

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

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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.



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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

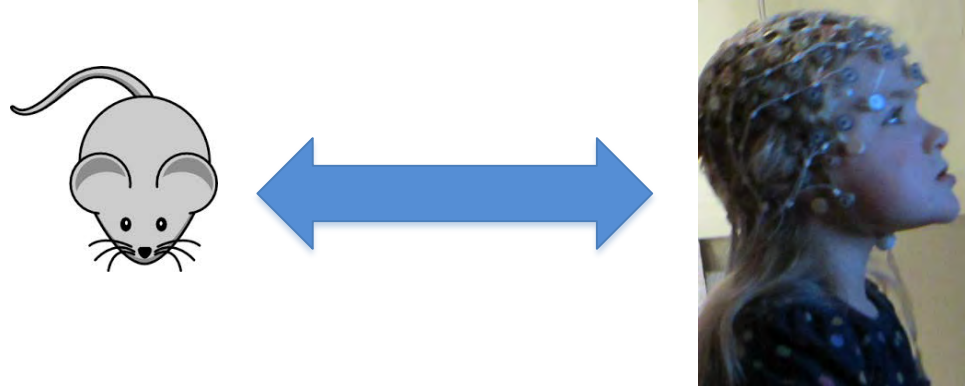
Part 1 – Evaluating cortical function with visual evoked potentials (VEPs)

– 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

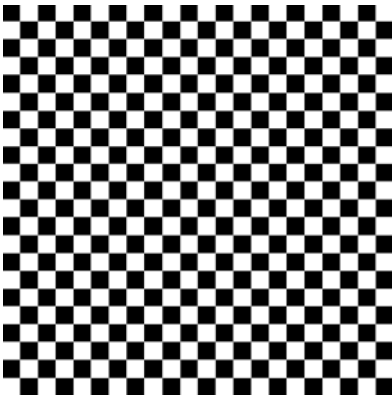
RTT subjects were recruited through the Natural History Study or the Rett Syndrome Program at Boston Children's Hospital (BCH)

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



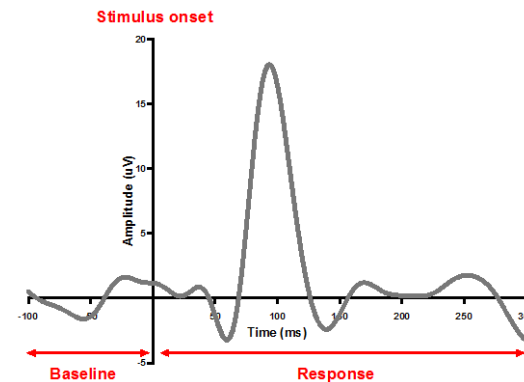
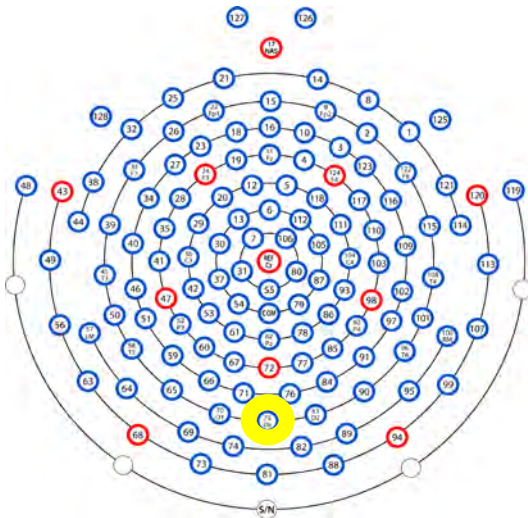
Stimulus

Eye-gaze contingent



Data collection

128-channel EEG net



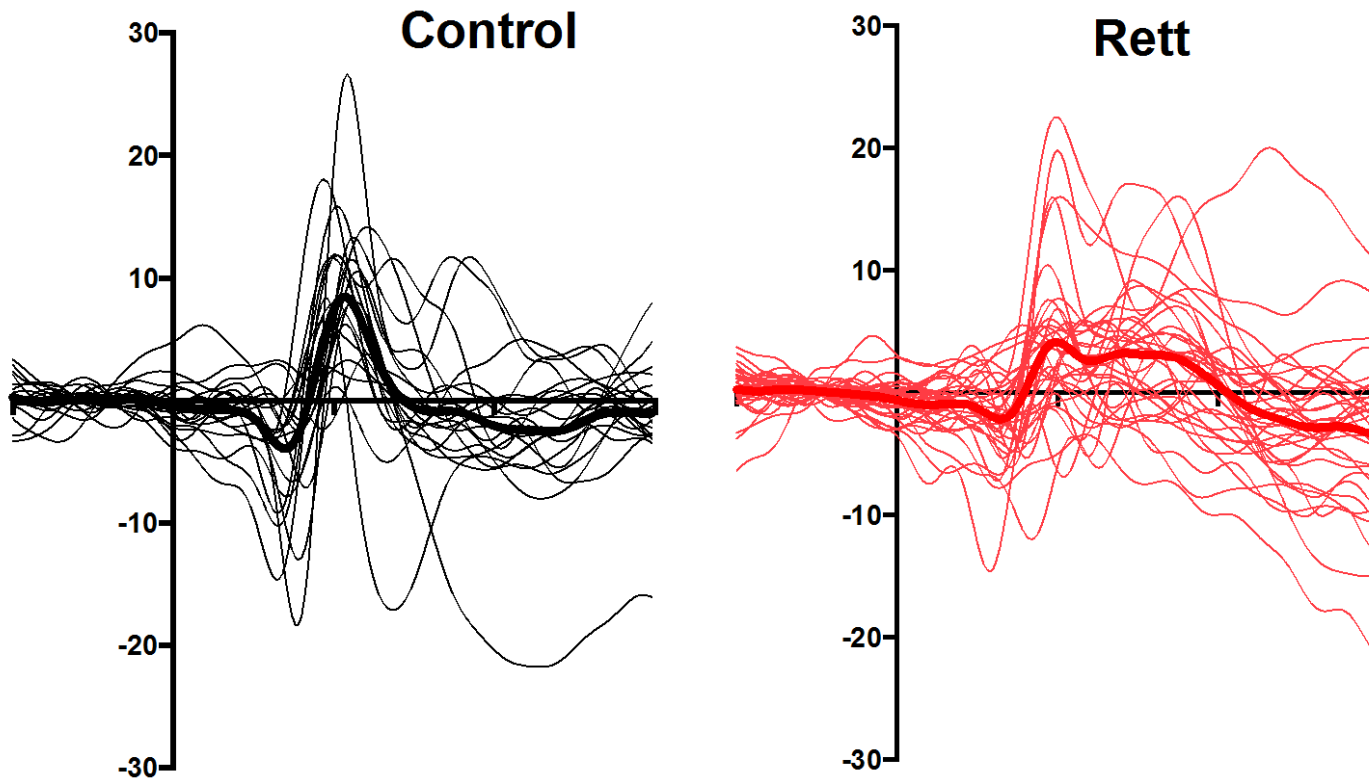
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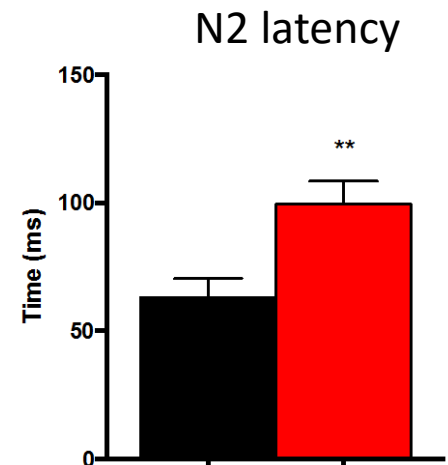
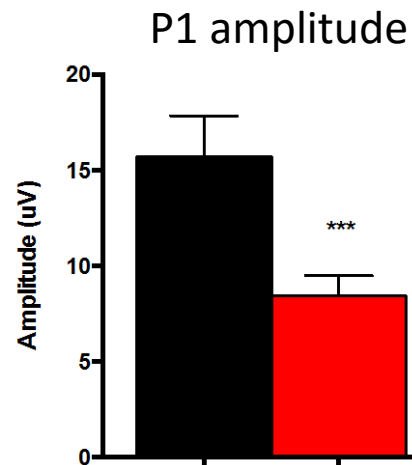
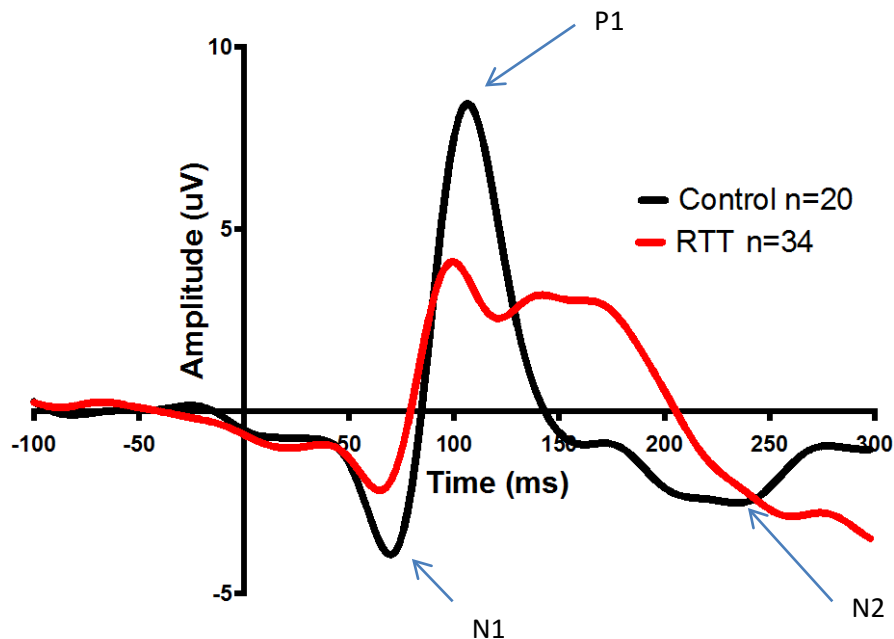
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VEP waveform is abnormal in children with RTT

(displayed are individual subject averages)



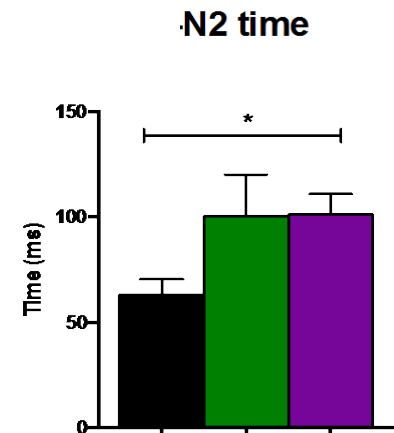
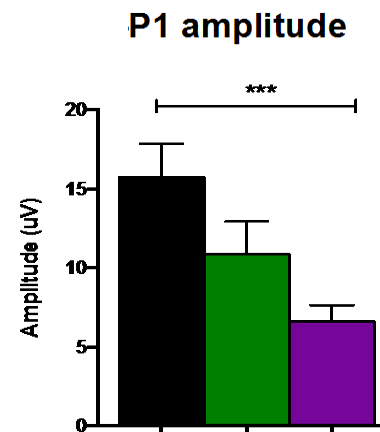
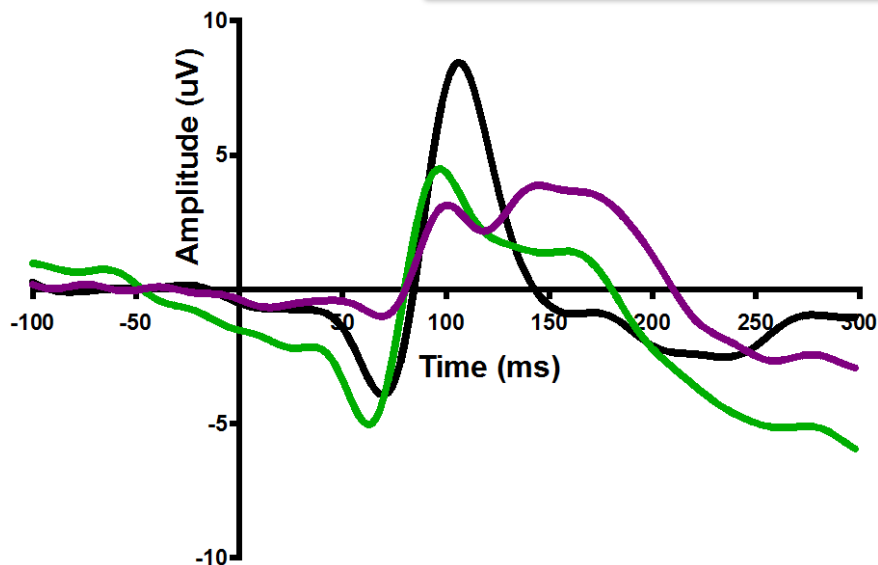
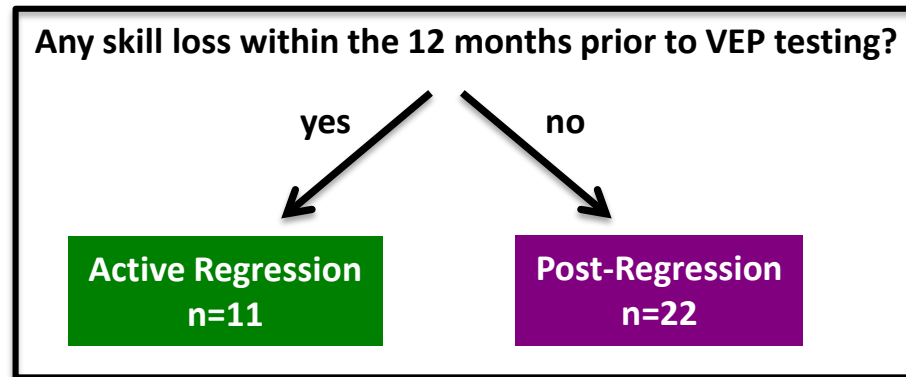
Group differences: Control vs. Rett



P1 amplitude is diminished and N2 time is increased in Rett



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

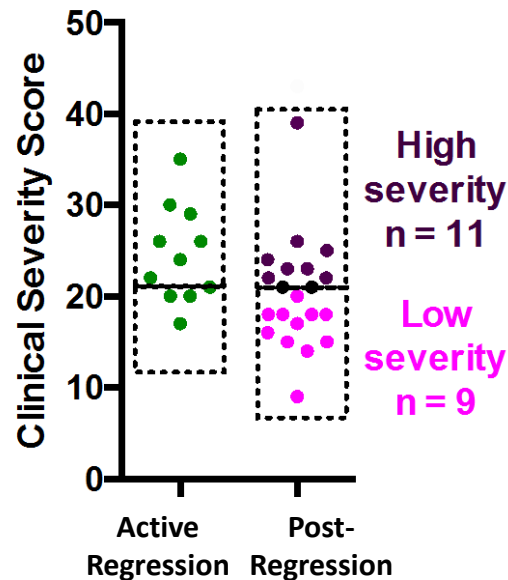
Feeding

Onset of stereotypies

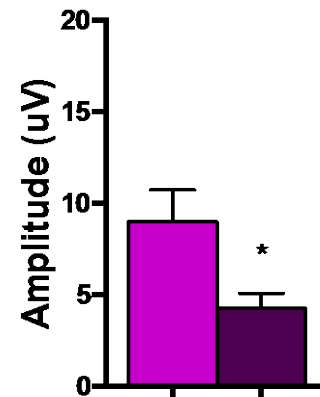
Somatic growth

Autonomic dysfunction

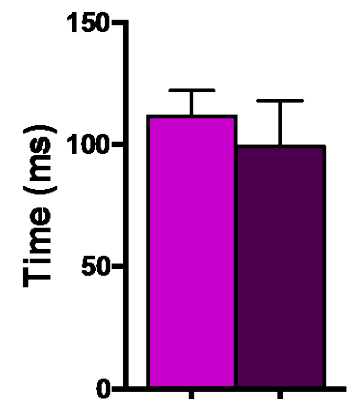
Scoliosis



P1 amplitude



N2 time



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



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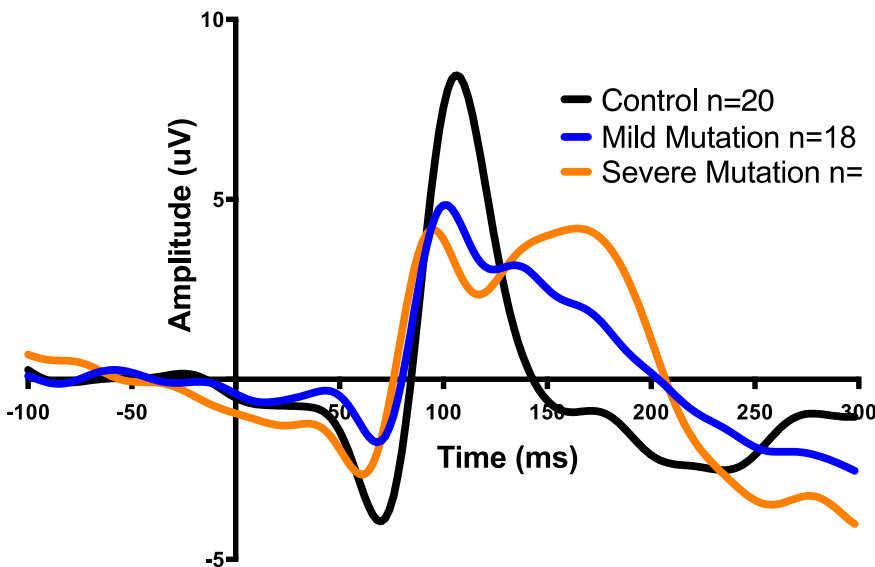
Is the VEP sensitive to MeCP2 mutation type?

Mild

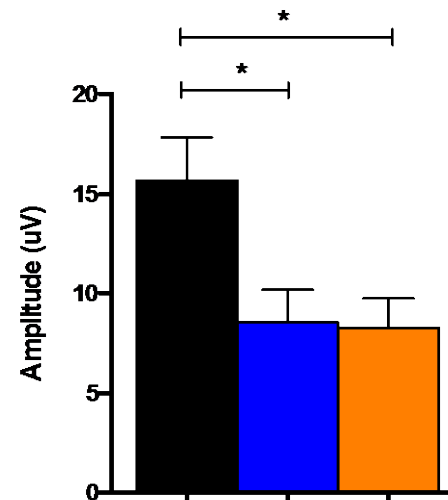
R133C (n=2)
R294X (n=1)
R306C (n=4)
T158M (n=3)
C-terminal trunc (n=5)
Other deletions (n=3)

Severe

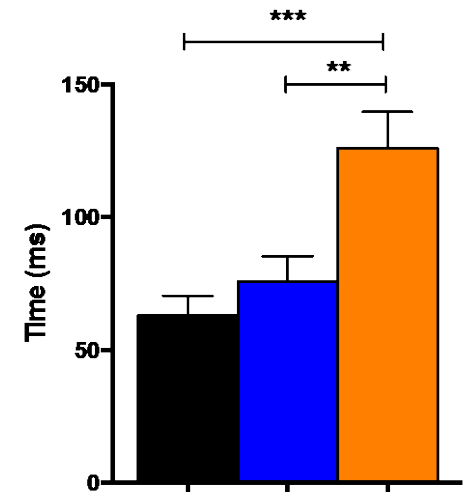
R168X (n=9)
R255X (n=3)
R270X (n=1)
Large deletions (n=2)



P1 amplitude



N2 time



MeCP2 mutation severity selectively impacts N2 time and not P1 amplitude

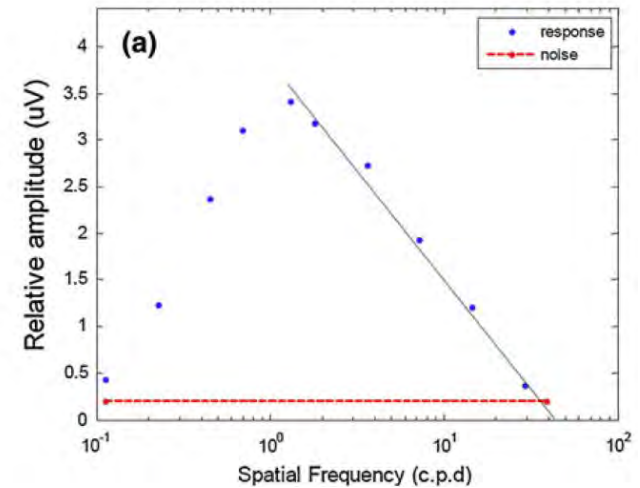
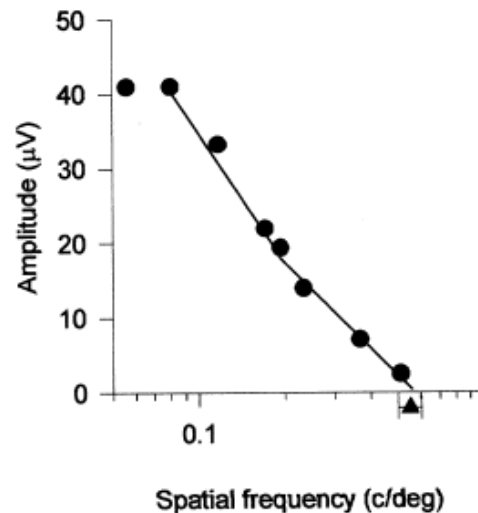
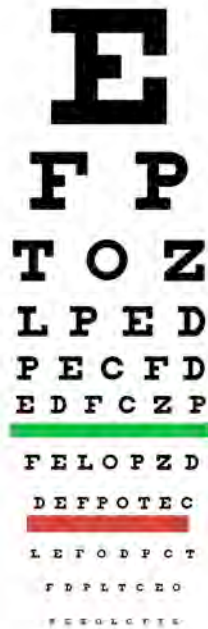


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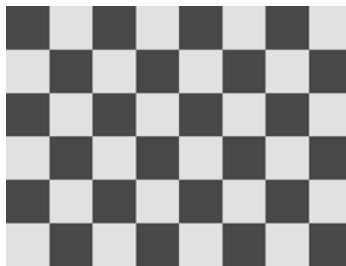
VEPs can be used to measure spatial resolution (acuity)



Low

High

Spatial
Frequency



Porciatti et al., *Vision Research*, 1999

Iyer et al., *Doc Ophthalmol*, 2013



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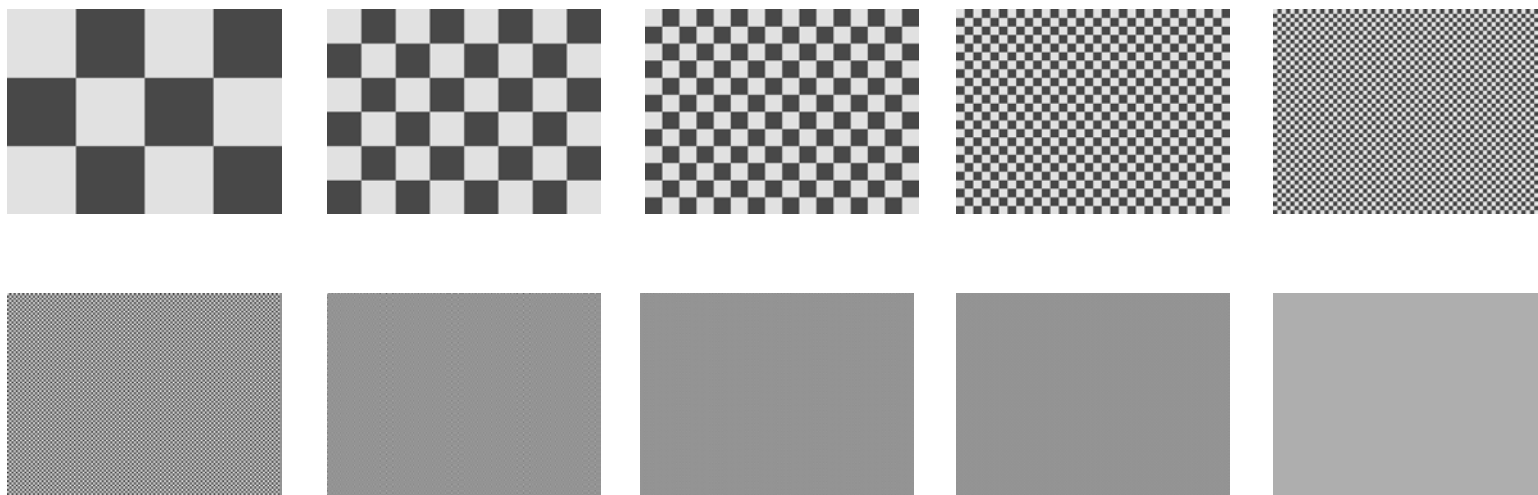


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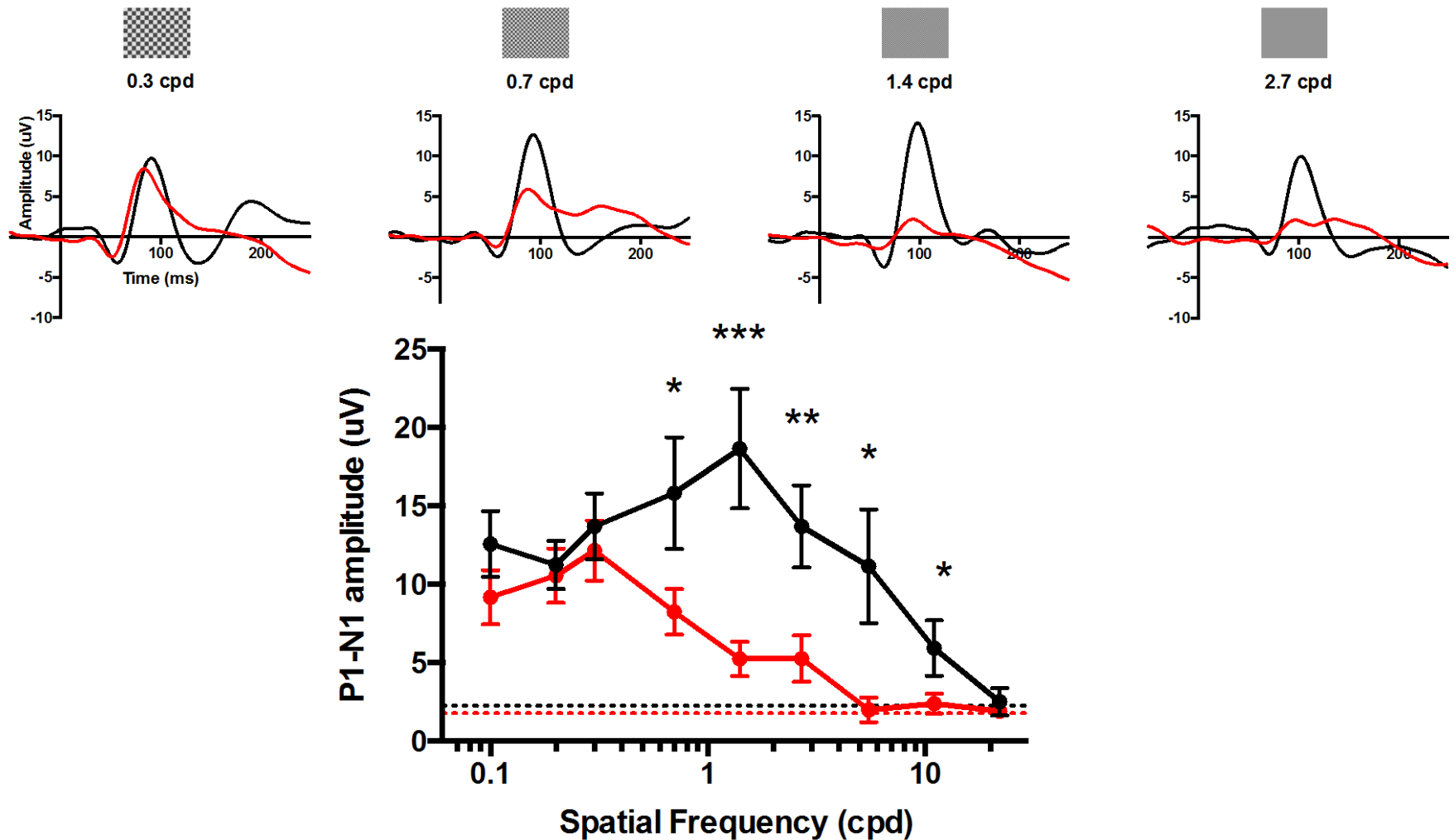
Testing acuity in Rett patients using VEP

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 1 – Evaluating cortical function with visual evoked potentials

– Cognitive function

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



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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:

Experimental Design

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

Subjects

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



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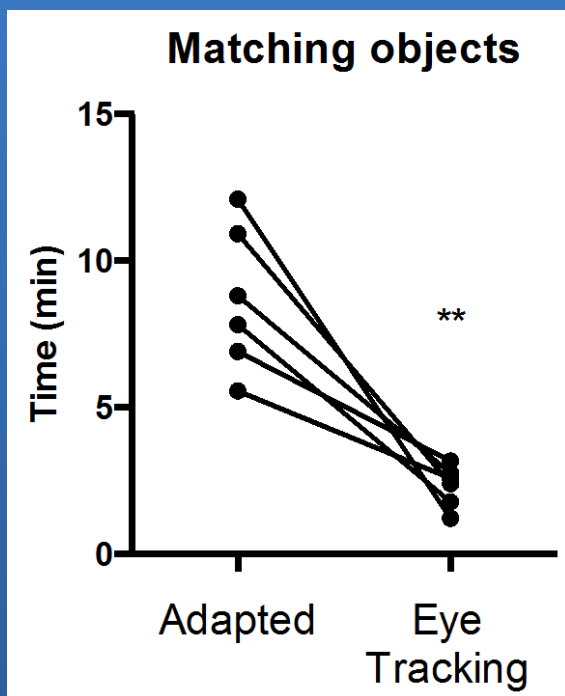
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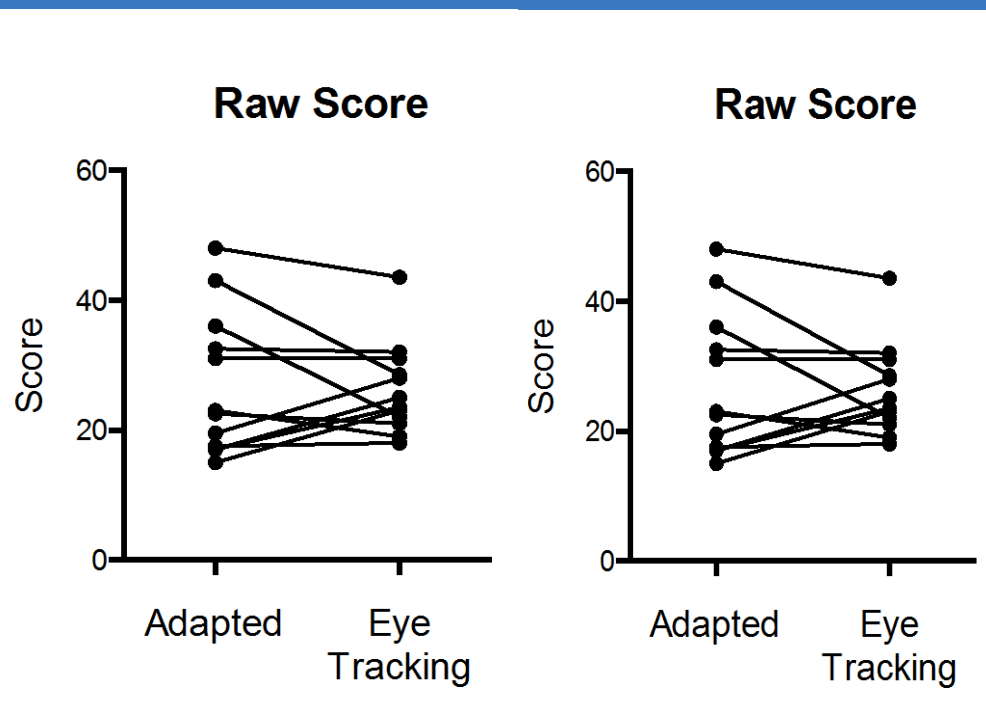
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Adapted vs. Eye Tracking MSEL outcomes

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?



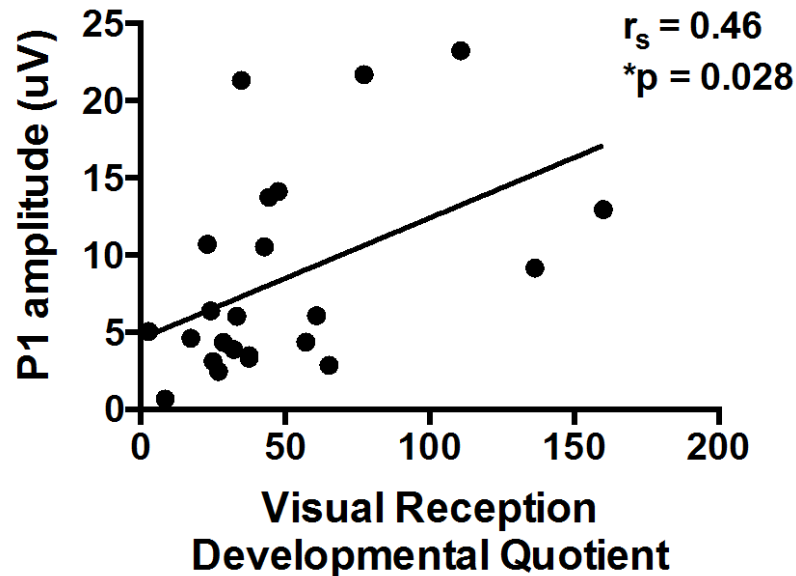
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VEP P1 amplitude positively correlates with visual reception skills on the Adapted MSEL

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

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