A multi-method, cross-population comparison of pragmatic language in autism spectrum disorder, fragile X syndrome, and Down syndrome

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Overview

• Pragmatics as a clinically and etiologically significant feature
  – Pragmatics in autism and the broad autism phenotype
  – Pragmatics across genetically based neurodevelopmental disabilities

• The importance of context
  – Structured vs. unstructured
  – Global pragmatic ability vs. specific pragmatic skills

• Implications
  – Clinical, neuropsychological, molecular genetic
Pragmatic as a clinically and etiologically significant feature

“when to say what to whom, and how much to say” --Hymes, 1971

*Persistent challenge for particular groups
*Overlapping and divergent profiles
*Complex cognitive underpinnings
Pragmatic Competence

“A child capable of any and all grammatical utterances, but not knowing which to use, not knowing even when to talk and when to stop, would be a cultural monstrosity”

Hymes (1967, p. 16)
Implications: Insights into core ingredients of typical development

“In any well-made machine one is ignorant of the working of most of the parts – the better they work the less we are conscious of them ... it is only a fault which draws our attention to the existence of a mechanism at all.”

--Kenneth Craik, *The Nature of Explanation* (1943)
• Autism/Autism Spectrum Disorder
  – Problems with social reciprocity, social communication
  – Restricted interests and repetitive behaviors
  – 1/68
  – Male>Female
Pragmatics a primary deficit in autism

But context matters...

• Relative strengths in highly structured contexts (e.g., storybook narratives)

• Relative weaknesses in more flexible environments (e.g., conversation, personal narrative)
  – Correlates: social cognition, structural language, etc.
Pragmatics a primary deficit in autism

Clinical and etiologic significance

• Clinical
  – Persistent barrier to social interaction in even highest functioning individuals

• Etiologic
  – Evidence of mild pragmatic differences in relatives (the broad autism phenotype)
  – Clues to etiologic subgroups? Endophenotypes?
Clinical heterogeneity a possible reflection of genetic subgroups

- Identify etiologically homogeneous subgroups
- Reduce “noise”
- Increase power to detect gene-behavior relationships

- Language
- Social features
- Repetitive behaviors
“It is not easy to evaluate the fact that all of our patients have come of highly intelligent parents ...

For the most part, the parents, grandparents and collaterals are persons strongly preoccupied with abstractions of a scientific, literary or artistic nature…”

Genetic basis of ASD
Evidence from families

- **Heritability**
  - MZ vs. DZ concordance: 60:3-20% ➔ heritability ~50-90%

- **Familiality**
  - Recurrence risk ~20% (> 30% in multiplex families)
  - Broad autism phenotype (BAP) in unaffected family members
Autism

- Repetitive
- Social
- Language

Broad autism phenotype (BAP)

- Perfectionistic, detail and routine oriented
- Socially reticent
- Pragmatic language differences (e.g., Narrative, conversation)

*Subtle, present in subgroup, often associated with exceptional talent*

Losh et al., 2008; 2009; 2011; Piven et al., 1994, 1997; LeCouteur et al., 1996; Bolton et al., 1994; Landa et al., 1991
ASD

Pragmatic language impairment

Broad autism phenotype

Subtle pragmatic language differences
BAP a sensitive marker of genetic risk: Multiplex > Simplex > Control Families

Personality Traits

Social Behavior (friendships)

Losh et al., 2008; 2009; 2011
Disaggregate complex traits in **unaffected relatives** to detect dissociable, genetically meaningful traits that may have a **simpler genetic basis**.
Underlying neuropsychological markers?

- Autism and BAP features proxies for underlying biological mechanisms
- Neuropsychological underpinnings related to the BAP (and pragmatics in particular?)
  - Social cognition
Social perception, Theory of mind, Mentalizing, Emotional intelligence...
Pragmatic violations associated with social cognition in parents

- Mean proportion correct +/- 1 SE
- Control	BAP (-)	BAP (+)
- Pragmatic language difficulties (PRS)
- % correct on the Eyes Test
- Irritated	Disappointed
- Depressed	Accusing
Social cognitive differences in ASD and the BAP

Losh et al., 2009, 2011, 2012
Tasks rely on the “social brain”

• Impaired performance in individuals with ASD and BAP
• Associated with specific neural regions in lesion, fMRI studies

--Adolphs, Baron-Cohen, Tranel, 2002; Baron-Cohen et al., 1999; Happé et al., 1996; Gallagher et al., 2000; Losh et al., 2009; 2011; Stone et al., 2003
Underlying biological mechanisms?

- ASD and BAP features clinically significant **proxies** for underlying biological causes?
- Neuropsychological features associated with pragmatic language
- Molecular genetic mechanisms?
  - Associated monogenic conditions - **fragile X syndrome**
Underlying biological mechanisms?

- ASD and BAP features *proxies* for underlying biological causes
- Neuropsychological features
- Molecular genetic mechanisms
  - Associated monogenic conditions – *fragile X syndrome*
- Clinical implications
Fragile X syndrome

- Caused by mutation in *FMR1* gene on the X chromosome
- Most common inherited cause of intellectual disability
- 1:4000 males; 1:8000 females
- Intellectual Disability, moderate to severe (IQ 40-70)
- Autistic features – most common single-gene disorder associated with autism
Fragile X syndrome and autism

Role of *FMR1* in features of autism?

- Fragile X as a *foothold* to understand complex genetics of autism
  - Fragile X full mutation
  - FMR1 premutation
  - FMRP
Fragile X Syndrome and FMRP

- FMRP: critical protein expressed in the brain
- Not produced when \( FMR1 \) is mutated
- Involved in synaptic plasticity

Fig. 3. Example of typical spine morphologies on Golgi-impregnated dendrites from a Fragile-X Subject (FraX) and an unaffected control subject (Control). Dendrites are at extremes of the range of spine densities and are not intended to depict the norm.
Autism susceptibility genes interacting with FMRP

> 60 known autism risk genes interact with FMRP

*FMR1/FMRP implicated in etiology of autism?

Fragile X syndrome and autism

Role of *FMR1* in features of autism?

- Fragile X as a *foothold* to understand complex genetics of autism
- Translating findings from clinical trials based on shared phenotypes
  - FMRP
- Unique clinical needs of subgroup with FXS and autism?
Autism underdiagnosed in fragile X syndrome

Klusek et al., in 2014

N=86

Autism in individuals with fragile X syndrome
Pragmatic language predicts autism status longitudinally

Unique Developmental Trajectory for Subgroup with Autism

*Early pragmatic language impairment predicts later autism diagnosis

-Lee et al., 2017
### Phenotypes associated with *FMR1* variation

<table>
<thead>
<tr>
<th>Category</th>
<th>CGG repeats</th>
<th>Associated Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable</td>
<td>6 to ~45</td>
<td>--</td>
</tr>
<tr>
<td>Gray zone</td>
<td>~45 to ~55</td>
<td>?</td>
</tr>
<tr>
<td>Premutation</td>
<td>~55 to ~200</td>
<td>FXTAS, FXPOI, anxiety, depression, <strong>autism</strong></td>
</tr>
<tr>
<td>Full mutation</td>
<td>&gt;200</td>
<td>Fragile X syndrome, <strong>autism</strong></td>
</tr>
</tbody>
</table>

*FMR1* premutation is common in general population (~1/150 women)
Pragmatic language features of the BAP in *FMR1* carriers

Losh et al., 2012
### Types of pragmatic language violations

<table>
<thead>
<tr>
<th>Dominating conversational style</th>
<th>Withdrawn conversational style</th>
<th>Atypical suprasegmental style</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overly detailed</td>
<td>0.82 [0.08]</td>
<td>0.07 [0.21]</td>
</tr>
<tr>
<td>Vague</td>
<td>-0.62 [0.14]</td>
<td>0.00 [0.01]</td>
</tr>
<tr>
<td>Tangential</td>
<td>0.91 [0.08]</td>
<td>0.15 [0.2]</td>
</tr>
<tr>
<td>Overly frank</td>
<td>0.70 [0.12]</td>
<td>0.00 [0.04]</td>
</tr>
<tr>
<td>Informal</td>
<td>0.16 [0.15]</td>
<td>-0.05 [0.25]</td>
</tr>
<tr>
<td>Pedantic</td>
<td>0.14 [0.16]</td>
<td>0.54 [0.18]</td>
</tr>
<tr>
<td>Overly talkative</td>
<td>0.89 [0.09]</td>
<td>0.25 [0.24]</td>
</tr>
<tr>
<td>Overly succinct</td>
<td>-0.65 [0.10]</td>
<td>0.11 [0.12]</td>
</tr>
<tr>
<td>No reciprocation</td>
<td>0.01 [0.02]</td>
<td>0.47 [0.19]</td>
</tr>
<tr>
<td>Odd humor</td>
<td>0.36 [0.16]</td>
<td>0.27 [0.21]</td>
</tr>
<tr>
<td>Topic preoccupication</td>
<td>0.77 [0.09]</td>
<td>0.24 [0.14]</td>
</tr>
<tr>
<td>Atypical eye contact</td>
<td>-0.24 [0.25]</td>
<td>0.67 [0.16]</td>
</tr>
<tr>
<td>Interruptions</td>
<td>0.38 [0.13]</td>
<td>0.43 [0.17]</td>
</tr>
<tr>
<td>Too loud</td>
<td>0.59 [0.12]</td>
<td>0.07 [0.19]</td>
</tr>
<tr>
<td>Too soft</td>
<td>-0.73 [0.15]</td>
<td>0.68 [0.28]</td>
</tr>
<tr>
<td>Rate too fast/slow</td>
<td>-0.16 [0.21]</td>
<td>0.87 [0.18]</td>
</tr>
<tr>
<td>Atypical intonation</td>
<td>-0.42 [0.19]</td>
<td>0.69 [0.15]</td>
</tr>
<tr>
<td>Atypical rhythm</td>
<td>0.00 [0.02]</td>
<td>0.69 [0.16]</td>
</tr>
<tr>
<td>Reformulations</td>
<td>0.21 [0.16]</td>
<td>0.36 [0.17]</td>
</tr>
</tbody>
</table>

Bolded items indicated factor loadings of .3 or greater, considered strong indicators of a given factor.

Losh et al., 2012
Types of pragmatic language violations

Losh et al., 2012
Pragmatic features in *FMR1* premutation carriers predict autism features children with FXS

<table>
<thead>
<tr>
<th>Child characteristics correlated with pragmatics in premutation carrier parents</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism symptoms (SRS)</td>
<td>.46*</td>
</tr>
<tr>
<td>Expressive vocabulary (EVT)</td>
<td>-.50*</td>
</tr>
<tr>
<td>Pragmatic language (CASL)</td>
<td>-.29*</td>
</tr>
<tr>
<td>Theory of mind</td>
<td>-.56*</td>
</tr>
</tbody>
</table>
Social cognition in *FMR1* premutation carriers

- **Control Group**
- **PM Carrier Group**

*Percent correct*
Social cognition in *FMR1* premutation carriers predicts autism symptoms in children with FXS

\[ r = -0.39 \]
Comparing pragmatic profiles in autism, fragile X, and Down syndrome
Down Syndrome

• Most common genetic cause of ID
• Caused by a third copy of chromosome 21
• 1 in 800 live births
• Disconnect between sociability and language competence
• Considerable variation in development, some overlap with autism
<table>
<thead>
<tr>
<th></th>
<th>FXS-O n = 13</th>
<th>FXS-ASD n = 51</th>
<th>ASD-O n = 40</th>
<th>DS n = 22</th>
<th>TD n = 22</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronological Age</strong></td>
<td>9.7 (3.3)</td>
<td>10.7 (2.4)</td>
<td>8.9 (2.6)</td>
<td>10.9 (2.1)</td>
<td>10.7 (2.4)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Leiter Mental Age</strong></td>
<td>5.7 (1.4)</td>
<td>5.0 (0.5)</td>
<td>6.4 (1.7)</td>
<td>5.3 (0.8)</td>
<td>6.5 (2.6)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PPVT AE</strong></td>
<td>5.0 (1.0)</td>
<td>5.4 (1.5)</td>
<td>5.9 (1.8)</td>
<td>5.3 (1.3)</td>
<td>5.4 (1.5)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EVT AE</strong></td>
<td>5.5 (1.0)</td>
<td>6.5 (2.6)</td>
<td>6.4 (2.6)</td>
<td>5.2 (1.4)</td>
<td>5.0 (0.5)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MLU</strong></td>
<td>4.0 (.73)</td>
<td>3.5 (.74)</td>
<td>4.3 (1.1)</td>
<td>3.1 (.75)</td>
<td>3.5 (.74)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Males only

**All analyses control for mental age, PPVT/EVT, and MLU
Methods for assessing pragmatic language

• Conversational interaction
  – Clinical-behavioral rating
  – Sociolinguistic hand coding

• Structured tasks tapping specific pragmatic skills
  – Repairing breakdowns
  – Signaling non-comprehension
Conversational Interaction

- Pragmatic Rating Scale-School Age – video-taped ratings of 34 different pragmatic skills in conversation

<table>
<thead>
<tr>
<th>Conversational skill</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Listener Appreciation</td>
<td>Appropriate length, ability to clarify conversational breakdowns</td>
</tr>
<tr>
<td>Discourse Management</td>
<td>Appropriate topic initiation, elaboration, conversational reciprocity</td>
</tr>
<tr>
<td>Speech Behaviors Impacting Pragmatics</td>
<td>Formality, natural vs scripted speech</td>
</tr>
<tr>
<td>Suprasegmentals</td>
<td>Rate, rhythm, volume, intonation</td>
</tr>
<tr>
<td>Nonverbal Communication</td>
<td>Gestures, eye contact, facial expressions</td>
</tr>
</tbody>
</table>
Conversational Interaction

• Pragmatic Rating Scale-School Age (Landa, 2011): Video-taped ratings of 34 different pragmatic skills in conversation

Examples:
• Lack of engagement, elaboration
• Difficulty monitoring topics
• Little reciprocity
• Eye contact
Conversational Interaction

- Hand coding of conversational skills

<table>
<thead>
<tr>
<th>Conversational variable</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncontingent language</td>
<td>% turns loosely or not at all related to current topic of conversation</td>
</tr>
<tr>
<td>Perseveration</td>
<td>% turns with repetition of phrases, sentences, or topics</td>
</tr>
<tr>
<td>Initiations</td>
<td>% nonobligatory turns out of all turns</td>
</tr>
<tr>
<td>Non-responsiveness</td>
<td>% direct requests child does not respond to</td>
</tr>
</tbody>
</table>
Conversational interaction: PRS-SA

*Controlling for IQ, and structural language ability

Pragmatic errors in semi-structured conversation (PRS-SA)

ASD & FXS-ASD > FXS-O, DS, TD
FXS-O > TD
Conversational interaction: Hand coding

Perseveration

Contingency

FXS-ASD, ASD-O > FXS-O, DS, TD

FXS-ASD, ASD-O > FXS-O, DS
Perseveration in FXS-ASD

Perseveration
C: What is this? What is it? What is this? What is this?
E: Hmm.
C: What is it?
E: I think (interrupted)
C: What is it?
E: It’s something that twirls.
...
C: What is this? What is this guy? What is, what is this?
E: He’s a fireman.
C: No. He’s a fireman. What is this guy?
Examples of pragmatic differences in conversation: FXS-O and FXS-ASD

**Individual with FXS-ASD**
- Age: 16;3
- VIQ: 55
- ToM: Failed 2 1st order false belief tests

**PRS-SA Characteristics**
- Poor response elaboration
- Mismanagement of personal space
- Topic perseveration

---

Video removed
Examples of pragmatic differences in conversation: FXS-O and FXS-ASD

- Video removed

**Individual with FXS-O**
- Age: 38;4
- VIQ: 55
- ToM: Passed 1 of 2 false belief tests

**PRS-SA Characteristics**
- Differences in social reciprocity
- Topic initiation (“I went to the airport...”)
- Expressive gesturing
- Eye contact (checks in visually)
Structured pragmatic tasks: Repairing communication breakdowns

Sources of misunderstanding: Responding to and initiating bids for clarification of misunderstanding

- Responding to bids for clarification
  - Repeat or revise message, emphasize original response

- Requesting clarification
  - “What?”, “I’m not sure I am following you.”
Conversational repair: **Responding to bids for clarification**

Huh?
What?
I don’t understand!
<table>
<thead>
<tr>
<th>Type</th>
<th>Utterance</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Request 1</td>
<td>E huh?</td>
<td></td>
</tr>
<tr>
<td>Repair 1</td>
<td>C <em>A octopus doing his hair.</em></td>
<td>Repetition</td>
</tr>
<tr>
<td>Request 2</td>
<td>E what?</td>
<td></td>
</tr>
<tr>
<td>Repair 2</td>
<td>C <em>A octopus doing his hair.</em></td>
<td>Repetition (Suprasegmental)</td>
</tr>
<tr>
<td>Request 3</td>
<td>E I don’t understand.</td>
<td></td>
</tr>
<tr>
<td>Repair 3</td>
<td><em>C The octopus is doing the guy’s hair!</em></td>
<td>Addition (Suprasegmental + Gesture)</td>
</tr>
<tr>
<td>Understanding</td>
<td>E there’s an octopus cutting a boy’s hair?</td>
<td></td>
</tr>
</tbody>
</table>
Responses Types: Appropriate revisions

**Inappropriate**: “A fish catching a hot dog”
→ “I want to watch my movie”

**Appropriate**: “Octopus and haircut”
→ ”Octopus is cutting his hair!”

FXS-ASD > DS & ASD-O
FXS-ASD > FXS-O, TD

FXS-ASD < TD
Conversational repair: Signaling non-comprehension

“Put the black planet in the sky”
Conversational repair: **Signaling non-comprehension**

“Put the ursine animal in the zoo”
Conversational repair: **Signaling non-comprehension**

- FXS-ASD, DS < ASD-O, TD
- FXS-ASD < FXS-O
Summary and significance

• Pragmatics highlighted as a clinically and etiologically significant domain of functioning
  – Evident in affected individuals and unaffected relatives

• Syndrome-specific profiles of pragmatic language across different contexts

• Importance of multimethod approach
  – FXS-ASD group standing out across all tasks
  – Shared global pragmatic profiles in ASD-O and FXS-ASD
  – Distinctions in specific pragmatic skills (ASD showing strengths in some areas)

• Clinical implications
Clinical and biological significance

Pragmatic features
• Impact on successful communication
• Social behavior and relationships

Underlying causes
• Pragmatic profiles linked with different genetic etiologies

Intervention
• Tailored to subgroups
• Translation across disorders