



American
Association of
Neurological
Surgeons

Jointly Sponsored by AANS

Electronic Poster presentation for the
**American Association of Neurological Surgeons, April
5-9, 2014. San Francisco, CA.**

*Improved autism behaviors after noninvasive cerebral trans-
magnetic stimulation using customized frequency
modulation: follow-up mean 24 months*

K. Anthony Kim, MD
&
Alexander Taghva, MD
23961 Calle Magdalena, suite 504
Laguna Hills, CA 92653

Kris A. Peterson, MD
Child, Adolescent and Family Assistance Center
Department of Psychiatry, Madigan Army Medical Center
Tacoma, WA 98431

Charles Y. Liu, MD, PhD
Professor, Keck-USC Department of Neurosurgery and Neurology
1200 N State Street
Suite 3036
Los Angeles, CA 90033

Keywords: autism, magnetic resonance stimulation, neuro-modulation, transmagnetic stimulation

DISCLOSURES

Authors have not received any monetary or financial compensation.

Abstract

- INTRODUCTION

- Autism represents a multi-factorial highly prevalent disorder of the developing human neo-cortex with no clear treatments. Trans-magnetic stimulation with customized frequency has been safe in the treatment of certain frontal lobe behavioral disorders. We hypothesize behavioral improvements in autism behaviors via TMS with customized frequency modulation.

-

- MATERIALS AND METHODS

- In a retrospective of prospectively collected data, 141 patients underwent TMS with customized frequency modulation. Serial EEGs were used to modify frequency delivered using resting alpha frequency combined with resting heart rate. 35 patients were excluded at 1 week due to lack of improvement on Child Autism Score (CARS). 1 patient was excluded at first week for seizure (0.7%). 44 patients are now past 12 months with mean 24 months follow-up. Age, sex, race, other treatments, number of treatments, CARS scores were sub-stratified.

-

- RESULTS

- 26 of 44 patients who are now beyond 12 months follow-up (mean 24 months) showed statistically-significant improvement of -11.7 ± 6.2 S.D. From an initial CARS of 33 - 51.5, ten patients' CARS fell below 26 (38%) consistent with minimization of autism behaviors. Most improvements were made in Taste, Smell, and Touch Response and Use (Item IX), Fear and Nervousness (Item X), and Verbal Communication (Item XI).

-

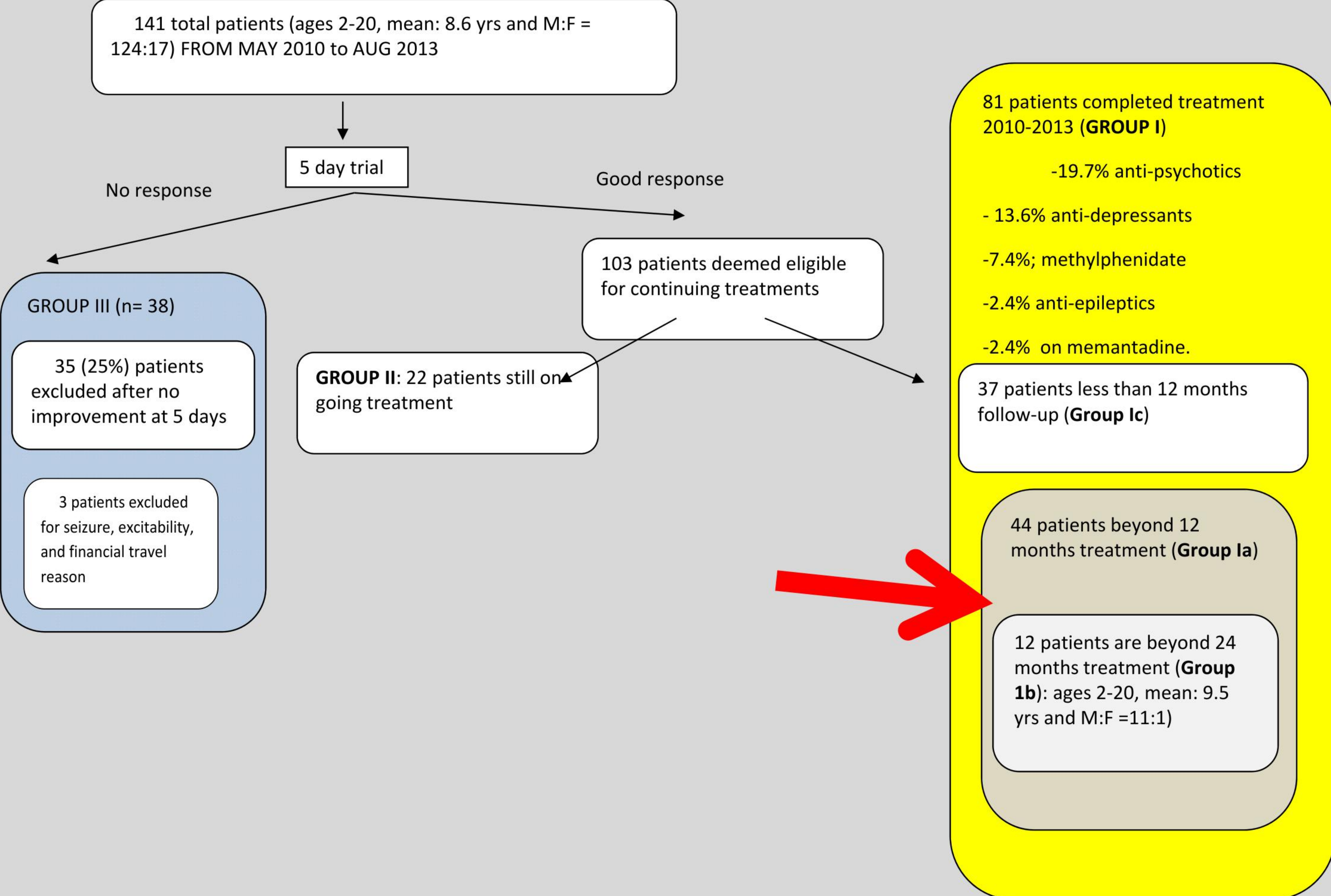
- CONCLUSION

- Non-invasive cerebral transmagnetic stimulation using customized frequency is safe at mean 24-month for the treatment of a child with autism behaviors. In those who completed 12 months (n=44), CARS was improved in 59.1% of cases by -11.7 ± 6.2 S.D. This improvement may reflect potentiation by TMS coupled with intensive behavioral interventions. Class I research will need to be performed to confirm this data.

Materials and Methods

- A retrospective review of prospectively collected data. From May 2010 to September 2013, 141 children (ages 2-20, mean: 8.6 and M:F = 124:17) underwent trial and/or treatment for autism behaviors. Three patients were over the age of 18 (ages 19, 19, 20).
- An initial five-day 'trial' period was used to determine benefit and safety. CARS was filled by the clinician-parent interview. Table 1 notes data collected and sub-stratified.
- For the trial, one 30-minute cranial trans-magnetic stimulation (TMS) session was performed each day for five days. After the trial, treatment was continued ONLY IF with parental consent, documentation of EEG changes, and IF the researcher saw benefit in CARS > 4 points.
- Each child had a verified diagnosis of autism documented by pediatrician and/or psychiatrist as per the DSM IV guidelines prior to TMS.
- End of treatment was determined by no further changes on serial EEG and *plateau-ing* of the CARS as well as parents'-documented lack of further efficacy. No further change in improvement of parents' CARS in five sequential sessions (< 5 points) was deemed *plateau-ing*.
- A CARS of 15-24 was considered minimization of autism behavior, 25 – 30 was considered borderline behavior, 31-37 mild to moderate autism, and 37-60 considered with severe autism .
- ***Exclusion from TMS and Grouping***
- Treatment was stopped after the trial period (five treatments over five days) if response was deemed lacking by the clinician and parent (i.e., change in CARS =< 4). Treatment was discontinued for seizures (n=1), worsening of symptoms (n=1), and medical reasons. Parents had the option of discontinuing treatment any time. All patients who did not continue with further treatment after the five day trial were entered into Exclusion group (Group III) (**Fig 1**).

Figure 1 – patient grouping – This electronic poster will focus on the 44 patients beyond 12 months treatment (Group 1a)



Results – main group of our focus is Group 1a

- ***81 patients continued with treatment until endpoint, i.e., plateau-ing of behavior improvement***
- 103 (73%) patients continued beyond the trial safety and efficacy period. 81 children completed the treatment (Group I). Of these, 12 children are now beyond 24-months follow-up (Group Ib; ages 2-20, mean: 9.5 and M:F =11:1).
- **44 children are *beyond 12-months follow-up with mean follow up 24 months (Group Ia; ages 2-20; mean age 10 +/- 5 S.D.; M:F=37:7)***. Of Group I, 37 patients have had less than 12-months follow-up (Group Ic). Group Ib is a subset of Group Ia. Once again, **Figure 1 shows grouping of patients (Fig. 1)**.
- Each of 103 children (Group I and II) underwent 5 -80 treatments (average 22.5 sessions) over an average 14.4 weeks (ranging 2 week to 52 weeks). In Group 1a, the average child had 35 +/-22 sessions (range 6-86) over a period of 3.9 +/- 4.9 months (0.8 – 27 months).
- **Figure 1 shows grouping and Table 1 substratification data.**

Table 1

Comparison and stratification of potential biases between Group 1, Group F, and Group S. Group I was chosen as basis for comparison to include widest variety of other concurrent non-TMS treatments

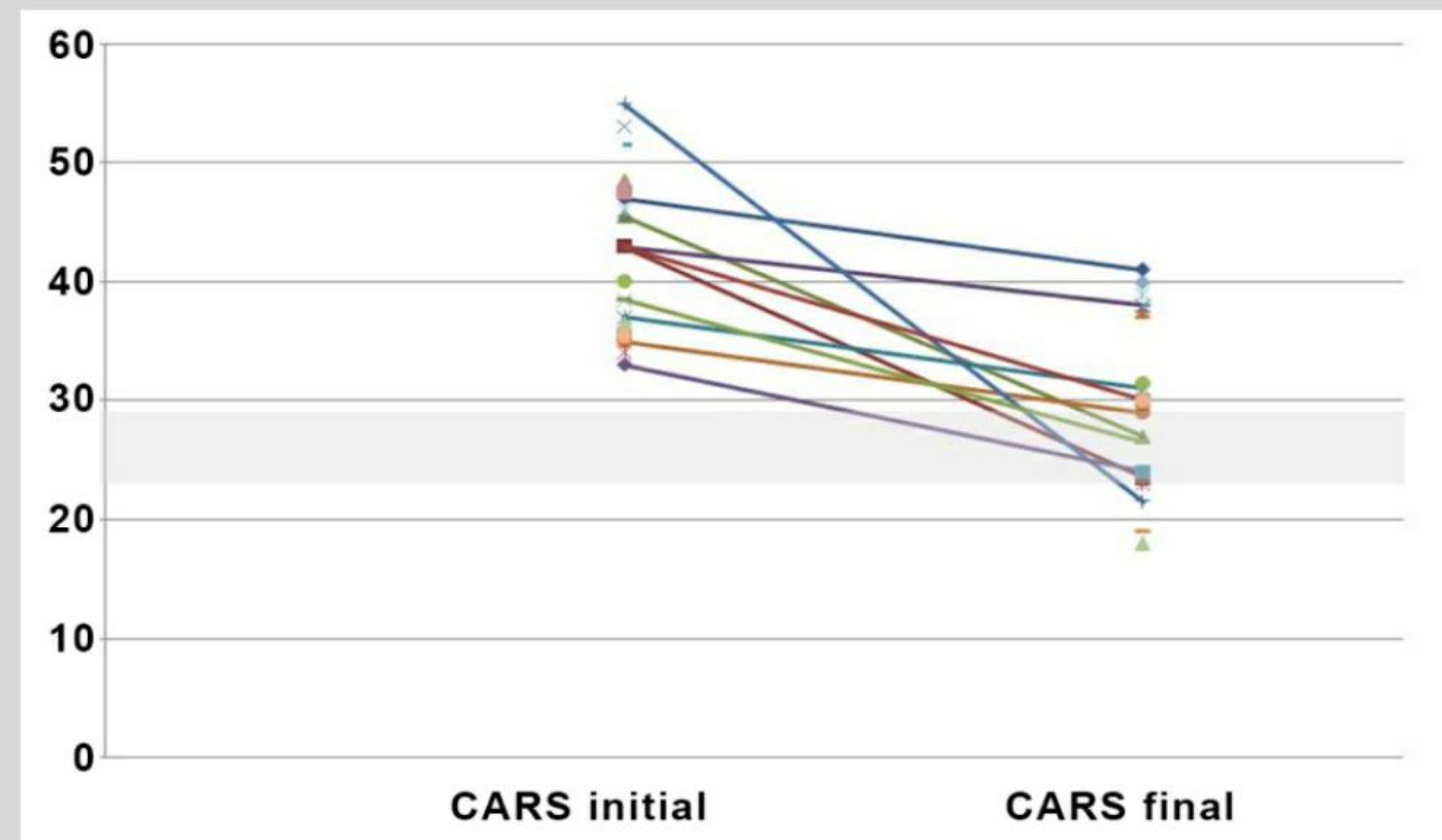
	Group S(n=26)	Group I (n = 81)	Group F (n=18)	p-value
Male	21 (0.8)	69 (0.85)	16 (0.89)	1.0
Female	5 (0.2)	12 (0.15)	2 (0.11)	
Age yrs (avg)	9.5+/-5.1	8.9 +/- 4.7	10.8 +/- 5.0	
Age yrs(range)	2-19	2-20	4-20	
No. of Tx	43.9 +/-23.6	35 +/- 22.1	22 +/- 10.5	
Tx duration(mo)	5.2+/-5.8	3.3 +/-4.9	2.0 +/- 1.8	
Hx of CBT	all	all	all	
Anti-psych meds	5 (0.2)	16 (0.20)	6 (0.3)	0.5
Anti-seizure meds	1 (<0.1)	2 (0.03)1	2 (0.1)	0.6
Anti-depressants	5 (0.2)	11 (0.14)	3 (0.17)	1.0
Stimulant	1 (<0.1)	6 (0.07)	0	1.0
Namenda	2 (0.1)	2 (0.03)	0	0.5
MVI	7 (0.3)	22 (0.27)	4 (0.2)	1.0
Melatonin	1 (<0.1)	10 (0.12)	2 (0.1)	0.6
L-carnitine / L-lysine	3 (0.1)	4 (0.05)	1 (0.1)	1.0
5-HTP	1 (<0.1)	5 (0.06)	0	
Daxitrol	0	2 (0.03)	0	
Anti-fungal	0	2 (0.03)	0	
Probiotic	0	6 (0.07)	0	
Initial CARS	41.1 +/- 7.6	38.7 +/-8.6	37.9 +/- 10.4	N.S.
FINAL CARS	29.4 +/- 7.73	33 +/- 8.7	36.7 +/- 10.4	N.S.
Change in CARS	-11.7 +/-6.2	-5.7+/- 5.9	-1.2 +/- 1.9	significant

Results 2 – within Group Ia

- *Within Group Ia, CARS Improvement is noted in 26 of 44 (59%) patients after 1 year and completed treatment*
- *Group II and Group Ic data was excluded at time of analysis due to less than one year follow-up.*
- All 44 patients (100%) in Group Ia had (a) all CARS completed, (b) TMS completed and (c) with at least one- year follow-up. In this group, data on sum 1537 treatments over 170 months was collected. On the surface, CARS demonstrated an improvement or reduction -7.4 ± 7.1 , i.e. no apparent improvement. Average Initial CARS was 39.8 ± 8.9 S.D. Average Final CARS was 32.4 ± 9.5 S.D. A subset analysis was performed:
- **Eighteen patients had CARS improvement of < 5 points (41%) and declared failure (Group F). Excluding the 18 failed patients, the remaining 26 patients (Group S) showed average initial CARS of 41 ± 7.6 S.D. and average final CARS 29.4 ± 7.73 S.D. with an average CARS improvement of -11.7 ± 6.2 . This represents average 28% improvement over mean 24 months.**
- Removing the exclusion of 27% in the beginning (n = 38), the CARS improvement of 26 of 44 patients at end-treatment represents a potential 59.1% positive statistically significant response rate of all patients after 1 year. Including the exclusion, significant response rate would be $0.73 \times 0.59 = 0.43$, or, 43% success rate.
- **FIGURE 2 and 3 show autism behavior improvements comparing the Successful 26 to the Failure 18 patients.**

Figure 2. Overall CARS improvement after 1 year of treatment in Group Ia. Comparison is made between Group S (successful) and F (failure). A CARS score of less than 25 is deemed to be “minimal autism behaviors.” In our paper, borderline autism behavior was defined as score 25-30.

Overall CARS improvement by or beyond 1 year in 26 patients (Group S)



Overall CARS lack of change by or beyond 1 year in 18 failed patients (Group F)

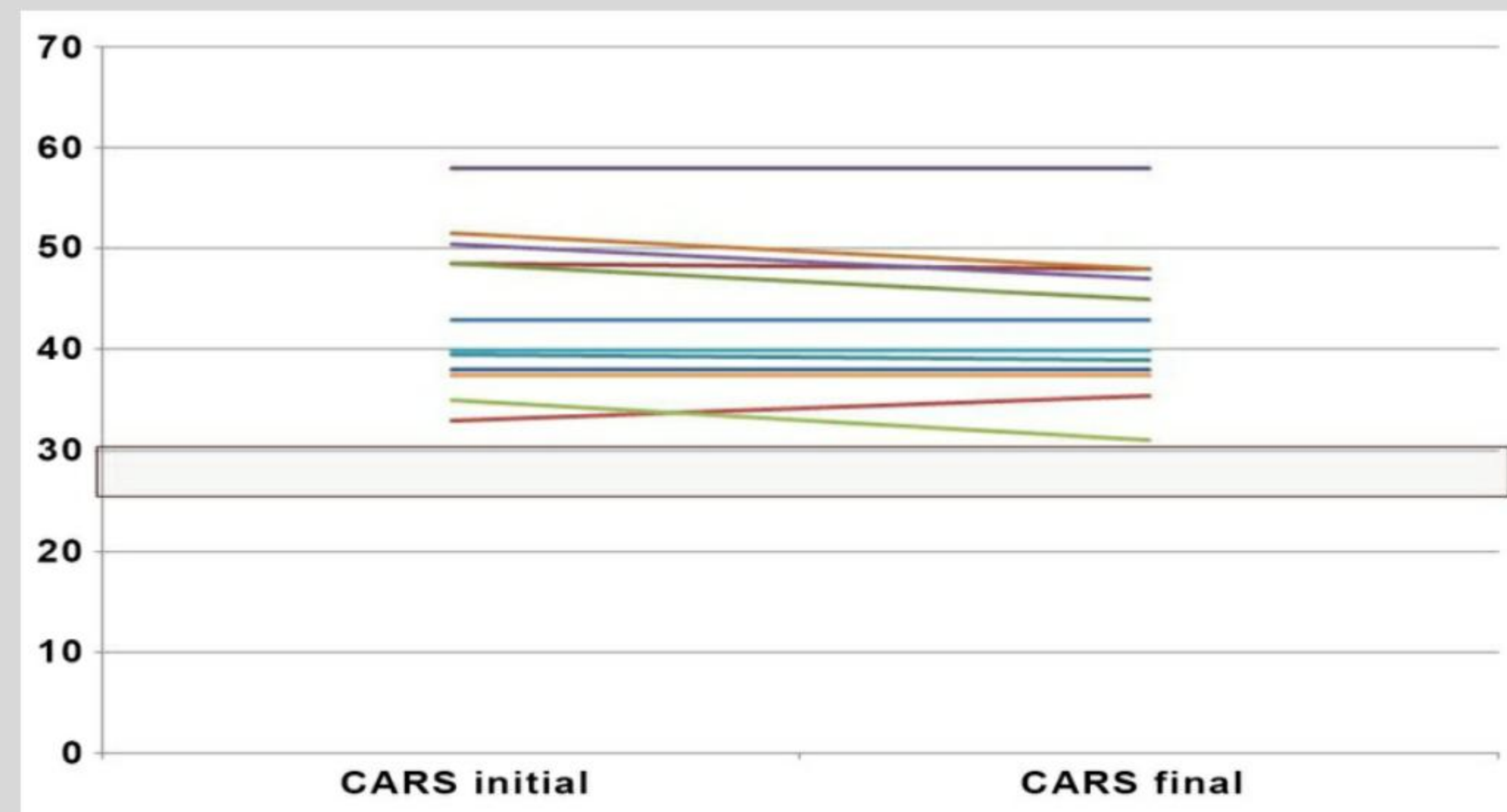
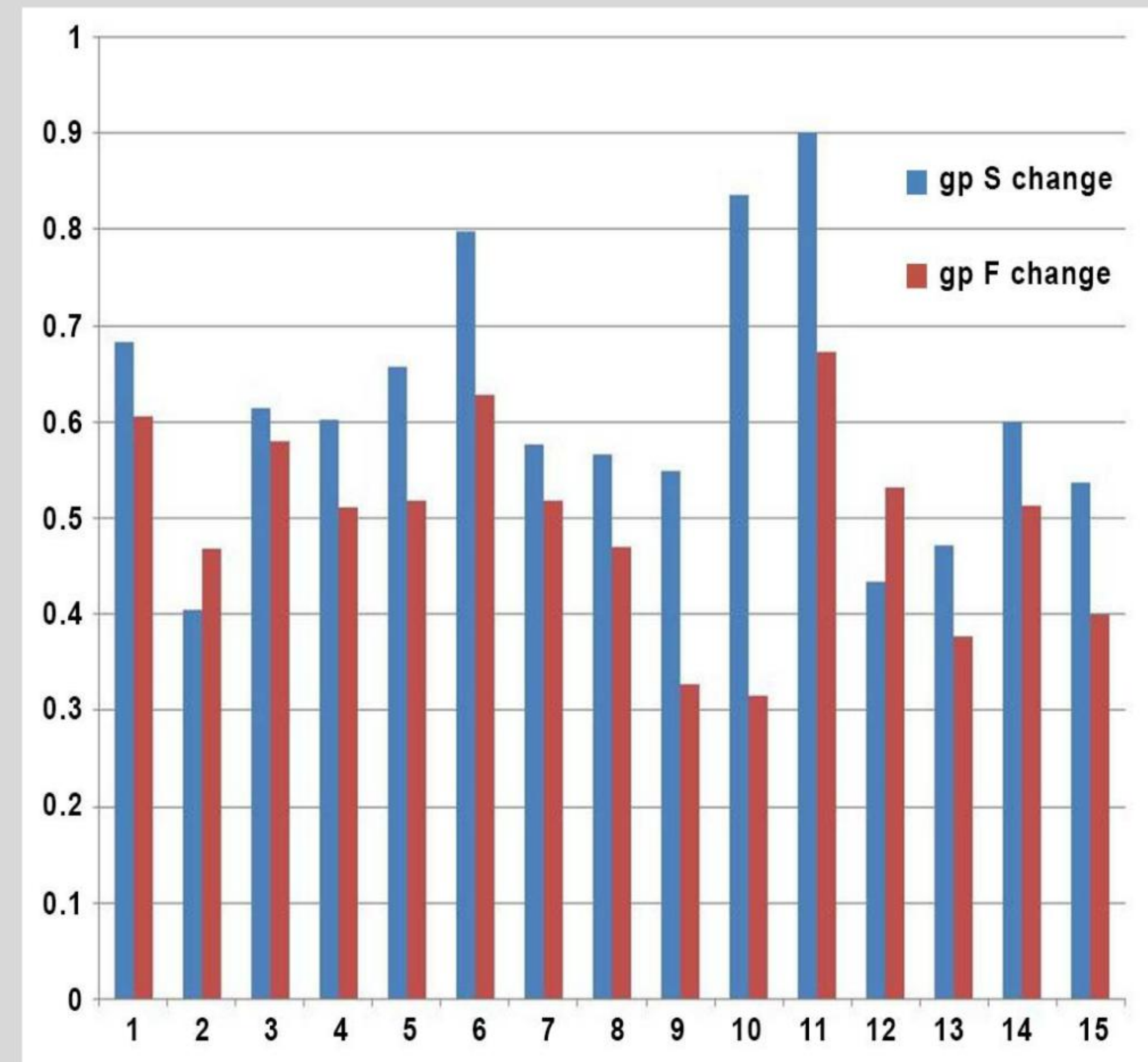


Figure 3. Absolute change of CARS final comparing Group S (successful) (Blue) and Group F (failure) (Red) within Group Ia sub-divided by item. Items 9-11 demonstrated the most improvement.

- 1 Relationship to people
- 2 Imitation
- 3 Emotional response
- 4 Body use
- 5 Object use
- 6 Adaption to change
- 7 Visual response
- 8 Listening response
- 9 Taste, smell,touch response,use
- 10 Fear and nervousness
- 11 Verbal communication
- 12 Non-verbal communication
- 13 Activity Level
- 14 Level and consistency of intellectual response
- 15 General impressions



Conclusion

- Non-invasive cerebral transcranial magnetic stimulation using customized frequency is safe at mean 24-month for the treatment of a child with autism behaviors. No significant increase in seizure activity was noted (0.7%). In those who completed treatment and follow-up (n=44), CARS was improved in 59.1% of cases by -11.7 ± 6.2 S.D. This improvement may reflect potentiation by TMS coupled with intensive behavioral interventions. Class I research will need to be performed to confirm this data.