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

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Disclosures

• Funding Sources

  • Autism Speaks – Autism Treatment Network – Autism Intervention Research Network on Physical Health

  • 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)


• 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.

Rest-and-digest: Parasympathetic activity dominates.

Fight-or-flight: Sympathetic activity dominates.
GI + Stress Relationship in ASD

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).

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

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

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

Presence of a co-occurring anxiety disorder significantly alters the lower GI tract-parasympathetic nervous system relationship.
GI, Problem Behavior, & Internalizing Symptoms in ASD

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

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4 Department of Psychology, Marietta College, Poughkeepsie, NY, United States.
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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

<table>
<thead>
<tr>
<th></th>
<th>Younger group (N = 200)</th>
<th></th>
<th>Older group (N = 140)</th>
<th></th>
<th>Statistical comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>M</td>
<td>SD</td>
<td>Range</td>
<td>M</td>
</tr>
<tr>
<td>Age in years</td>
<td>2–5</td>
<td>3.03</td>
<td>1.07</td>
<td>6–18</td>
<td>9.19</td>
</tr>
<tr>
<td>IQ§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal</td>
<td>57–128</td>
<td>90.02</td>
<td>15.25</td>
<td>50–136</td>
<td>92.71</td>
</tr>
<tr>
<td>Nonverbal</td>
<td>43–127</td>
<td>94.20</td>
<td>15.11</td>
<td>56–137</td>
<td>92.83</td>
</tr>
<tr>
<td>Full scale</td>
<td>71–121</td>
<td>92.34</td>
<td>12.96</td>
<td>49–127</td>
<td>90.30</td>
</tr>
<tr>
<td>Dietary problems</td>
<td>0–12</td>
<td>3.72</td>
<td>2.30</td>
<td>0–10</td>
<td>2.75</td>
</tr>
</tbody>
</table>
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
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.**

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

*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.*
Association between electrodermal activity and problem behavior

- 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

<table>
<thead>
<tr>
<th>ID</th>
<th>PB assessed</th>
<th>Valid EDA records</th>
<th>Number of times anticipatory rise prior to PB (%)</th>
<th>Mean EDA prior to PB (µS) (SD)</th>
<th>Mean anticipatory rise time (s) (SD)</th>
<th>Number of times returned to BL after PB (%)</th>
<th>Mean time to return to BL (s) (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>Jumping in seat</td>
<td>9</td>
<td>6 (67%)</td>
<td>0.99 (0.85)</td>
<td>590 (466)</td>
<td>5 (56%)</td>
<td>2,165 (673)</td>
</tr>
<tr>
<td>S6</td>
<td>Repetitive body hitting</td>
<td>11</td>
<td>6 (55%)</td>
<td>1.09 (1.06)</td>
<td>1,076 (1,009)</td>
<td>6 (55%)</td>
<td>2,436 (1,919)</td>
</tr>
<tr>
<td>S7</td>
<td>General classroom disruption</td>
<td>9</td>
<td>8 (89%)</td>
<td>2.22 (1.92)</td>
<td>945 (1,201)</td>
<td>2 (22%)</td>
<td>4,939 (2,742)</td>
</tr>
<tr>
<td>S8</td>
<td>Aggression</td>
<td>8</td>
<td>1 (13%)</td>
<td>0.74 (0.81)</td>
<td>681 (403)</td>
<td>2 (25%)</td>
<td>3,759 (356)</td>
</tr>
<tr>
<td>S9</td>
<td>Out of seat</td>
<td>9</td>
<td>5 (56%)</td>
<td>0.48 (0.42)</td>
<td>403 (389)</td>
<td>8 (88%)</td>
<td>6,389 (4,289)</td>
</tr>
<tr>
<td>S11</td>
<td>Self-injurious behavior</td>
<td>9</td>
<td>8 (89%)</td>
<td>0.89 (0.61)</td>
<td>490 (385)</td>
<td>5 (50%)</td>
<td>3,536 (4,138)</td>
</tr>
<tr>
<td>S12</td>
<td>Agitation</td>
<td>7</td>
<td>3 (43%)</td>
<td>0.18 (0.20)</td>
<td>95 (86)</td>
<td>0 (0%)</td>
<td>X</td>
</tr>
<tr>
<td>S13</td>
<td>Repetitive motor movement</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>8</td>
<td>37 (60%)</td>
<td>0.94 (0.64)</td>
<td>611 (806)</td>
<td>28 (45%)</td>
<td>3,870 (1,586)</td>
</tr>
</tbody>
</table>

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

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 G ISI, 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!

• Thompson Center patients and their families
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• Kristen Dovgan, PhD – Marist College
• Nicole Takahashi, MS - MU Thompson Center
• Department of Defense
• The Center for Discovery
• AS ATN AIR-P