MR imaging of autism: Mining for biomarkers

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Dept. of Psychology

Brain Development Imaging Laboratory

www.sci.sdsu.edu/bdil
• Founding faculty:
  • Karen Emmorey, Tracy Love, Lew Shapiro (SLHS)
  • Sarah Mattson, Ed Riley, Ralph-Axel Müller (Psych.)
• New core faculty (cluster hire):
  • Alyson Abel-Mills (SLHS), Ksenija Marinkovic (Psych.)
• Affiliates
  • N. Amir, I. Fishman, P. Gilbert, D. Goble, P. Holcomb, K. Moon, I. Nip, K. Midgley, C. Murphy, F. Valafar
• Populations:
  • Deafness & use of sign language
  • Dyslexia
  • Aphasia
  • Fetal alcohol syndrome
  • ADHD
  • Autism
  • Anxiety disorders
  • Parkinson’s
  • Alzheimer’s
  • Huntington’s
Autism

- Neurodevelopmental disorder
  - High prevalence
    - 1/88 for whole spectrum (CDC, 2012)
    - 1/38 (Kim et al. 2011)
  - Diagnosed in terms of consensus-based array of *behavioral* criteria
- DSM-IV: Impairments or delays
  - Social interaction
    - Eye contact
    - Peer relations
  - Communication
    - Language delay (or total lack)
    - Inadequate or stereotyped use of language
  - Restricted and repetitive behaviors
    - Preoccupation with specific objects
    - Hand flapping etc.
An example of a multimodal autism study

- **MRI**
  - Functional MRI
  - Functional connectivity MRI
  - High-resolution anatomical MRI
    - E.g.: White matter volume, regional cortical thickness
  - Diffusion weighted MRI/tractography
  - Several indices of white matter integrity, tract organization
  - Restriction spectrum imaging
  - Several indices of cortical architecture
  - MR spectroscopy
    - Measures of brain metabolites
- **Physiological measures**
  - Heart rate, breathing
- **EEG**
  - Power spectra at frequencies of interest (e.g., gamma)
- **MEG**
  - Event-related
  - Coherence in different frequency bands
- **Questionnaires**
  - Medical history
  - Sensory profiles
  - Sociocommunicative, executive, etc.
- **Behavior-based measures**
  - Diagnostic scores
  - Neuropsychological tests
  - Performance data from fMRI task or other
- **For study including 120 participants**

<table>
<thead>
<tr>
<th>~# features per pt</th>
<th>10,000</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>100,000</td>
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<tr>
<td></td>
<td>1,000</td>
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<tr>
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<td>4,000</td>
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fMRI: Tip of the activity iceberg

- 180-450 time points per scan
- ~100,000 brain voxels
- 120 participants
- Billions of measurements for fMRI alone
- Massive data reduction in conventional activation analysis

<table>
<thead>
<tr>
<th>Cluster size (µl)</th>
<th>Peak Talairach coordinates</th>
<th>Peak t value</th>
<th>Location of peak activation (approximate Brodmann area)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4568</td>
<td>-13 -17 15</td>
<td>8.9</td>
<td>Left thalamus</td>
</tr>
<tr>
<td></td>
<td>-16 -6 13</td>
<td>8.0</td>
<td>Left lentiform nucleus</td>
</tr>
<tr>
<td>4336</td>
<td>-34 17 17</td>
<td>12.5</td>
<td>Left inferior frontal (44/45)</td>
</tr>
<tr>
<td>2608</td>
<td>-4 17 39</td>
<td>9.3</td>
<td>Left cingulate (32)</td>
</tr>
<tr>
<td>2336</td>
<td>-24 2 52</td>
<td>9.5</td>
<td>Left middle frontal (6)</td>
</tr>
<tr>
<td>1752</td>
<td>-9 -58 -2</td>
<td>7.7</td>
<td>Left lingual (19)</td>
</tr>
</tbody>
</table>
fcMRI: Focus on regions of interest...

Underconnectivity findings from same group:
- Just et al. (2006): Executive (Tower of London)
- Cherkassky et al. (2006): Rest (default mode network)
- Kana et al. (2006, 2007): Sentence comprehension; response inhibition
- Koshino et al. (2008): Nonverbal working memory
- Mason et al. (2008), Kana et al. (2009): Theory of mind
- Damarla et al. (2010): Visuospatial
- Mizuno et al. (2012): Perspective-taking

... and from other groups:
- Villalobos et al. (2005): Visuomotor coordination
- Bird et al. (2006): Selective visual attention
- Kleinhans et al. (2008): Face processing
- Lee et al. (2009): Response inhibition
- Mostofsky et al. (2009): Finger movement
- Solomon et al. (2009): Cognitive control
... may be missing the bigger picture

IFG: Less consistent local activity, but diffusely increased BOLD correlation

ASD: Cross-talk rather than underconnectivity?

- Overconnectivity *between* mentalizing network and mirror neuron system in ASD
- Between-network “cross-talk” correlated with sociocommunicative impairment

I. Fishman et al., *JAMA Psychiatry* 2014
Popper or not?

• Hypotheses for ASD are “cheap”
  • Some supportive evidence for virtually any pet idea
• No strong hypotheses for *unique* biomarkers

=> Need for data-driven approaches
Data-driven approaches: ICA

- 17 non-noise components (=functional networks)
  - Matched to components from previous TD studies (Smith et al., 2009; Laird et al., 2011)
- 10 show group differences in asymmetry index
  - Exclusively: rightward shift in ASD

Cardinale et al. (JAMA Psychiatry, 2013)
Diagnostic classification

- **Machine learning** (Random Forest)
- **Low-motion subsample**
  - (selected from ABIDE)
  - N=252
- **220 ROIs** (Power et al., 2011)
  => 24090 features
- **Selection of 100 most informative features**
- **Classification accuracy**
  - 90.9%
  - “Out of bag” (validation sample) error: 9.1%

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<thead>
<tr>
<th></th>
<th>ASD (n=126)</th>
<th>TD (n=126)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Gender (M/F)</td>
<td>108 / 18</td>
<td>95 / 31</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>17.3 ± 6.0</td>
<td>17.1 ± 5.7</td>
<td>0.8</td>
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<tr>
<td></td>
<td>(8.2 - 35.7)</td>
<td>(6.5 - 34)</td>
<td></td>
</tr>
<tr>
<td>Motion (RMSD; mm)</td>
<td>.06 ± .02</td>
<td>.06 ± .02</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>(.02-.1)</td>
<td>(.02-.1)</td>
<td></td>
</tr>
<tr>
<td>Non-verbal IQ</td>
<td>106.9 ± 17</td>
<td>106.3 ± 12.8</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>(37-149)</td>
<td>(67-155)</td>
<td></td>
</tr>
<tr>
<td>ADOS_total</td>
<td>12 ± 4 (4-22)</td>
<td>N/A</td>
<td></td>
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C. Chen et al. (under review)
Functional connectivity

- Matrix of signal correlations between 220x220 regions of interest
- >24,000 features
Informative features: Top 10
Informative features: Top 25

![Graph showing informative features with TD > ASD and ASD > TD connections.](image-url)
Informative features: Top 50
Informative features: Top 75

- TD > ASD
- ASD > TD
Informative features: Top 100
Informative ROIs: normalized* numbers per network

*Number of times network ROIs participate in informative connection / total number of ROIs in network

- SMM: 2.6
- SMH: 1.5
- SUB: 1.2
- VIS: 0.9
- MR: 1.0
- DMN: 0.9
- SAL: 0.9
- VA: 0.9
- UN: 0.8
- COTC: 0.5
- DA: 0.5
- FPTC: 0.5
- CEB: 0.3
Machine learning for detection of biomarkers

• Issues

  • Large functional dataset only from ABIDE
    • Multisite data sources introduce many factors of variability that are hard to control

  • No solution for validation problem
    • Separate validation sets cannot be fully matched to training sets
      – Unknown subtypes
    • Random Forest: Out of Bag validation

  • Multimodal imaging more likely to capture complex signature of disorder
    • Usually not available for very large samples
Why all this?

• Autistic symptomatology likely due to complex patterns of brain network abnormalities

• Conventional hypothesis-driven techniques have not succeeded in identifying distinct patterns of brain anomalies

• Need for biomarkers of ASD
  • Measures of network connectivity a potential source for such markers
    • Detection requires data-driven methods (e.g., machine learning)
    • Biomarkers may be highly complex
  • Identification of brain-based subtypes of ASD
    = Clusterings of patterns of biomarkers

• Perspectives:
  • More transparent links between such subtypes and specific genetic (+ environmental) factors
  • Mechanistic models of developmental disturbances
  • Taylored treatments
Thanks!

To parents and participants

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Brain Development Imaging Lab:
• Faculty: Inna Fishman, Ruth Carper, Dinesh Shukla
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