

Neuroimaging Tools Suitable for Young Children: EEG, ERP, fNIRS, MEG

H-126: Typical and Atypical Neurodevelopment
18 September 2017



Armamentarium

- Behavioral assays with neural specificity
 - Generally derived from animal studies (where brain tissue can be manipulated) or human neuropsychology (e.g., following injury or surgery to the brain)
 - delayed match-to-sample (ability to recognize a stimulus as familiar after some period of time has passed)
 - Wisconsin card sort (cognitive flexibility; sort cards on color, then shape)



Armamentarium (con't)

- Electrophysiological Tools (assessment of brain's electrical activity)
 - EEG
 - Event-related potentials



Armamentarium (con't)

- Metabolic Tools
 - MRI
 - Near Infrared Spectroscopy (NIRS)
- Magnetic Tools
 - MEG



Pros/Cons

- All methods have advantages and disadvantages
 - Behavioral assays
 - **PRO:** inexpensive; can be applied to broad range of ages
 - **CON:** does not visualize brain directly; little neural specificity; same tool may work well at one age but not another; when it comes to lesion approaches (think back to last week's lecture) we do not know if it was the lesion or the interruption of fibers that connect different regions that is responsible for the deficit)
 - EEG-based tools
 - **PRO:** relatively inexpensive; can be used across entire life span; excellent temporal resolution; non-invasive
 - **CON:** relatively poor spatial resolution

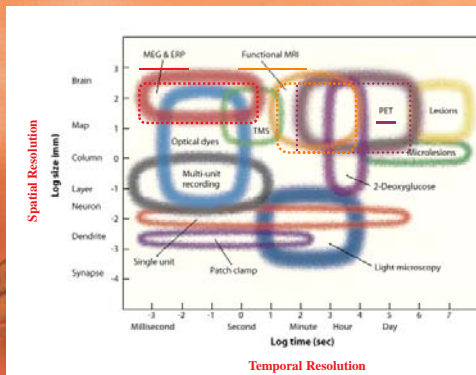


Pros/Cons (con't)

- Metabolic tools
 - **PRO:** excellent spatial resolution; non-invasive
 - **CON:** subject must remain motionless (difficult to use <5 years); expensive (\$600+/hour); contraindications for scanning; relatively poor temporal resolution
- Magnetic Tools
 - **PRO:** good spatial, excellent temporal resolution
 - **CON:** subject must remain motionless; expensive.



Spatial and Temporal Resolution of Various Neuroimaging Methods



Electroencephalography (EEG)



Why use EEG?

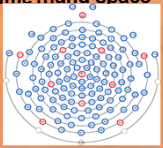
- Provides a direct measure of neural activity



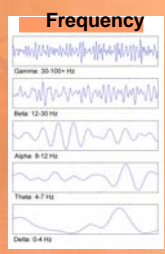
Why use EEG?

- The EEG signal is multidimensional


Voltage changes over time...and space



Frequency

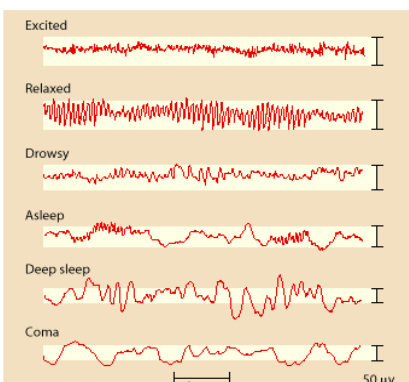


Power



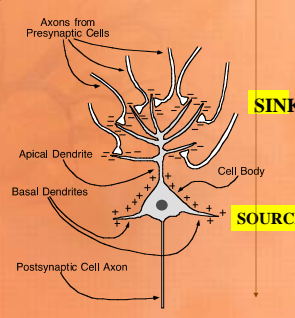
Frohlich et al., 2015

Electroencephalogram (EEG)



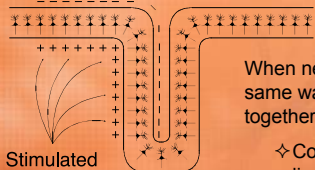
Electrical fields around neurons

- Neurotransmitters activate ion channels on the cell membrane, ions flow into and out of neuron
- Summation of postsynaptic potentials at the dendrites
- Creates electrical fields that surround the neuron (current dipole)
- Can't measure the activity of a single neuron from the scalp – only if activity is synchronous across many neurons
 - oscillations or response to event
- Estimated that 10,000 - 50,000 neurons contribute to the EEG signal



from Luck, S. J., & Girelli, M. (1998)

Electrical fields in the cortex




When neurons are oriented the same way, their electrical fields sum together

✧ Cortical pyramidal cells are lined up perpendicular to the cortical surface

Whether a component is + or – is determined by:

- ✧ Orientation of neurons with respect to the electrode
- ✧ Location of reference electrode
- ✧ Part of neuron where neurotransmission is occurring
- ✧ Excitatory vs. inhibitory neurotransmission

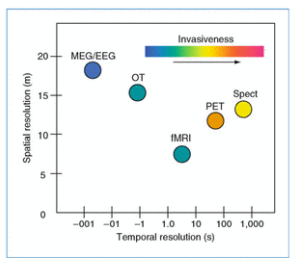


from Luck, S. J., & Girelli, M. (1998)

Why Use EEG to Study Development?

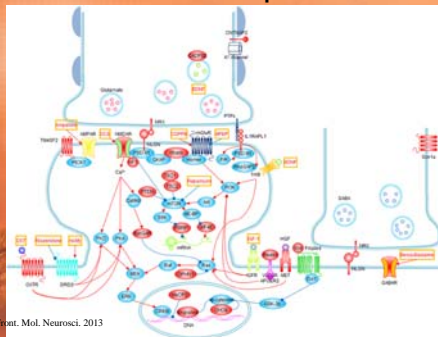
- Practical reasons
 - Easy to place (especially nets)
 - Portable
 - Inexpensive
 - No sedation required
 - This is key for studying at-risk populations
- Scientific reasons
 - EEG reflects synchrony between large numbers of neurons. The network-level resolution of EEG thus provides a link between the microscopic level (synapses) and the macroscopic level (behavior).
 - There are data to suggest that EEG has promise as a tool for studying development.

EEG has good temporal resolution.



C.E. Panayiotopoulos (ed.), *Atlas of Epilepsies*, DOI 10.1007/978-1-84882-128-6_11
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The Microscopic Level



From Synapses to Behavior



How to record brain activity from infants and children





How We Net Babies & Young Children



Caveats

- It is thought that Pyramidal cells make the biggest contribution to EEG currents, as these cells tend to be aligned and fire together (synchrony).
 - Thus, not all neurons and therefore not all structures, are capable of generating EEG currents (e.g., amygdala has no pyramidal cells)
- Voltage falls off as a function of the square of the distance so very deep structures are unlikely to generate currents that can be recorded at the scalp surface (but perhaps with improved signal detection tools....).
- Because currents volume conduct to scalp surface, it is challenging to identify underlying sources

Examples of EEG work



ELECTROENCEPHALOGRAPHY



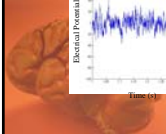
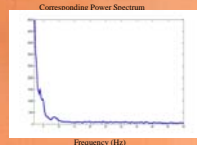
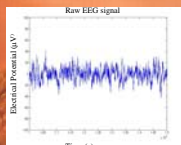
Collecting EEG

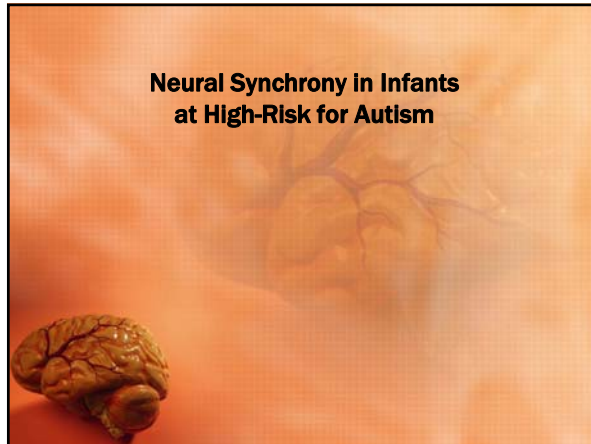


Reading EEG

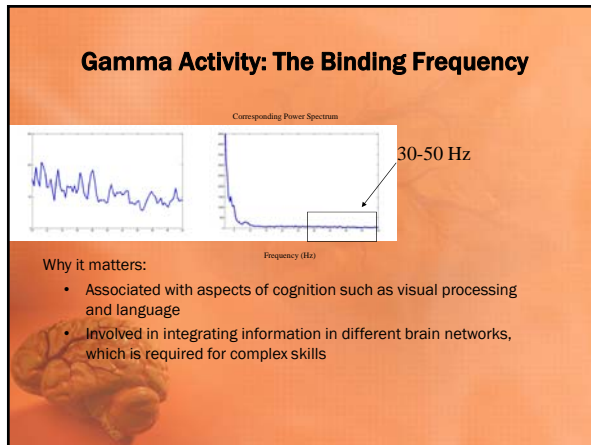


Resting EEG: Data Collection and Analysis








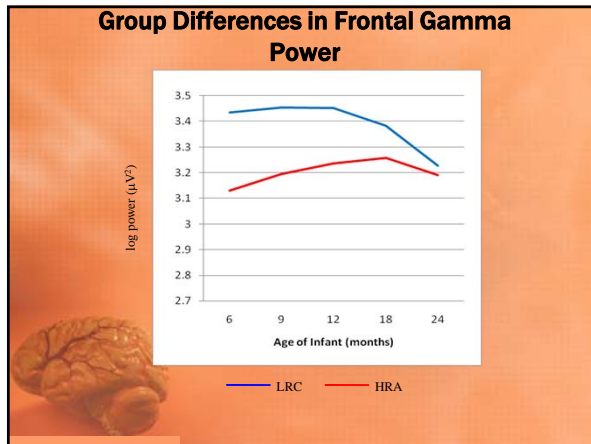
Neural Synchrony in Infants at High-Risk for Autism

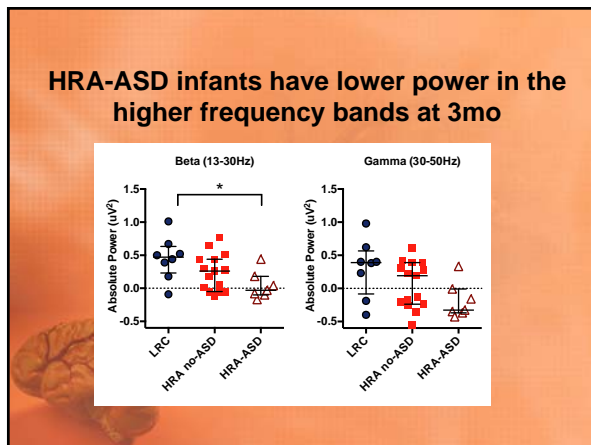


Research Question

- In comparison to infants at low-risk for autism:
- Do infants at high-risk for autism have *lower* levels of gamma activity in the first year of life, which may reflect less neural integration, particularly in the frontal areas of the brain?

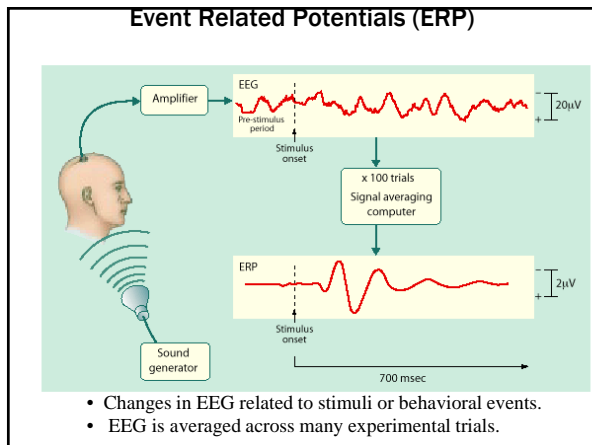


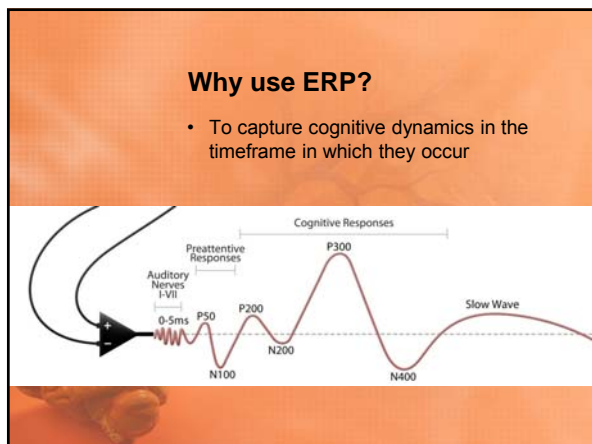


Summary

- 6 Months: 35% reduction in gamma among HRA vs. LRC;
- By 24 months, HRA=LRC.
- In the intervening period, HRA infants show a remarkably flatter trajectory of change than LRC.
- Finally, EEG power in gamma band at 3 months predicts who develops autism at 36 months








ERPs

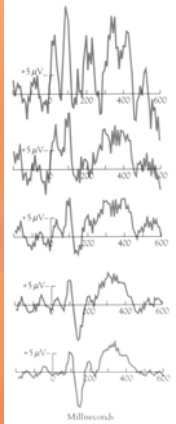
- Reflect a subset of the EEG (essentially deflections in the continuous EEG)
- Are captured by time-locking brain response to stimulus (if external stimulus, is "evoked" (e.g., flashes of light or bursts of sound); if endogenous, is "invoked" [e.g., "keep track of the number of times a face is NOT presented"])
- Examine three elements of ERP:
 - Amplitude
 - Latency
 - topography



ERP Averaging

One Trial


Many Trials



ERP Signal < Noise

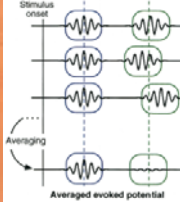

ERP Signal > Noise

Milliseconds

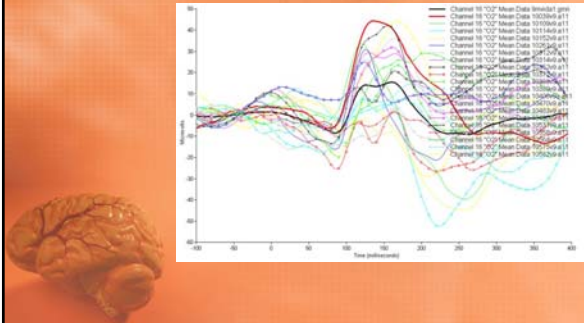


ERP Averaging Assumptions

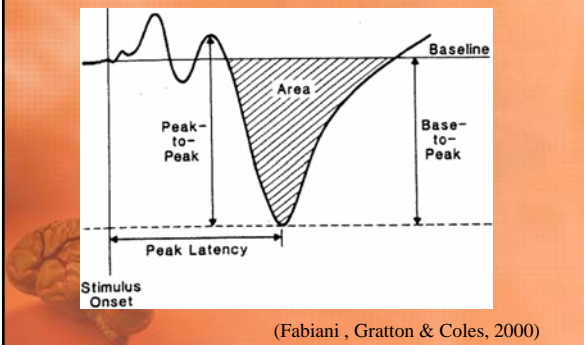
- ERP signals are consistent over trials
 - Minimal "latency jitter"
 - Alternative of single-trial pattern recognition
- Noise is random across trials
- ERP signals are independent of noise

Individual Averages vs. Group Averages

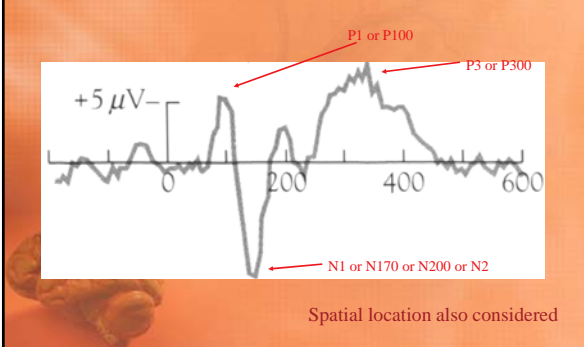


Peak Measurement



(Fabiani, Gratton & Coles, 2000)

Peak Identification



Spatial location also considered

Event-related Potentials (ERPs) can be used to study:

- Visual and auditory sensory responses
- Somatosensory, olfactory and gustatory responses
- Language processing and specialization
- Face/object processing and specialization
- Memory
- Attention
- Error detection and monitoring
- Response inhibition
- Reward processing
- Learning
- Motor and cognitive preparation
- And more...

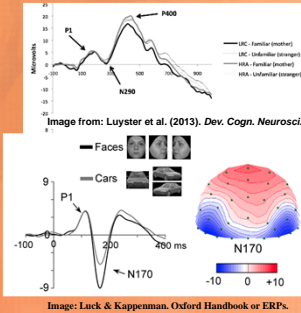


TABLE 1
Overview of Some ERP Components Commonly Examined in Studies of Typical and/or Atypical Development and Some Relevant Adult Components

Process	Component	Age Observed	Function	Scalp Distribution, Timing, ms	Notes
Auditory sensory	MMN	Birth onward	Obligatory auditory discrimination and/or sensory memory	Frontocentral, 100–250	Plotted as a difference wave (deviant stimulus-response minus standard stimulus-response)
	P50/P71 repetition suppression	Early adolescence onward	Reduction of amplitude after repetition, index sensory inhibition	Ventral, ~50 in adults	This function may be observable in neonates. This may also be observable in the visual domain.
Visual sensory	N2	Infancy onward	Stimulus complexity, scene processing, speech vs. non-speech in children and adults	Frontocentral, 150–250 in adults; ~250–300 in children	
	P100	Birth/infancy	Visual pattern reversal, visual thresholds, visual discrimination	Occipital, ~100 in adults; 250–300 in neonates	
	C1	Adulthood	Initial cortical processing in V1	Occipital, ~60 (~56 ms)	
	P1	Infancy, adulthood	Under unique circumstances, may index magnocellular visual pathway functioning	Occipital, ~100	
Face processing	N1	Birth/infancy, adulthood	Under unique circumstances, may index magnocellular visual pathway functioning	Occipital, 65–85	
	N290	Infancy and early childhood	Sensory-perceptual processing of faces	Occipitotemporal, ~290	See also N170 and P400
	P400	Infancy and early childhood	Sensory-perceptual and early cognitive processing of faces	Occipitotemporal, ~400	See also N290 and N170
	P1/P100	Birth onward	Face processing during childhood, face inversion during childhood	Occipitotemporal, ~100 in adults	Significant developmental changes, sometimes indexing face processing, and P400
	N170/N1	Middle childhood onward	Sensory-perceptual processing of faces, perceptual experience	Occipitotemporal, ~170	See also VPP, P100, N290, and P400
	VPP	Adulthood	Sensory-perceptual processing of faces	Centrontal, ~170	Highly similar functionally to the N170

(Continued on next page)

TABLE 1
Continued

Process	Component	Age Observed	Function	Scalp Distribution, Timing, ms	Notes
Memory/attention	Nc	Infancy and childhood	Attention, perceptual memory	Frontocentral, ~350	Auditory, visual, and cross-modal. Also relevant for face processing and cognition
	NSW		Recognition memory	Frontocentral, ~1,000–1,500	Auditory, visual, and cross-modal
	PSW		Updating of memory representation	Frontocentral, ~600–1,200	
Language	P7a	Middle childhood onward	Attentional engagement, sensory working memory	Midline with frontal maximum, 280–300	Time locked to a target stimulus in oddball paradigms. Part of the P900/TEFAC. See also P7b.
	P7b	Middle to late childhood onward	Gender updating relevant to memory storage	Midline with parietal maximum, 350–550	Time locked to a target stimulus in oddball paradigms. Part of the P900/TEFAC. See also P7a.
	N200–400	Toddlerhood	Word familiarity, hemispheric specialization for words	Temporal-parietal, 200–400	Analyzed as mean amplitude differences
	N400	Early childhood onward	Semantic content mismatch, semantic integration	Centroparietal, ~400	An N400-like response has been observed in toddlers
	P600/SPS	Early childhood, adulthood	Syntactic violations, rule-based violations	Centroparietal, ~600	See also LAN/ELAN
	LAN/ELAN	Middle childhood onward	Syntactic structure violations, rule-based sequence violations	Left frontal, ELAN; ~200, LAN, 300–700	See also P600/SPS
Executive functioning	ERNS/e	Late childhood onward	Error monitoring, sequence evaluation	Centrontal, 50–150	Time locked to subjects' meta-response bias response; see also N2
	N2	Late adolescence onward	Response inhibition	Frontocentral, 200–300	Time locked to correct response on incongruent trials or to going up trials
	Pc	Adulthood onward	Cognitive/monitorial evaluation or response errors	Centroparietal, 300–400	Time locked to subjects' motor response errors; see also ERN and N2
	CNV	Late childhood onward	Stimulus evaluation, motor and cognitive preparation	Frontocentral, 400–800	Occurs between a warning stimulus and a stimulus requiring a response

Note: CNV = Contingency negative variation; ELAN = Early left anterior negativity; ERN = Error-related negativity; LAN = Left anterior negativity; MMN = Mismatch negativity; N = Negative; Nc = Negative central; Nc = Error negativity; NSW = Negative slow wave; P = Positive; Pc = Error positivity; PSW = Positive slow wave; SPS = Syntactic positivity shift; VPP = Visual positivity potential.

Components are typically labeled according to the polarity of the deflection (i.e., P = positive; N = negative), and the peak latency of the components are in milliseconds (e.g., N170 peak approximately 170 milliseconds after the presentation of a visual stimulus). Alternatively, components are sometimes labeled based on the topography of the ERP waveform (e.g., the auditory N2 is the second negative deflection observed in response to an auditory stimulus). Finally, the names of other components are derived from their apparent functional significance (e.g., error-related negativity is observed after an error motor response or their scalp topography (e.g., left anterior negativity).

Advantages of ERPs

- Fast to compute and require few analysis assumptions
- High temporal precision (to study online processing)
- Extensive literature (spanning decades) on ERP components
- Can study a range of processes (spanning sensory to cognitive) in a wide range of domains (e.g., social, language, motor, perceptual) in a non-invasive manner
- Low cost



Limitations of ERPs

- Not well-suited to examine cognitive processes that are slow and have an uncertain or variable time course (e.g., emotion)
- Many types of oscillatory dynamics in the EEG signal are not represented in ERPs
- Limited in the ability to link results to physiological mechanisms



Summary

- Deflections=components
- Each component assumed to reflect a unique neural operation, and thus, a unique mental operation
- Because of poor signal:noise, generally average individual trials, and then average the averages (grand average).
- Can examine individual differences by examining individual subjects or clusters of subjects
- Infer something about function from individual components




Examples of ERP studies

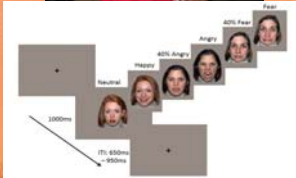
- Neural correlates of emotion processing in the first year of life
- Association between such correlates and later outcomes (age 3)



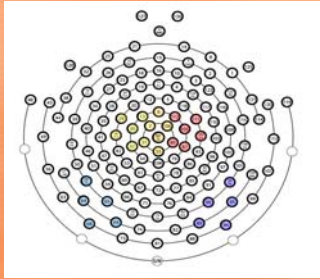
A)



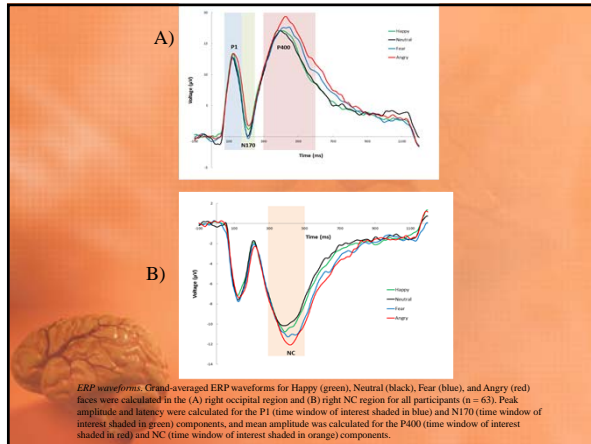
B)

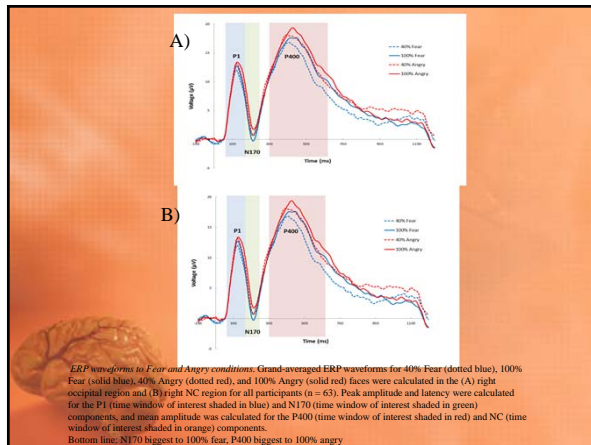


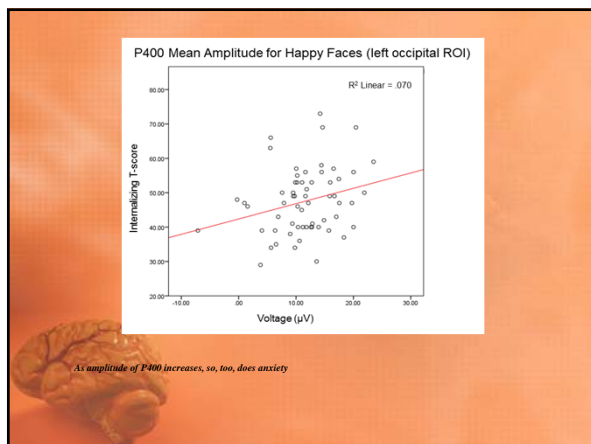
Experimental design. (A) Children wore a 128 electrode Hydrocel Geodesic Sensor Net for the ERP task, which was presented as a "Finding Nemo" game. (B) Subjects were shown a total of 300 static female faces (from 5 different models), displaying 6-emotions (50 faces per emotional condition) from the NimStim Face Stimulus Set (Tottenham et al., 2009). Each stimulus appeared for 1000ms, followed by an inter-stimulus time interval (ITI) of 650 - 950ms during which a fixation cross was shown before the next stimulus appeared. After each block of 15 trials, a still image from the "Finding Nemo" movie appeared.



Electrode groupings. Subjects were fitted with a 128 electrode Hydrocel Geodesic Sensor Net for the ERP task. Data was analyzed from electrodes in the occipital and NC regions of interest, represented by the colored circles. The P1, N170, and P400 were analyzed in the occipital region (left: electrodes 58, 64, 65, 68, and 69 [in blue]; right: electrodes 89, 90, 94, 95, and 96 [in purple]). The NC was analyzed in the NC region (left: electrodes 13, 29, 30, 31, 36, and 37 [in yellow]; mid: electrodes 6, 7, 55, 106, and vREF [in orange]; right: electrodes 80, 87, 104, 105, 111, and 112 [in red]).







Summary

- ERPs can be used as an index of differential response to facial expressions
- And, at least one ERP component is associated with anxiety

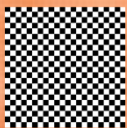


Use of ERPs in the study of rare genetic disorders

- Rett syndrome: mutation in MECP2 gene leads to dysregulation of synapses formation throughout brain
- These girls (nearly always fatal in boys) develop in typical fashion till 18 or so months, then progressively regress and lose skills.
- Have used visual evoked potential to "interrogate" brain function (next slides)



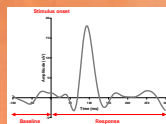
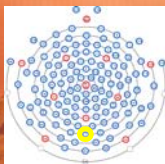
Pattern-reversal VEP paradigm



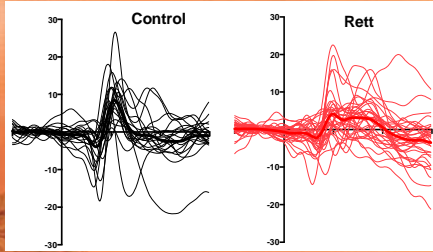
Stimulus
Eye-gaze contingent



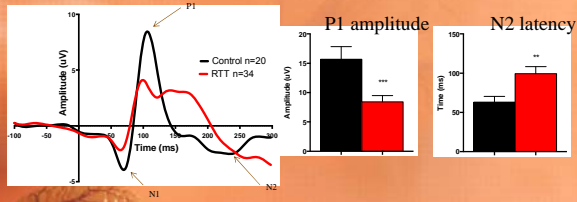
Data collection
128-channel
EEG net



VEP waveform is abnormal in children with RTT (displayed are individual subject averages)

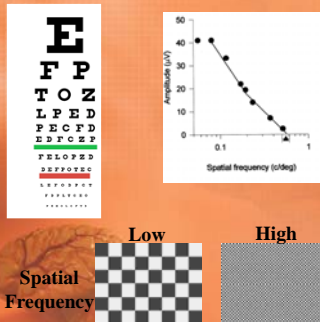


Group differences: Control vs. Rett



P1 amplitude is diminished and N2 time is increased in RTT

VEPs can be used to measure spatial resolution (acuity)



Porciatti et al., *Vision Research*, 1999
Iyer et al., *Doc Ophthalmol*, 2013

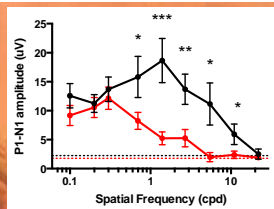
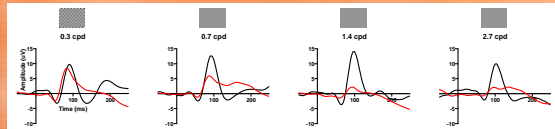
Testing acuity in Rett patients using VEP

Modifications:

- lower contrast (83%) to avoid eye strain
- faster frequency (4 Hz) to fit in more trials
- 50 trials instead of 100 to reduce total time
- varied spatial frequency



Spatial frequency tuning and acuity



Summary

- We identified quantifiable alterations in waveform morphology that reflect cortical processing deficits
- These alterations were differentially impacted by disease stage and mutation type, indicating that VEP may be used as a biomarker
- We identified a functional impact on spatial resolution (acuity) in the girls that directly supports results in the mouse model



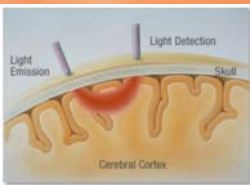
Conclusions

- ERPs have excellent temporal resolution and are very useful for examining variety of perceptual and cognitive operations and their neural correlates
- Other advantages:
 - Non-invasive
 - Relatively inexpensive
 - Easily tolerated
 - Same measure can be used across the lifespan, making it an ideal tool to use in longitudinal studies
 - Can be used in low resource environments
- *But*, have poor spatial resolution, making it very difficult to know where brain activity actually originates

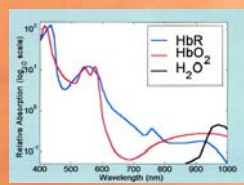
Using fNIRS to assess brain function

62

What is Near-Infrared Spectroscopy (NIRS)?

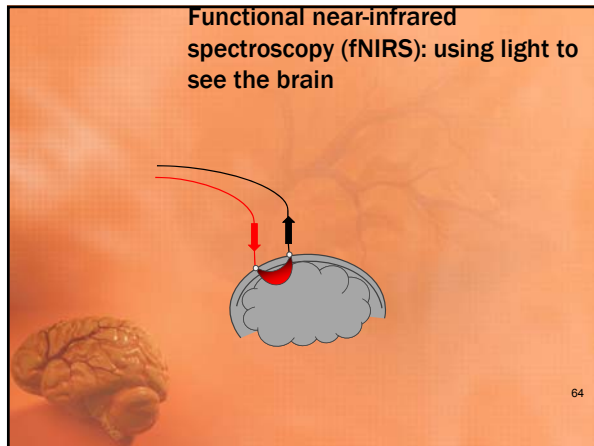


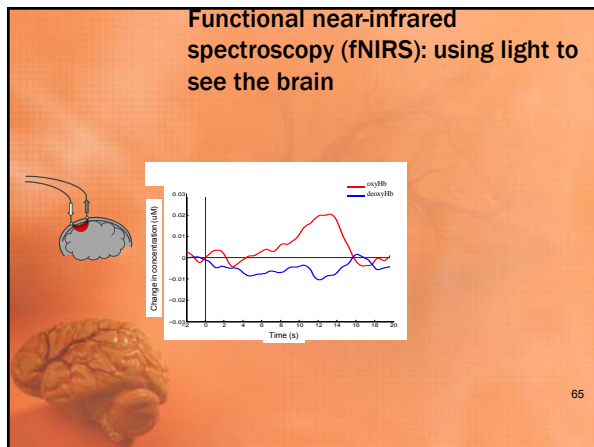
(courtesy of Aslin Lab, University of Rochester)

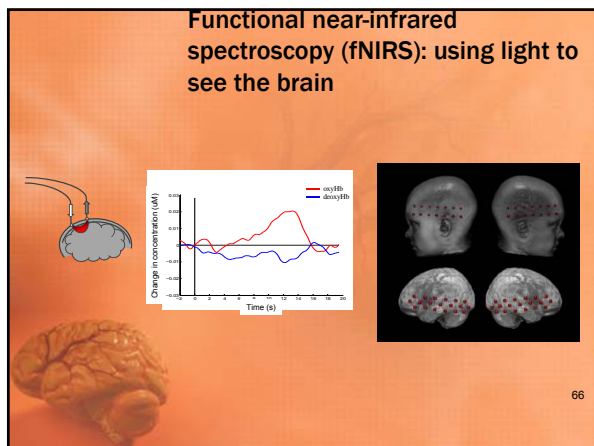


(Strangman et al. 2002)

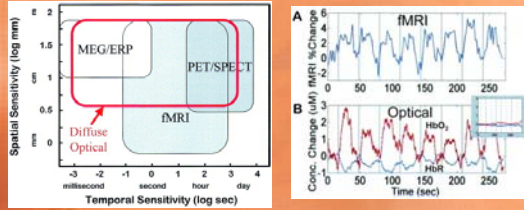
- Same concept as pulse oximetry → but measure **OxyHb** and **DeoxyHb** separately
- Emit light at two (or more) wavelengths through an optical fiber into the head
- Measure the exiting light for *each* wavelength at a detector location some distance away







NIRS for Brain Imaging

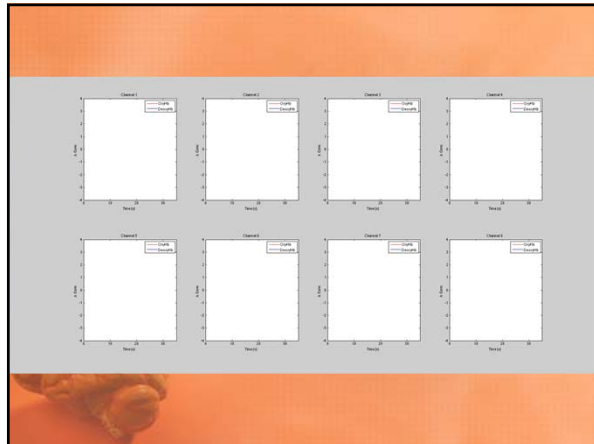


- Spatial resolution depends upon probe placement
- Hemodynamic responses:
 - HbO (OxyHb) has greater signal to noise
 - HbO (deOxyHb) most closely correlated with fMRI

(Strangman et al. 2002)

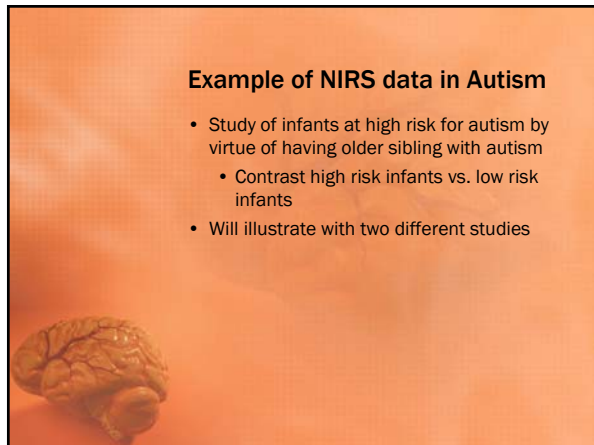
Two types of NIRS “caps”





Example of NIRS data in Autism

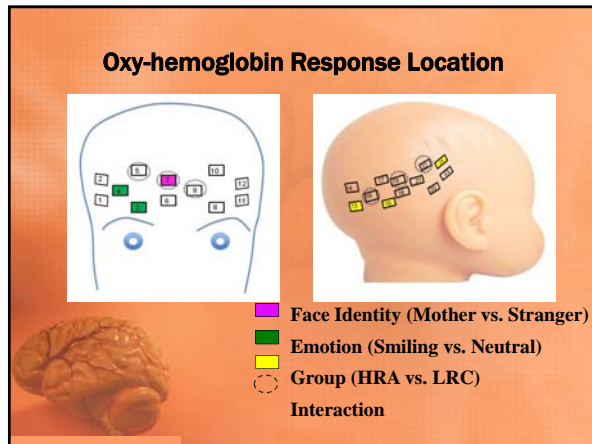
- Study of infants at high risk for autism by virtue of having older sibling with autism
 - Contrast high risk infants vs. low risk infants
- Will illustrate with two different studies

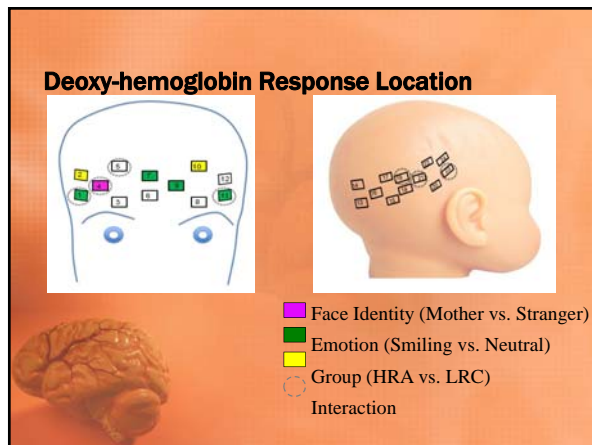


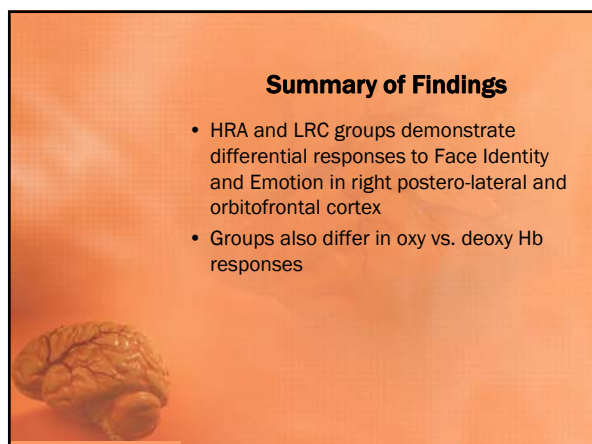
Face-Emotion Paradigm

- Stimuli: Videos of mothers displaying neutral and smiling expressions while speaking (sound is removed)









Functional Connectivity NIRS in Autism

- Autism likely represents a “connectopathy” rather than a disorder of localized and specific brain regions (see subsequent lecture on social communication and autism)
- Do infants at-risk for ASD show a atypical intra- and inter-hemispheric functional connectivity during the first year of life?



Study Design & Participants

- Auditory processing paradigm: ABB vs. ABC syllables
 - Infants listened to 28 blocks of artificial “words” with syllables in either an ABB or ABC pattern (e.g., penana vs. baloti)
- Participants
 - Infants at high-risk for ASD (HRA) and low-risk comparison (LRC) infants were tested at 3-, 6-, 9-, and 12-months



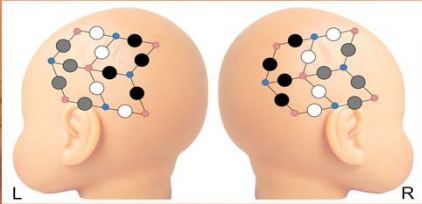
Methods

- Functional connectivity NIRS (fcNIRS) analysis
 - Averaged time course for 4 regions of interest (ROI)
 - 4 probes per ROI
 - Correlation between average time course for each ROI pair calculated



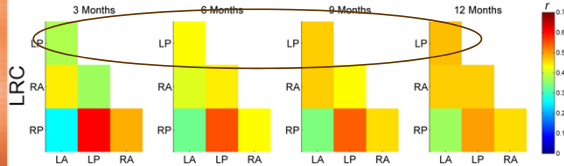
Functional Connectivity (fcNIRS)

- Averaged time course for 4 regions of interest (ROI)
- Correlation between average time course for each ROI pair calculated
- Regions of Interest (ROI):
 - Anterior (grey) and posterior (black) ROIs for each hemisphere

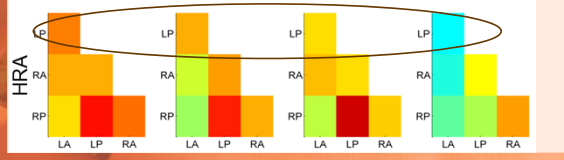


Results

Low-Risk Comparison Group



High-Risk for Autism Group



Summary

- HRA infants evidenced altered trajectory of connectivity across the first years of life
 - Increased connectivity in HRA infants at 3 months of age
 - However, by the second half of the first year we see *reduced* connectivity in HRA infants – similar to findings of Dinstei et al (2011) using fMRI



Caveats/Constraints to fNIRS

- Can only examine first few mm beneath scalp; thus, can only examine cortical surface
- Thick skull/hair impediments to NIRS; thus, are ideally suited to early development, when skull is thinner and hair is more sparse
- Has excellent spatial resolution (but see caveat 1 above); but,
 - Has relatively poor temporal resolution
 - Can't see "inside" a sulcus
- Limited utility in adults ...although advances in probe development are changing this



...con't

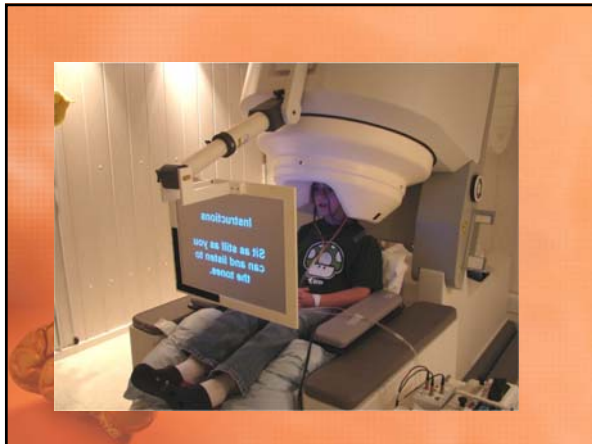
- Similar to fMRI, NIRS provides measures of deOxy – but also provides OxyHB and Total HB.
- In contrast to fMRI, however,
 - Quiet environment
 - Permits head movement
 - Can be performed in very young children
 - Is *relatively* inexpensive



Magnetoencephalography (MEG)

- MEG detects small magnetic fields associated with electrical currents
- Involves super conducting quantum interference device (SQUID) housed in magnetically shielded room (see next slide)



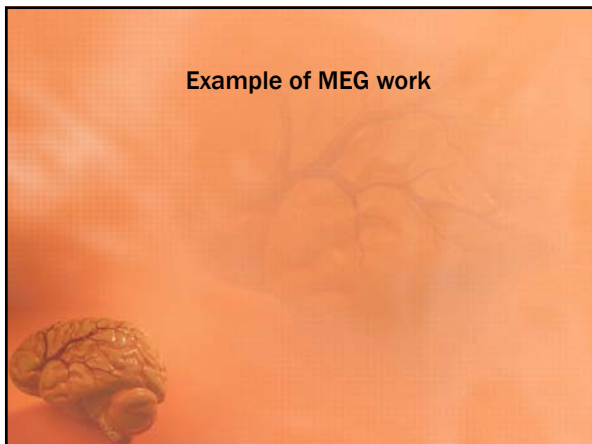


MEG (con't)

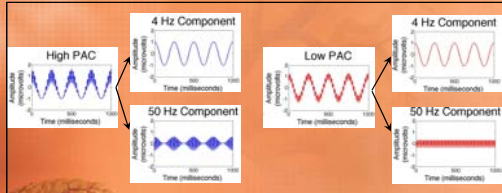
- Pros: excellent spatial and temporal resolution; completely non-invasive
- Cons: very expensive; requires subject to sit very still (like MRI)
- **Bottom Line:** may or may not be tool of the future in context of development (mostly due to limitations in cost, test constraints, technological demands); but, has great potential in context of clinical neuroscience



Example of MEG work

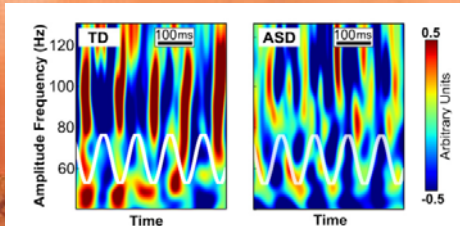


Phase Amplitude Coupling (PAC)



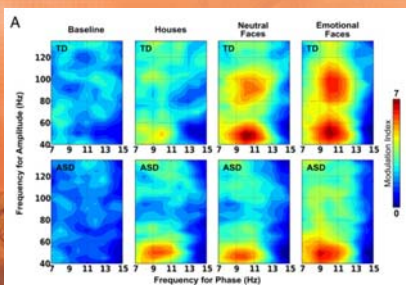
Phase-Amplitude Coupling:

The phase of the lower frequency (e.g., alpha) modulates the amplitude of the higher frequency (e.g., gamma)



Khan et al, *PNAS* 2013

Local functional connectivity, as measured by Phase Amplitude Coupling in the fusiform face area on MEG, is reduced in 14-20 year old males with autism.



Khan et al, *PNAS* 2013

CONCLUSIONS

- The armamentarium of imaging tools has greatly expanded in recent years
- Each tool has advantages and disadvantages;
 - Thus, neuropsychological measures are inexpensive but lack precise structure-function relations.
 - ERPs have excellent temporal resolution (but poor spatial resolution) and can be used throughout the entire lifespan, whereas
 - fMRI has excellent spatial resolution (but poor temporal resolution), and is best used >5/6 years of age (except Nadine Gaab, who is successful with 4 year olds)
 - fNIRS has excellent spatial resolution (but poor temporal resolution) but
 - May not be able to image more than a few mm beneath cortical surface
 - MEG has excellent temporal and spatial resolution but
 - May not be able to image deep structures and
 - it is very expensive
- In the end, which tool is employed should be determined by the question being targeted.
- Future: multi-modal recordings



THE END





Alterations in the Mu rhythm?

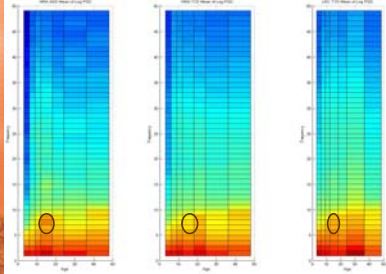


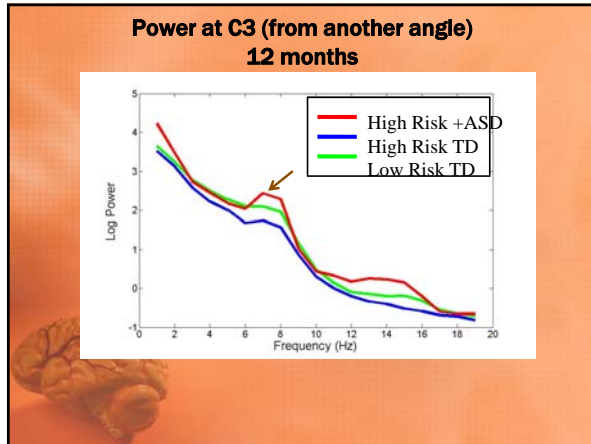
THE TASK

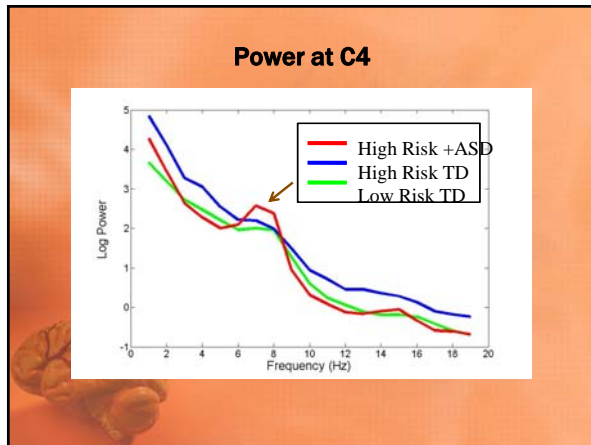


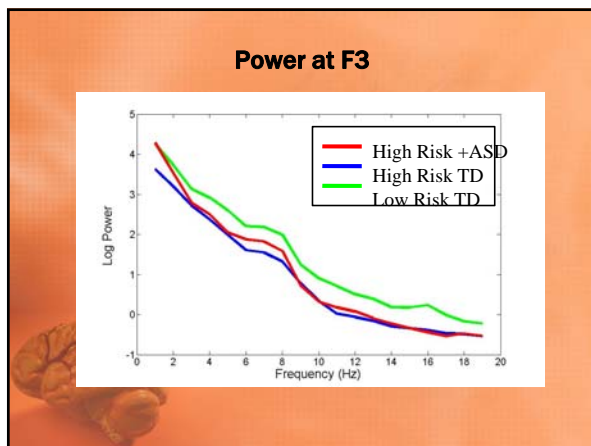
Power at C3

High Risk +ASD High Risk TD Low Risk TD









Could it be Mu?



- Mu rhythm oscillates at approximately 5-9 Hz in babies
 - Seen predominantly at electrodes C3 and C4
- Mu is suppressed both when a subject performs an action and observes someone else perform the same action
 - Mirror neuron hypothesis
- Mu suppression is seen in infants as young as 8 months
 - Increases with age
- Children with ASD show decreased mu suppression when watching a stranger perform an action
- *Does watching an RA blow bubbles → mu suppression?*



Summary

- EEG reflects multiple neuronal sources acting in synchrony
- Signal itself is complex, containing different frequencies
- Are simple (e.g., FFT) and complex (machine learning, multiscale entropy) ways to make sense of the EEG
- Signal decomposition permits inference about
 - Underlying networks and
 - Functional significance of signal