Using the visual system as a means to quantitatively evaluate cortical function and cognitive performance in Rett syndrome

Charles A. Nelson
Professor of Pediatrics and Neuroscience
Professor of Psychology in Psychiatry
Harvard Medical School
Richard David Scott Chair in Pediatric Developmental Medicine Research
Boston Children's Hospital

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Rett Syndrome Marked by Developmental Regression

ABOUT RETT SYNDROME

- X-linked, spontaneous mutation of MeCP2
- < 1% cases inherited
- Primarily affects females
- Prevalence: ~1/10,000 females
- Classified by toddlerhood regression, loss of purposeful hand use, loss of acquired speech, gait abnormalities, and stereotypies.

Source: Rett, 1966; Hagberg, 1983; NINDS, 2015.

Nelson Lab Rett Syndrome Studies

Specific Aims

1. to **quantitatively evaluate cortical function** in girls with RTT using electroencephalography (EEG), event-related potentials (ERP) and visual evoked potentials (VEP).
2. to monitor and **measure neurological signs of response to pharmacological treatment** through changes in VEPs, and resting state EEG over treatment course. *This work being done in parallel with work in mouse (Michela Fagiolini)*
3. to **develop a cognitive assessment that circumvents confounds of impairment in motor function and expressive language** when assessing domains of receptive language and visual reception.

Gaps of knowledge in Rett syndrome research

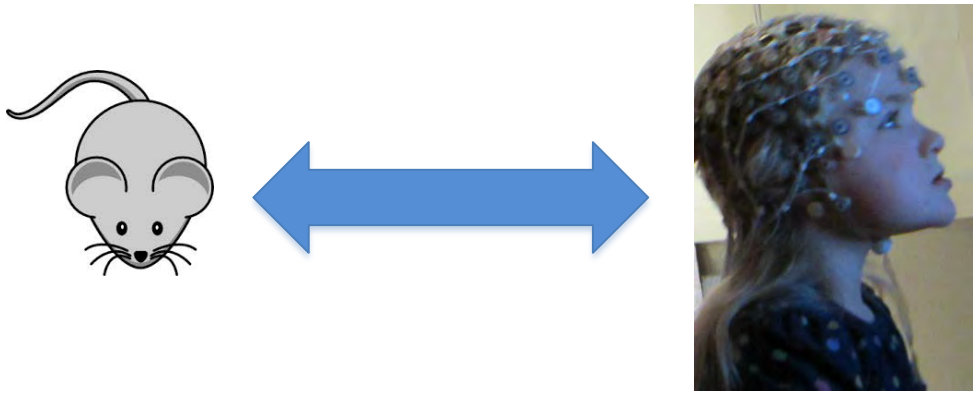
– **Cortical function**

Part I – Evaluating cortical function with visual evoked potentials (VEPs)

– **Cognitive function**

Part 2 – Evaluating cognitive function with a developmental behavioral assessment (MSEL) and eye-tracking

VEP as a translational biomarker in RTT



- Reflects the summation of cortical response to a visual stimulus
- Robust signal with distinct, quantifiable components
- Matures within the first year of life
- Passive task not dependent on attention
- Non-invasive, quick, and cost-effective
- *Can use the knowledge gained in mouse models of RTT to better understand the cellular and circuit impairments in RTT patients and inform treatments*

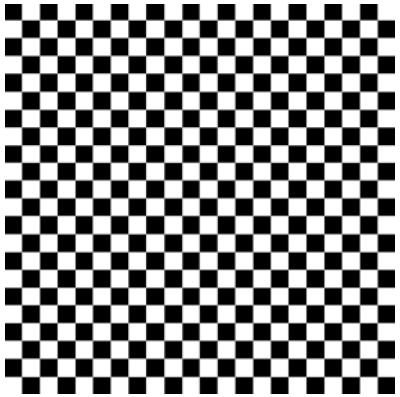
Population for VEP study

RTT subjects were recruited through the Natural History Study or the Rett Syndrome Program at Boston Children's Hospital (BCH)

20 typically developing girls recruited as controls

	Control	RTT
Number of subjects	20	34
Mean age in months	57	56
Age range	24-112	22-103

Pattern-reversal VEP paradigm

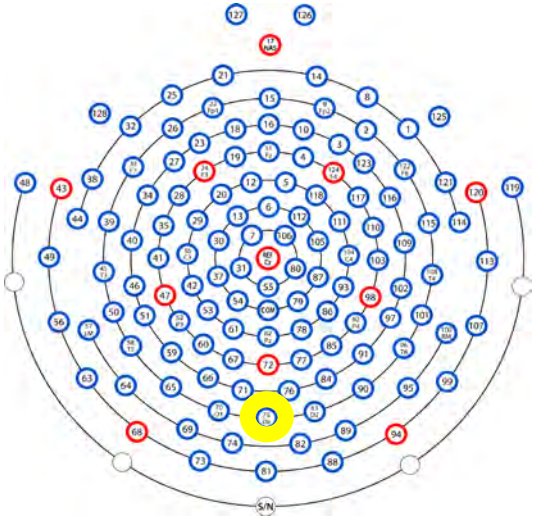


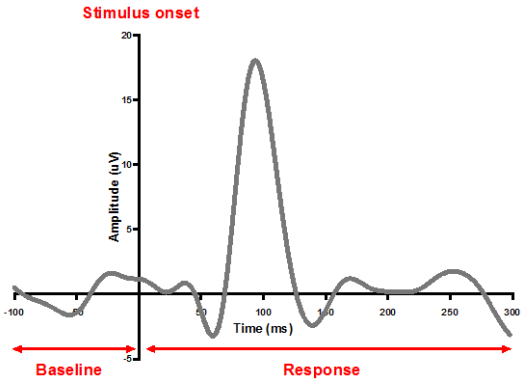
Stimulus

Eye-gaze contingent

Data collection

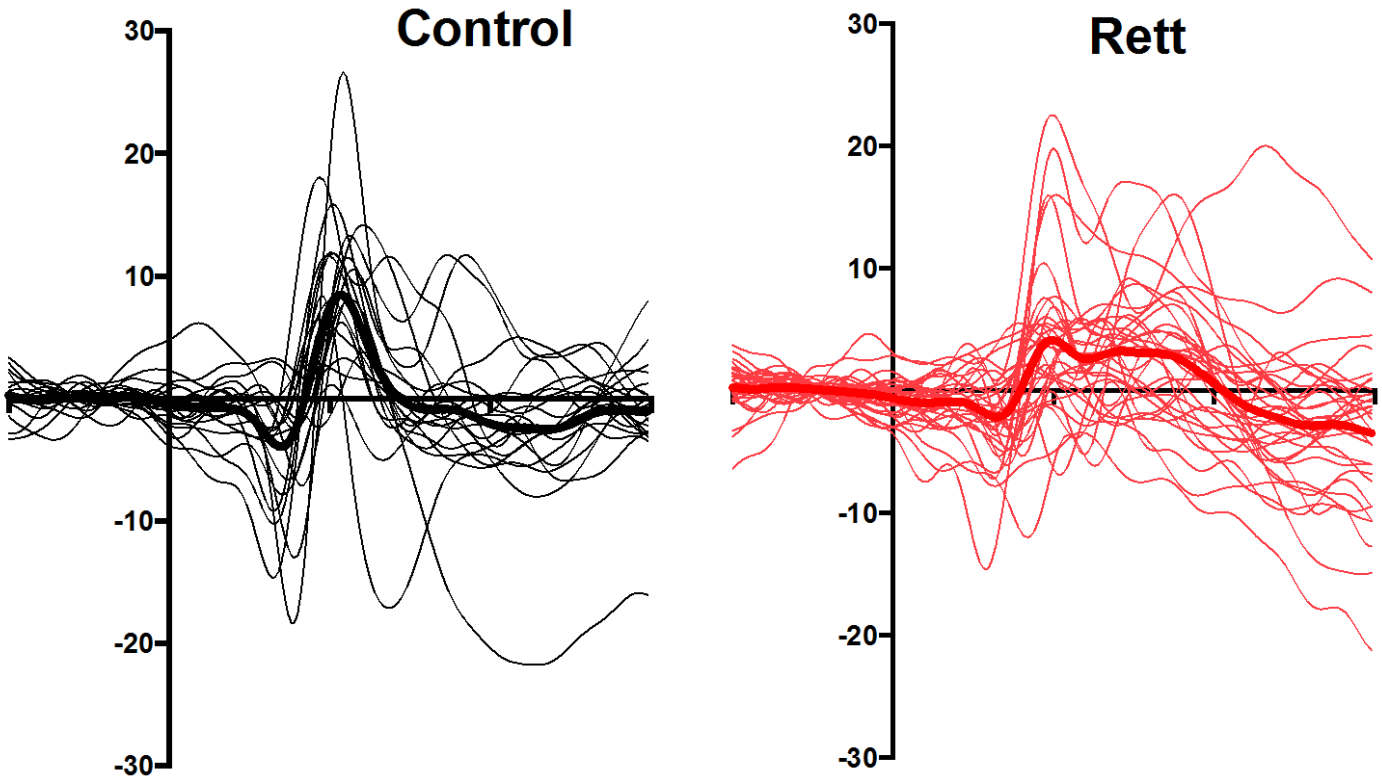
128-channel EEG net



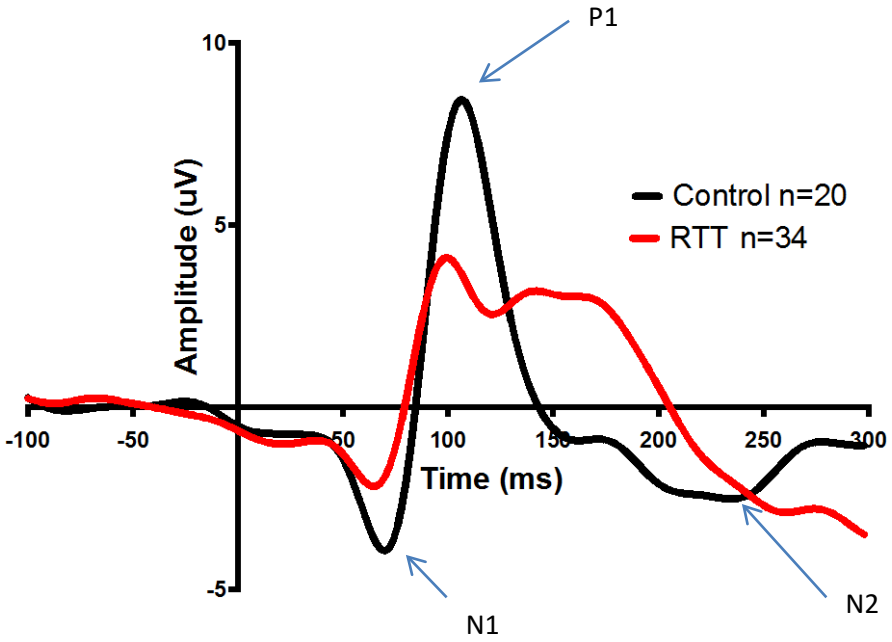


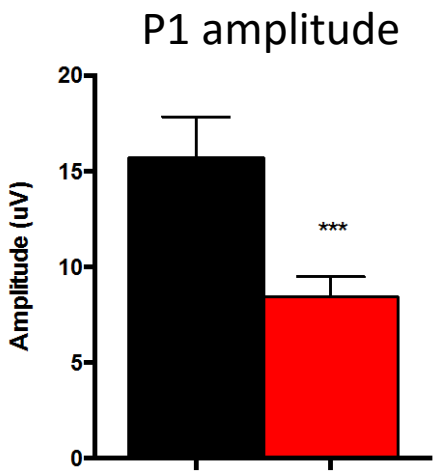
VEP waveform is abnormal in children with RTT

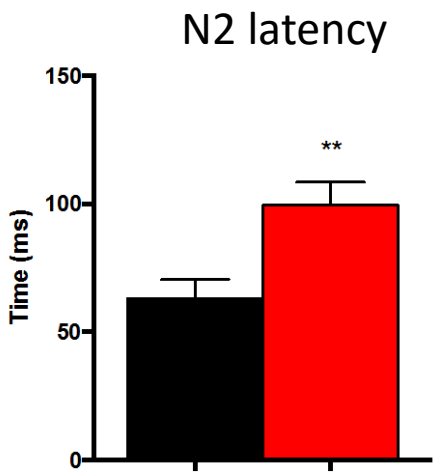
(displayed are individual subject averages)



Group differences: Control vs. Rett

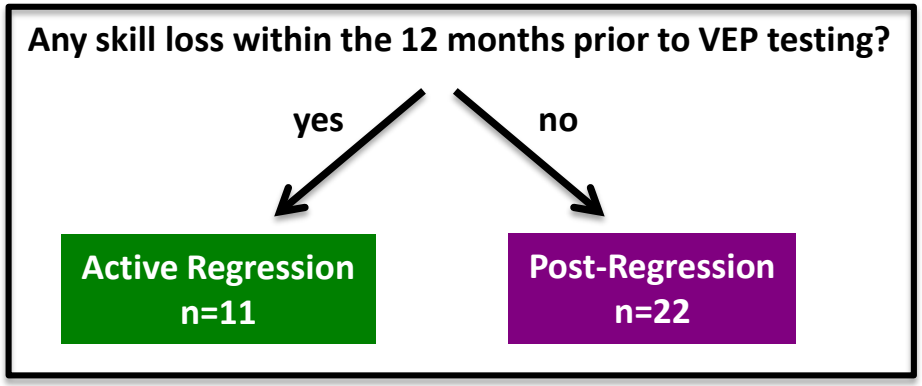


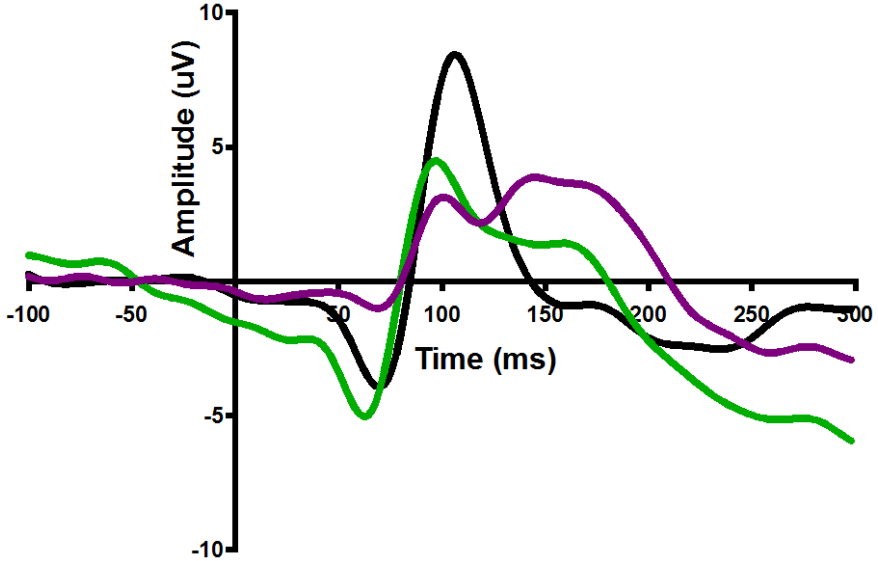


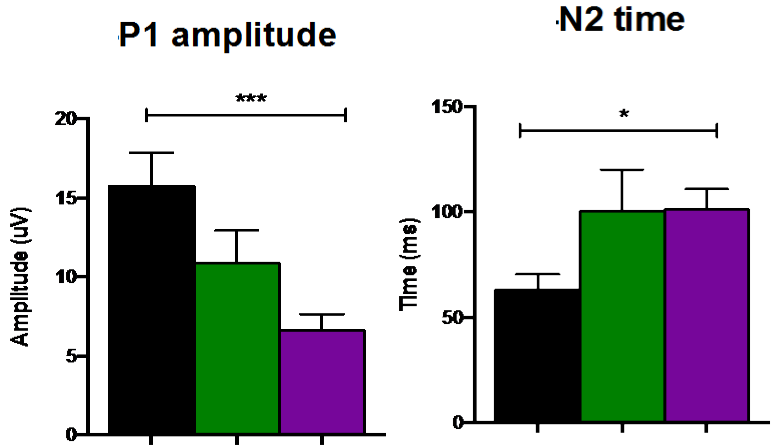


P1 amplitude is diminished and N2 time is increased in RTT

How does the VEP change with developmental progression in RTT?



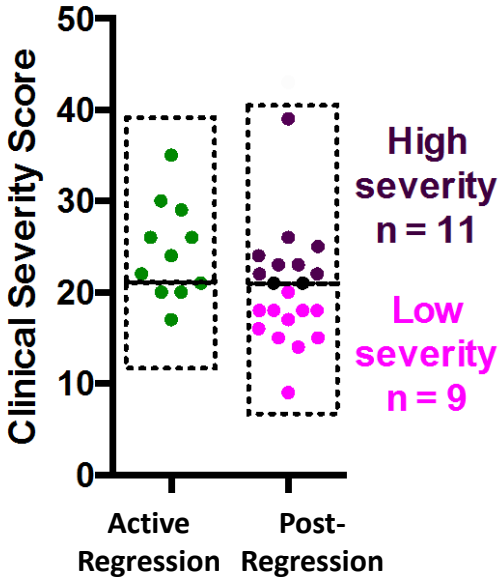


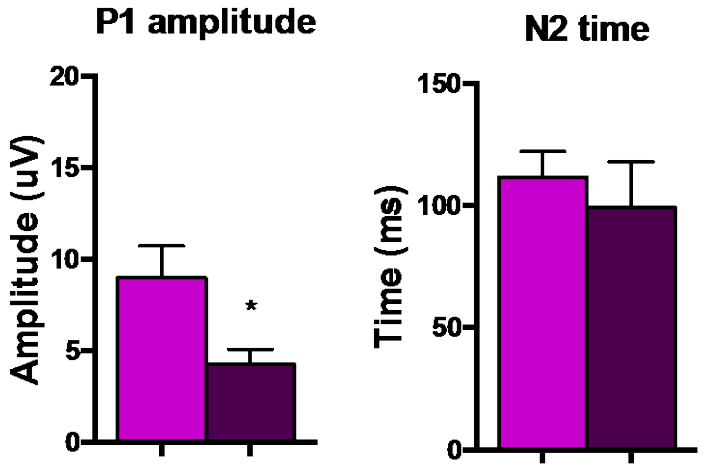


- **P1 amplitude diminishes with progression of the disorder**
- **Longer N2 time is a consistent feature of RTT throughout the stages**

Is the VEP sensitive to clinical severity?

Clinical severity score
Age of onset of regression
Head Growth
Sitting
Crawling
Ambulation
Non-verbal comm.
Language
Respiration
Seizures
Hand use
Feeding
Onset of stereotypies
Somatic growth
Autonomic dysfunction
Scoliosis



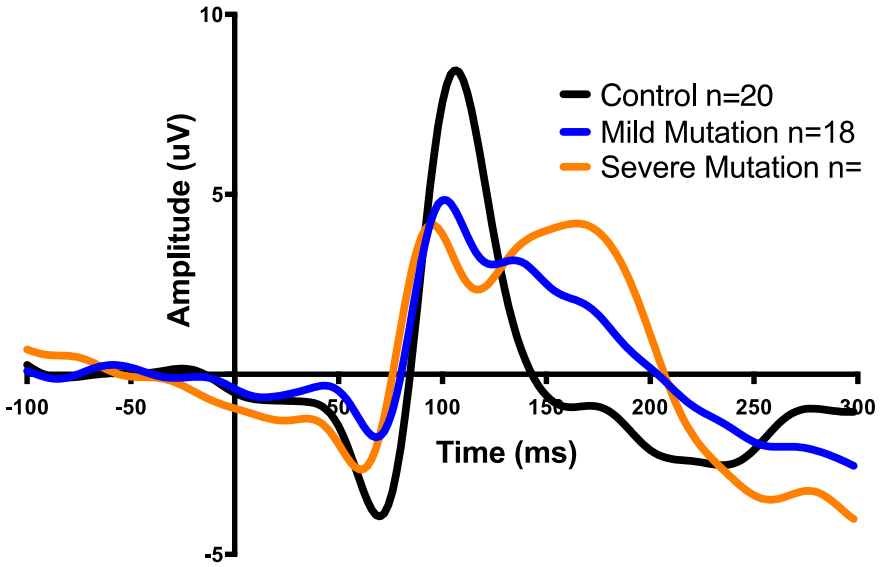


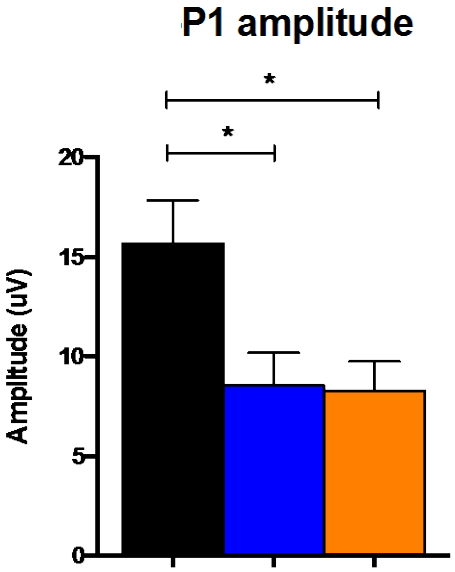
P1 amplitude is an index of clinical severity during the Post-Regression stage

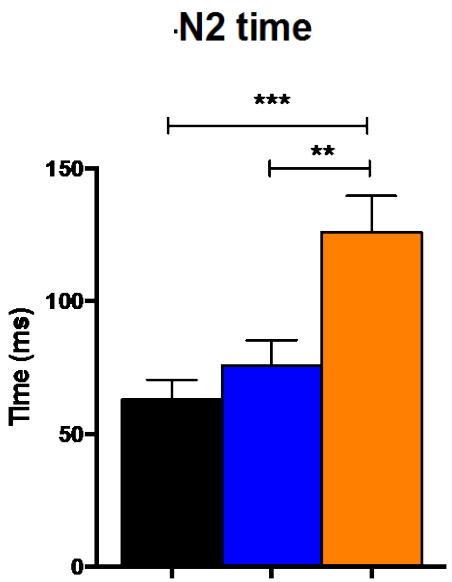
Is the VEP sensitive to MeCP2 mutation type?

Mild
R133C (n=2)
R294X (n=1)
R306C (n=4)
T158M (n=3)
C-terminal trunc (n=5)
Other deletions (n=3)

Severe
R168X (n=9)
R255X (n=3)
R270X (n=1)
Large deletions (n=2)

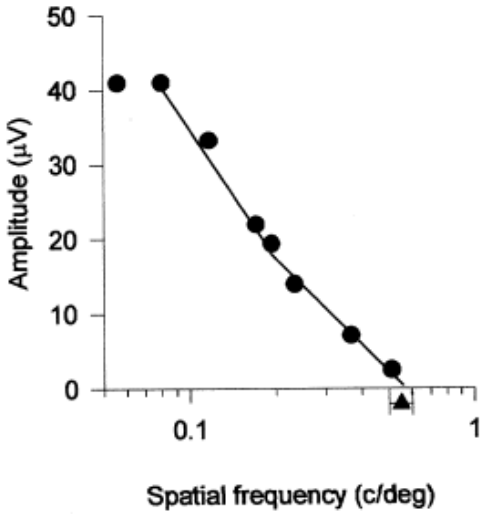


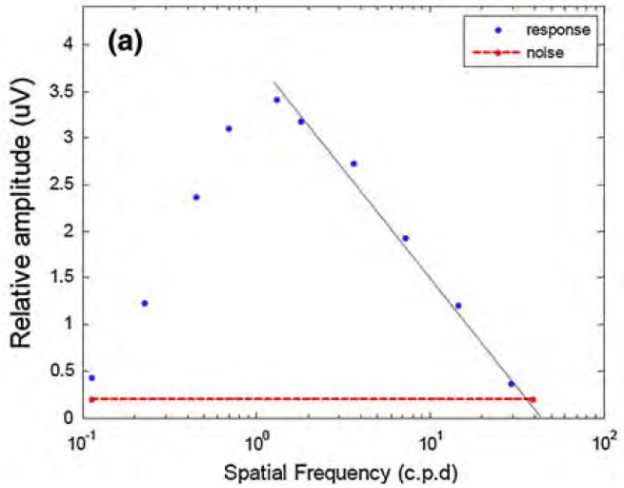




MeCP2 mutation severity selectively impacts N2 time and not P1 amplitude

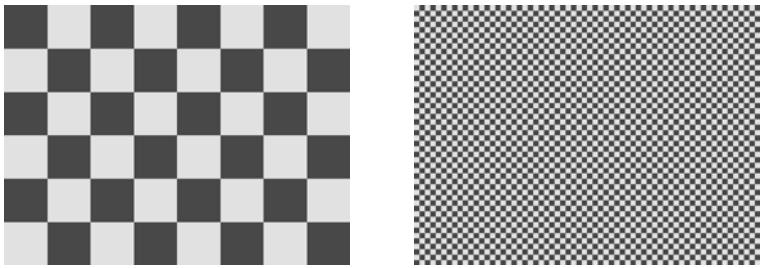
VEPs can be used to measure spatial resolution (acuity)





Low **High**

Spatial Frequency



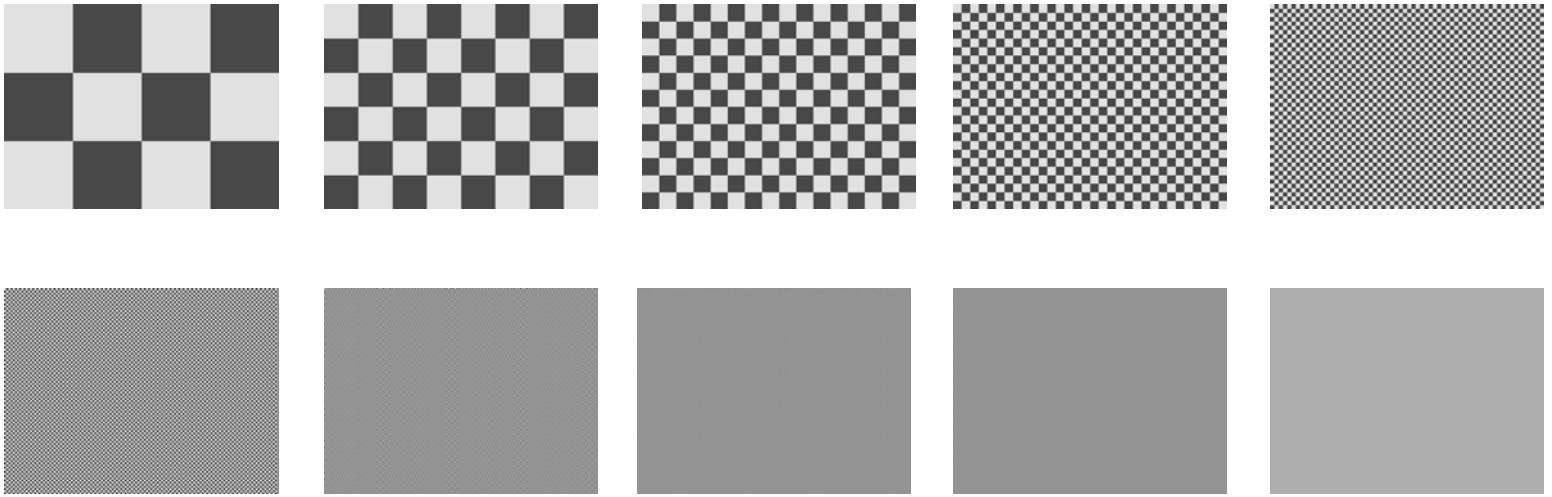
Porciatti et al., *Vision Research*, 1999

Iyer et al., *Doc Oph*thalmol, 2013

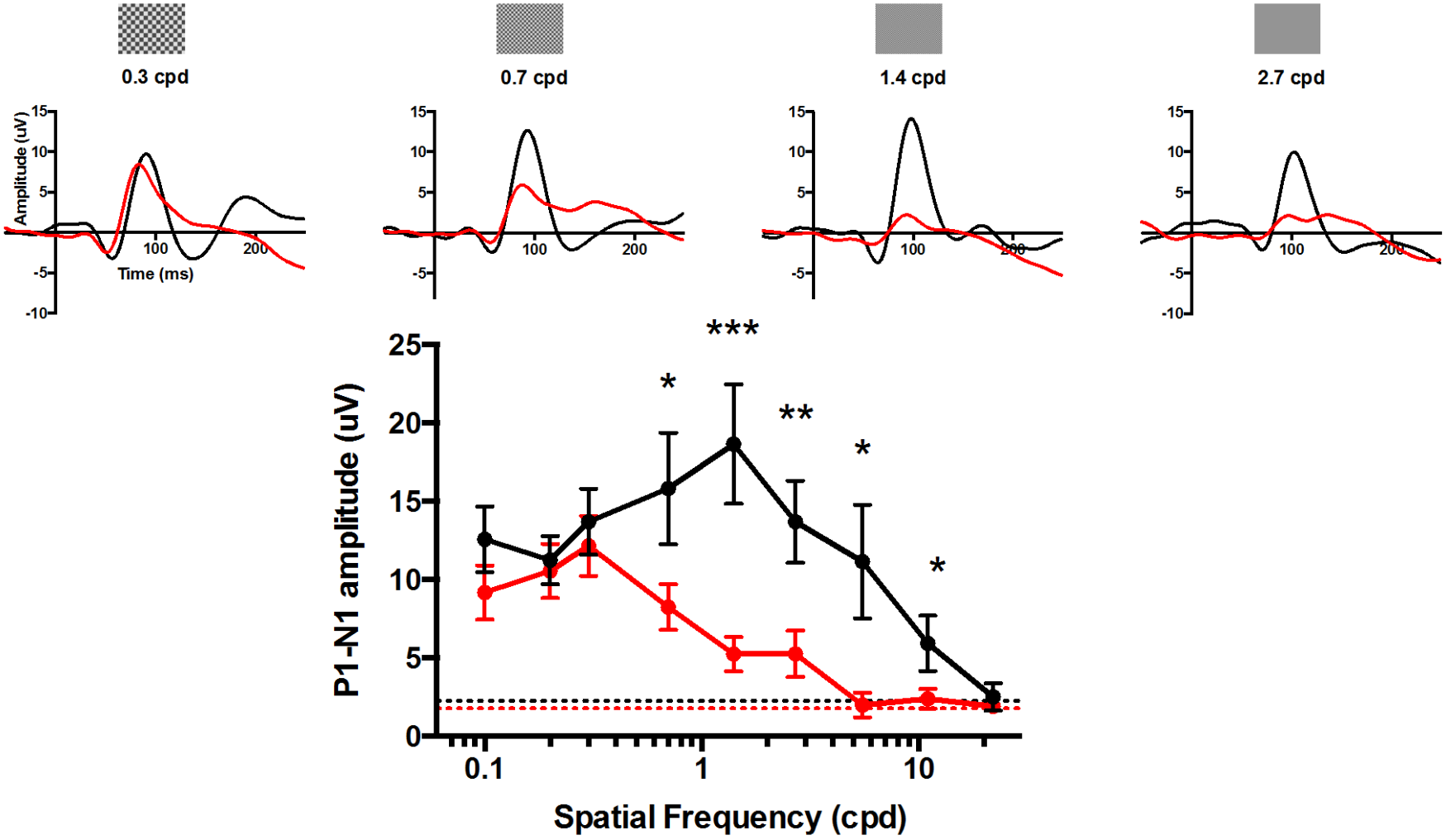
Testing acuity in Rett patients using VEP

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

- The Fagiolini lab found that MeCP2 knock-out mice displayed reduced behavioral and VEP acuity
- This inspired recording VEPs in humans with RTT in the Nelson lab
- 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

Summary: Part 1

- Intracortical processing of sensory stimuli is impaired in RTT
- Reduction in P1 amplitude worsens with progression of the disorder and is an index of clinical severity
  - Weak or asynchronous excitation
  - Local hypoconnectivity
- Prolonged N2 time is a consistent feature of Rett throughout the progression of the disorder but *does* reflect mutation type
  - Impaired intracortical signaling, ineffective inhibition, demyelination
- The VEP provides a quantitative unbiased biomarker for cortical function

Gaps of knowledge in Rett syndrome research

– **Cortical function**

Part I – Evaluating cortical function with visual evoked potentials

– **Cognitive function**

Part 2 – Evaluating cognitive function with a developmental behavioral assessment (MSEL) and eye-tracking

Part 2: Cognitive functioning

- We need cognitive assessments to
  - provide a functional correlate for research measures
  - provide an outcome measure for interventions or treatments
  - better understand needs and improve quality of life

- Current evaluations underestimate the cognitive abilities of children with RTT

Goal:

To assess cognitive skills while minimizing confounds from fine motor and expressive language deficits

Method:

Adapt the conventional administration of the MSEL for girls with RTT (n=36, mean age is 58 months, range is 22-123 months) for use with eye tracker

Mullen Scales of Early Learning (MSEL)

- 5 domains or "scales"
  - Gross Motor
  - Fine Motor
  - Expressive Language
  - Receptive Language
  - Visual Reception

- Play-based, interactive assessment
- For use from birth to 6 years old

- Output:
  - Raw score
  - Equivalent age
  - Descriptive category
  - Developmental quotient

Limitation for RTT: basic verbal and/or motor skills needed for most items

Incorporating eye tracking technology into the Adapted MSEL

- Girls use eye gaze to "greet, point, request, and refuse"
- Previous pilot studies have suggested that eye gaze tracking can be an effective method for assessing some aspects of cognition*
- Our lab has expertise with eye tracking systems

Pilot Study:

<u>Experimental Design</u>

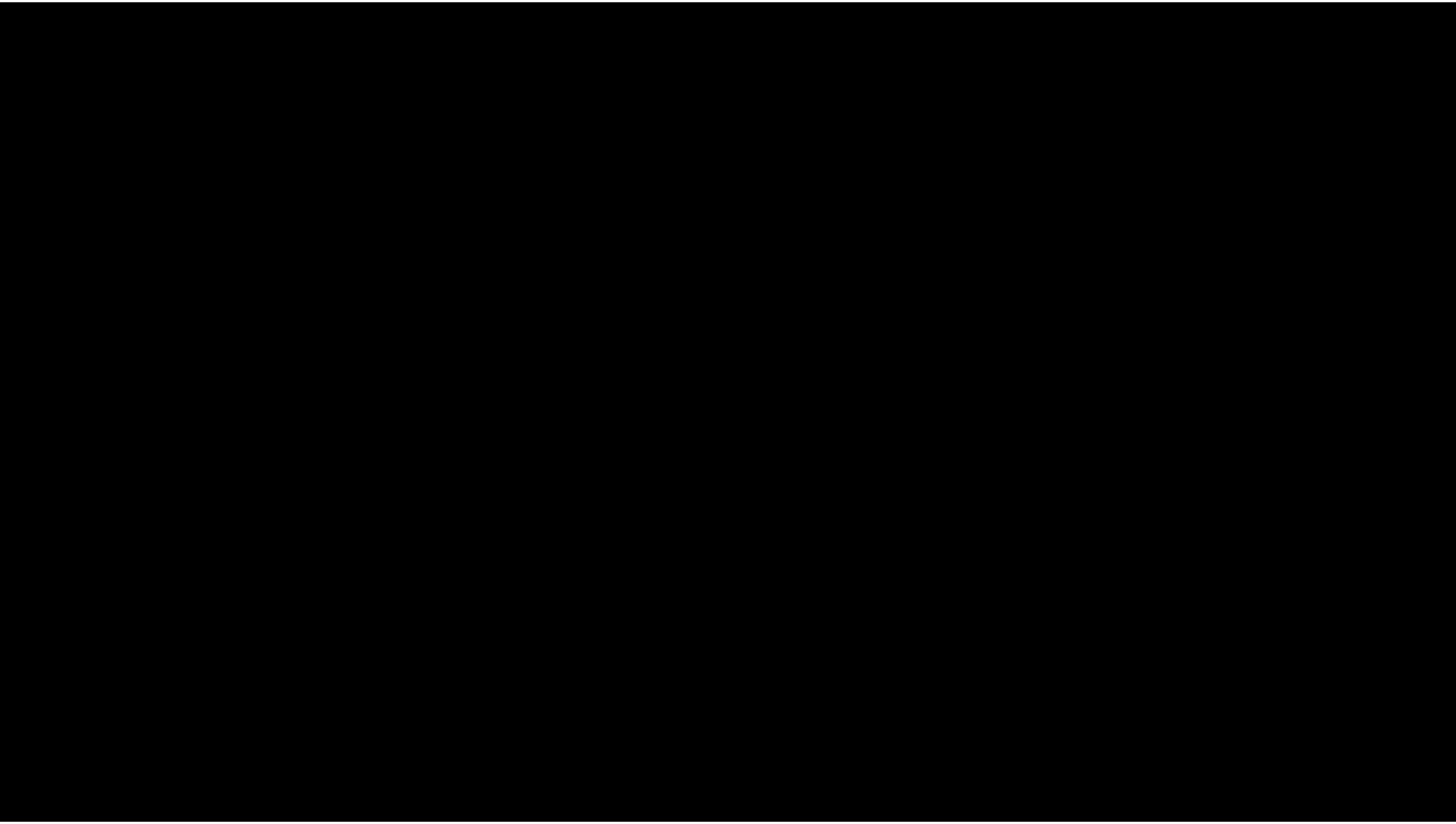
Translate Visual Reception and some Receptive Language MSEL items into PowerPoint slides presented on a Tobii® eye tracker monitor

<u>Subjects</u>

12 girls with RTT, 2-4 years old

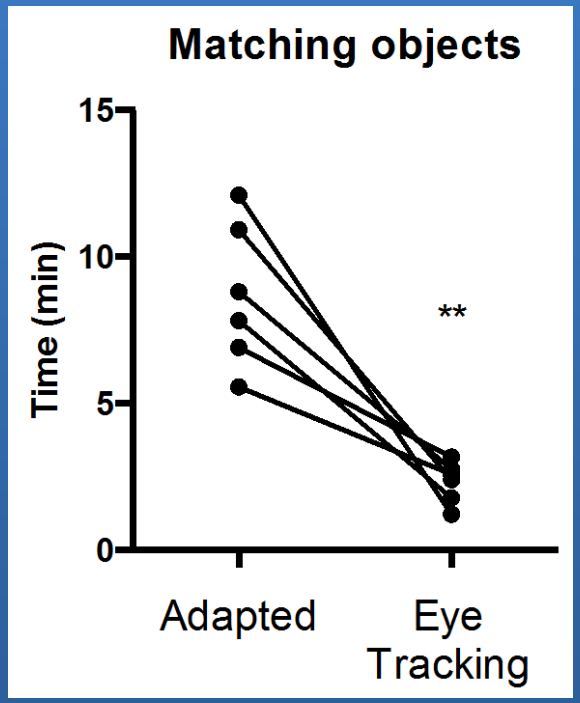
Administered both Adapted and Eye tracking MSEL to same individual

*von Tetzchner *et al.*, 1996; Baptista *et al.*, 2006; Djukic *et al.*, 2012; Rose *et al.*, 2013

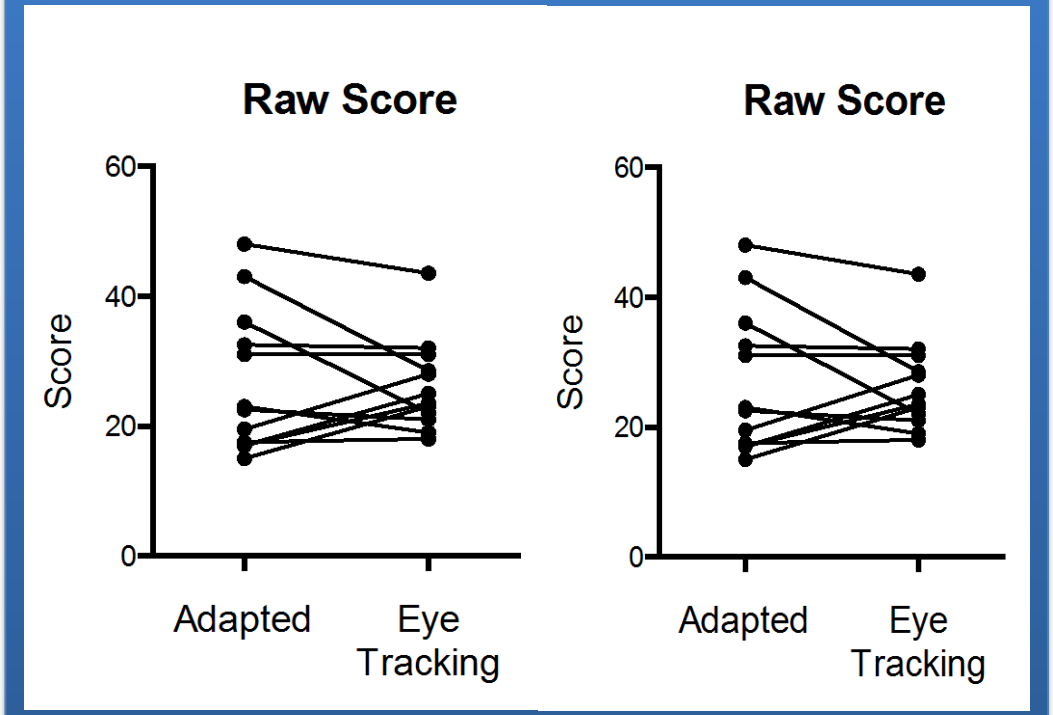


Adapted vs. Eye Tracking MSEL outcomes

Less time to administer items on the Eye Tracking MSEL



Similar outcomes on both paradigms for Visual Reception



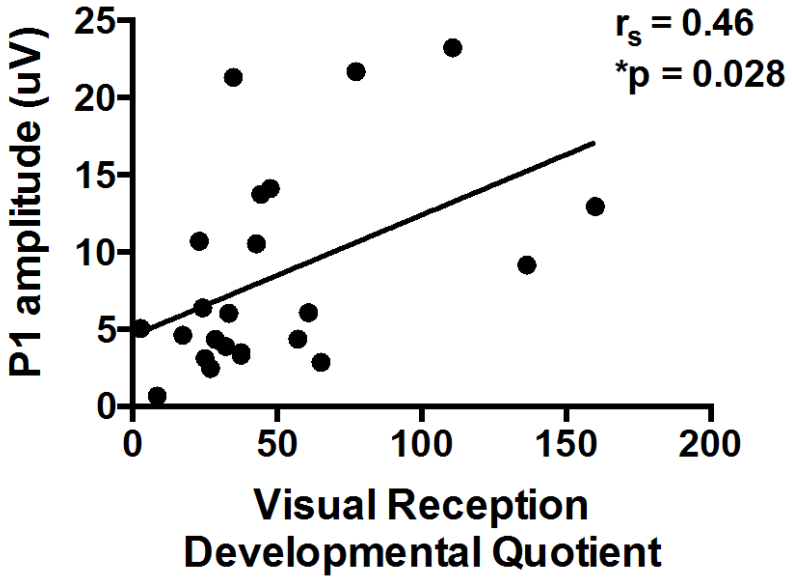
Summary: Part 2

- Cognitive impairment is a significant feature of RTT
- HOWEVER, some do surprising well, indicating some “hidden abilities” that might not be detected by standard assessments
- Impacts how parents interact and communicate with their child
- Eye gaze represents an important avenue for cognitive assessment in RTT and other disorders with fine motor or expressive language limitations

Does the VEP reflect cognitive function?

VEP P1 amplitude positively correlates with visual reception skills on the Adapted MSEL

We have both VEP and Adapted MSEL data from 23 girls



Overall summary and future directions

Summary

1) The VEP provides a promising biomarker of cortical function

2) Adaptation of the MSEL improves assessment of cognition in RTT

Future Directions

- Complete eye tracker version for Receptive Language domain
- Continue to further adapt items for RTT
- Incorporate both VEP and eye tracking MSEL into clinical trials
- Further ground human VEP work in animal models

THE END

- charles_nelson@harvard.edu