

The Relationship among Gastrointestinal Symptoms, Problem Behaviors, and Internalizing Symptoms in Autism Spectrum Disorder

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**Thompson Center for Autism
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Health Psychology
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Disclosures

- Funding Sources
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 - Department of Defense
 - The Center for Discovery
 - No other disclosures

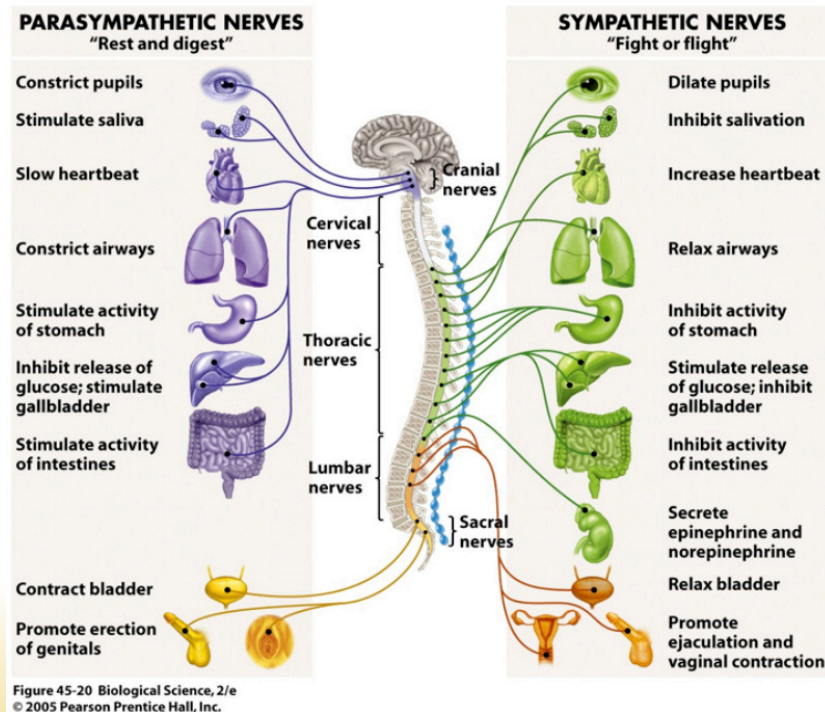


Prevalence of GI Disorders in ASD

- GI issues common in ASD
 - Prevalence = 9-91% (Buie et al., *Pediatrics*, 2010)
- Many suffer from constipation (Buie et al, *Pediatrics*, 2010; McElhanon et al., *Pediatrics*, 2014; Ferguson et al., *Autism Res.*, 2017; Ferguson et al. *Brain, Beh. Immun.*, (2016).
- Using Rome III Criteria:
 - 42.5% met criteria for functional constipation
 - 12% irritable bowel syndrome (Ferguson et al., *Autism Res.*, 2017)
- Etiology is unclear, however...

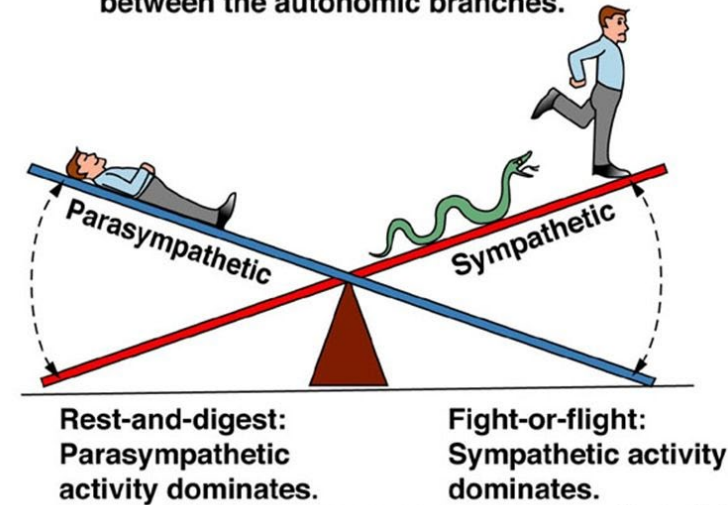


Altered Autonomic Nervous System Response to Stress in ASD



The autonomic nervous system balances between "fight or flight," and "rest and digest"

Homeostasis is a dynamic balance between the autonomic branches.



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Figure 11-1



GI + Stress Relationship in ASD

Table 1

Partial Pearson correlations between biomarkers and QPGS Rome III GI scores, FSIQ, and selected ABC and Vineland variables, controlling for age, gender, and cortisol pre-stress values (cortisol response only). Significant correlations are in bold ($p < 0.05$).

Biomarker	Covariate	Correlation (95% CI)	p-Value	n
Cortisol Response	Upper GI Score	-0.00 (-0.24, 0.23)	0.9755	75
	Lower GI Score	0.27 (0.04, 0.47)	0.0207	75
	IQ	0.27 (0.02, 0.49)	0.0365	64
	ABC Inappropriate Speech	-0.27 (-0.47, -0.04)	0.0231	74
	ABC Hyperactivity	-0.28 (-0.48, -0.05)	0.0186	74
IL-6 Concentration	Upper GI Score	0.13 (-0.06, 0.31)	0.1910	110
	Lower GI Score	-0.01 (-0.20, 0.18)	0.9320	110
	IQ	-0.29 (-0.46, -0.08)	0.0062	92
	Vineland Socialization SS	-0.27 (-0.47, -0.05)	0.0169	77
TNF- α Concentration	Upper GI Score	0.20 (0.01, 0.38)	0.0391	108
	Lower GI Score	0.08 (-0.12, 0.26)	0.4430	108
	IQ	-0.06 (-0.26, 0.15)	0.6026	91
	ABC Irritability	0.20 (0.01, 0.38)	0.0433	105

Positive relationship between cortisol response to stressor and and symptoms of lower GI tract (mainly constipation)



HHS Public Access

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Associations between cytokines, endocrine stress response, and gastrointestinal symptoms in autism spectrum disorder

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GI + Stress Relationship in ASD

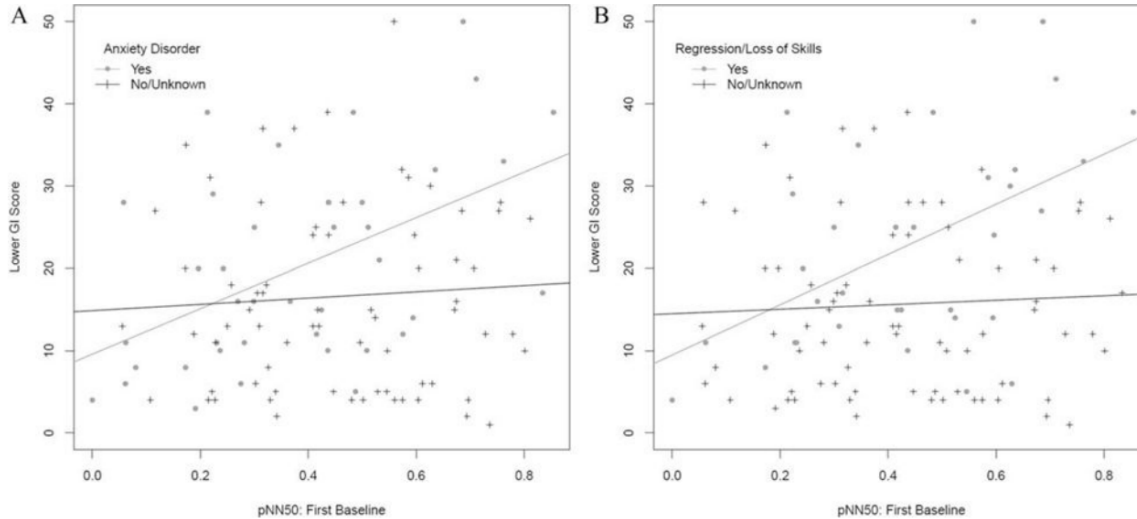


Figure 2.
Impact of effect modifiers on the ANS- gastrointestinal symptomatology relationships. (A) Effect of presence or absence of anxiety on the relationship between lower GI tract scores and pNN50 baseline. (B) Effect of presence or absence of history of regression/loss of skills on the relationship between lower GI tract scores and pNN50 baseline.

Presence of a co-occurring anxiety disorder significantly alters the lower GI tract-parasympathetic nervous system relationship



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Psychophysiological Associations with Gastrointestinal Symptomatology in Autism Spectrum Disorder

Bradley J. Ferguson, Sarah Marler, Lily L. Altstein, Evon Batey Lee, Jill Akers, Kristin Sohl, Aaron McLaughlin, Kaitlyn Hartnett, Briana Kille, Micah Mazurek, Eric A. Macklin, Erin McDonnell, Mariah Barstow, Margaret L. Bauman, Kara Gross Margolis, Jeremy Veenstra-VanderWeele, and David Q. Beversdorf



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GI, Problem Behavior, & Internalizing Symptoms in ASD



BRIEF RESEARCH REPORT
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The Relationship Among Gastrointestinal Symptoms, Problem Behaviors, and Internalizing Symptoms in Children and Adolescents With Autism Spectrum Disorder

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Methods

- Participants
 - 340 children and adolescents with ASD
 - Age: 2-18 years ($M = 5.56$, $SD = 3.67$)
 - Clinic patients from MU Thompson Center for Autism & Neurodevelopmental Disorders in Columbia, Missouri, USA
 - ASD Diagnosis confirmed using the ADI-R or ADOS



Methods

- Measures
 - Caregivers completed the following questionnaires:
 - **Dietary problems** (score 0-12; did child experience feeding issues in infancy, current feeding issues, picky eating, milk aversion, nonfood item cravings, food group aversion, food reactions, special diet, difficulty with solids/liquids, lethargy, dehydration)
 - **Nutrition Problems** “Is the child’s nutrition adequate?” (0 = adequate, 1 = inadequate)
 - **Current GI Symptoms** (constipation, diarrhea, nausea or vomiting, stomachaches (range of scores = 1-4)
 - **Internalizing + Externalizing Symptoms** – Child Behavior Checklist (CBCL) (3 point Likert scale; 0 = not true, 1 = somewhat true, 2 = very true or often true)



Methods

- Statistical Analysis
 - Bivariate correlation matrix to determine which demographic or descriptive child and family covariates to include in main analysis
 - 2-5: dietary problems, medications, GI medications, nutrition problems
 - 6-18: gender, dietary problems
 - Then, separate logistic regressions with each of the four GI symptoms as outcome variables for each age group
 - Predictors of interest were internalizing and externalizing subscales of the CBCL
 - 2 groups created based on different versions of CBCL (2-5 years old, 6-18 years old)



Results

	Younger group (<i>N</i> = 200)			Older group (<i>N</i> = 140)			Statistical comparison
	Range	M	SD	Range	M	SD	
Age in years	2–5	3.03	1.07	6–18	9.19	2.94	
IQ [#]							
Verbal	57–128	90.02	15.25	50–136	92.71	17.78	$t_{(153)} = -0.989$
Nonverbal	43–127	94.20	15.11	56–137	92.83	16.90	$t_{(182)} = 0.578$
Full scale	71–121	92.34	12.96	49–127	90.30	16.40	$t_{(168)} = 0.869$
Dietary problems	0–12	3.72	2.30	0–10	2.75	2.12	$t_{(224)} = 3.182^{**}$



Results

- For both older and younger groups:
 - 65% experienced constipation
 - 50% experienced stomachaches or stomach pain
 - 29% experienced diarrhea
 - 23% experienced nausea
 - 93% not taking GI medication (e.g. Miralax)
 - 53% taking medications for other reasons (e.g. ADHD, aggression, seizures)



Results

In children 2-5 years of age, do GI symptoms predict internalizing or externalizing symptoms?

- Nausea significantly predicted aggression ($B = 0.106$, $SE = 0.052$, $p < 0.05$)



Results

In children 6-18 years of age, do internalizing or externalizing symptoms predict GI symptoms?

- Anxiety = 11% more likely to experience constipation, but 9% less likely to experience stomachaches.
- Withdrawn behavior = 11% more likely to experience stomachaches, but 9% less likely to experience constipation.
- Greater somatic complaints = 11% more likely to experience nausea and 11.5% more likely to experience stomachaches.



Discussion

- Majority of participants reported constipation
 - Corroborates previous research (Ferguson et al., 2016, 2017)
- Young children with ASD who are non-verbal may use aggression to communicate their somatic complaints.



Discussion

- Older children + adolescents with ASD have more internalizing behaviors associated with GI symptoms
 - Anxiety and constipation
 - Withdrawn/depressed and increased stomachaches but decreased constipation
- GI disorders and behavior problems are related in ASD and may serve a communicative function of discomfort



Electrodermal Activity & Problem Behavior in ASD



BRIEF RESEARCH REPORT
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Examining the Association Between Electrodermal Activity and Problem Behavior in Severe Autism Spectrum Disorder: A Feasibility Study

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Association between electrodermal activity and problem behavior

TABLE 1 | Participant demographics and descriptive statistics.

ID	Age	Gender	Ethnicity	Intelligence quotient (type) (<i>M</i> = 100, <i>SD</i> = 15)	Adaptive functioning	ASRS <i>T</i> -score (<i>M</i> = 50, <i>SD</i> = 10)	Co-occurring conditions
S01	18	M	Caucasian	44 (NV)	41 (ABAS)	82	OCD, ADHD, constipation
S06	15	M	Caucasian	52 (SB abbreviated)	45 (VAB)	84	OCD, ADHD, vomiting
S07	13	M	Caucasian	42 (NV)	35 (VAB)	74	Constipation
S08	15	M	Caucasian	NS	38 (VAB)	85	Movement disorder
S09	13	M	Hispanic	NS	59 (VAB)	68	None
S11	15	M	Caucasian	NS	35 (VAB)	76	Constipation, ADHD, GERD
S12	20	M	Caucasian	53 (NV)	48 (ABAS)	70	Constipation
S13	18	M	Hispanic	42 (NV)	43 (ABAS)	73	Constipation

NV, non-verbal; *SB*, Stanford-Binet; *NS*, attempted but unable to obtain score; *ABAS*, Adaptive Behavior Assessment System General Adaptive Composite; *VAB*, Vineland Adaptive Behavior Scales Adaptive Behavior Composite; *OCD*, obsessive-compulsive disorder; *ADHD*, attention-deficit hyperactivity disorder; *ODD*, oppositional defiant disorder; *ASRS*, Autism Spectrum Rating Scales; *GERD*, gastroesophageal reflux disease.



Baseline



Anticipatory rise



Problem Behavior



Association between electrodermal activity and problem behavior

TABLE 2 | Frequency and percentage of the occurrence of an anticipatory rise in EDA prior to the problem behavior, mean anticipatory rise time, number of times that a student returned to baseline EDA after engaging in problem behavior, and the mean time for EDA to return to baseline. Note for S13, no statistics for anticipatory rise and return to baseline were able to be calculated as the student's repetitive behavior was continuous for the duration of each session.

ID	PB assessed	Valid EDA records	Number of times anticipatory rise prior to PB (%)	Mean EDA prior to PB (μ S) (SD)	Mean anticipatory rise time (s) (SD)	Number of times returned to BL after PB (%)	Mean time to return to BL (s) (SD)
S1	Jumping in seat	9	6 (67%)	0.99 (0.85)	590 (466)	5 (56%)	2,165(673)
S6	Repetitive body hitting	11	6 (55%)	1.09 (1.66)	1,076 (1099)	6 (55%)	2,436 (1, 919)
S7	General classroom disruption	9	8 (89%)	2.22 (1.92)	945 (1, 201)	2 (22%)	4,939 (2, 742)
S8	Aggression	8	1 (13%)	0.74 (0.81)	681 (0)	2 (25%)	3,759 (356)
S9	Out of seat	9	5 (56%)	0.48 (0.42)	403 (399)	8 (89%)	6,389 (4, 289)
S11	Self-injurious behavior	9	8 (89%)	0.89 (0.61)	490 (385)	5 (56%)	3,536 (4, 138)
S12	Agitation	7	3 (43%)	0.18 (0.20)	95 (86)	0 (0%)	X
S13	Repetitive motor movement	X	X	X	X	X	X
TOTAL	8	62	37 (60%)	0.94 (0.64)	611 (306)	28 (45%)	3,870 (1, 586)

s, seconds; SD, standard deviation; BL, median baseline EDA level; PB, problem behavior; μ S, microsiemens.

- Rise in skin conductance occurred 60% of the time prior to problem behavior occurring
- Skin conductance returned to baseline (“normal”) 45% of the time after problem behavior
- Average rise in skin conductance before problem behavior = ~10 minutes



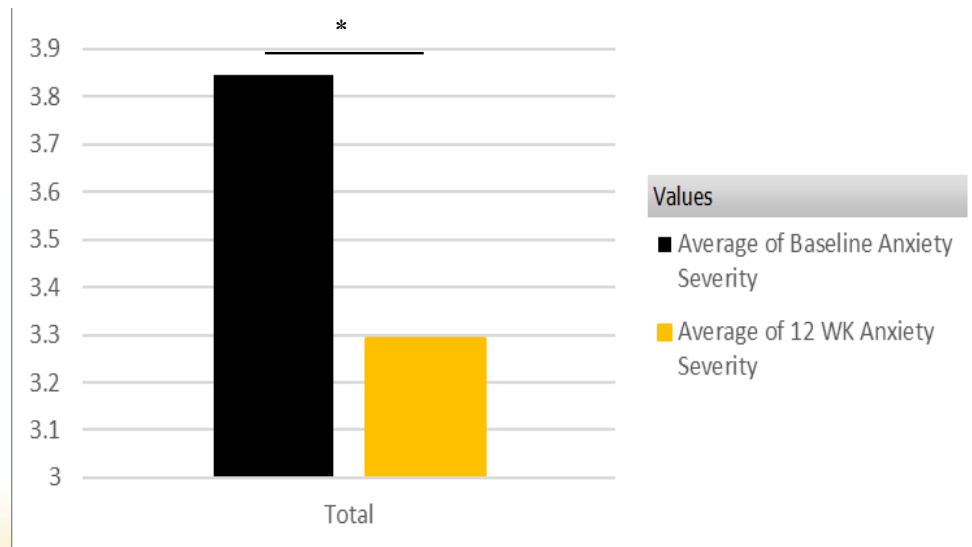
What can we do about it?

- What happens when we treat the stress response?
 - “Trial of Propranolol in Children and Youth with Autism Spectrum Disorder and Predictors of Response” (ClinicalTrials.gov Identifier: NCT02871349)
 - Examining effects of propranolol on:
 - Core ASD symptoms
 - Language
 - Gastrointestinal Symptoms



Effects of propranolol on anxiety and GI symptoms in ASD

Change in Anxiety Scores after 12-weeks of propranolol



Change in Constipation Scores after 12-weeks of propranolol

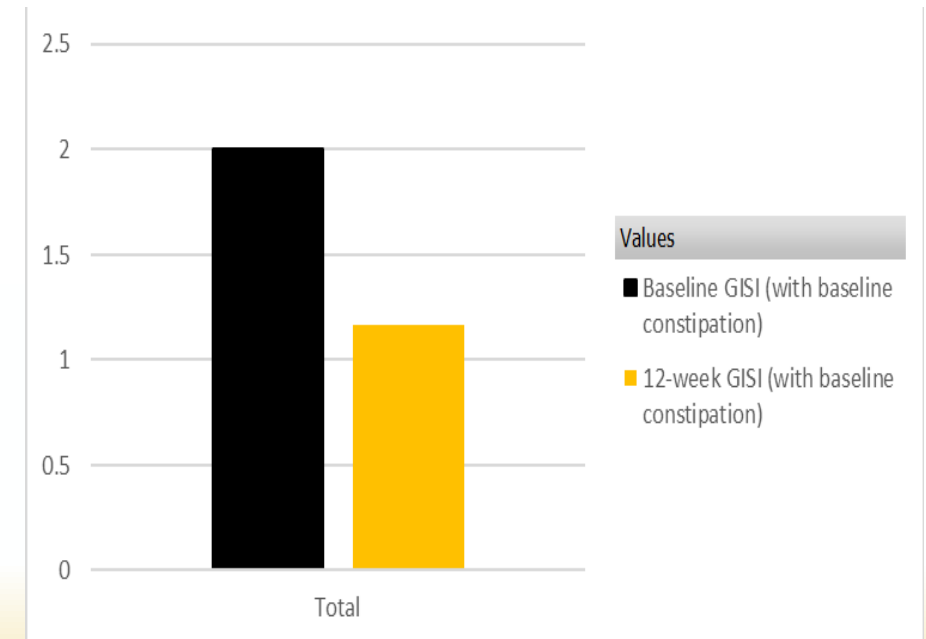


Figure 1 (left): Significant reductions in Clinical Global Impression of Severity scores after 12-weeks of administration of propranolol $*p=0.012$. (right): additionally, for the 6 patients with a score of at least 2 on constipation for the GIS, there is already a trend towards reduction in constipation with propranolol $p=0.09$. Data presented are from an open-label portion of an ongoing randomized clinical trial.



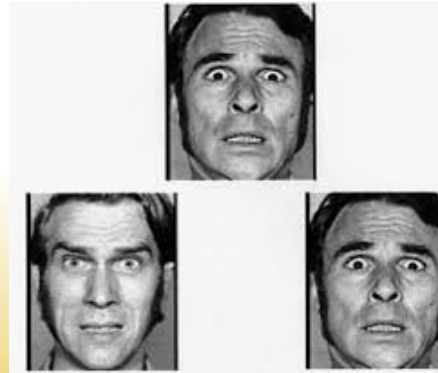
Effects of propranolol on the relationship between GI and amygdalar reactivity

- N= 12 (11 male, 1 female)
- FSIQ = 80 or above
- 3 sessions
 - Placebo
 - Nadolol
 - Propranolol
- GI Questionnaire
 - Autism Treatment Network GI Symptoms Inventory
 - Screens for abdominal pain, nausea, diarrhea, or other GI symptoms

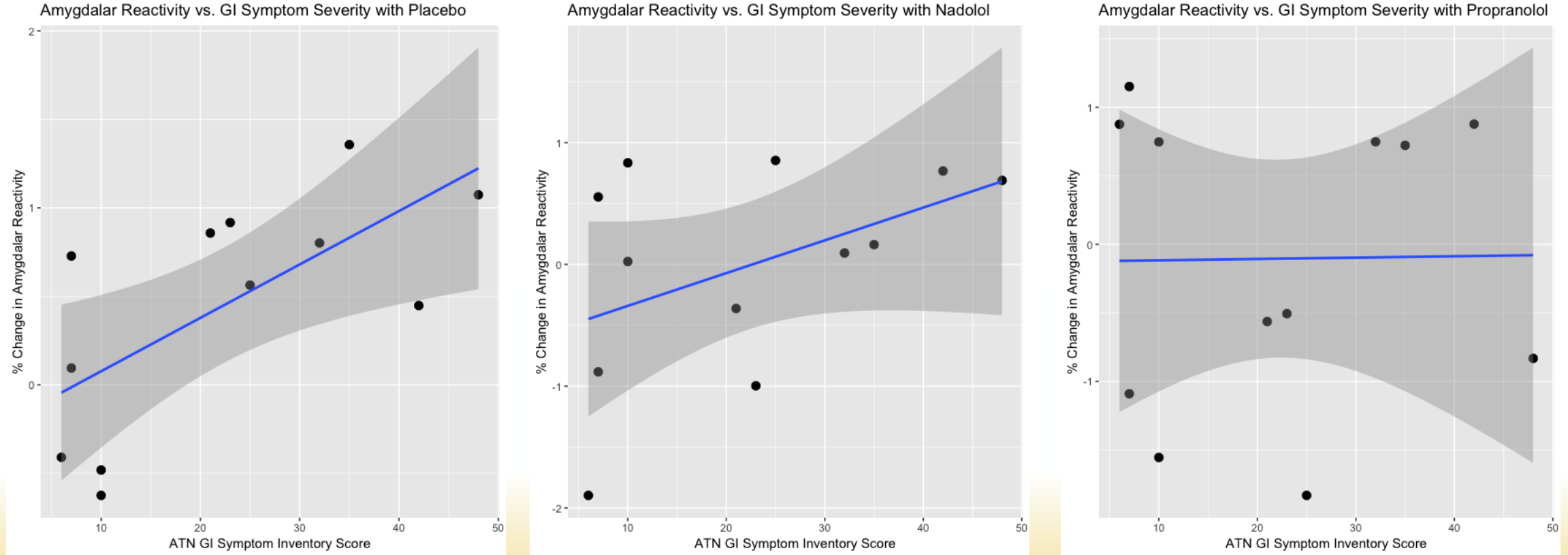


Effects of propranolol on the relationship between GI and amygdalar reactivity

- fMRI
 - Examined amygdalar responses to emotional faces (angry, afraid, neutral)
 - Face matching task
 - Shown to activate the amygdala in ASD and is correlated with social anxiety (Kleinhans, et al., 2010)



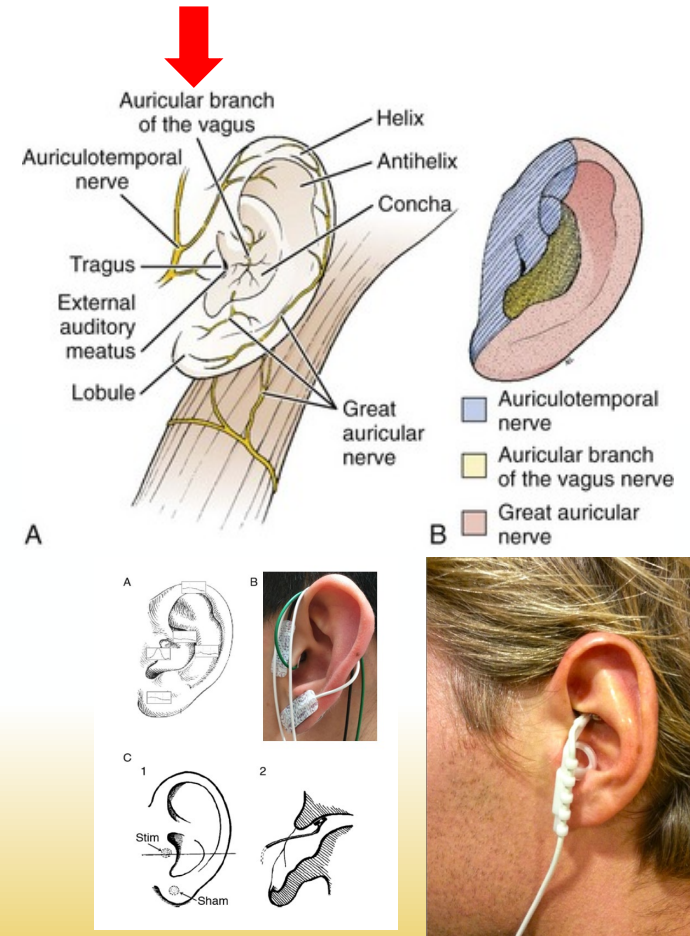
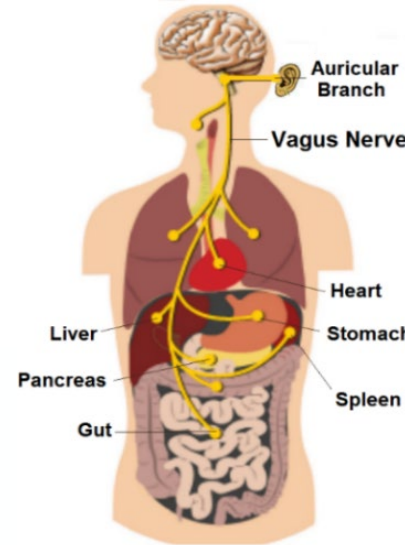
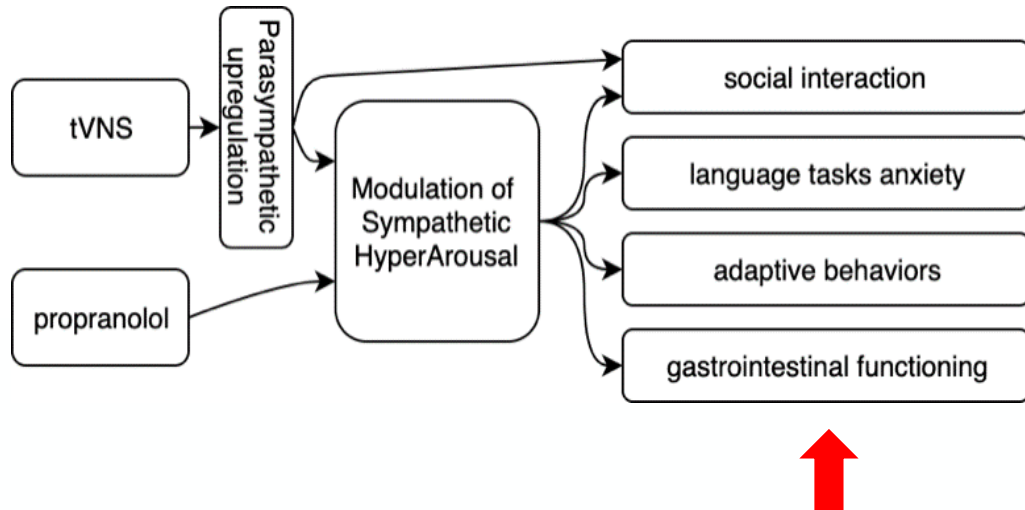
Effects of propranolol on the relationship between GI and amygdalar reactivity



Riecken et al., Manuscript submitted for publication.



Future directions: Transcutaneous Vagus Nerve Stimulation (tVNS)



Take home messages

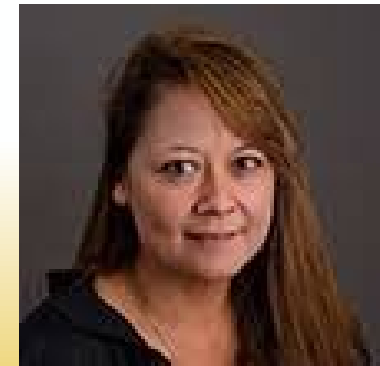
- GI symptoms are common in ASD, especially constipation
- GI symptoms are associated with an enhanced stress response, particularly for lower GI tract symptoms (e.g., constipation)
- GI symptoms are associated with internalizing symptoms and problem behavior
 - May differ by age
- Stress response may precede problem behavior in ASD
- Potential treatments may involve reducing stress response (pharmacological, vagal, behavioral) to reduce GI and problem behavior
 - More research needed in this area



Thanks!



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- The Center for Discovery
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