Effects of a beta-adrenergic antagonist on social and cognitive functioning in autism spectrum disorder

Zamzow, R. M., Ferguson, B. J., Hegarty II, J. P., Lewis, M. L., Ragsdale, A. S., Christ, S. E., Stichter, J. P., & Beversdorf, D. Q.

University of Missouri

INTERDISCIPLINARY NEUROSCIENCE PROGRAM

Thompson Center
For Autism & Neurodevelopmental Disorders
University of Missouri

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social communication impairments and restricted, repetitive behaviors.[1] Current pharmacological interventions for ASD focus primarily on psychiatric symptoms, including agitation and obsessive behaviors.[2] Few agents target core symptomatology, such as social communication. As autonomic dysregulation has been previously observed in this population,[3] agents targeting the sympathetic or parasympathetic nervous systems may provide therapeutic effects. Propranolol, a non-selective beta-adrenergic antagonist with known anxiolytic effects, reduces noradrenergically mediated sympathetic tone. This agent has been previously reported to improve verbal fluency and working memory in ASD.[4,5] The present single dose challenge study explores the effects of propranolol on performance on social and cognitive tasks in ASD. In addition, we sought to determine if sympathetic or parasympathetic tone could predict response to propranolol, establishing a potential treatment response marker.

Methods

Twenty individuals with high-functioning ASD [mean age = 21.39 ± 4.55 (SD)] participated in two study sessions. All participants had an IQ greater than 85. At the beginning of each study session, baseline sympathetic and parasympathetic tone was measured via galvanic skin response (GSR) and electrocardiography (ECG) respectively for a period of 5 minutes, after 3 minutes of acclimation, using a BIOPAC MP150 system (BIOPAC Systems, Inc., Goleta, CA). Participants were then administered propranolol (40 mg) or placebo in a counterbalanced, double-blinded manner. Following a 60 minute wait period to allow for peak drug effects, participants performed several tasks, during which sympathetic/parasympathetic tone was recorded.

Social Competence Assessment
Participants were given a component of the General Social Outcome Measure (GSOM),[6] in which they engaged in a short conversation with the researcher after choosing between two topics. Scores ranging from 0 - 2 were recorded for six domains: staying on topic, sharing information, reciprocity, transitions/interruptions, nonverbal communication, and eye contact.

Cognitive Tasks
To assess verbal problem solving, the Anagrams task was administered, in which participants were asked to solve 20 anagrams (e.g. IRBCK for BRICK). The number solved and latency to correct response (maximum = 120 s) were recorded. Verbal memory was assessed using the Hopkins Verbal Learning Test (HVLT), in which participants are asked to memorize a list of 12 words. Scores were recorded for free recall, delayed free recall, and recognition phases.

Sympathetic/Parasympathetic Tone Analysis
GSR data was represented as the mean level over the 5 minute data collection period. Following motion artifact removal, R-R intervals were extracted from ECG data and heart rate variability (HRV) was determined using AcqKnowledge 4.1 (BIOPAC Systems, Inc) and Kubios HRV (University of Eastern Finland, Kuopio, Finland).

Statistical Analysis
Paired samples t-tests were used to compare task performance between drug conditions. Simple linear regressions were used to explore relationships between sympathetic/parasympathetic tone and response to drug (propranolol score – placebo score).
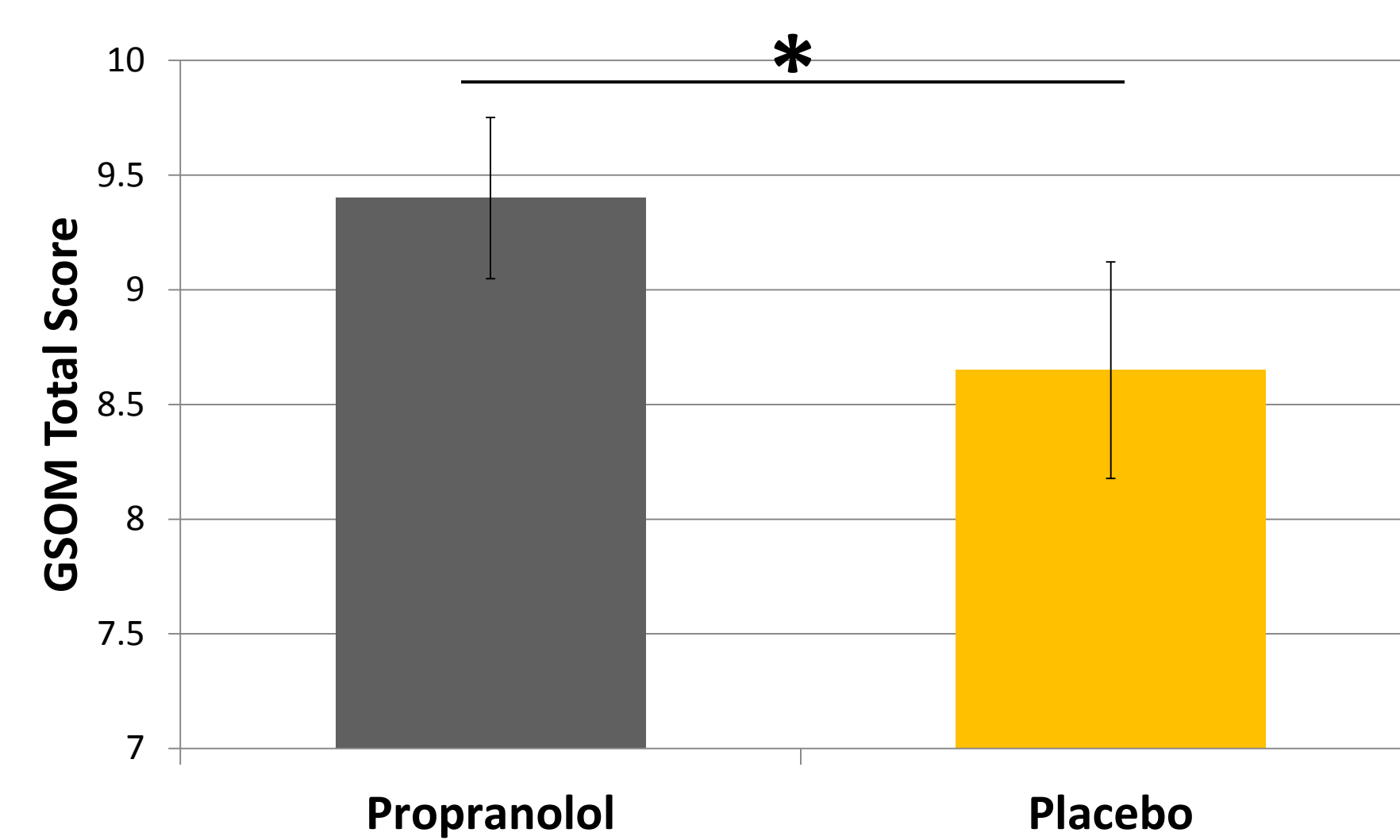
Social Competence Task Performance

Figure 1. Mean GSOM total scores for the propranolol and placebo conditions. Bars represent S.E.M. * $p < .05$
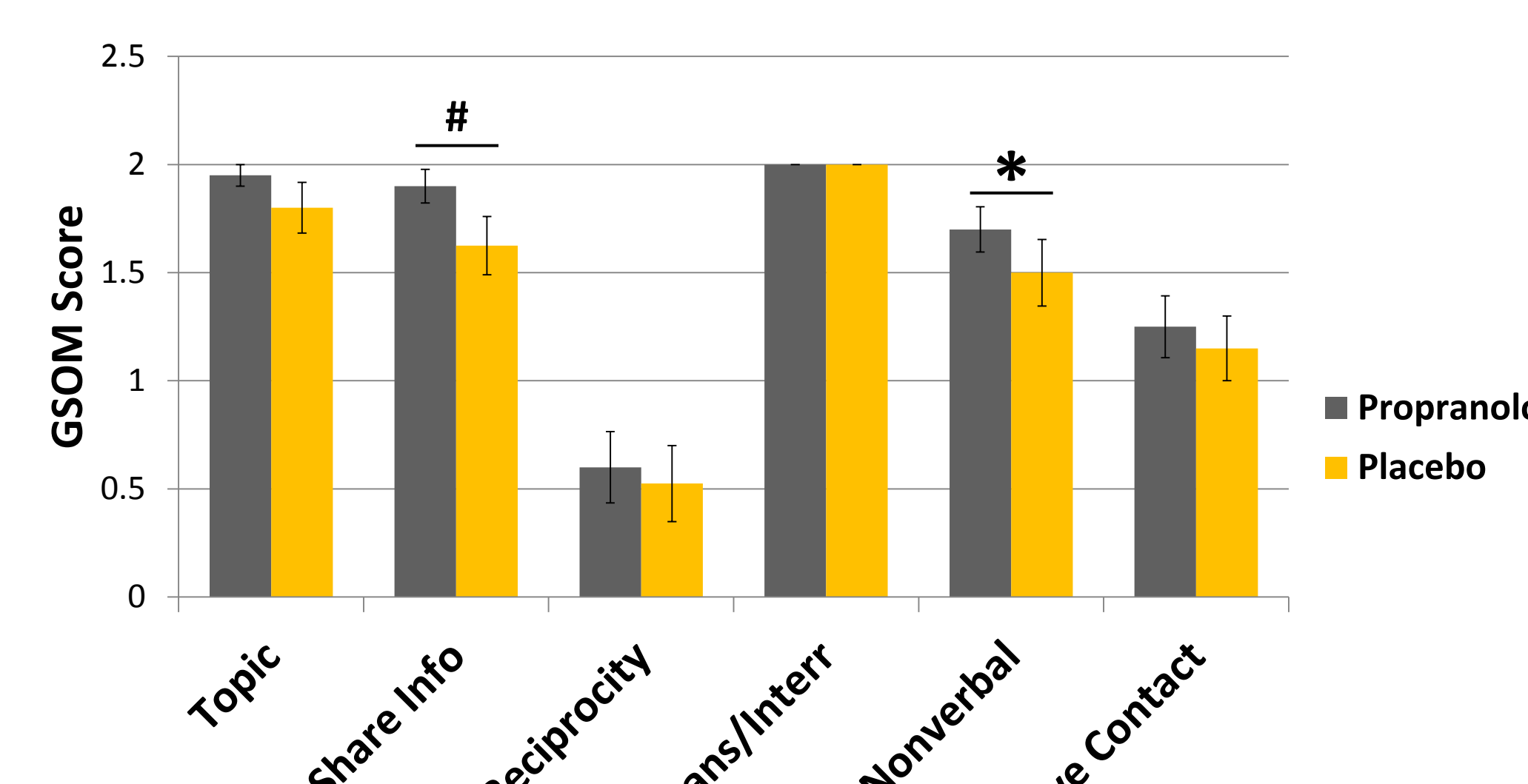

Figure 2. Mean GSOM subscale scores for the propranolol and placebo conditions. Bars represent S.E.M. * $p < .05$, # $p < .10$
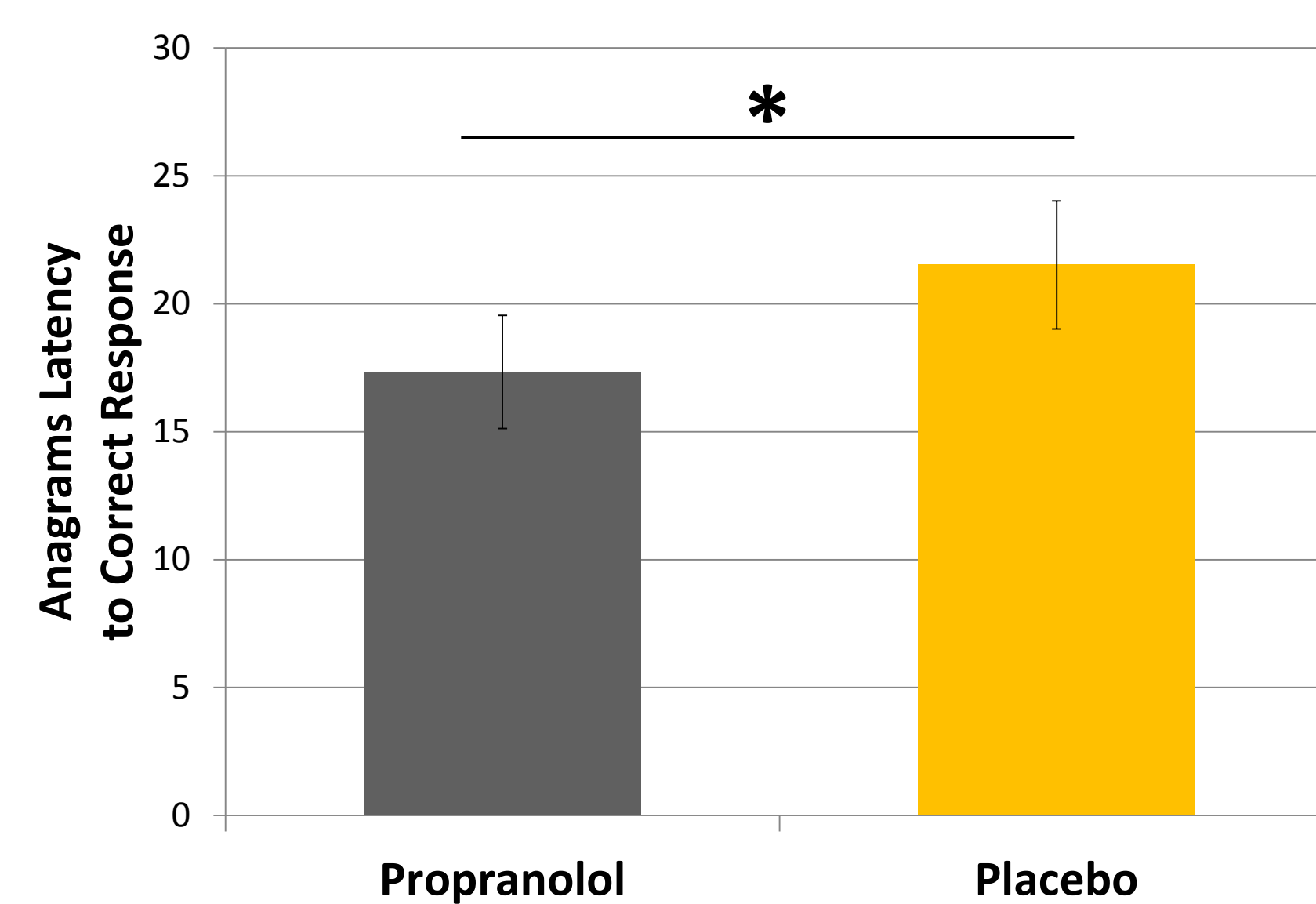
Cognitive Task Performance

Figure 3. Mean latency to correct response for the Anagrams task in the propranolol and placebo conditions. Bars represent S.E.M. * $p < .05$
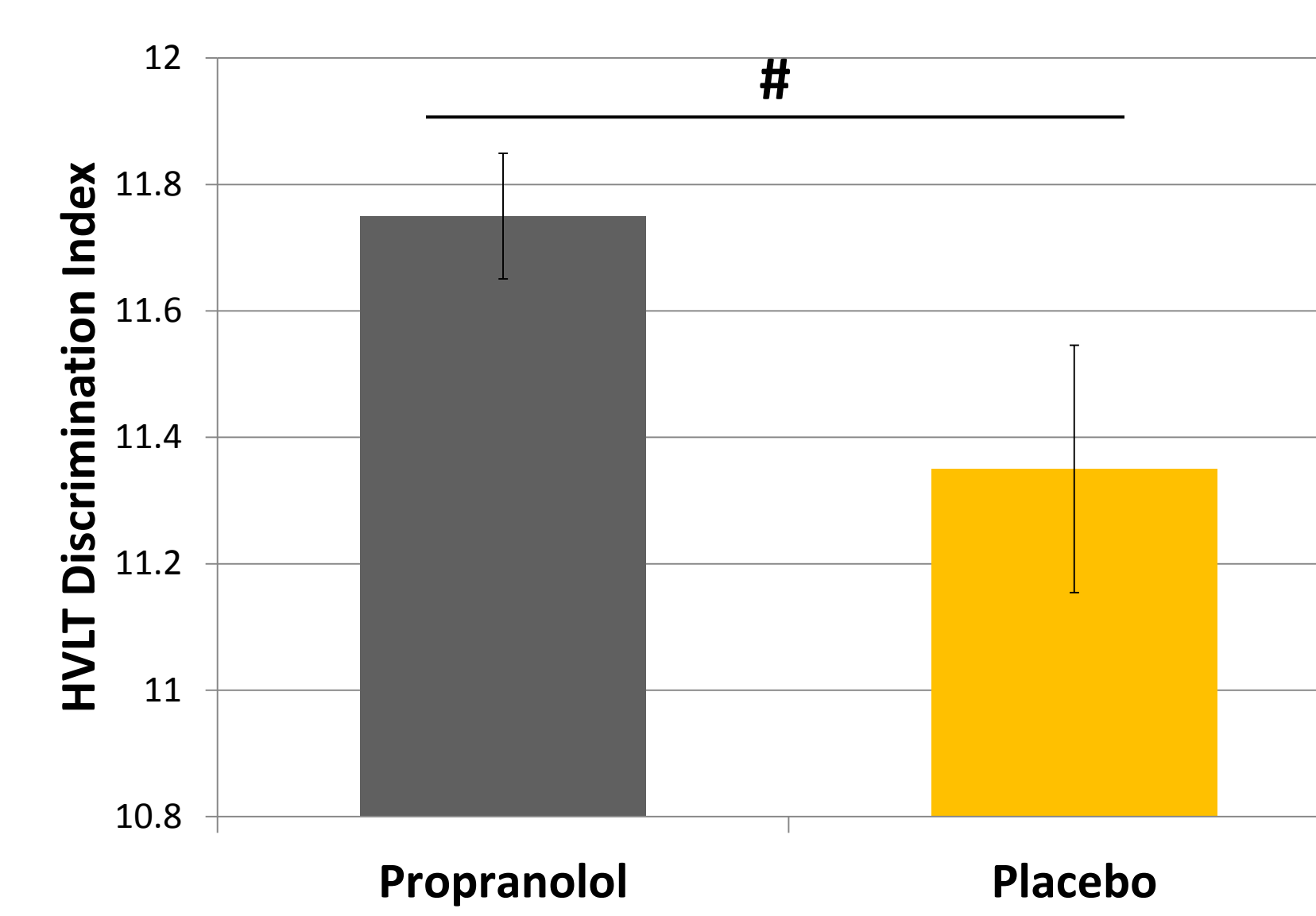

Figure 4. Mean Discrimination Index (DI) for the HVLT in the propranolol and placebo conditions. DI = (# True Positives) – (# False Positives). Bars represent S.E.M. # $p < .10$
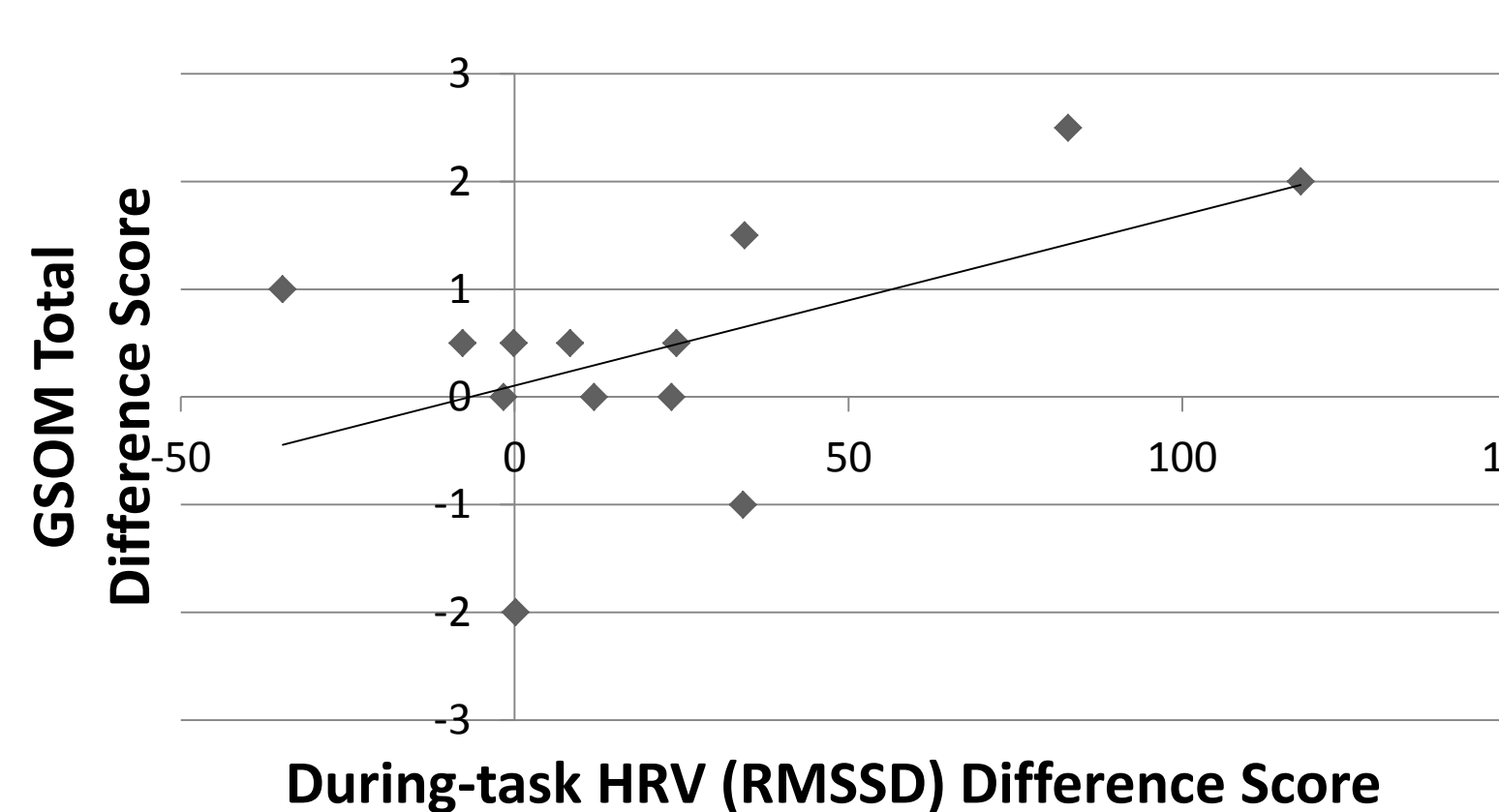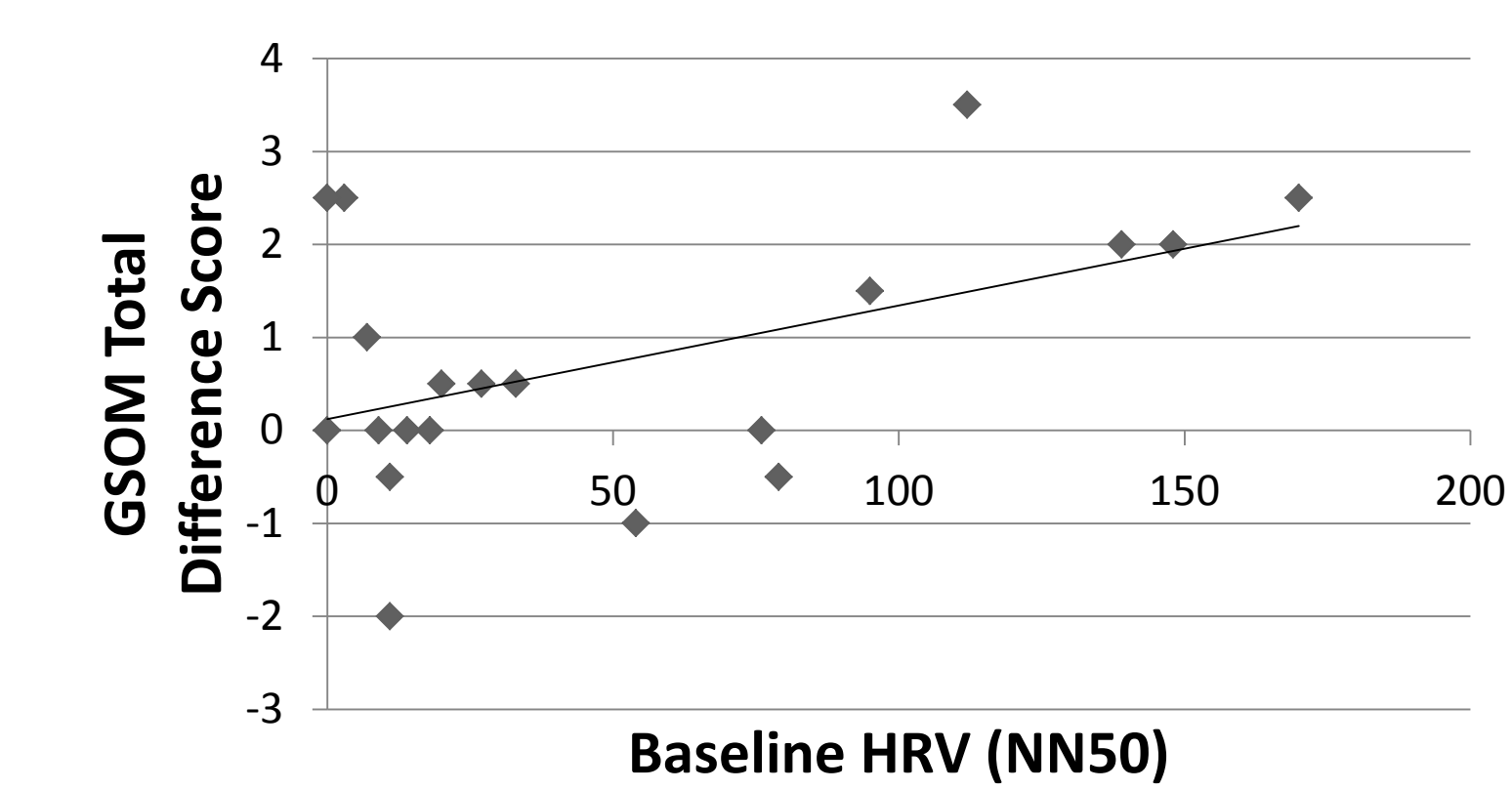
Social Competence & Parasympathetic Tone

Figure 5. Scatterplot showing response to drug (propranolol – placebo) as a function of baseline ($p < .05$) and during-task ($p = .06$) HRV for the GSOM total score with the corresponding linear regression lines. NN50 - number of successive R-R intervals that differ by greater than 50 ms. RMSSD - root mean square of successive differences between adjacent R-R intervals.

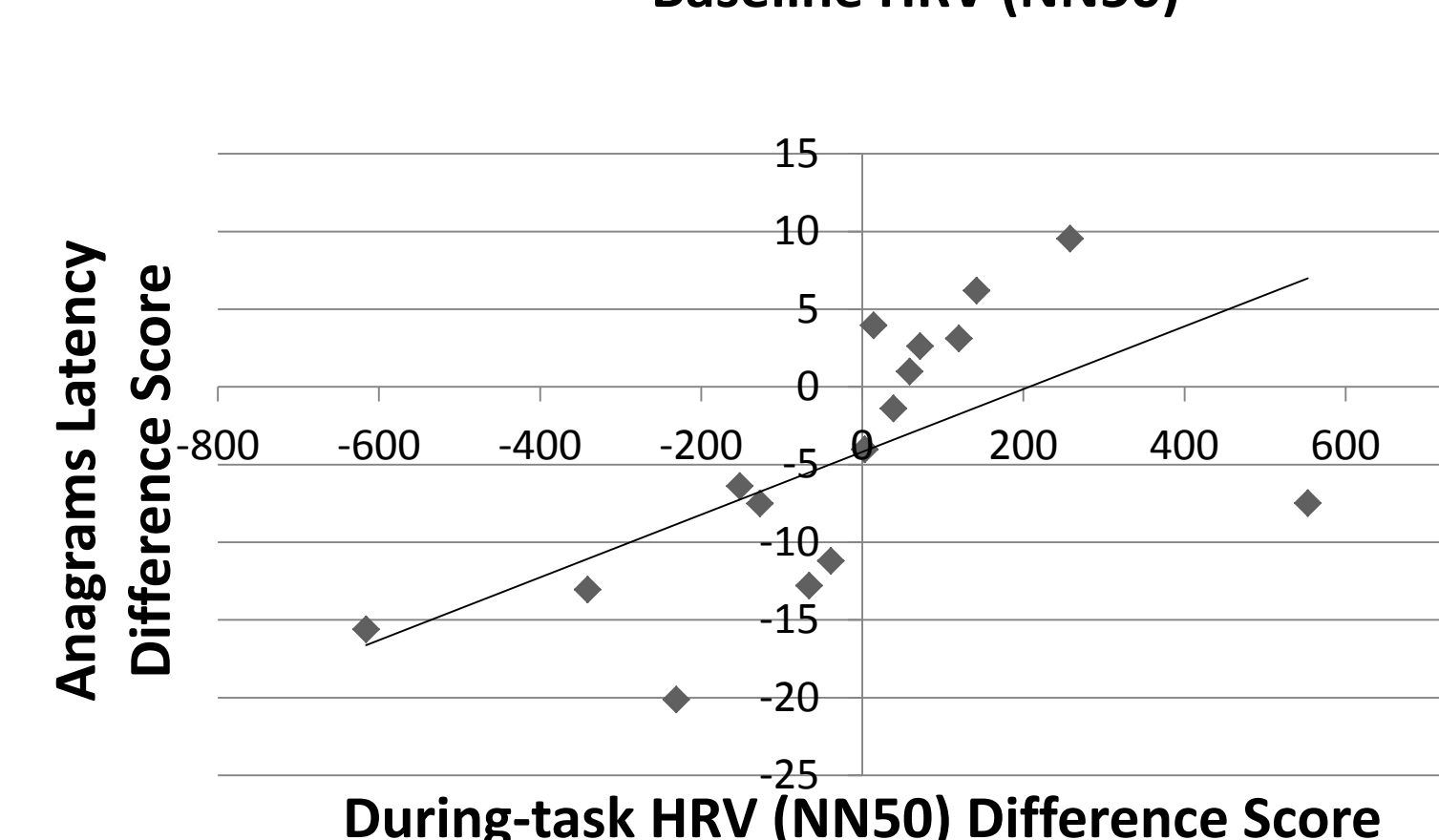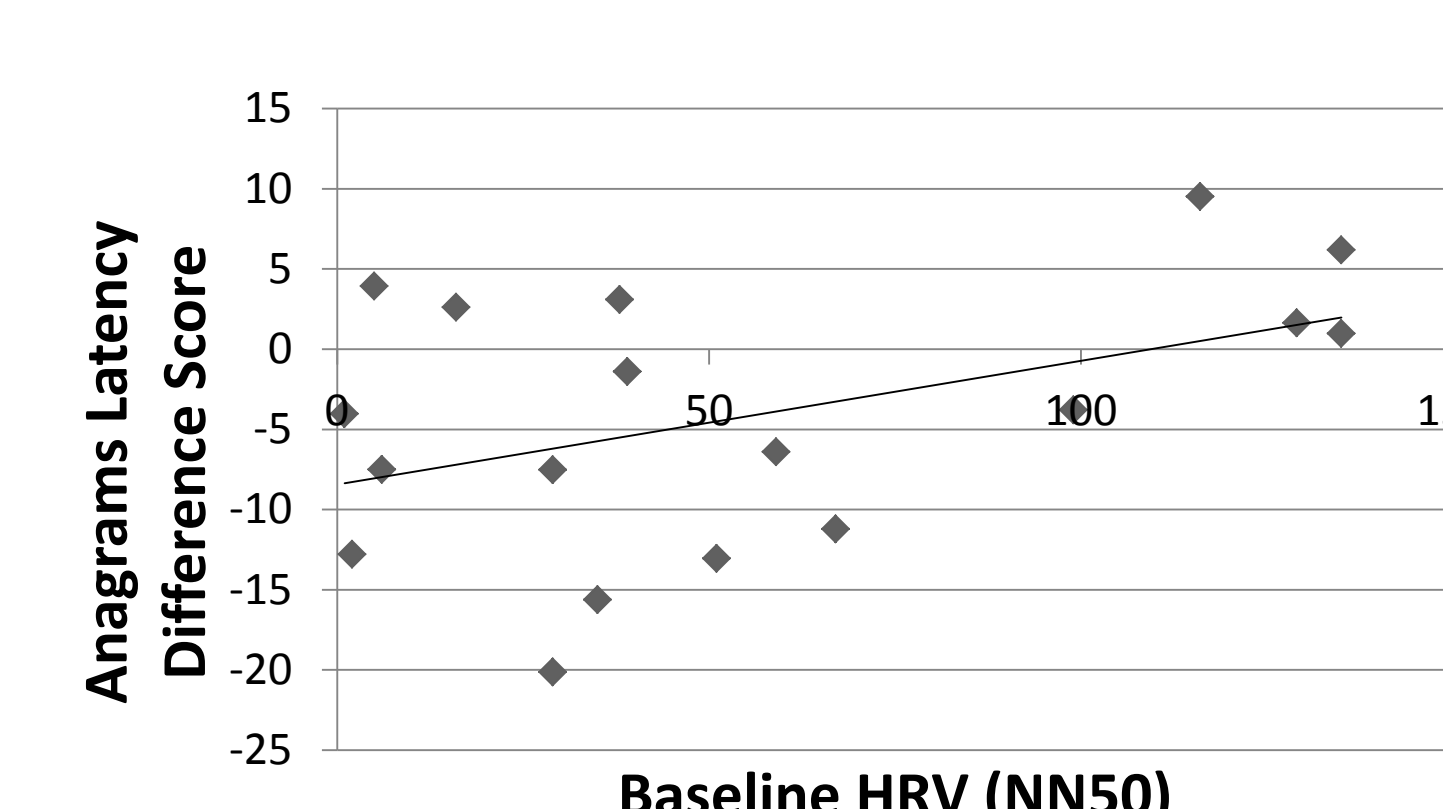### Verbal Problem Solving & Parasympathetic Tone

Figure 6. Scatterplot showing response to drug (propranolol – placebo) as a function of baseline ($p = .06$) and during-task ($p < .05$) HRV for the Anagrams latency to correct response with the corresponding linear regression lines. NN50 - number of successive R-R intervals that differ by greater than 50 ms.

Results

Task performance

• The total score [$t(19) = 2.36$, $p = .03$] and the nonverbal communication score [$t(19) = 2.18$, $p = .04$] for the GSOM were significantly higher in the propranolol condition, as compared to the placebo condition (Figs. 1 & 2).

• A trend for an increased sharing information score for the GSOM in the propranolol condition was also observed [$t(19) = 1.76$, $p = .09$] (Fig. 2).

• The latency to correct response for the Anagrams task was significantly lower in the propranolol condition, as compared to the placebo condition [$t(18) = 2.17$, $p = .045$] (Fig. 3).

• There was a trend for a greater discrimination index for the HVLT recognition phase in the propranolol condition [$t(19) = 1.80$, $p = .09$] (Fig. 4).

Sympathetic & Parasympathetic Tone

• A significant positive relationship was observed between baseline HRV (NN50) and response to propranolol for the GSOM total score [$F(1,18) = 5.05$, $p = .04$, $R^2 = .22$] (Fig. 5).

• There was a trend for the same relationship between change in HRV (RMSSD) and change in total score in response to propranolol during the GSOM [$F(1,11) = 4.40$, $p = .06$, $R^2 = .29$] (Fig. 5).

• A trend for a positive linear relationship was also revealed between baseline HRV (NN50) and response to propranolol for the latency to correct response on the Anagrams task [$F(1,16) = 4.00$, $p = .06$, $R^2 = .20$] (Fig. 6).

• A significant relationship was found between change in HRV (NN50) and the change in latency in response to propranolol during the Anagrams task [$F(1,14) = 8.24$, $p = .01$, $R^2 = .37$] (Fig. 6).

• No significant relationships were observed between GSR and task performance in response to propranolol [$p > .05$ in all instances].

Conclusions

• Propranolol may improve both social competence and aspects of cognition, specifically verbal problem solving and memory, in ASD.

• Improvements in these domains may be predicted by autonomic nervous system activity at baseline as well as in response to propranolol, where individuals with greater parasympathetic tone exhibited greater responses to propranolol.

• Future studies are needed to explore the effects of serial doses of propranolol on social and cognitive abilities in ASD, as well as the role of autonomic nervous system activity in response prediction.

References

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