

Beta-adrenergic antagonism alters functional connectivity during associative processing in a preliminary study of individuals with and without autism

Autism

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John P Hegarty^{1,2} , Rachel M Zamzow¹,
Bradley J Ferguson¹ , Shawn E Christ¹, Eric C Porges³,
Jeffrey D Johnson¹  and David Q Beversdorf¹

Abstract

Beta-adrenergic antagonism (e.g. propranolol) has been associated with cognitive/behavioral benefits following stress-induced impairments and for some cognitive/behavioral domains in individuals with autism spectrum disorder. In this preliminary investigation, we examined whether the benefits of propranolol are associated with functional properties in the brain. Adolescents/adults (mean age = 22.54 years) with ($n = 13$) and without autism spectrum disorder ($n = 13$) attended three sessions in which propranolol, nadolol (*beta*-adrenergic antagonist that does not cross the blood–brain barrier), or placebo was administered before a semantic fluency task during functional magnetic resonance imaging. Autonomic nervous system measures and functional connectivity between language/associative processing regions and within the fronto-parietal control, dorsal attention, and default mode networks were examined. Propranolol was associated with improved semantic fluency performance, which was correlated with the baseline resting heart rate. Propranolol also altered network efficiency of regions associated with semantic processing and in an exploratory analysis reduced functional differences in the fronto-parietal control network in individuals with autism spectrum disorder. Thus, the cognitive benefits from *beta*-adrenergic antagonism may be generally associated with improved information processing in the brain in domain-specific networks, but individuals with autism spectrum disorder may also benefit from additional improvements in domain-general networks. The benefits from propranolol may also be able to be predicted from baseline autonomic nervous system measures, which warrants further investigation.

Keywords

beta-blockers, fronto-parietal control network, functional magnetic resonance imaging, noradrenergic, propranolol, semantic fluency

The mechanisms underlying autism spectrum disorder (ASD) are not yet known, but the autonomic nervous system (ANS) may contribute to some degree based on reports of heightened sympathetic nervous system (SNS) arousal/stress reactivity (Hirstein, Iversen, & Ramachandran, 2001) and reduced parasympathetic nervous system (PNS) tone (Porges, 2005). Considering that the PNS exerts modulatory influences on SNS activity and these influences may be reduced in ASD, pharmacological modulation of the SNS may provide some clinical benefit. For instance, the administration of propranolol (a central nervous system and peripheral nervous system *beta*-adrenergic antagonist) to individuals with ASD in case series and single-dose studies has indicated the potential for benefits in aggression (Ratey

et al., 1987), verbal problem-solving/semantic fluency (Beversdorf, Carpenter, Miller, Cios, & Hillier, 2008; Beversdorf et al., 2011; Zamzow, Ferguson, Ragsdale, Lewis, & Beversdorf, 2017), working memory (Bodner,

¹University of Missouri, USA

²Stanford University School of Medicine, USA

³University of Florida, USA

Corresponding author:

John P Hegarty, Autism and Developmental Disorders Research Program, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Road, Stanford, CA 94305, USA.

Email: hegartyj@stanford.edu

Beversdorf, Saklayen, & Christ, 2012), and social communication (Ratey et al., 1987; Zamzow et al., 2016).

Based on research by our team (Hegarty et al., 2017; Narayanan et al., 2010) and other groups (Hermans et al., 2011), it appears that the cognitive benefits of propranolol may be due to modulation of network-level processing in the brain. Propranolol has been shown to alter functional network properties in the default mode network (DMN) in individuals with ASD during passive rest (Hegarty et al., 2017) and in language regions during the performance of a phonological processing task (Narayanan et al., 2010). However, target engagement of functional network differences in individuals with ASD with propranolol and its relationship with alterations in cognitive performance has not yet been examined. In addition, only a few functional networks have been assessed, which limits our understanding of the dynamic effects of *beta*-adrenergic antagonism. For instance, upon stimulus presentation, the fronto-parietal control (FPC) network generally shifts access from the DMN to the dorsal attention network (DAN) to allow orientation to the stimulus, and the domain-specific network then processes the information necessary to complete the task. Once the stimulus is removed, the FPC shifts network access back to the DMN until the next stimulus occurs (Corbetta & Shulman, 2002; Fox et al., 2005; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). Individuals with ASD exhibit functional differences in regions comprising all of these networks (Cherkassky, Kana, Keller, & Just, 2006; Fitzgerald et al., 2015; Just, Cherkassky, Keller, & Minshew, 2004; Kana, Keller, Cherkassky, Minshew, & Just, 2006; Kana, Keller, Minshew, & Just, 2007; Solomon et al., 2009). Thus, additional research will be necessary to elucidate the effects of *beta*-adrenergic antagonism on functional network integration in the brain in individuals with ASD. The objective of this preliminary investigation was to examine whether the cognitive benefits of propranolol are associated with drug-induced alterations in functional network properties in the brain and assess whether these drug-related changes differ in individuals with ASD compared to typically developing (TD) controls. Control conditions included the administration of placebo and nadolol, a *beta*-adrenergic antagonist that does not cross the blood-brain barrier and yet yields identical peripheral physiological effects as propranolol, to ensure that any propranolol-mediated effects on functional magnetic resonance imaging (fMRI) data were not due to peripheral changes in blood flow and pressure.

Methods

Detailed information regarding our experimental design was outlined previously in an examination of the resting-state data that were acquired during these imaging sessions (Hegarty et al., 2017).

Participants

Our sample was comprised of 13 individuals with ASD and 13 matched TD controls who were recruited from a local neurodevelopmental disorder treatment and research center as well as the greater local community. All participants provided informed consent, and all procedures were conducted in accordance with the ethical standards of the Helsinki Declaration and approved by the Institutional Review Board.

Drug administration

Participants attended three counterbalanced sessions in which propranolol (40 mg), nadolol (50 mg), or placebo was orally administered in a blinded manner as described in the study by Hegarty et al. (2017). Participants then waited in a quiet study room for peak drug effects before data were acquired.

ANS measurement

Baseline ANS measures included heart rate (HR)/blood pressure (BP) and electrocardiogram (ECG). ECG data were collected for 8 min using three-lead electrodes and a BIOPAC MP150 System (BIOPAC Systems, Inc., Goleta, CA). The first 3 min were discarded and the remaining 5 min were analyzed for R-R interbeat intervals, as previously described (Zamzow et al., 2016).

Magnetic resonance imaging acquisition

Magnetic resonance imaging (MRI) utilized a Siemens 3T Trio scanner (Siemens, Malvern, PA) and standard eight-channel head coil. Structural T1-weighted three-dimensional (3D) MR images were acquired for anatomical localization (magnetization-prepared rapid gradient echo (MPRAGE), repetition time=1920ms, echo time=2.92ms, flip angle=9°, field of view=256 × 256, matrix size=256 × 256, 1-mm³ resolution with sagittal acquisition) and functional T2*-weighted images (echo-planar imaging (EPI), repetition time=2200ms, echo time = 30 ms, flip angle = 90°, field of view = 256 × 256, matrix size=64 × 64, 35 anterior to posterior commissure-aligned slices at 4-mm³ resolution) were acquired to measure the blood oxygenation level-dependent (BOLD) response during the completion of a semantic fluency task.

Task design

Semantic fluency was assessed because our previous research indicated that propranolol is beneficial for individuals with ASD who are completing this task (Beversdorf et al., 2011). Although TD individuals may also exhibit some performance benefits from propranolol for verbal problem-solving, these improvements are primarily reported for more difficult tasks (Campbell, Tivarus,

Hillier, & Beversdorf, 2008). Thus, we expected some ASD-specific effects for semantic fluency. Stimuli consisted of the presentation of a cross-hair fixation point for 11 s (five TRs) of passive rest followed by a verbal cue for 33 s (15 TRs). In response to the cue (e.g. ANIMALS), each participant verbally named as many items as possible that belonged to that category. Each run included three separate verbal cues, and each session included two independent runs. A rater blinded to the diagnostic group and drug condition recorded each response.

MRI preprocessing

Preprocessing procedures for functional connectivity (FC) analyses were previously outlined (Hegarty et al., 2017). Briefly, preprocessing included slice timing correction, rigid body realignment, intensity normalization, brain extraction, and registration to the structural T1-weighted image with the FMRIB Software Library (FSL) (Smith et al., 2004). Translation/rotation parameters and average BOLD signals (whole brain, ventricles, white matter, and their temporal derivatives) were regressed out of the time series data with the REST toolkit (Song et al., 2011), and temporal band-pass filtering ($0.01 < f < 0.08$ Hz) was applied. Any image acquisitions that exceeded two standard deviations from the within-subject within-run mean for any translation, rotation, or intensity parameter or exceeded motion of more than 2 mm in any direction were removed. Initial analyses were conducted on time series with a regression of stimulus design to account for activation magnitude differences between groups and drug conditions and to focus the analyses on residual fluctuations in the BOLD response. Due to methodological concerns regarding the influence of preprocessing procedures on group-related differences in fMRI data (Müller et al., 2011), we also examined the BOLD response only during task blocks as a secondary control.

Non-overlapping 10-mm diameter spherical regions of interest were determined a priori for a language-based network that is activated during semantic fluency (Wagner, Sebastian, Lieb, Tuschler, & Tadic, 2014), hereafter referred to as the semantic association network (SAN), as well as the fronto-parietal control (FPC) network, dorsal attention network (DAN), and default mode network (DMN), as described in the study by Spreng, Sepulcre, Turner, Stevens, and Schacter (2013). More detailed information on these networks is provided in the supplementary materials (Supplemental Figure 1 and Supplemental Table 1). Partial correlation matrices containing all possible region of interest (ROI) pairs within each network were generated for each participant. Fischer's z transformation was applied, and self-correlations and negative correlations were removed or set to zero as to not further impact the analyses. Graph theory analytical techniques were applied to examine additional functional properties. Weighted

partial correlations were utilized instead of binarization and were divided by the average across all cells in order to standardize the matrix. Graph metrics were calculated using the Brain Connectivity Toolbox (Rubinov & Sporns, 2010) and included measures of local- (i.e. local efficiency (*Elocal*)) and global-level processing (i.e. global efficiency (*Eglobal*)).

Statistical analyses

Analyses were conducted with IBM SPSS software (IBM Corp, Armonk, NY) and included a set of 2×3 repeated measures multivariate analyses of variance (MANOVAs; between subject: diagnostic group, within subject: drug condition) for the maximum number of words produced during each session as well as average FC and graph metrics separately for each network. These analyses were repeated controlling for task performance and baseline respiratory sinus arrhythmia (RSA). Post hoc paired samples or independent samples t tests were conducted and corrected for multiple comparisons by controlling for the false discovery rate (FDR) (Benjamini & Hochberg, 1995). Uncorrected p values are displayed and those surviving correction for multiple comparisons are indicated (*). Correction for multiple comparisons was only applied within networks or across drug conditions, which may increase Type I error but will allow hypothesis generation for future investigations. In an exploratory analysis, the associations between performance, FC, and ANS measures were examined with Spearman's ρ and curve estimation. Importantly, researchers were blinded to the diagnostic group and treatment condition during all data processing and analyses.

Results

Participants

Detailed information regarding our sample was reported previously (Hegarty et al., 2017). Importantly, the ASD (11 males/2 females aged 18–31 years, $M=22.21$ (4.16) years) and TD control (11 males/2 females aged 17–27 years, $M=22.86$ (2.68) years) groups did not significantly differ in age, full-scale intelligence quotient (FSIQ), years of education, gender, ethnicity, handedness, or family income, $p > 0.05$ in all instances. The ASD and TD groups also did not differ in regard to motion during MRI scanning, and there were no significant changes in motion across drug conditions, $p > 0.05$ in all instances (Supplemental Table 2).

Task performance

TD controls performed significantly better on the semantic fluency task compared to individuals with ASD, $F(1, 24)=25.67$, $p < 0.001$, $\eta_p^2 = 0.23$, and exhibited higher

Table 1. Baseline (placebo) functional network properties of the fronto-parietal control network.

Network metrics	ASD	TD	Statistics	p	Cohen's d
FC	0.33 (0.05)	0.26 (0.05)	$t(24) = 4.61$	$<0.001^*$	1.40
Eglobal	0.95 (0.04)	0.98 (0.05)	$t(24) = -1.67$	0.11	-0.66
Elocal	0.47 (0.13)	0.62 (0.06)	$t(24) = -3.87$	0.001^*	-1.48

Comparisons between individuals with autism spectrum disorder (ASD) and typically developing (TD) controls are shown for functional connectivity (FC) and global (*Eglobal*) and local (*Elocal*) efficiency of the fronto-parietal control network following placebo administration. Group mean values and standard deviation are indicated.

*Significant at false discovery rate correction for functional measures within networks.

scores on average across all sessions, including placebo ($M_{ASD} = 27.31$ (5.84), $M_{TD} = 41.69$ (10.50); $t(24) = -5.03$, $p < 0.001$, $d = 1.69$). Examining the within-subject effects of *beta*-adrenergic antagonism, there was a trend toward a main effect of drug, $F(2, 48) = 3.00$, $p = 0.06$, $\eta_p^2 = 0.11$, which appeared to be due to an increase in the maximum number of words produced following propranolol compared to placebo ($M_{Diff} = 2.85$ (6.77); $t(25) = 2.14$, $p = 0.04$, $g = 0.23$). This general performance benefit, compared to a previously reported ASD-specific effect (Beverdort et al., 2011), may have been due to a heightened stress reaction to the imaging environment that was reduced following *beta*-adrenergic antagonism. Although there was no significant drug-by-group interaction, $F(2, 48) = 1.81$, $p = 0.18$, $\eta_p^2 = 0.07$, there did appear to be a larger performance benefit in TD controls, $t(12) = 2.84$, $p = 0.02$, compared to individuals with ASD, $t(12) = 0.34$, $p = 0.74$. However, the anticipated benefits were found in individuals with ASD when controlling for FSIQ and age, $F(1, 10) = 5.09$, $p = 0.05$, suggesting that age and general cognitive abilities may be associated with drug response.

Functional connectivity

Baseline group comparisons. Comparing diagnostic groups during the placebo condition (Table 1), individuals with ASD exhibited altered functional properties of the FPC, $F(3, 22) = 6.55$, $p = 0.002$, $\eta_p^2 = 0.47$. Within the FPC, individuals with ASD exhibited higher FC, $p < 0.001$ (Figure 1(a)) and lower *Elocal*, $p = 0.001$, compared to controls. Importantly, these diagnostic group differences remained when controlling for task performance (FC, $p = 0.01$; *Elocal*, $p = 0.02$) as well as when examining only task blocks (FC, $p = 0.001$; *Elocal*, $p = 0.004$). There were no indications of diagnostic group differences in the SAN, $F(3, 22) = 2.20$, $p = 0.12$, $\eta_p^2 = 0.23$, DAN, $F(3, 22) = 1.48$, $p = 0.25$, $\eta_p^2 = 0.17$, or DMN, $F(3, 22) = 1.60$, $p = 0.22$, $\eta_p^2 = 0.18$, at the omnibus level for baseline (placebo) data.

Drug condition comparisons. On examining within-subject effects of *beta*-adrenergic antagonism (Table 2), there was a trend at the omnibus level suggesting drug-related

differences in functional properties of the SAN, $F(6, 94) = 2.11$, $p = 0.06$, $\eta_p^2 = 0.12$, but not the FPC, $F(6, 94) = 0.71$, $p = 0.64$, $\eta_p^2 = 0.04$, DAN, $F(6, 94) = 1.23$, $p = 0.30$, $\eta_p^2 = 0.07$, or DMN, $F(6, 94) = 0.39$, $p = 0.89$, $\eta_p^2 = 0.02$. Within the SAN, *Elocal* was significantly higher following propranolol administration compared to placebo, $p = 0.01$, as well as nadolol, $p = 0.04$. These differences remained when controlling for task performance between propranolol and placebo ($p = 0.02$) and also exhibited a trend comparing propranolol and nadolol ($p = 0.07$). However, they were not found when controlling for baseline RSA, suggesting it may be related to drug response. In addition, *Eglobal* was higher following propranolol administration compared to nadolol, $p = 0.03$, and this difference remained when controlling for task performance, $p = 0.03$. However, they did not survive correction for multiple comparisons or when controlling for baseline RSA, $p < 0.05$. None of the drug-related changes in the SAN remained when examining only task blocks, which may have been related to the reduction in data points. There were no significant drug-by-group interactions, $p > 0.05$ in all instances.

Based on our a priori hypotheses, we conducted an exploratory analysis of the effects of *beta*-adrenergic antagonism on FC in individuals with ASD. FC was significantly lower in the FPC following propranolol administration compared to placebo, $t(12) = -2.61$, $p = 0.02$, $g = -1.04$. This difference remained when examining only task blocks, $p = 0.05$, and when controlling for task performance, $p = 0.03$, but not baseline RSA, $p = 0.39$. Interestingly, this change was not found in TD controls, and the baseline (placebo) group difference in FC of the FPC was no longer evident following propranolol administration, $p > 0.05$, in both instances (Figure 1(b)). Baseline FC was also associated with the change in FC of the FPC following propranolol administration in individuals with ASD, $r = -0.75$, 95% CI = -0.92 to -0.34 , $p = 0.003$ (Figure 1(c)), but not in TD controls, $r = -0.45$, 95% CI = -0.80 to 0.13 , $p = 0.13$.

Brain-behavior relationships. On examining the relationships between task performance and FC, there was a significant correlation between the maximum number of words produced and baseline (placebo) FC in the FPC,

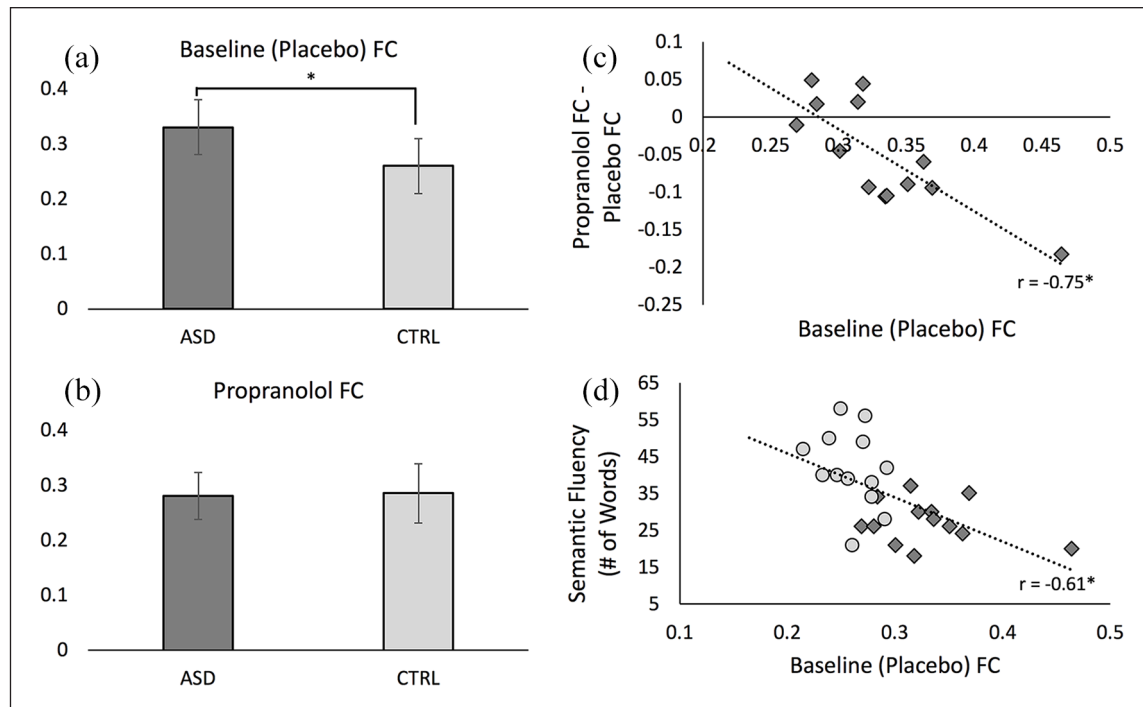


Figure 1. Beta-adrenergic antagonism of the fronto-parietal control network. Comparisons between individuals with autism spectrum disorder (ASD: dark gray/rhombus) and typically developing controls (TD: light gray/circle) regarding functional connectivity (FC) after (a) placebo (baseline) and (b) propranolol administration as well as correlations between baseline FC and (c) propranolol-mediated changes (propranolol–placebo) in FC, which are not shown for TD controls because they were not correlated, and (d) baseline semantic fluency performance. Error bars represent standard deviation.

*Significance at $p < 0.05$.

$r = -0.61$, 95% CI = -0.81 to -0.29 , $p = 0.001$ (Figure 1(d)), and DAN, $r = -0.59$, 95% CI = -0.80 to -0.26 , $p = 0.001$. There were no significant relationships between baseline FC or RSA and drug effects on task performance (propranolol–placebo), $p > 0.05$ in all instances, but the HR (beats/minute (bpm)) from the placebo condition was significantly associated with the performance benefit from propranolol, $r = -0.53$, 95% CI = -0.76 to -0.18 , $p = 0.01$.

Discussion

Beta-adrenergic antagonism of the central nervous system has been associated with cognitive/behavioral benefits for individuals experiencing performance anxiety, those struggling to complete difficult problems (Campbell et al., 2008), and those with differences in cognitive and behavioral processing, such as ASD (Beverdort et al., 2008; Beverdort et al., 2011; Bodner et al., 2012; Ratey et al., 1987; Zamzow et al., 2017; Zamzow et al., 2016). In the current investigation, we examined the effects of beta-adrenergic antagonism on functional network properties in the brain (Hegarty et al., 2017; Hermans et al., 2011) during task performance (Narayanan et al., 2010) and evaluated whether the performance benefits in individuals with ASD were associated with modulation of FC differences in the brain compared to TD controls.

At baseline (placebo condition), individuals with ASD performed worse on the semantic fluency task and exhibited hyper-connectivity in the FPC, which was associated with impaired performance. Following propranolol administration, there was a performance benefit, regardless of the diagnostic group, that was accompanied by increased efficiency of subnetwork processing in the SAN. The baseline hyper-connectivity of the FPC in individuals with ASD was also ameliorated following propranolol administration, and this change in FC was associated with the magnitude of baseline hyper-connectivity. Thus, it appears that some performance benefits from beta-adrenergic antagonism may be associated with increased functional integration of domain-specific networks in the brain, such as the SAN, but individuals with ASD may also benefit from beta-adrenergic modulation of inherent functional differences in domain-general networks, such as the FPC. Furthermore, the performance benefits from propranolol were associated with the baseline resting heart rate, suggesting that peripheral ANS measures may be able to help predict treatment response. These drug-mediated alterations were also no longer evident when controlling for baseline PNS tone, suggesting that inherent ANS regulation may be involved.

Due to the pilot nature of this investigation, correction for multiple comparisons was not applied across all

Table 2. Beta-adrenergic effects on functional network properties of the semantic association network.

Network metrics	FC	Statistics	p	Hedge's g
PROP-PLC				
FC	-0.01 (0.07)	t(25) = -0.41	0.68	-0.11
Eglobal	0.02 (0.12)	t(25) = 1.01	0.32	0.27
Elocal	0.16 (0.27)	t(25) = 3.03	0.01*	0.83
PROP-NAD				
FC	0.00004 (0.07)	t(25) = 0.003	0.99	0.00
Eglobal	0.05 (0.10)	t(25) = 2.39	0.03	0.60
Elocal	0.14 (0.33)	t(25) = 2.17	0.04	0.62
NAD-PLC				
FC	-0.01 (0.07)	t(25) = -0.44	0.66	-0.09
Eglobal	-0.02 (0.09)	t(25) = -1.35	0.19	-0.26
Elocal	0.02 (0.27)	t(25) = 0.42	0.68	0.10

Comparisons between propranolol (PROP), nadolol (NAD), and placebo (PLC) conditions for all participants are shown for functional connectivity (FC) and global (*Eglobal*) and local (*Elocal*) efficiency for the semantic association network. Group mean values and standard deviation are indicated. *significant at false discovery rate correction across drug conditions.

statistical tests, so the potential for increased Type I error should be considered. However, the within-subject assessment provides some additional support for our findings. A larger sample including younger individuals with higher variability of ASD severity should be examined. We were also unable to fully blind all research staff during data acquisition because of the differences in time to reach peak effects between drugs. To eliminate as many confounds as possible, testing was either conducted by a laboratory member blinded to diagnosis and drug condition or consisted of automated computer responses and questionnaires. All researchers were also blinded to diagnosis and drug condition during data processing and analysis. The effects of *beta*-adrenergic antagonism on peripheral blood flow and pressure should also be considered regarding interpretation of these findings, but the lack of drug-related changes in the nadolol condition suggests that peripheral cardiovascular effects were not the primary contributing factor to the observed changes in FC. Overall, our observations support continued investigation into the effects of *beta*-adrenergic antagonists on cognitive processing and functional network integration in the brain, especially regarding the potential relationships between ANS balance and functional network properties with treatment response in individuals with ASD.

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ORCID iDs

John P Hegarty II  <https://orcid.org/0000-0002-3533-5527>

Bradley J Ferguson  <https://orcid.org/0000-0002-1636-7849>

Jeffrey D Johnson  <https://orcid.org/0000-0001-7651-6992>

Supplemental material

Supplemental material for this article is available online.

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