Application of Psychophysiological and Neuromodulation Methods for Autism Research and Treatment

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Cognitive Neuroscience Lab., Dept. Psychiatry

Autism theories

- Executive function deficits *(Ozonoff, 1997)*
- Impaired neural connectivity *(Welchew, 2005)*
- Weak central coherence *(Happe, 1999)*
- Baron-Cohen's theories (e.g., "theory-of-mind", "empathy" & similar deficits, *Baron-Cohen, 2002*)
- "Broken Mirror Neuron System" *(Pineda, 1999)*
- Cerebellar dysfunction *(Courchesne et al., 1995)*
- "Minicolumnar" neuropathology *(Casanova, 2002)*

Reviews in: Sokhadze, E. M., Baruth, J., Tasman, A., & Casanova, M. F. (2014). Event-related potential studies of cognitive processing abnormalities in autism. In M. F. Casanova, A. El-Baz and J. S. Suri (Eds.), *Imaging the Brain in Autism,* Springer. 61-86 (ch.4)

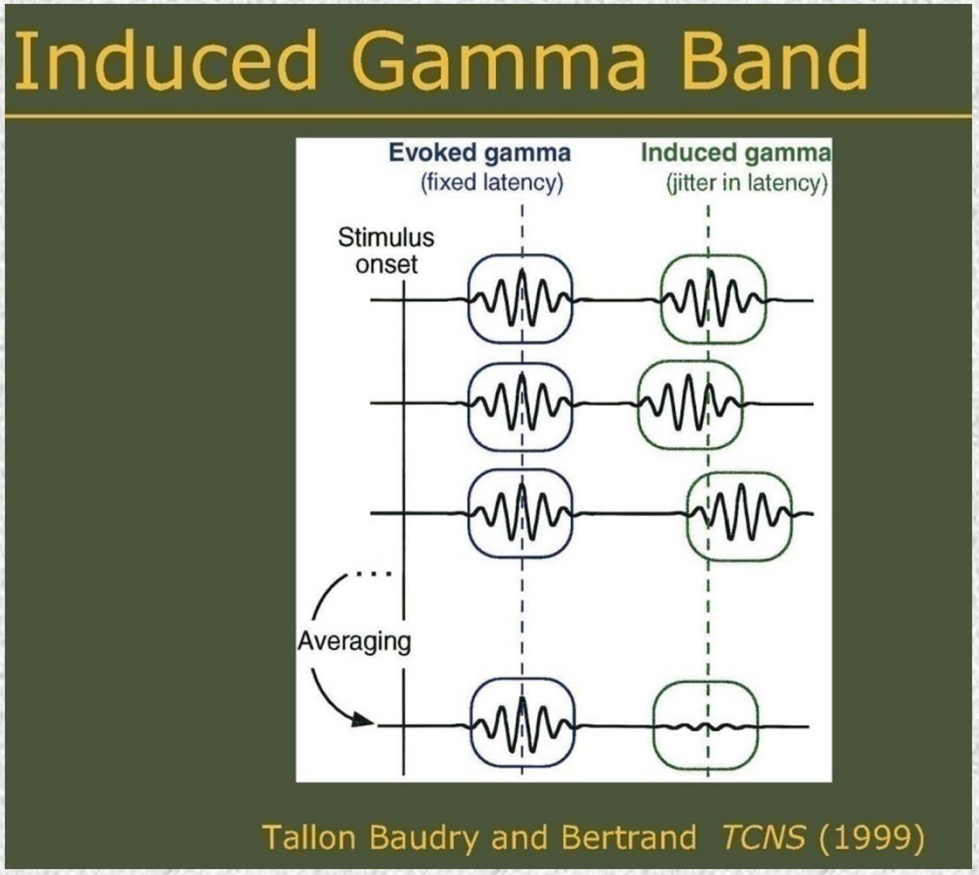
Casanova, M. F., Baruth, J., El-Baz, A. S., Sokhadze, G. E., Hensley, M., & Sokhadze, E. M. (2014). Evoked and induced gamma- frequency oscillation in autism. In M. F. Casanova, A. S. El-Baz, and J. S. Suri (Eds.), *Imaging the Brain in Autism*, Springer, New York, pp 87-106. (chapter 5)

Outline

- Focus on electrophysiological responses in autism using psychophysiological methods
- Event-related potentials (ERP) in visual oddball tests (novelty, illusory figures, cued reaction time)
- Evoked and induced gamma oscillations in EEG
- Autism, ADHD & typical children ERP/EEG comparisons in visual and auditory modalities
- Application of rTMS and other neuromodulation methods (neurofeedback, tDCS, prism lenses, AIT, VR) using ERP, EEG & autonomic activity outcomes
- Other clinical applications of combined neuromodulation methods in autism research (e.g., rTMS+neurofeedback)

Evoked and Induced EEG Gamma:

There are two types of event-related gamma oscillations



The “early” gamma response occurs within the 0-150 ms post-stimulus, is related to the earlier operations of information processing that culminate in sensation and early perception.

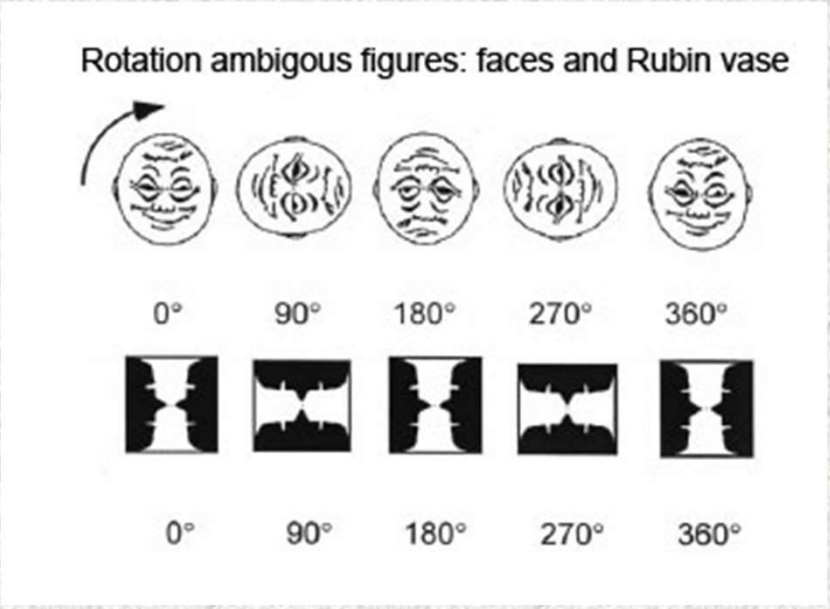
The “late” (induced) gamma occurs in the 200–400 ms post-stimulus time window and has an induced character, reflects perceptual and cognitive processes.

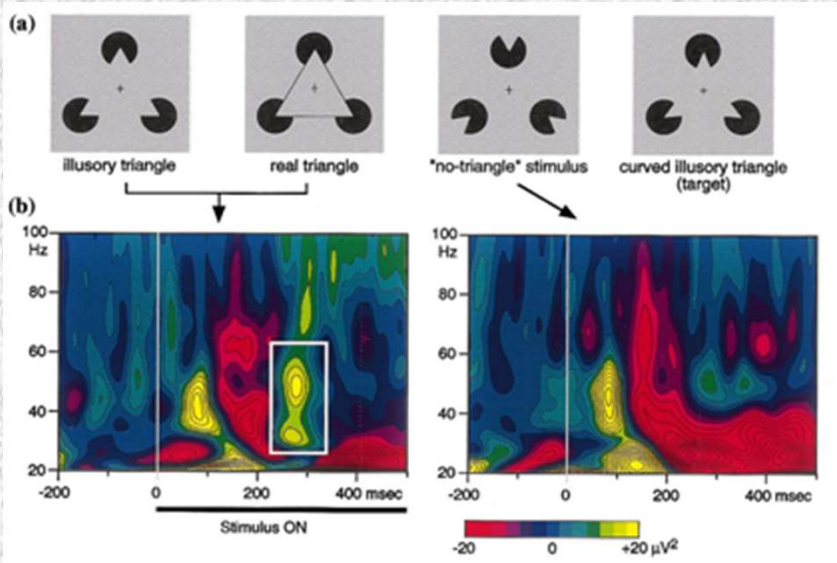
Gamma abnormalities in autism

- Brock et al., 2002 predicted that disordered connectivity would be manifested in task-specific abnormalities in gamma activation in autism.

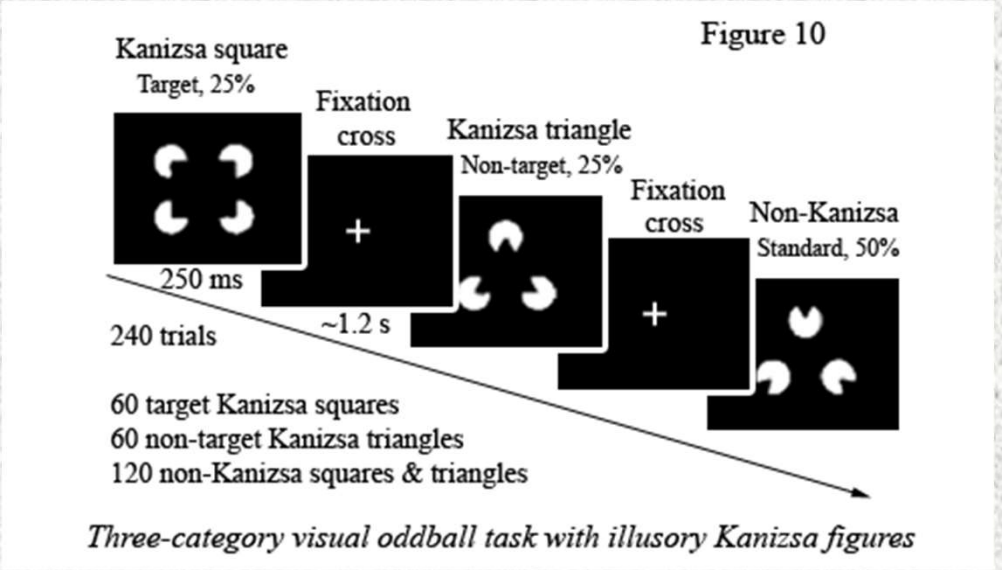
- Grice et al. (2001) observed that, whereas unimpaired adults demonstrated increased frontal gamma activity to upright faces and decreased activity to inverted faces, adults with autism showed an increase in induced frontal gamma activity to both upright and inverted faces.

- Brown et al. (2005) found that, relative to controls, adolescents with autism showed a significant peak increase in induced parietal gamma activity when presented with an illusory Kanizsa shape.





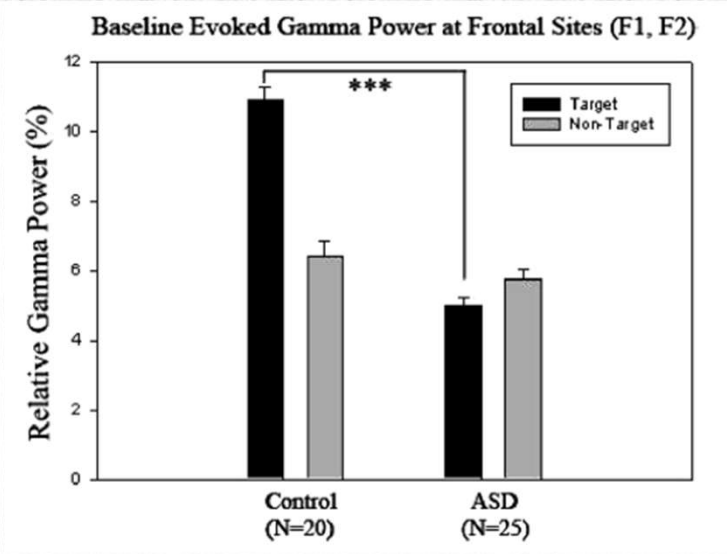
Kanizsa Illusory Figure Oddball Test

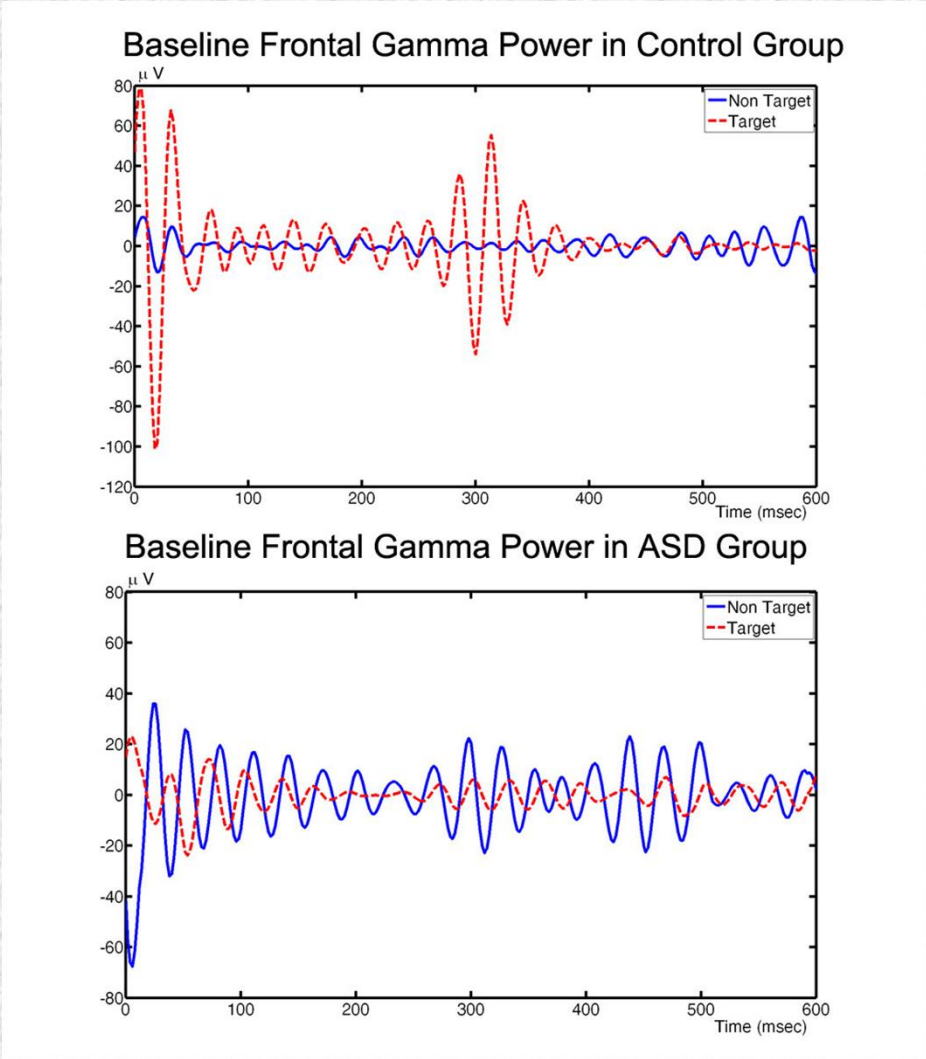


Three-category visual oddball task with illusory Kanizsa figures

Subjects were instructed to press a button with their index finger when the target stimulus appears on the monitor and ignore both non-target Kanizsa and standard stimuli.

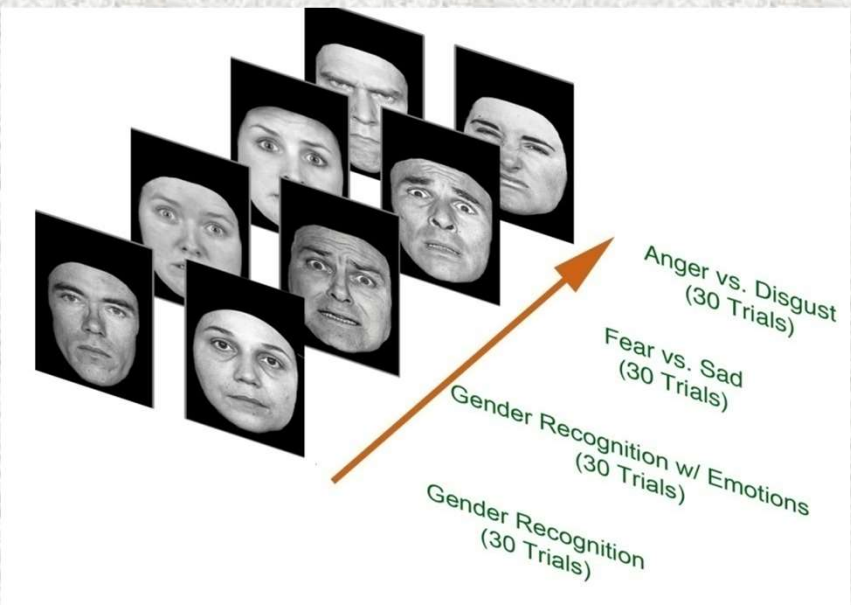
Evoked and Induced Gamma in Autism and Controls

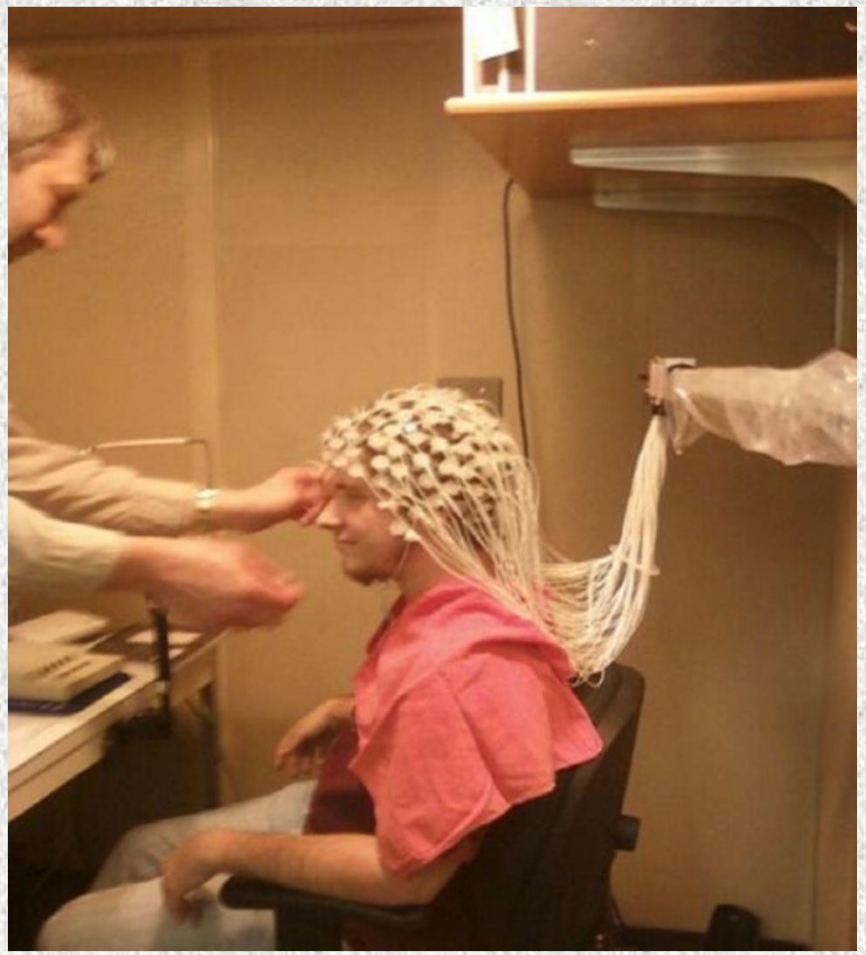




Sokhadze, E., El-Baz, A., Baruth, J., Mathai, G., Sears, L., &Casanova M. (2009). Effect of a low-frequency repetitive transcranial magnetic stimulation (rTMS) on induced gamma frequency oscillations and event-related potentials during processing of illusory figures in autism spectrum disorders. *Journal of Autism & Developmental Disorders*, 39, 619-634.

Facial gender and emotional categorization task (Autism, ADHD, controls)

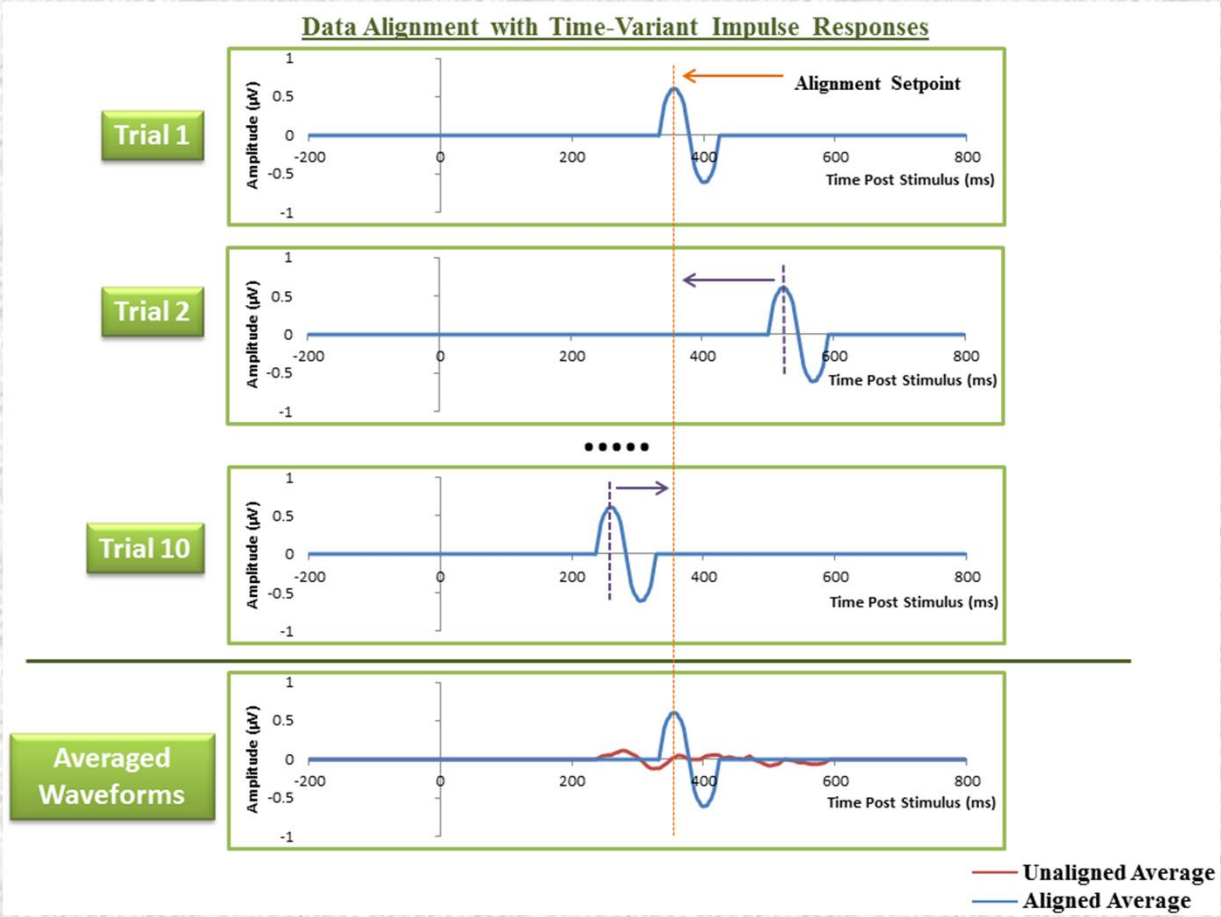


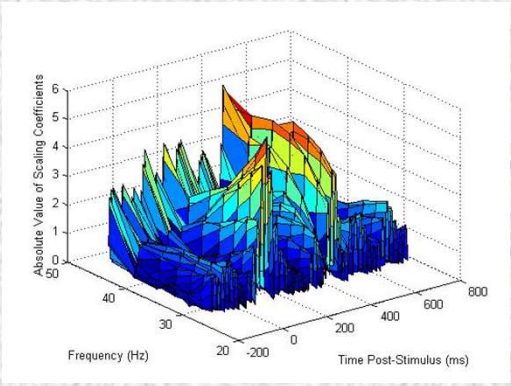


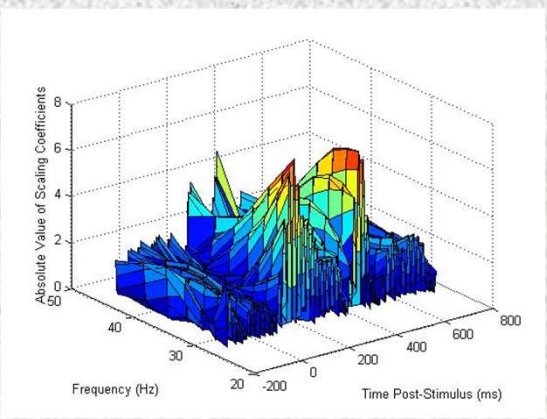
Gender categorization (man vs. women)
neutral, emotional
Emotional recognition (anger vs. disgust,
fear vs. sad)
Gender vs. Emotion difference waves

Gross, E., El-Baz, A. S., Sokhadze, G. E., Sears, L., Casanova, M. F., & Sokhadze, E. M. (2012). Induced EEG gamma oscillation alignment improves differentiation between autism and ADHD group responses in a facial categorization task. *Journal of Neurotherapy, 16,* 78-91.

Illustration of induced gamma response alignment

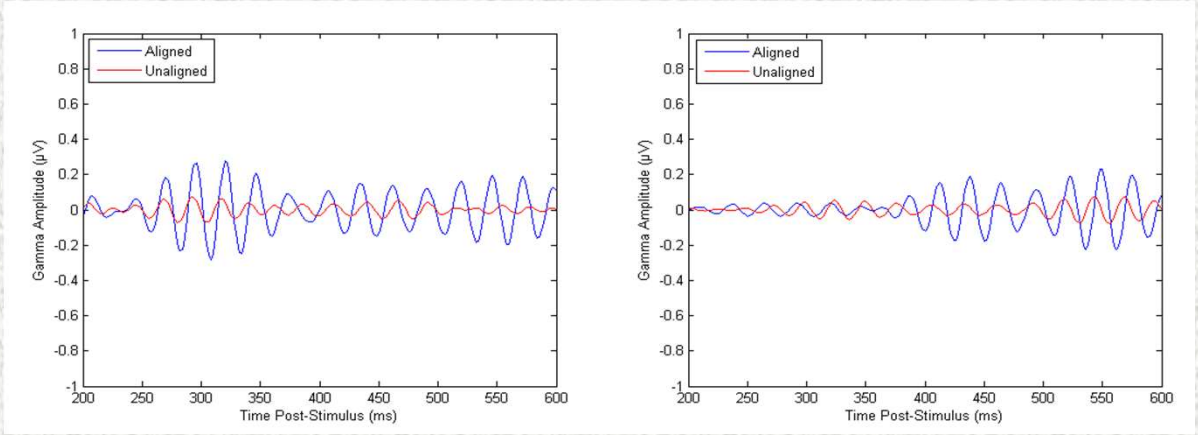


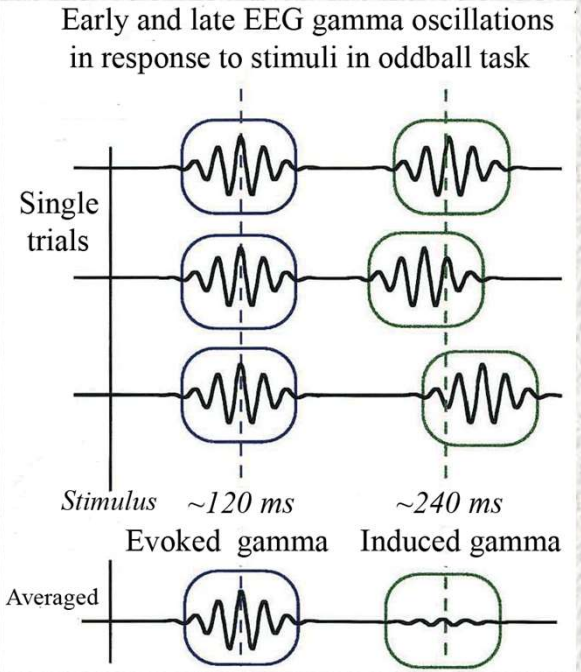


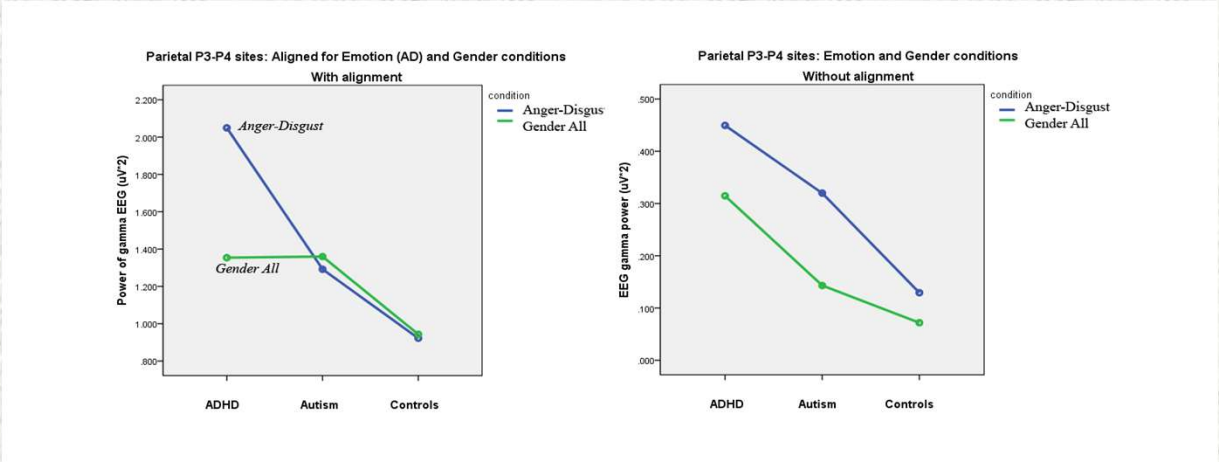


Gross, E., El-Baz, A. S., Sokhadze, G. E., Sears, L., Casanova, M. F., & Sokhadze, E. M. (2012). Induced EEG gamma oscillation alignment improves differentiation between autism and ADHD group responses in a facial categorization task. *Journal of Neurotherapy, 16,* 78-91.

The aligned averaged signal (blue) is less attenuated in the late induced gamma region (200-600 ms) than the unaligned averaged signal (red) at the parietal sites.







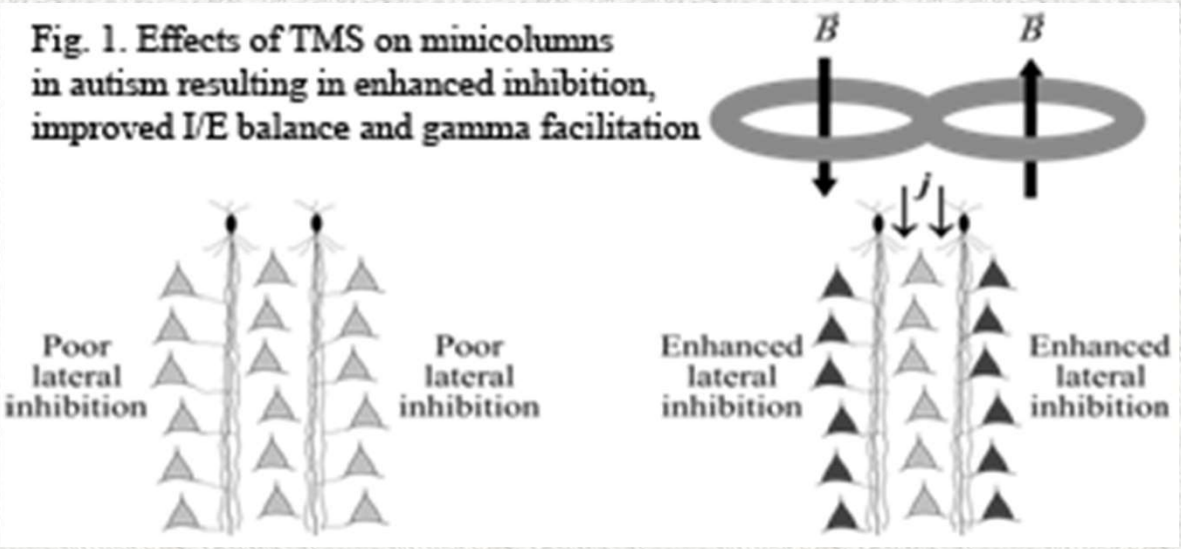
Conclusions on Specifics of Information Processing in Autism Spectrum Disorder

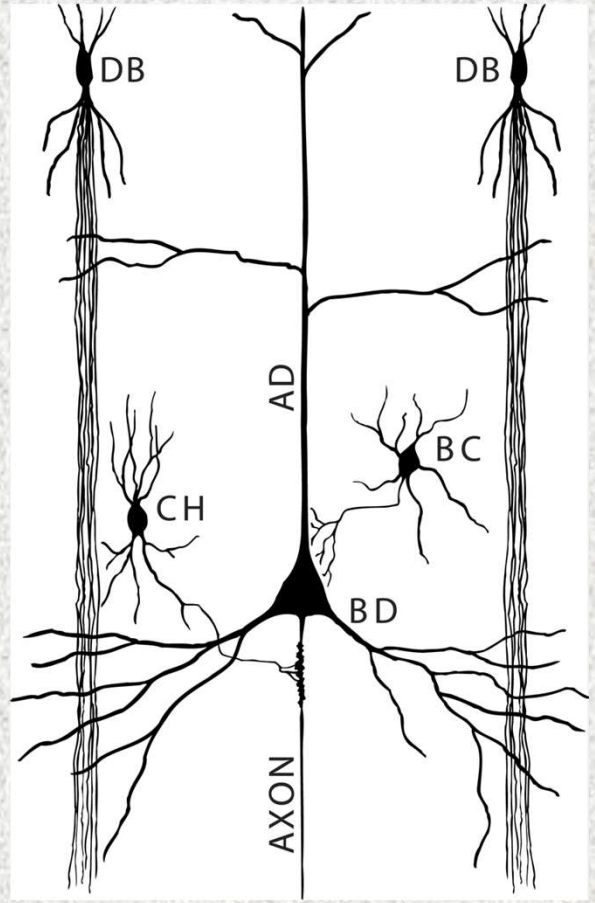
- In visual oddball tasks children with ASD have comparable early ERPs and evoked and induced EEG gamma oscillations to target and non-target cues, thus demonstration low early selectivity, which results in delayed late ERPs.
- Children with ASD tend to do not slow down in RT task after committed errors and have low ERN/Pe reflecting deficits in error monitoring.
- Children with ASD have difficulties in processing emotion facial expressions & they struggle in more simple facial recognition tests too.
- Children with ASD have problems in cued spatial attention task, manifested both in delayed ERP and slow motor preparation potentials (LRP) in incongruent trials.
- Children with ASD also have MMN abnormalities in simple auditory evoked potential tests.
- Children with ASD have less differentiated autonomic responses, and are featured by excess of sympathetic arousal along with low vagal tone.

Experimental Treatments/Interventions

- rTMS – Transcranial Magnetic Stimulation
- tDCS- Transcranial Direct Current Stimulation
- EEG biofeedback – neurofeedback
- Autonomic activity biofeedback
- Visuo-motor training with ambient prism lenses
- Berard's Auditory Integration Training
- Neurofeedback-based games
- Virtual Reality based Social Skills Training
- Combination/integration of above interventions

Rationale to use low frequency inhibitory rTMS in treatment of autism (based on Dr Casanova's "minicolumnar" neuro-developmental theory of autism

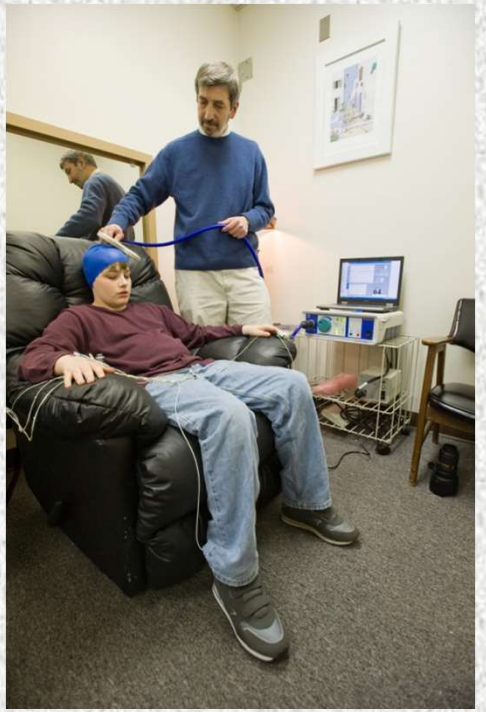




- The magnetic field induces a perpendicularly orientated electric field.
- Double-bouquet inhibitory interneurons are perfectly situated to interact with a magnetic field applied parallel to the cortex.

Low-Frequency Repetitive Transcranial Magnetic Stimulation in Autism Spectrum Disorder (NIH Eureka R01)

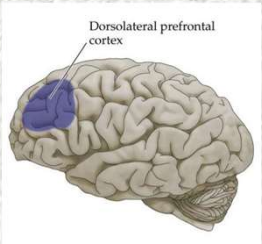
- 0.5-1 Hz
- 90% of motor threshold (MT)
- Once per week (or 2/week)
- 150-300 pulses per day (~10 trains /~20 stimuli per train).
- 12 Sessions (6 Left DLPFC, 6 Right DLPFC)
- Currently run 18 sessions
- Several follow-up cases with ~24 rTMS session



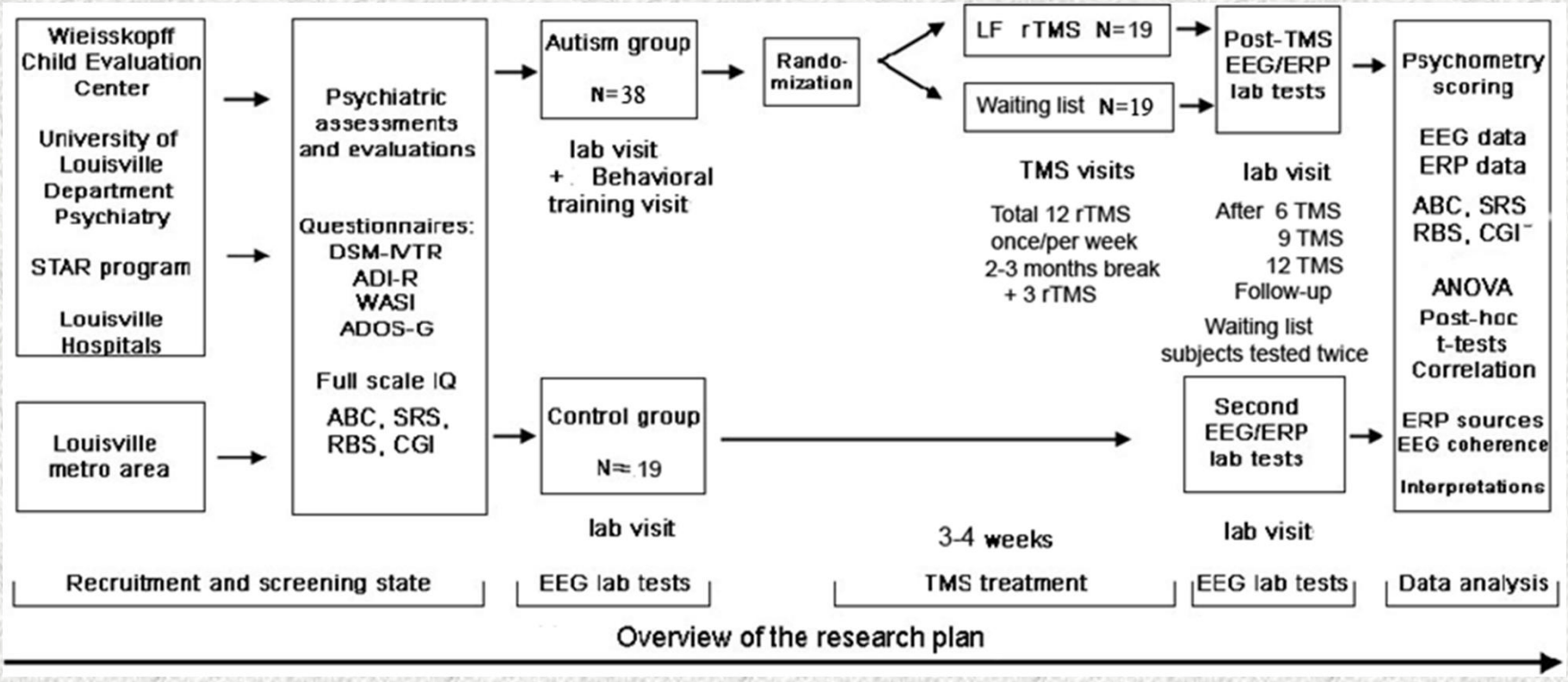
First results reported for 6 rTMS sessions in:

Sokhadze, E., Baruth, J., Tasman, A., Mansoor, M., Ramaswamy, R., Sears, L., Mathai, G., El -Baz, A., & Casanova, M. F. (2010). Low-frequency repetitive transcranial magnetic stimulation (rTMS) affects event-related potential measures of novelty processing in autism. *Applied Psychophysiology & Biofeedback, 35(2),* 147-161.

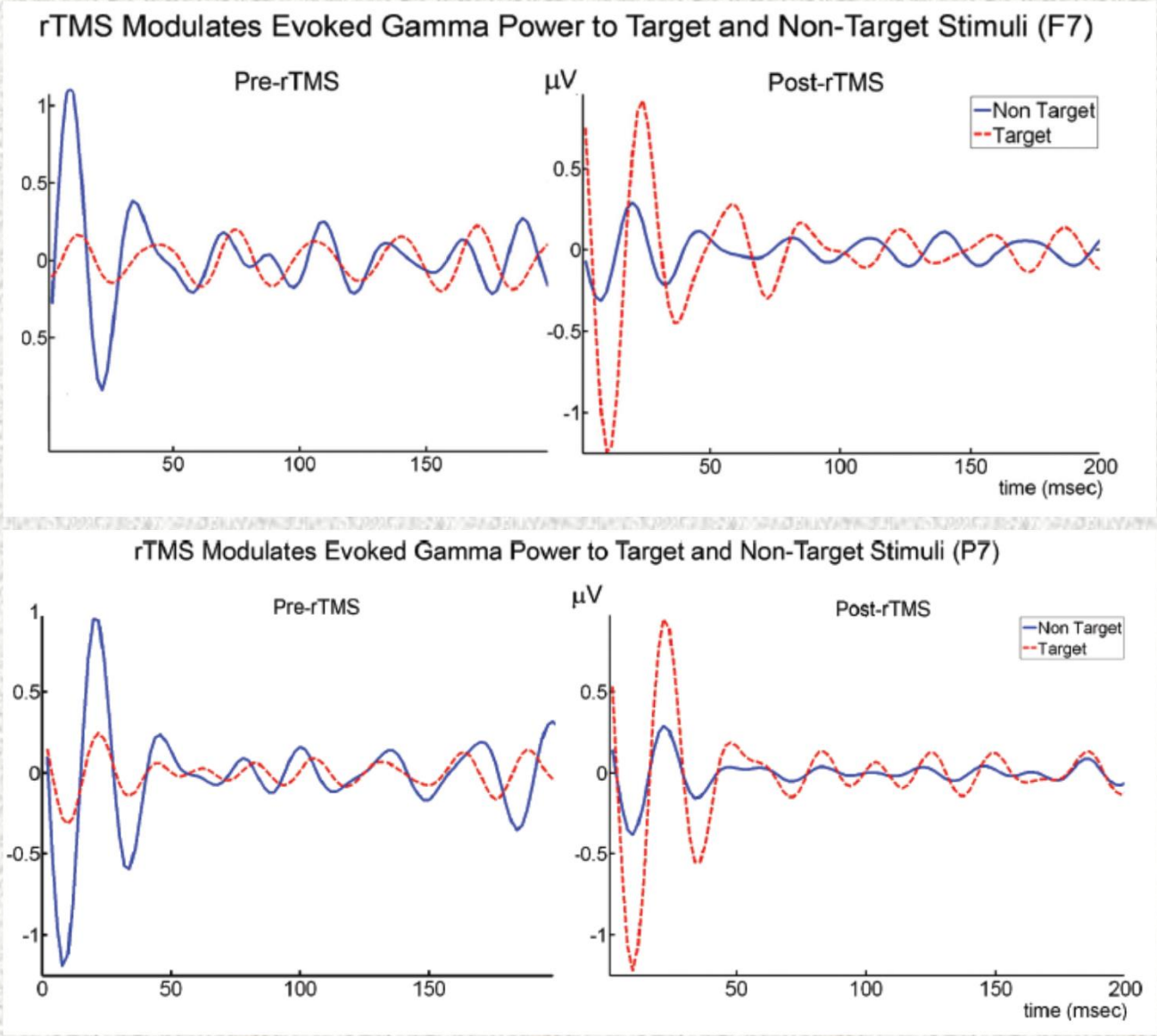
Review in: Sokhadze, E. M., Casanova, M. F., & Baruth, J. Transcranial magnetic stimulation in autism spectrum disorders. (2013). In L.Alba-Ferrara (Ed.), *Transcranial Magnetic Stimulation: Methods, Clinical Uses and Effects on the Brain*. New York: NOVA Science Publishers, Inc. 219-231 (chapter 13)



Research Design (12 TMS session course)

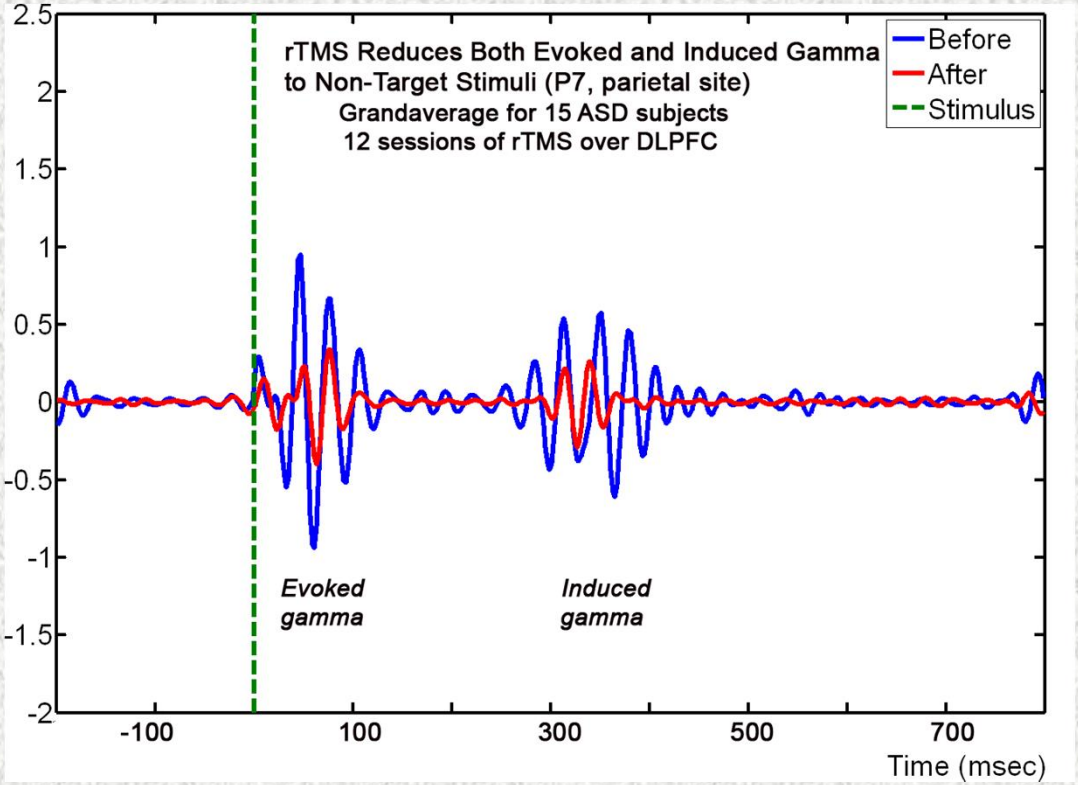


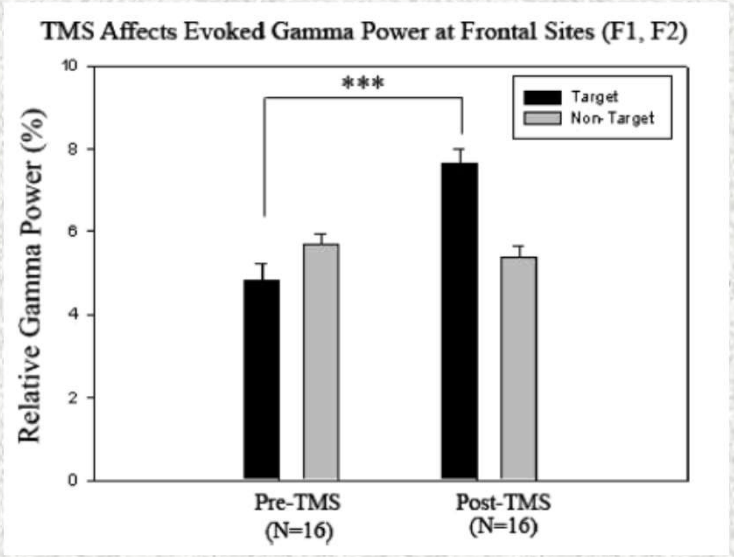
Average Amplitude of Evoked Gamma Oscillations



Baruth, J., Casanova, M., El-Baz, A., Horrell, T., Mathai, G., Sears, L., & Sokhadze, E. (2010). Low-frequency repetitive TMS modulates evoked-gamma frequency oscillations in autism spectrum disorders. *Journal of Neurotherapy,* 14 (3), 179-194.

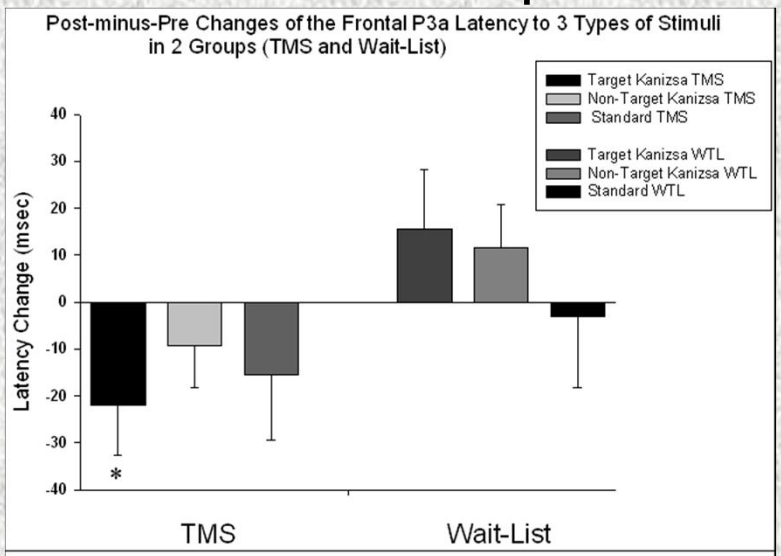
Effects of rTMS on evoked and induced gamma to non-target stimuli in autism

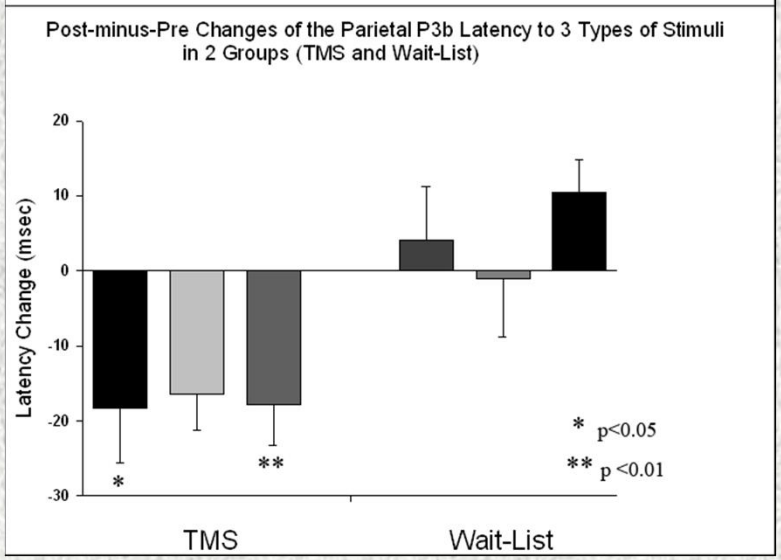


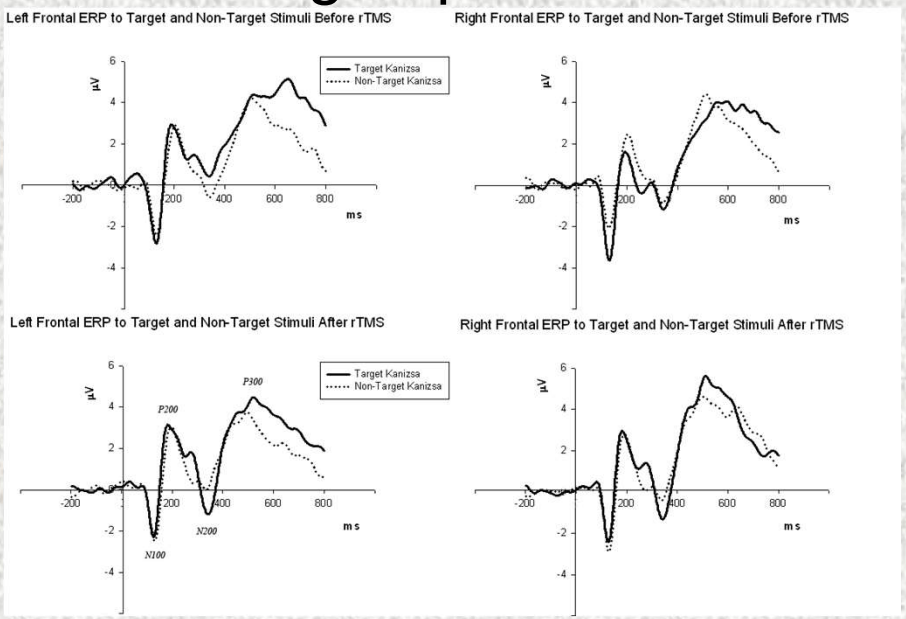


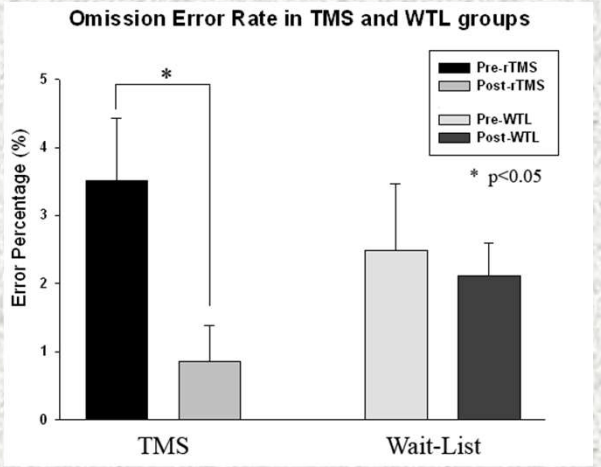
Post-TMS Group Differences to target and non-target Kanizsa stimuli

Post-TMS improvements in active group vs. wait-list



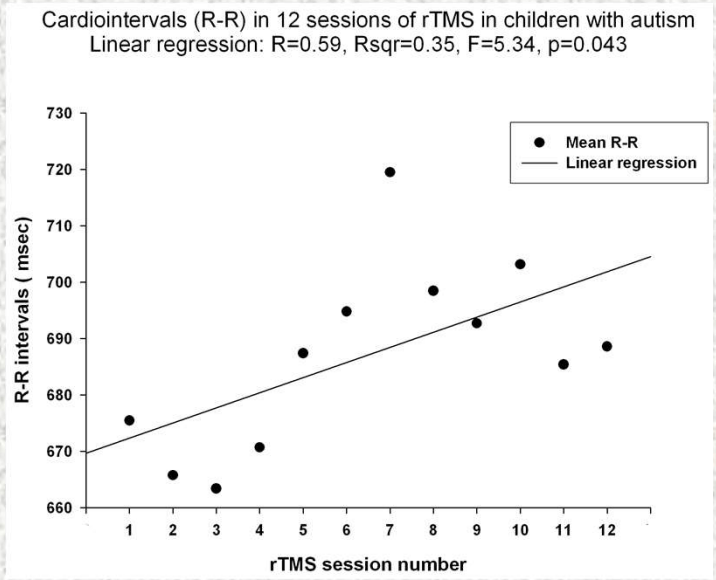


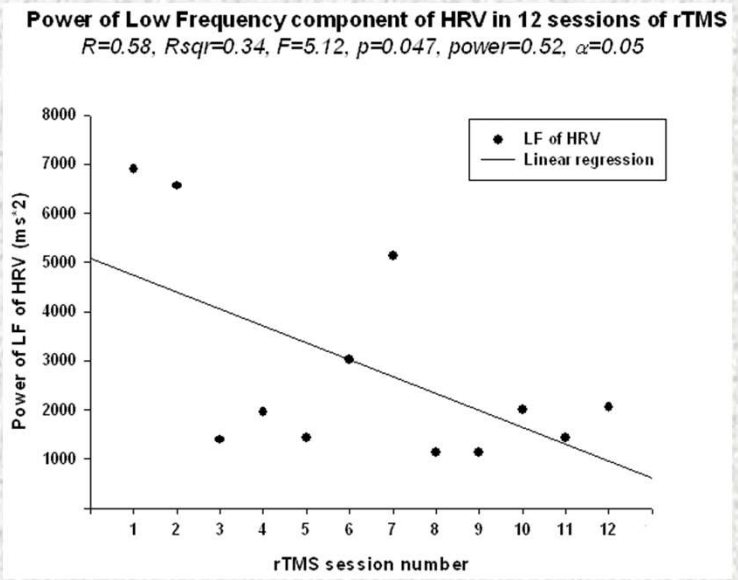


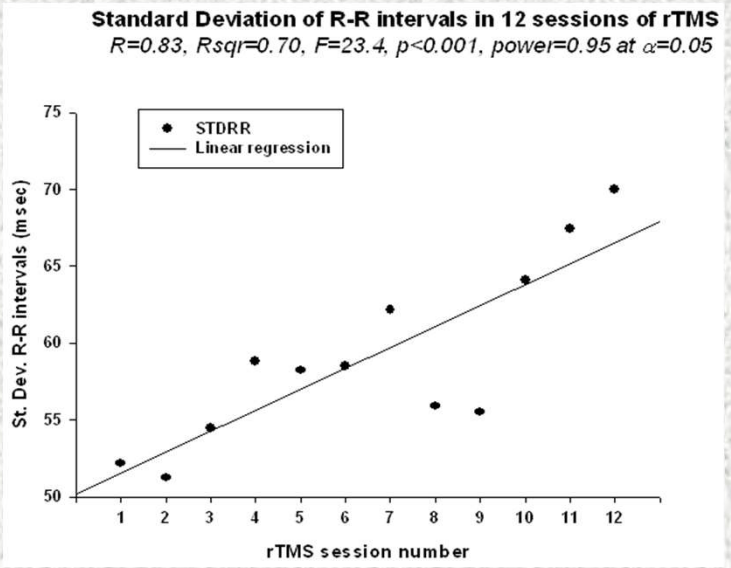


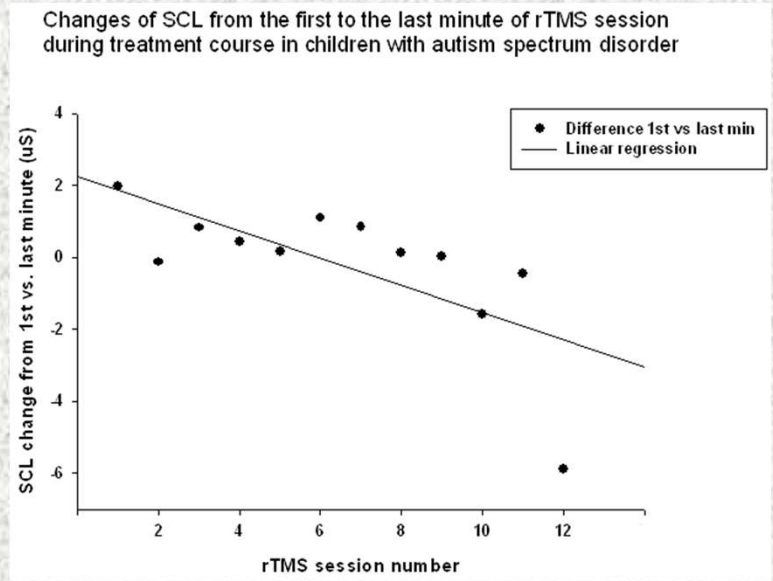
Baruth, J., Williams, E., Sokhadze, E., El-Baz, A., Sears, L., & Casanova, M.F. (2011). Repetitive transcranial stimulation (rTMS) improves electroencephalographic and behavioral outcome measures in autism spectrum disorders (ASD). *Autism Science Digest*, 1(1), 52-57.

Autonomic activity in 12 session long course of rTMS





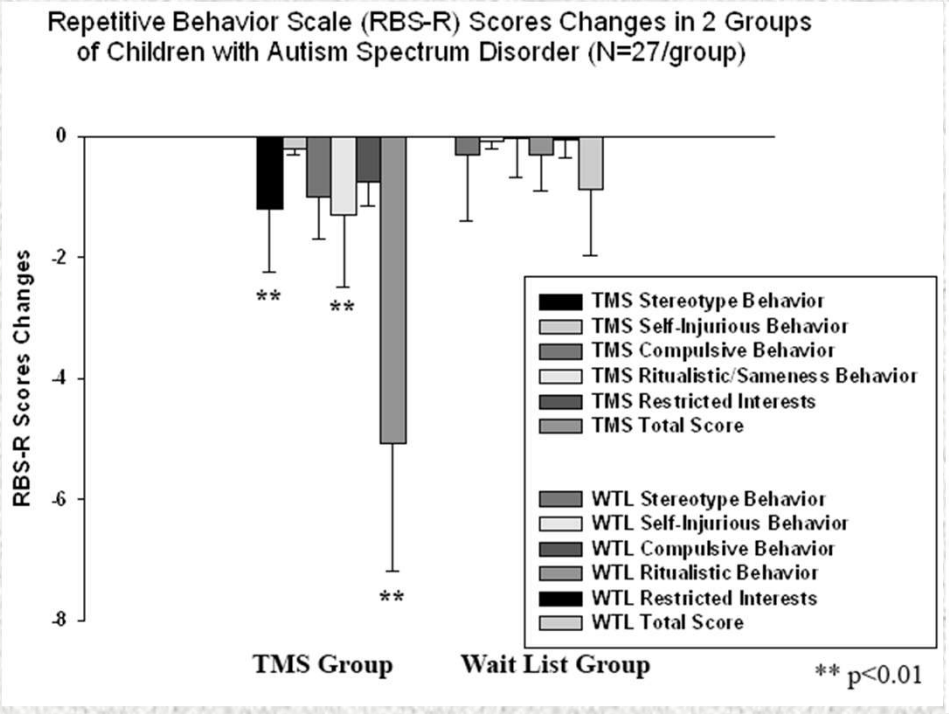


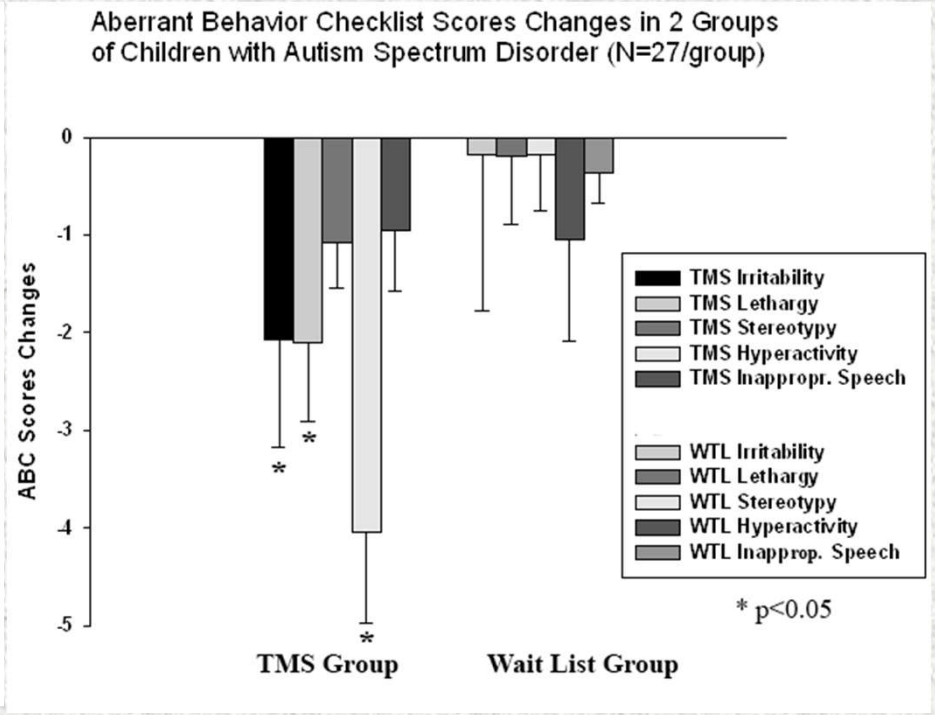


Conclusions on 12 session rTMS effects on executive functions in autism

- In individuals with ASD evoked gamma activity was not discriminative of stimulus type
- Following rTMS individuals with ASD showed significant improvement in discriminatory gamma activity between relevant and irrelevant visual stimuli, both evoked and induced gamma measures. Distal scalp coherence and dipole source coherence in gamma range also increase.
- Several ERP components improved post-rTMS
- Post-error RT increased along with response accuracy
- We also found significant improvement in the responses on behavioral questionnaires (i.e., irritability, repetitive behavior) as a result of rTMS.
- HR, LF of HRV and SCL decreased over rTMS course

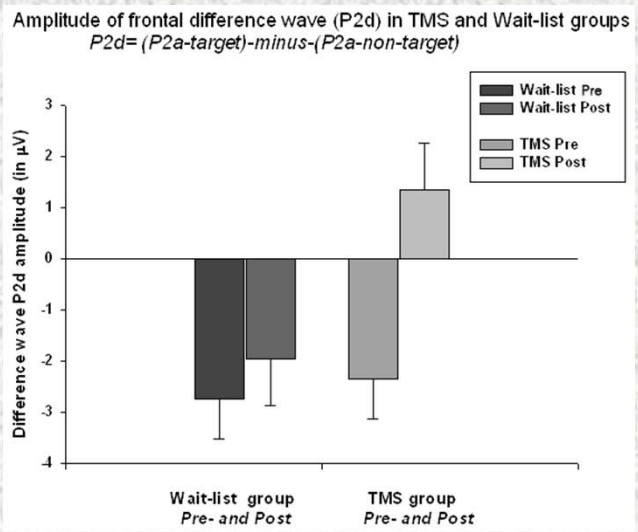
Effects of 18 sessions of rTMS in active treatment and wait-list ASD groups (N=27)

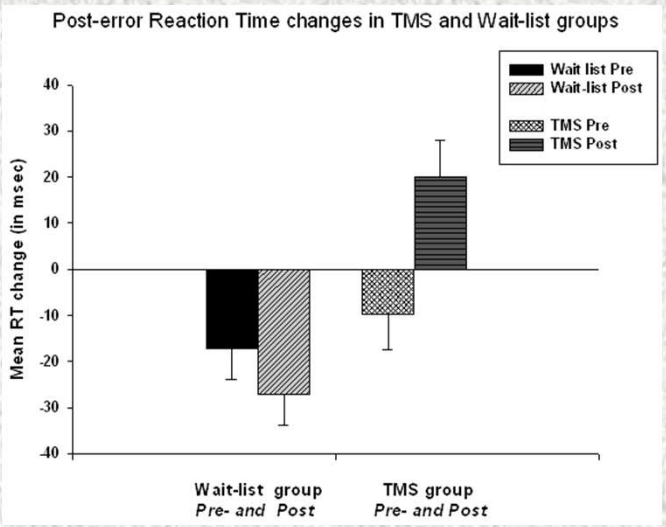


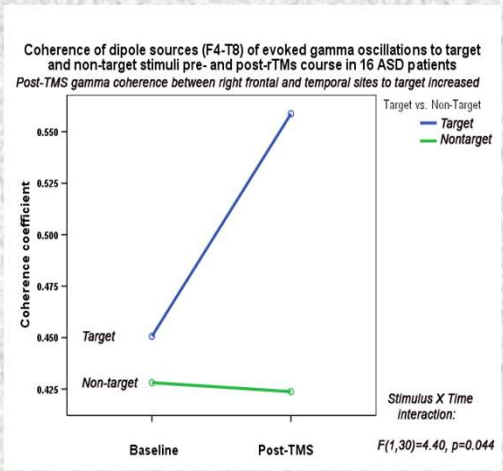


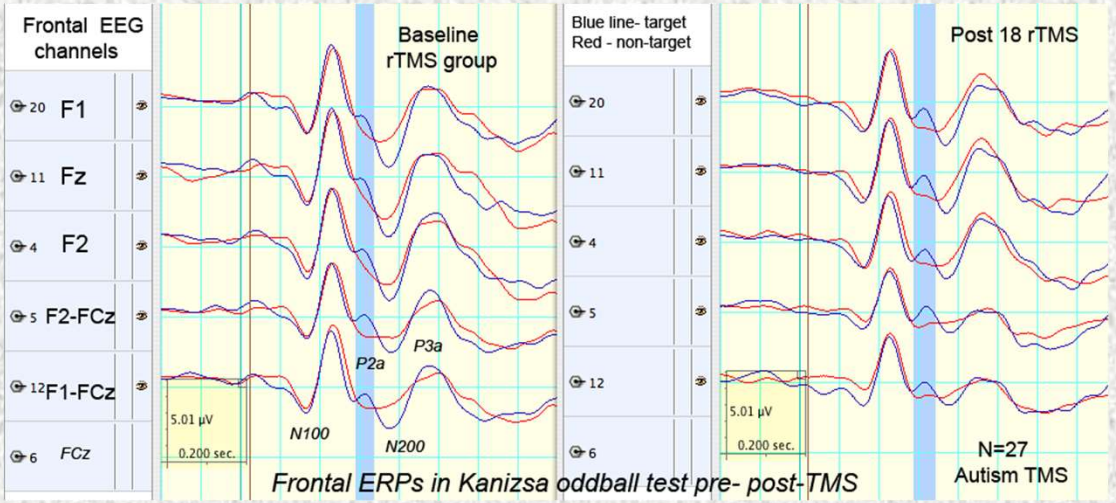
Sokhadze, E., El-Baz, A., Sears, L., Opris, I., & Casanova, M. (2014) Neuromodulation based on rTMS improves electrocortical functional measures of information processing and behavioral responses in autism. *Frontiers in System Neurosciences, vol. 8, art. 134.*

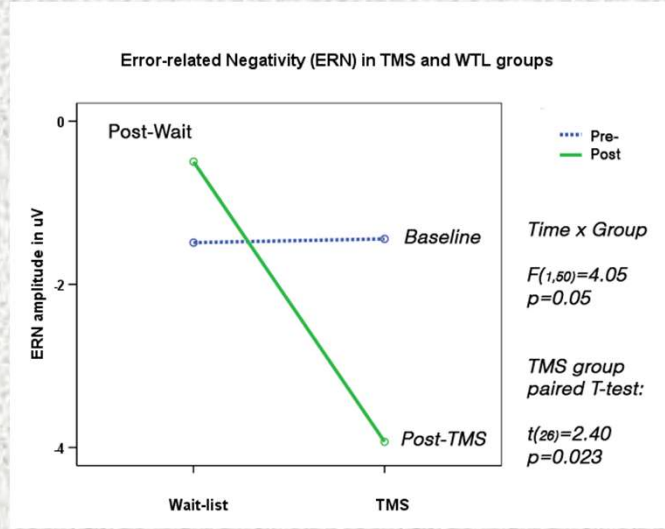
Effects of 18 sessions of rTMS in 27 ASD and 27 ASD wait-list



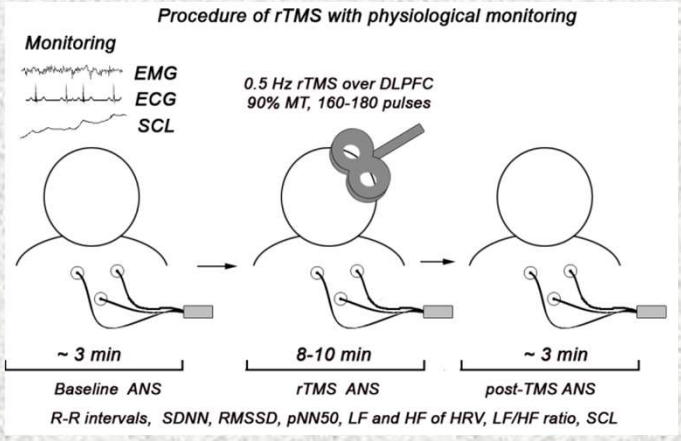


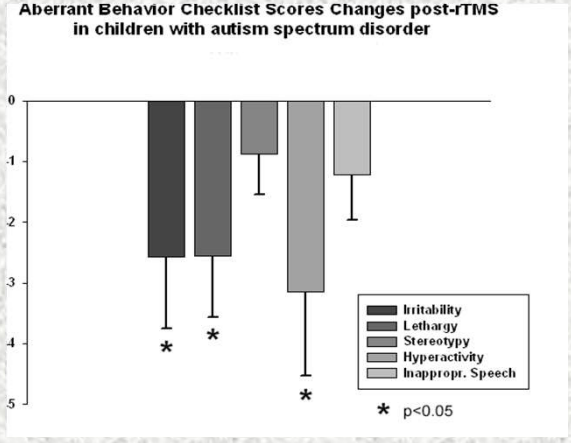


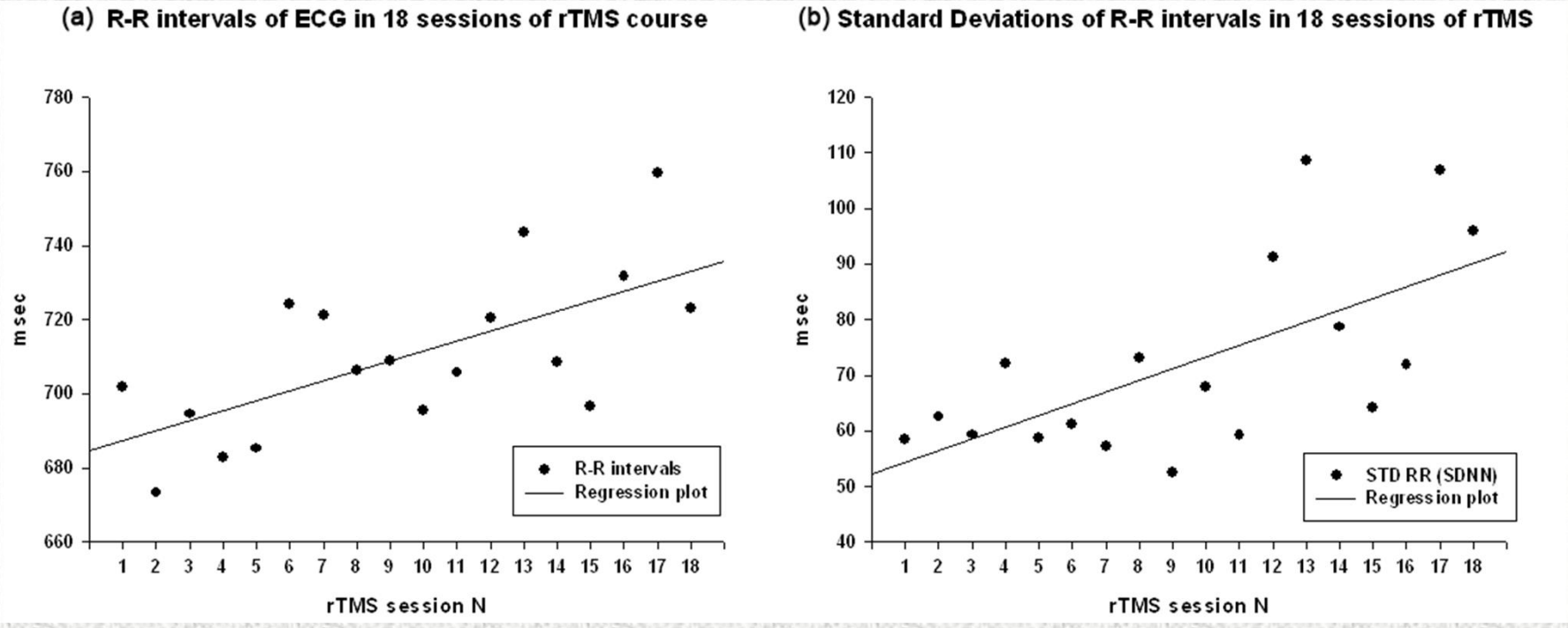




Effects of 18 session rTMS course on autonomic functions (HRV and SCL) in ASD

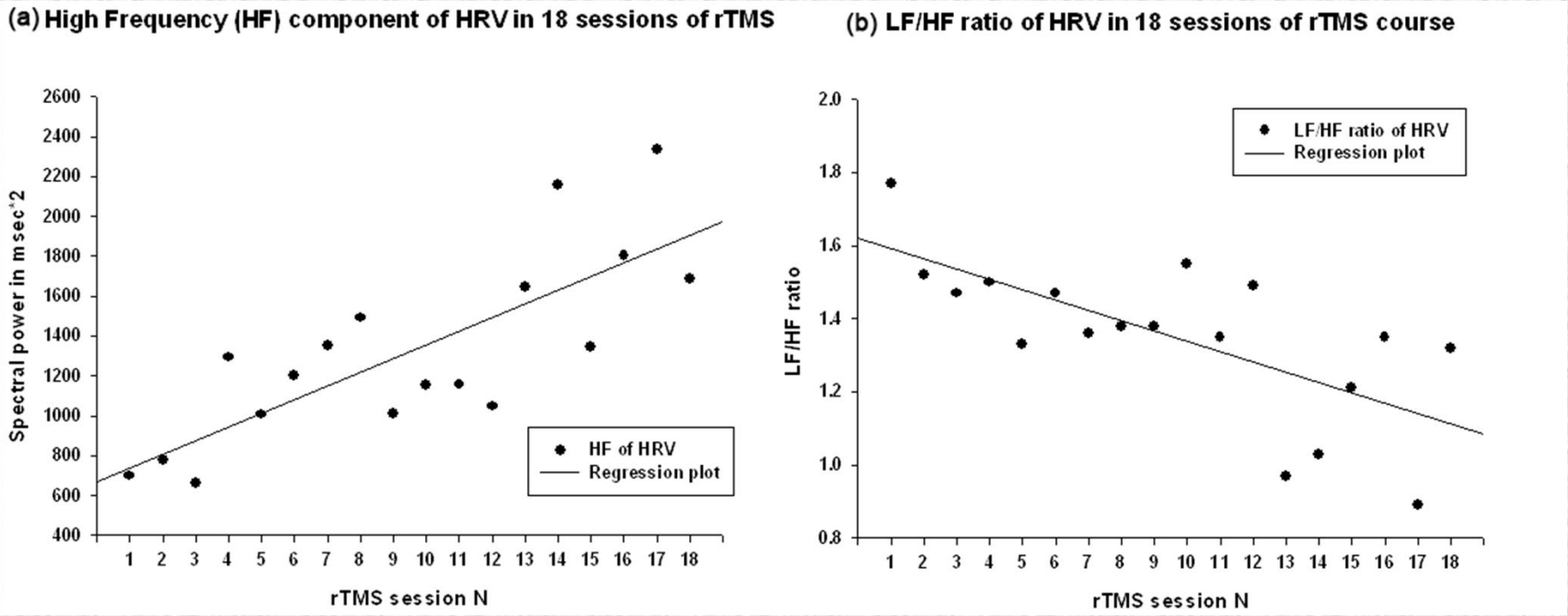




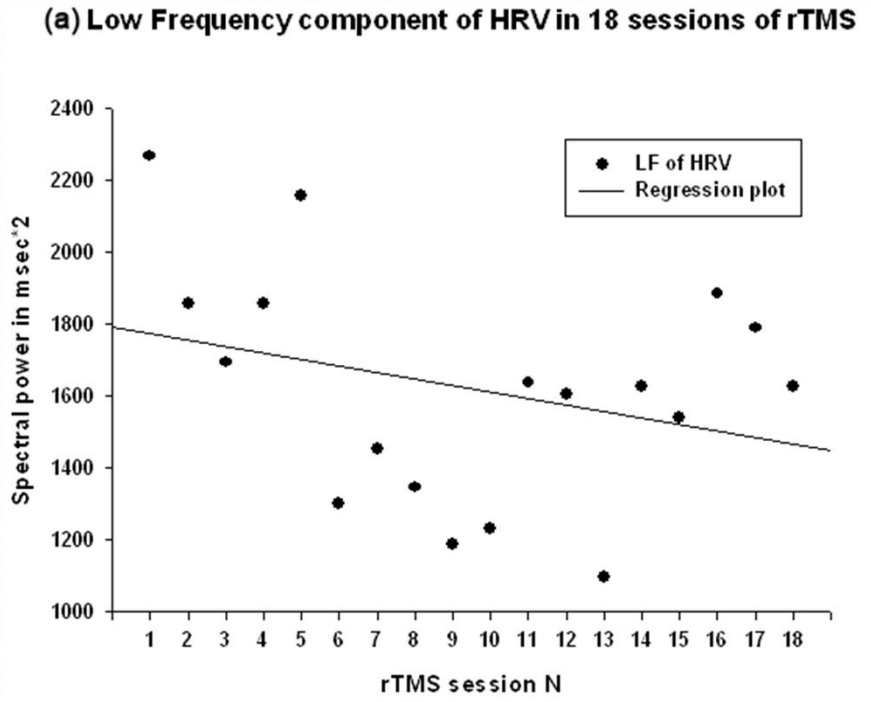


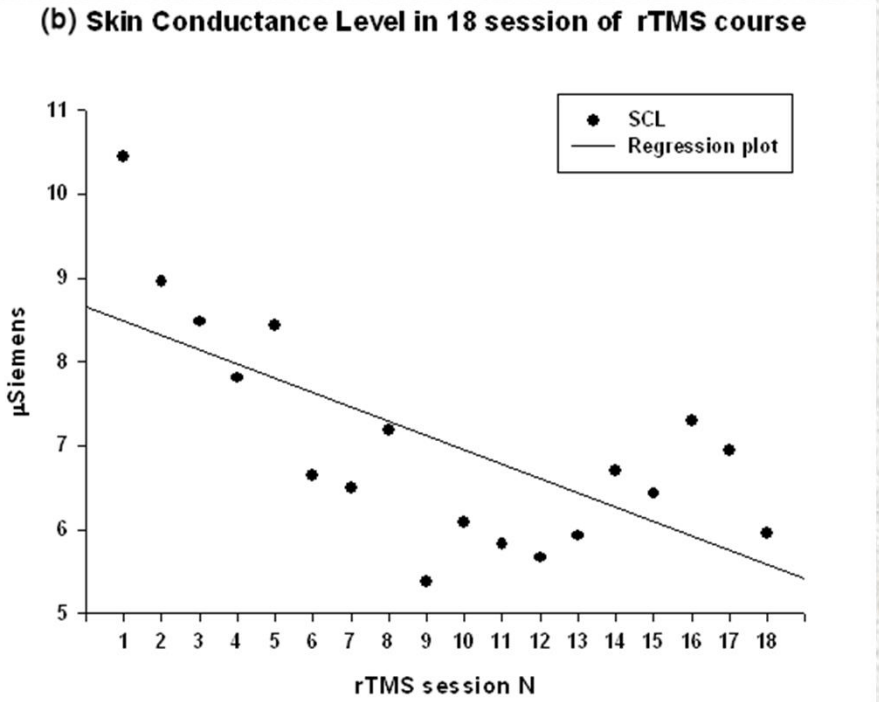
Effects of 18 session rTMS course on autonomic functions (HF of HRV and LF/HF) in ASD

Casanova, M., Hensley, M.K., Sokhadze, E., El-Baz, A., Wang, Y., & Sears, L. (2014) Effects of rTMS on autonomic functions in autism spectrum disorder. *Frontiers in Behavioral Neurosciences, doi:10.389/fnsys.2014.00134*



Effects of 18 session rTMS course on autonomic functions (LF of HRV and SCL) in ASD





Protocol of gamma neurofeedback

- The protocol used in the study is based on the Peak Achievement Trainer (PAT, Neurotek LLC) application and uses EEG gamma and theta/beta ratio as a training target

Hillard, B., El-Baz, A., Sears, L., Tasman, A., & Sokhadze, E. (2013). Neurofeedback training aimed to improve focused attention and alertness in children with ADHD: a study of relative power of EEG rhythms using custom-made software application.

Clinical EEG & Neuroscience. 44, 193-202.

Sokhadze, E. (2012). Peak performance training using prefrontal EEG biofeedback. *Biofeedback, 39*, 7-15.

EEG gamma neurofeedback screen

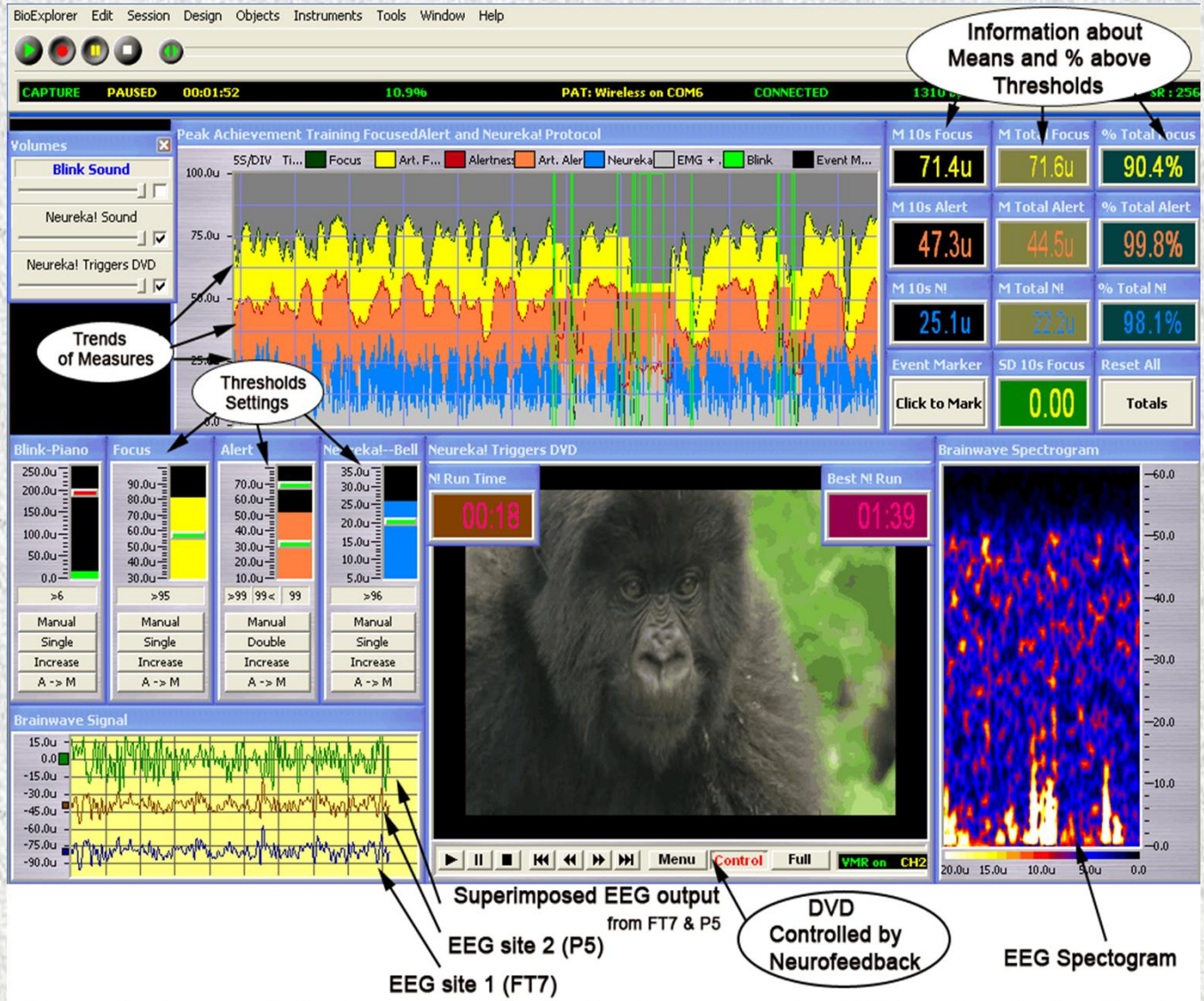
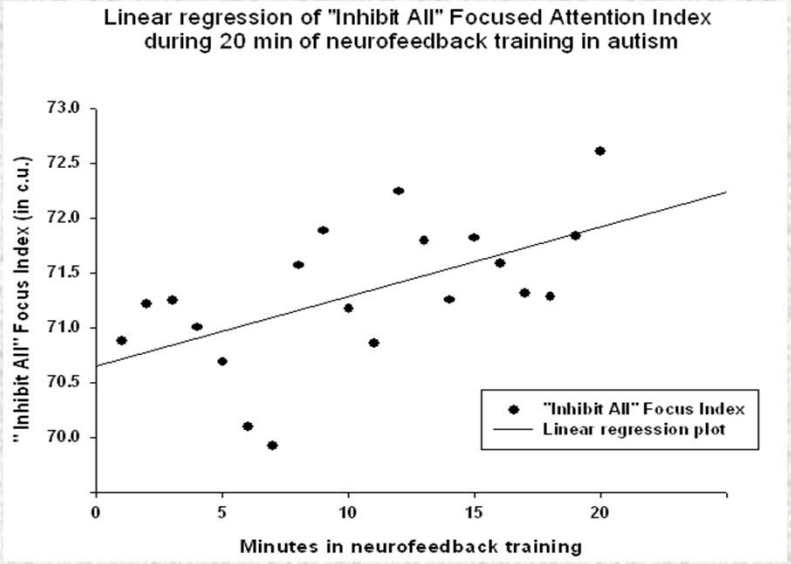
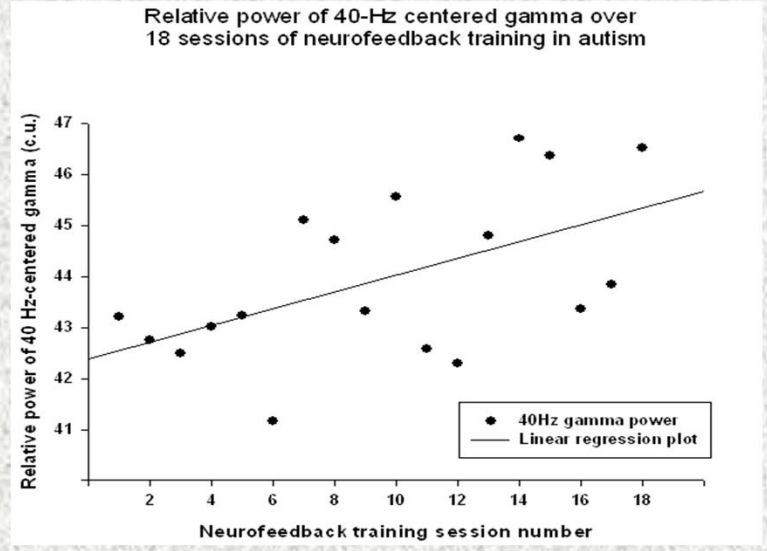
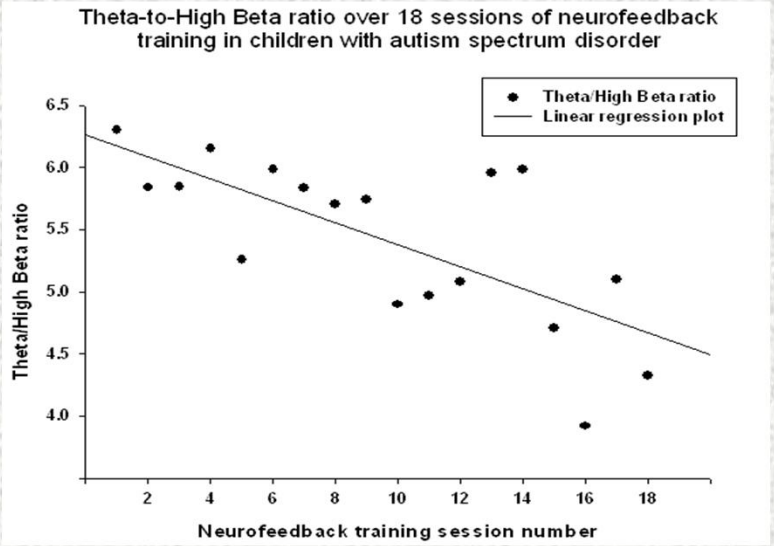
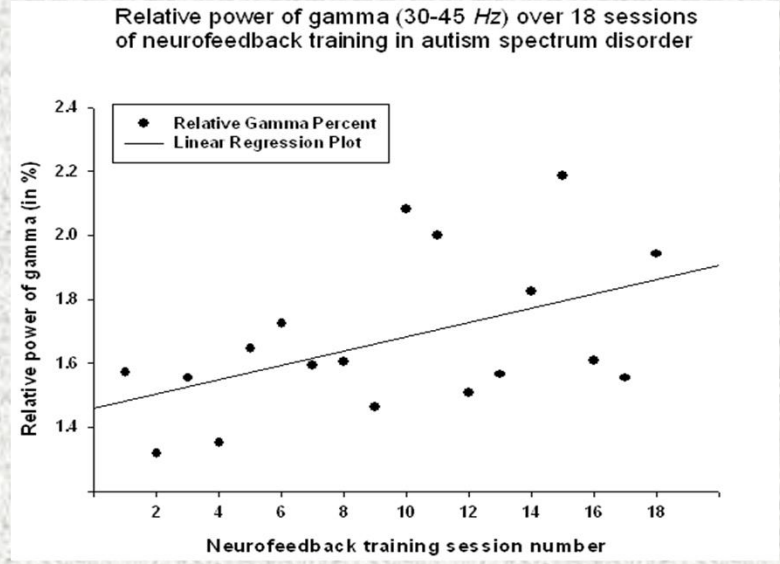


Figure 2. Screenshot of gamma neurofeedback screen using DVD and audio feedback



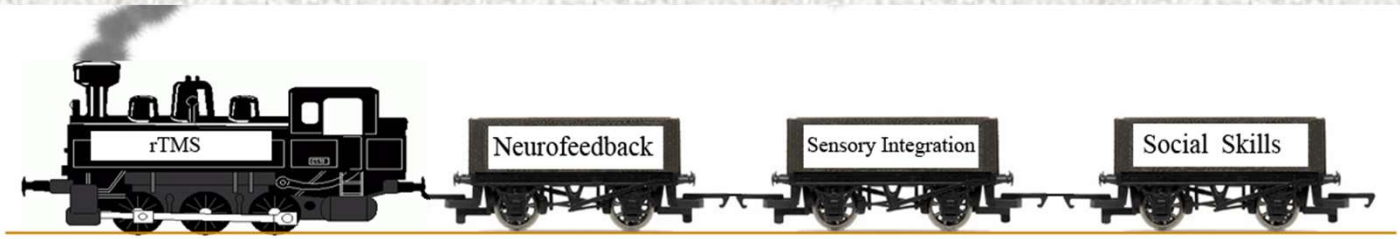






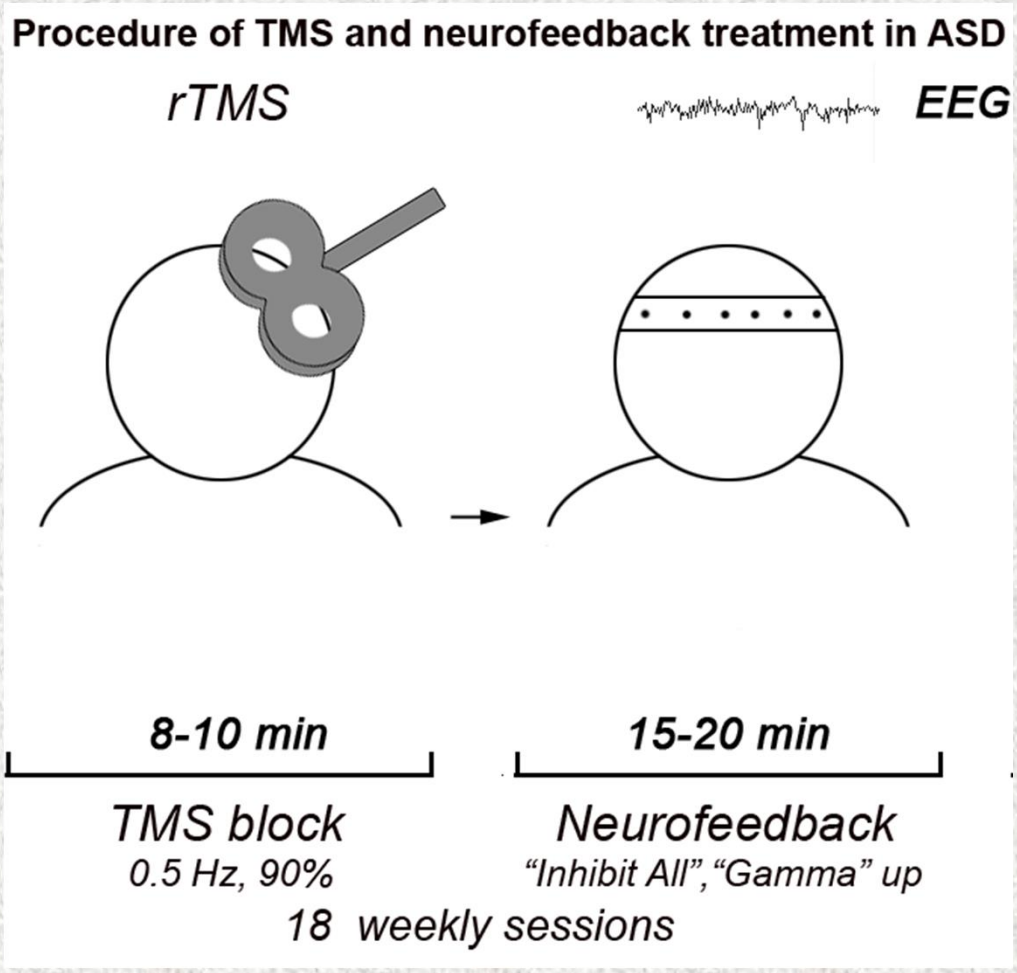
Wang, Y., Li, X., Sears, L., Casanova, M., Tasman, A., & Sokhadze, E. (2014) A study of relative power of specific EEG bands and their ratios during neurofeedback training in children with autism spectrum disorder. *Autism Research (submitted)*

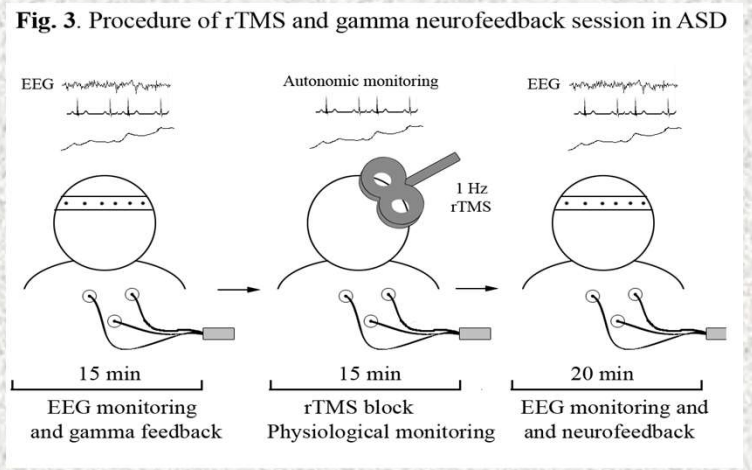
Combined Neuromodulation Approach to Autism Treatment of Our Research Team

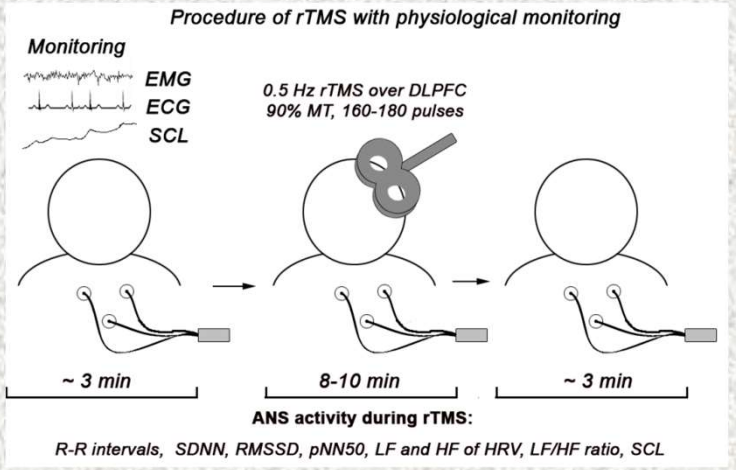


- We have a neuropathological theory of autism *(Casanova, 2002)*
- We believe that slow *rTMS* will target autism-specific deficits
- We use rTMS and reinforce EEG effects using *Neurofeedback*
- We continue using specific *Sensory Integration* techniques such as
  - Ambient Prism Lenses for visuo-motor coordination *(Kaplan,2006)*
  - Auditory Integration Training *(AIT, Berard & Brockett, 2011)*
- We are in process of developing Virtual Reality (Oculus Rift) and biofeedback based *Social Skills and Joined Attention Training* program

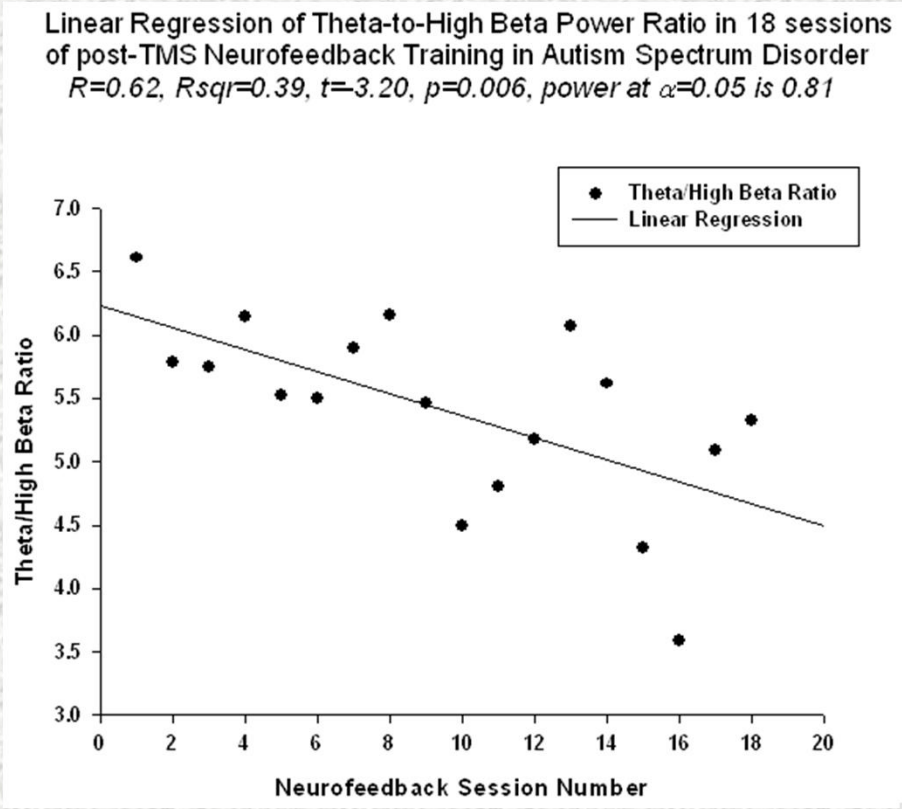
Procedure of combined rTMS-plus-Neurofeedback treatment in autism

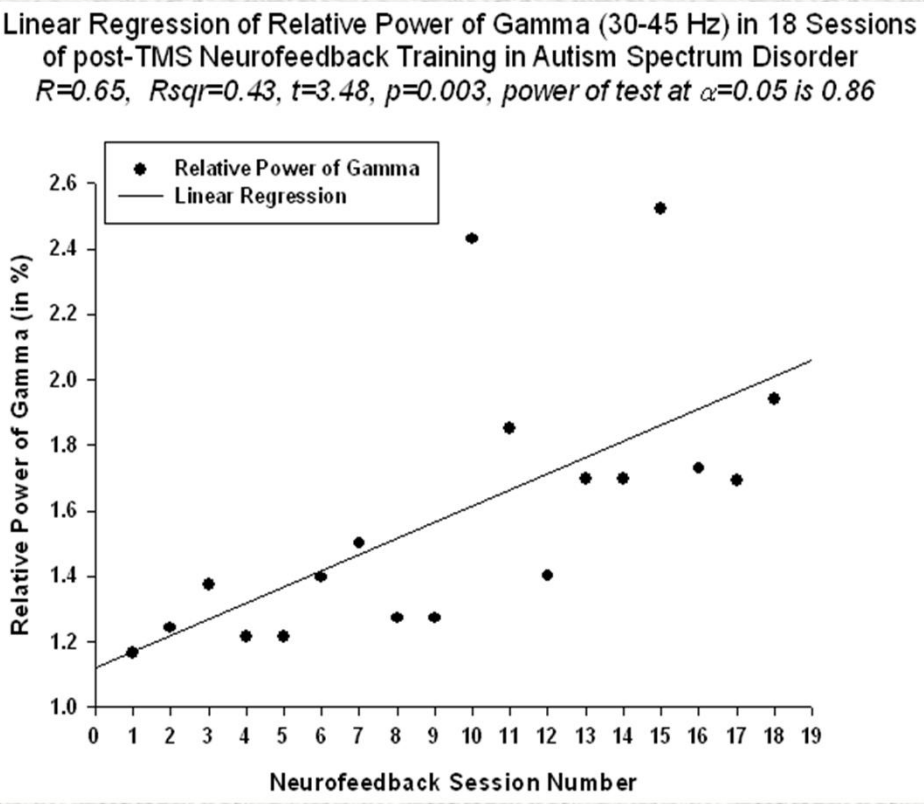






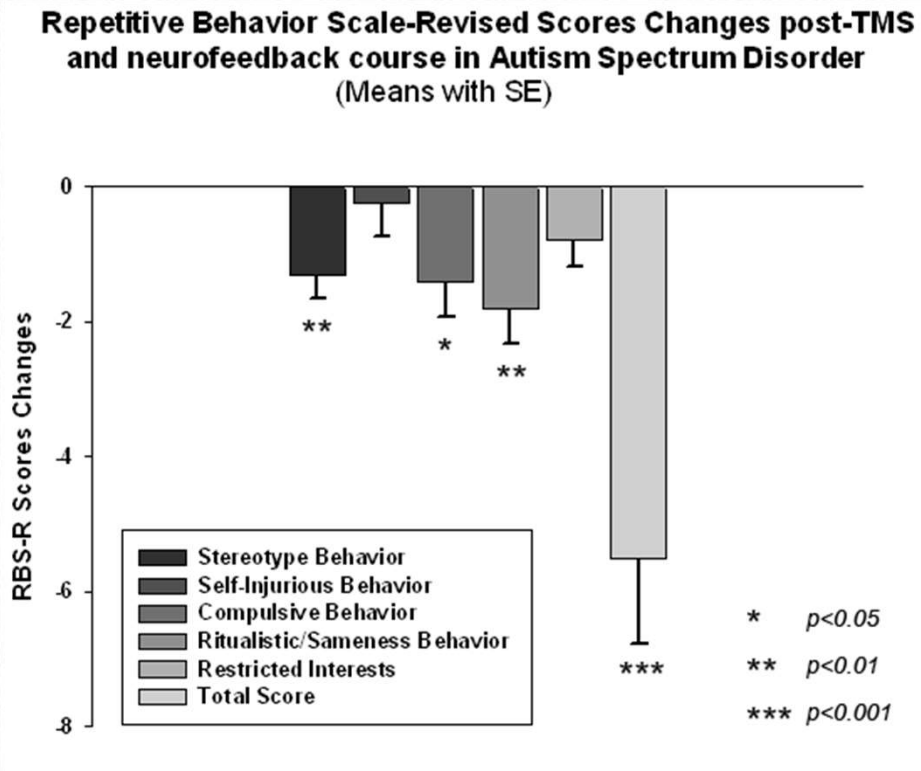
Preliminary results of rTMS+NFB in autism (N=20)

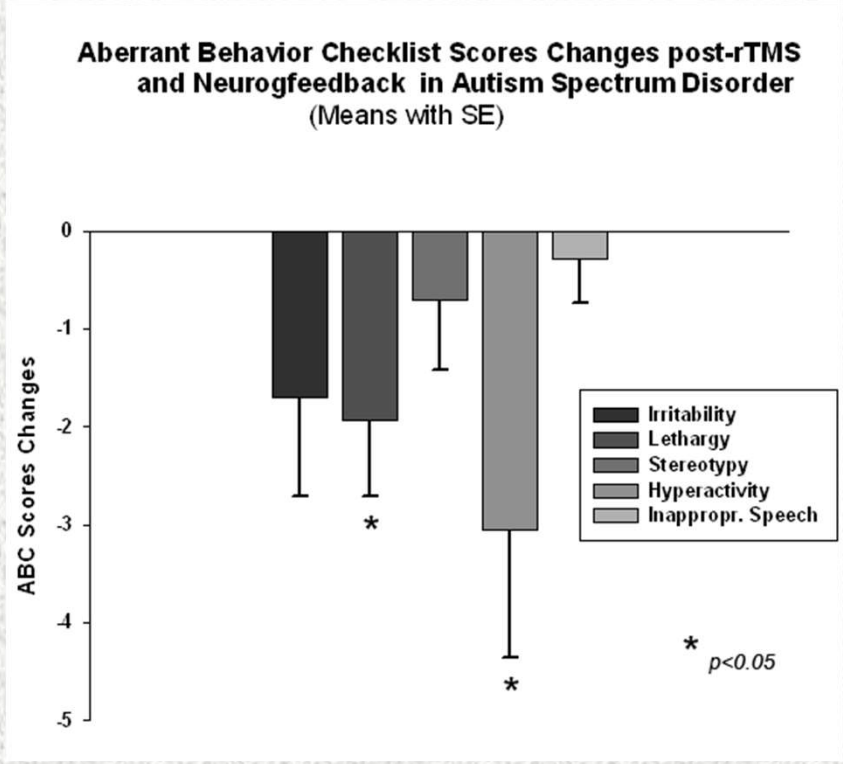




Sokhadze, E.M., El-Baz, A.S., Tasman, A., Sears, L.L., Wang, Y., Lamina, E.V., and Casanova, M.F.: Neuromodulation integrating rTMS and neurofeedback for the treatment of autism spectrum disorder: An exploratory study. *Appl. Psychophysiol. Biofeedback* 39 (3-4):237-257, 2014.

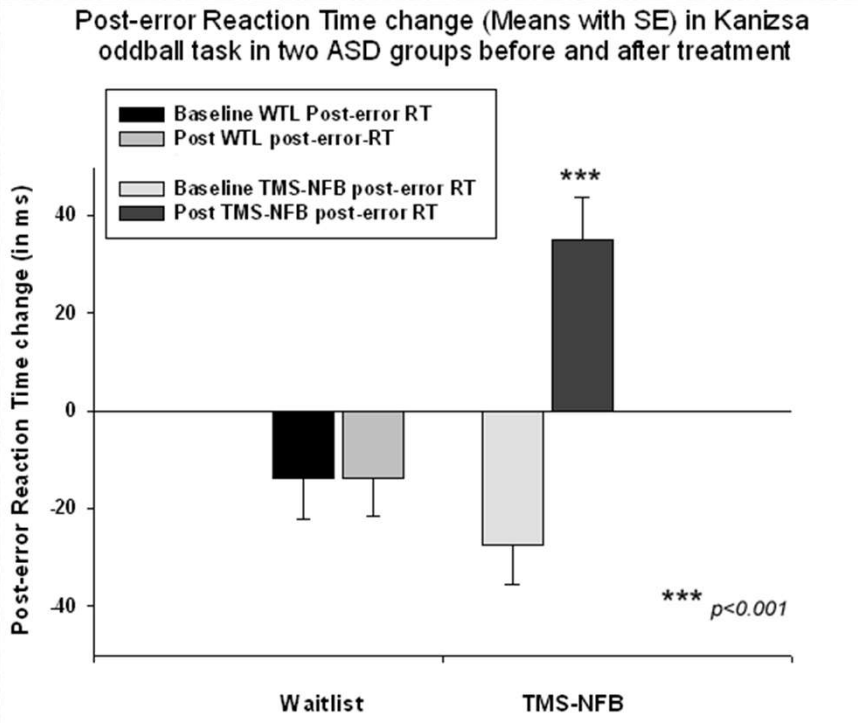
Clinical behavioral outcomes

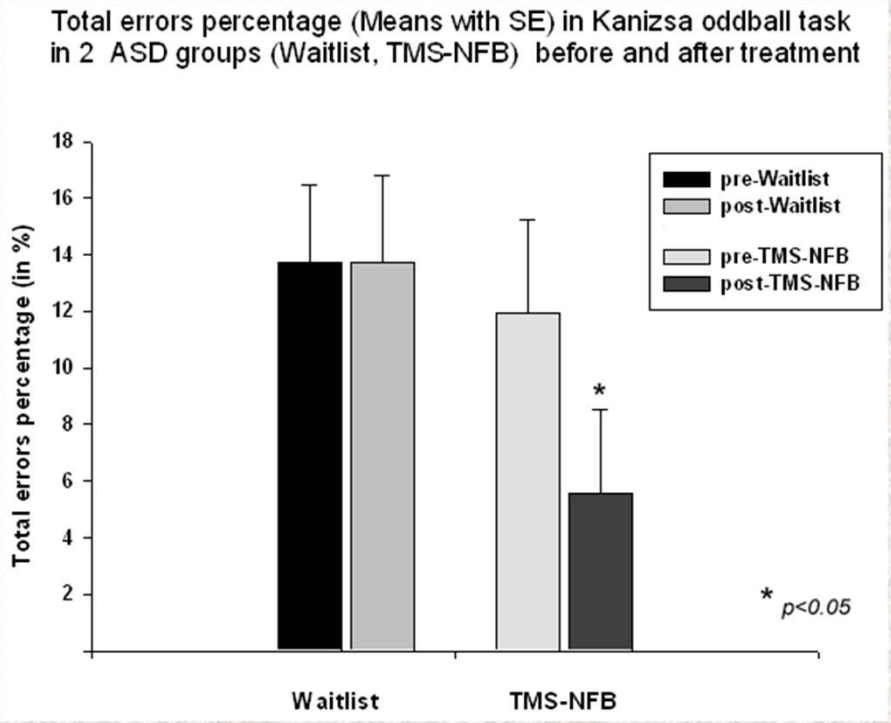




Behavioral outcomes (RT, accuracy)

- Sokhadze, E.M., El-Baz, A., Tasman, A., Sears, L., Wang, Y., Lamina, E. & Casanova, M.F. (2014) neuromodulation integrating rTMS and neurofeedback for the treatment of Autism Spectrum Disorder: An exploratory study. *Applied Psychophysiology and Biofeedback*. *E-pub. September 30*





Follow-up study

- Currently 12 subjects in rTMS+NFB group
- In addition to 12 rTMS-only group
- And also 12 in Neurofeedback-only group

- The main secret of being able to bring subjects with ASD for follow-up tests and evaluations:
- - offer them other research treatments

Thank you for the interest

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