infants now being born very early/very small, who may have subtle (and not so subtle) birth "injuries" – might this be associated with learning disabilities?

(don't know)

Infants of Diabetic Mothers (IDMs)

- Why Important: 10% of all pregnancies characterized by diabetes
- Characterized by:
  → an adverse fetal environment
  chronic hypoxia
  Iron deficiency
  Intermittent, acute repetitive insults such as hypoglycemia and hyperinsulinemia

- *All of these factors can selectively target the hippocampus, which is vulnerable to a variety of metabolic disturbances.*
- If development of hippocampus is altered, will that impact development of memory?

Infants born to diabetic mothers

Infants of Diabetic Mothers (IDMs)

Newborn Recognition of Mother’s Voice

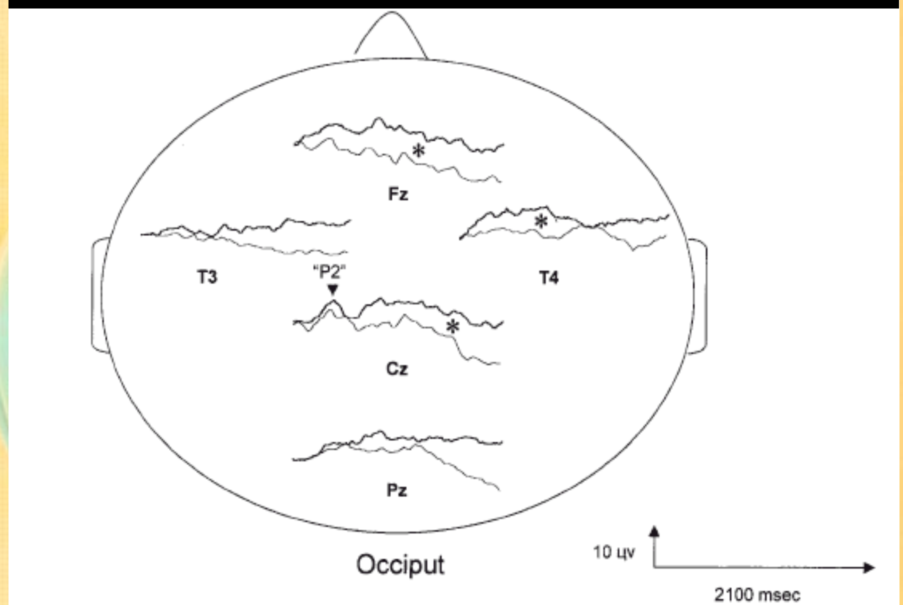
- What is the neural basis for ability to recognize material that should be recently established in memory?

- Present newborns with alternating sound clips of mother’s vs. stranger’s voice while recording ERPs.

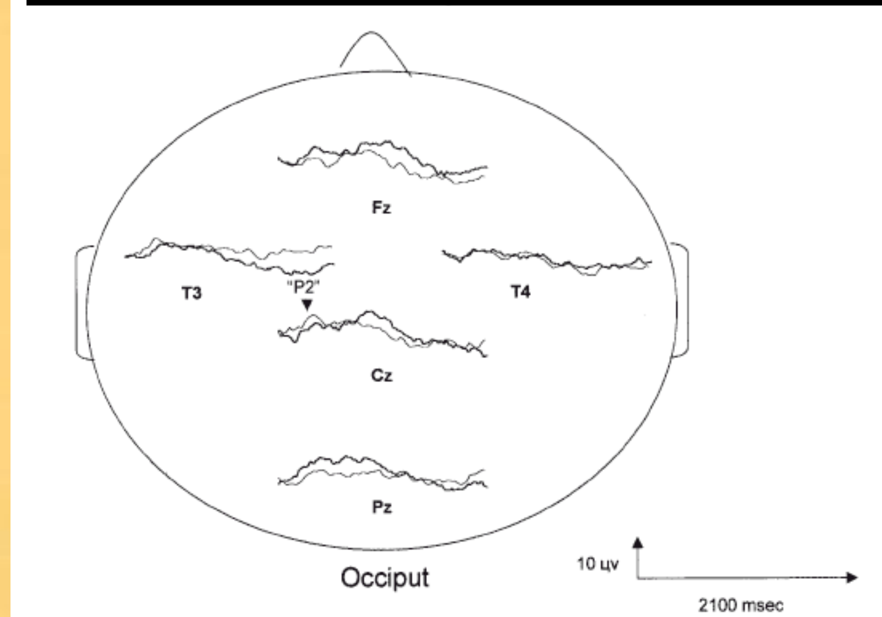
Infants of Diabetic Mothers (IDMs)

Newborn Recognition of Mother's Voice

Brain Iron Sufficient



Brain Iron Deficient

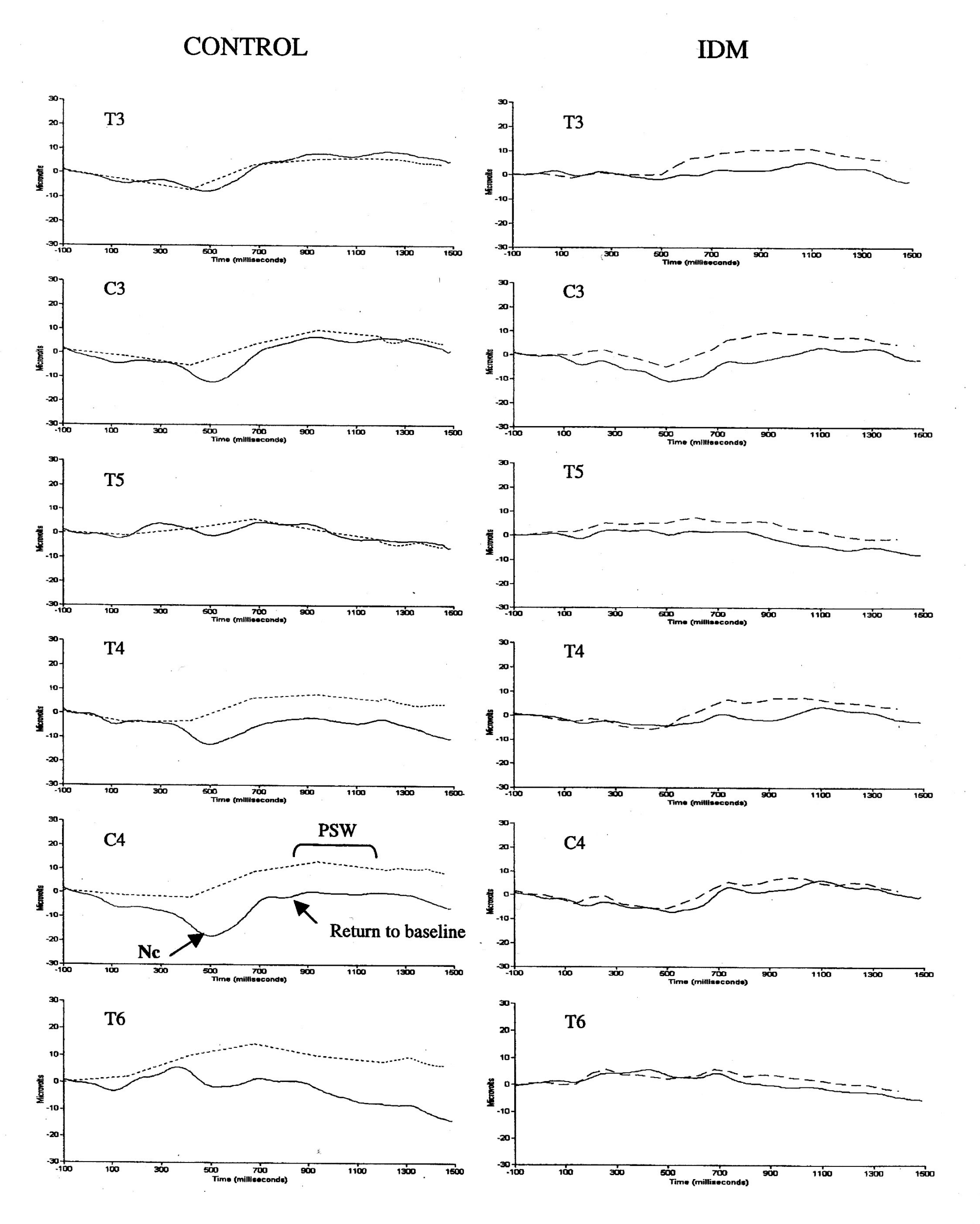


Siddappa et al., 2004

Infants of Diabetic Mothers (IDMs)

Long-Term Memory:
Recognition of Mother's Face

- What is the neural basis for ability to recognize material that should be well-established in memory?
- Present 6-month-old infants with alternating pictures of mother's face vs. stranger's face while recording ERPs.



Nelson et al., 2000

Infants of Diabetic Mothers (IDMs)

Cross-Modal Recognition Memory

- More demanding type of memory involving delay and multiple modalities
- Amygdala involvement (in addition to hippocampus)?
- Present 8-month-old infant with object they can feel but not see; then
- Present pictures of familiar object and novel object while recording ERPs

Cross-Modal Recognition Memory in 8-month-old Infants

Left Hemisphere

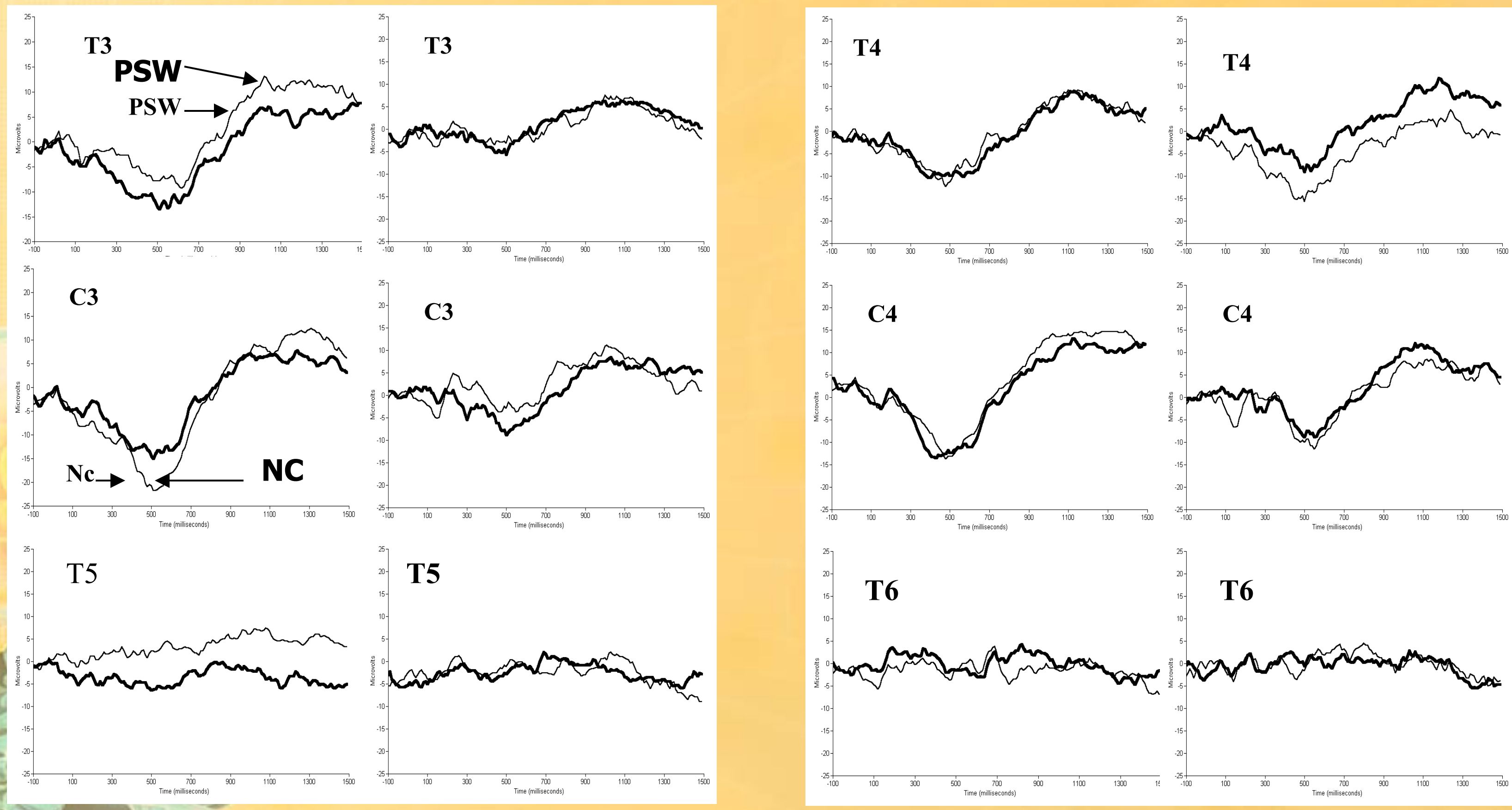
Right Hemisphere

Control IDM Control IDM

Frontal

Central

Posterior



Familiar Stimulus

Novel Stimulus

Infants of Diabetic Mothers (IDMs)

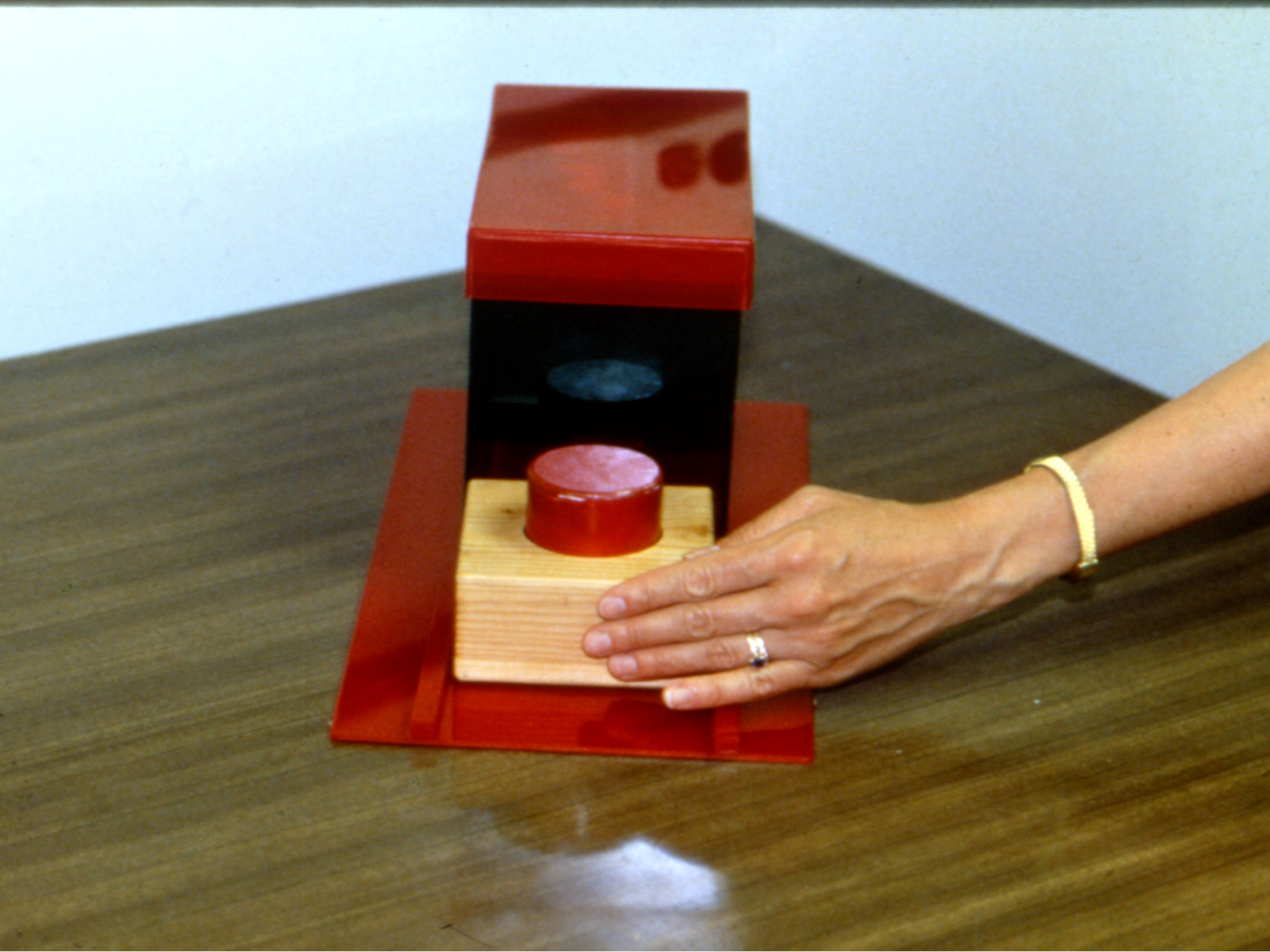
Deferred imitation

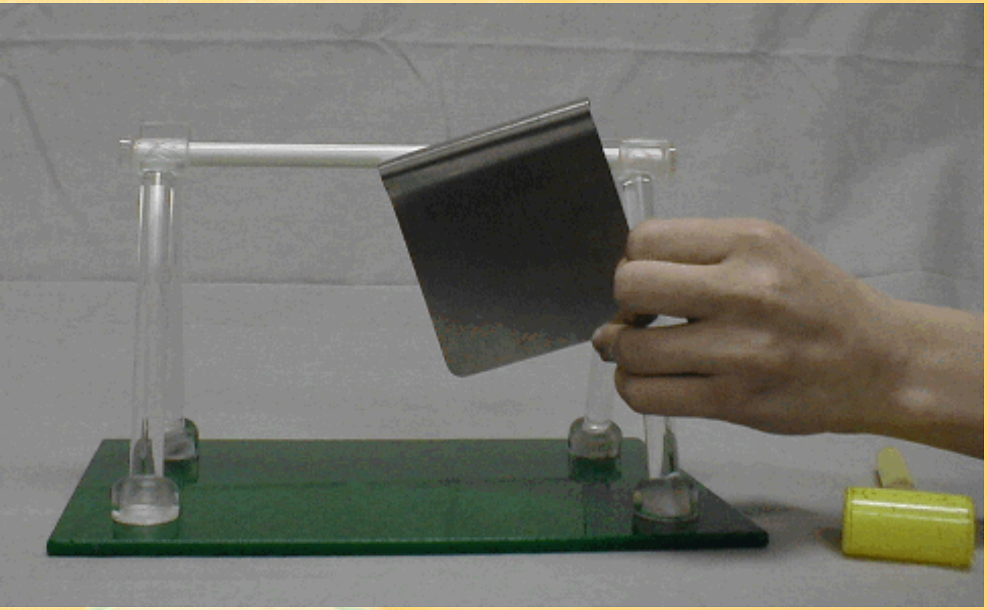
- Can ERPs be used to predict memory performance across lengthy delay
- Question: is there a difference in “recall” memory in infants who do vs. do not show earlier recognition of individual objects?

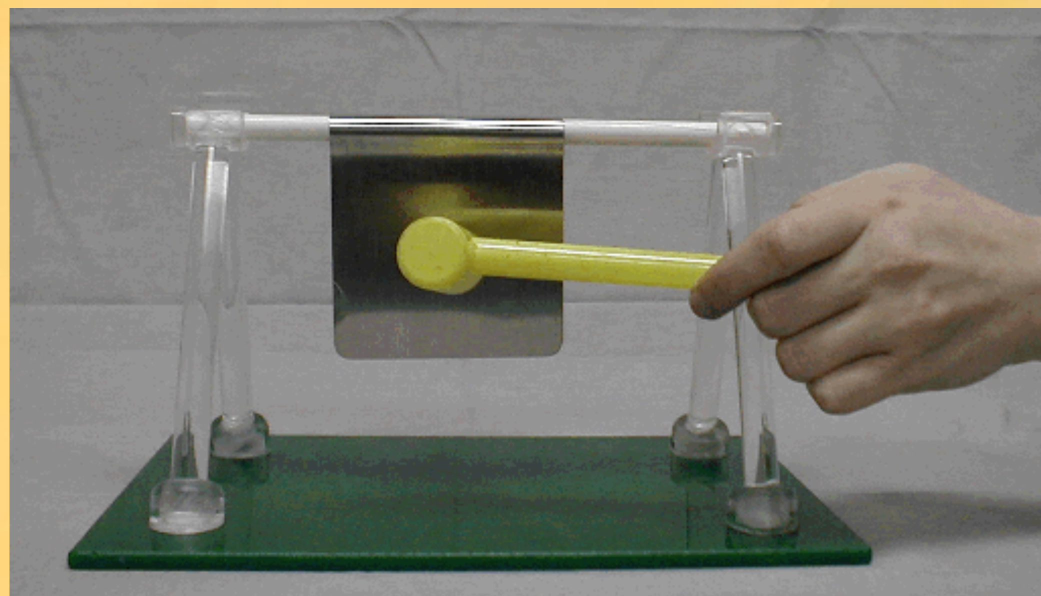
Infants of Diabetic Mothers (IDMs)

Deferred imitation

- Expose 12 month old infants to 2 and 3 step sequences
- 1 week later record ERPs while showing infants pictures of familiar and novel objects
- 4 weeks later test for recall memory
- Question: what is relation between ERPs and subsequent recall?



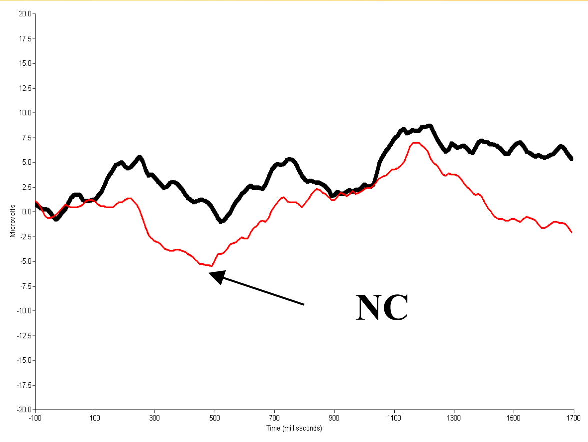




12-Month Old Infants' Explicit Memory for Event Sequences

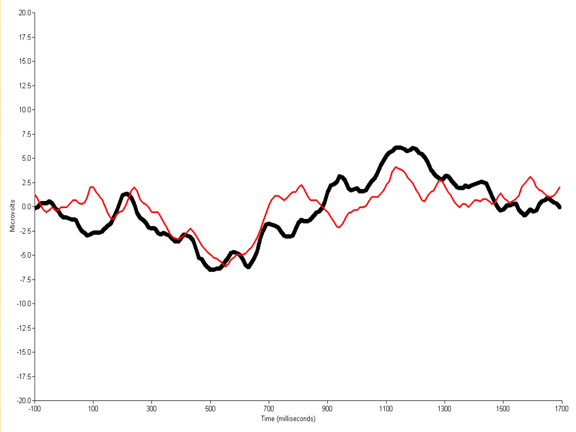
Control

Cz



IDM

Cz

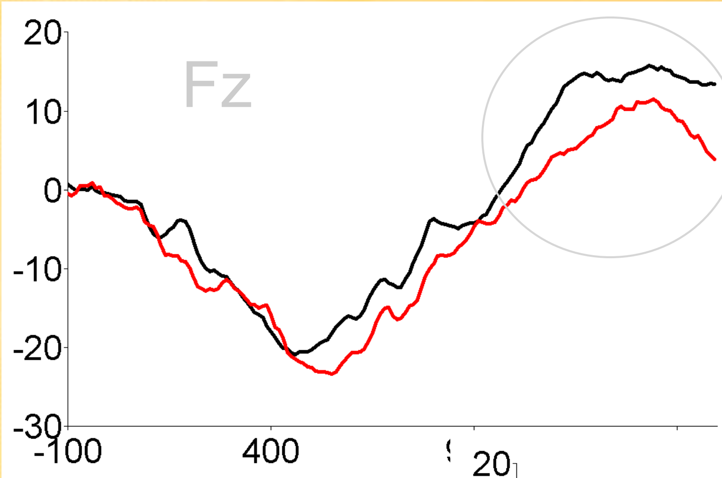


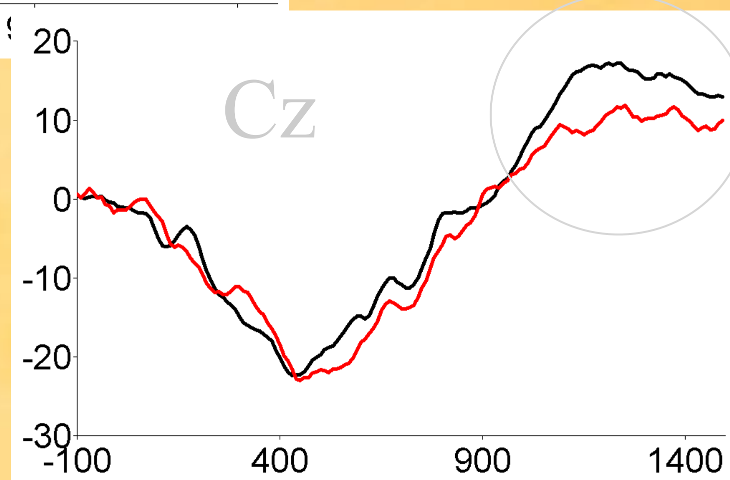
Familiar
Novel

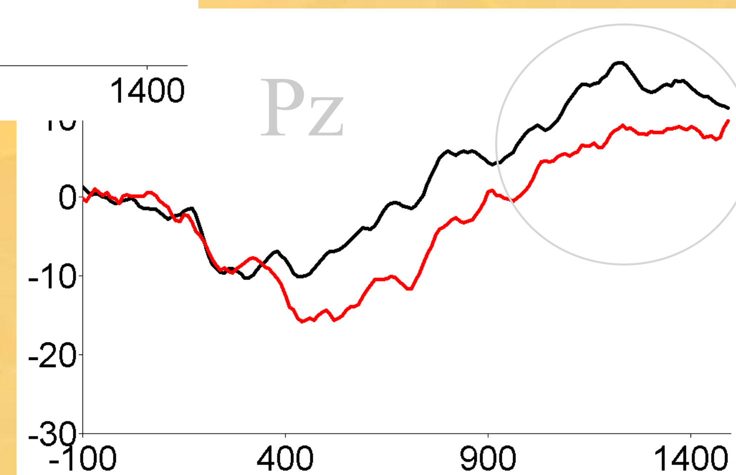
What happens at 24 and 36 months?
9-item sequence:
“Go Camping”

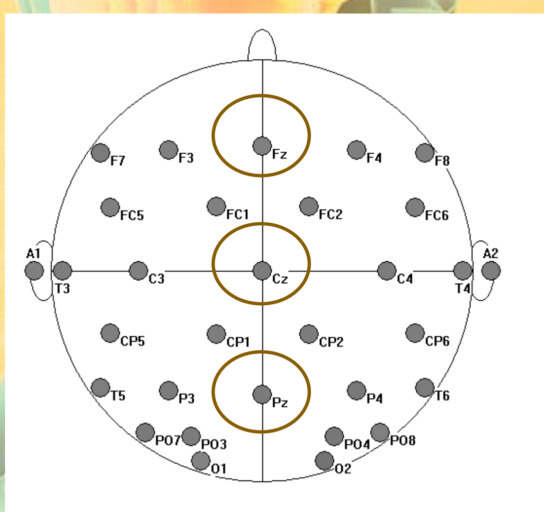
24 months

Control
IDM







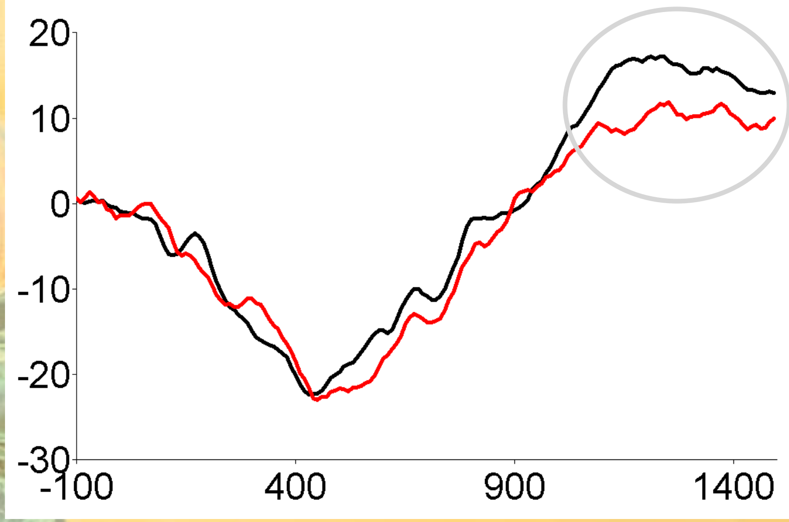


36 Month Results

Control

IDM

Cz



Infants of Diabetic Mothers (IDMs)

Associations between ERP and behavioral recall

- PSW was related to memory for individual target actions after the 1-week delay (i.e., larger PSW for infants with better “recall”)

Conclusions

- From birth through 36 months, IDMs show consistent electrophysiological evidence of hippocampal impairment as revealed in altered patterns of ERPs*
- *BUT*, developmental testing at 1 and 4 years reveals both groups score in the normal range of IQ
- These data, coupled with data from our comparison group, suggest that the tasks we have been employing reflect a form of hippocampally-based memory (generally recognition memory, or in some cases "recall" memory)
- **But how do we interpret disconnect between ERP data and behavior (e.g., IQ)?**
  - Compensation?
  - Perhaps ERPs simply had greater sensitivity than behavioral assays in detecting memory issues but there is no functional impairment

* note: there is a strong dose/response relation in our data, such that the heavier the child is at birth (with birth weight being a proxy for maternal diabetic control), or the lower the ferritin, the poorer outcome; see Siddappa, Georgieff, Wewerka, Worwa, Nelson, & deRegnier, Pediatric Research, 2004

SUMMARY

- Elements of declarative memory system come on line in the first months of life (pre-explicit memory); rest of the components of this system emerge over next few years
- Big improvement in memory from preschool – adolescence, in part due to changes in meta elements of memory (e.g.., development of prefrontal cortex/strategies for remembering things)
- Infantile amnesia is not infantile at all; we generally cannot remember events of our lives below the age of 2-4 years

SUMMARY (CON'T)

- Two prevalent forms of memory impairment include infants deprived of oxygen at birth (HII) and *possibly* infants born to diabetic mothers

The End