16p11.2 duplication as a model of psychosis in autism spectrum disorder

Amandeep Jutla, MD

Postdoctoral Fellow
Whitaker Scholars in Developmental Neuropsychiatry Program
Columbia University
New York State Psychiatric Institute

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Disclosures

- Postdoc funding:
  - Whitaker Scholar in Developmental Neuropsychiatry Award
  - Marilyn and James Simons Family Giving

Why care about psychosis in autism?

Autism spectrum disorder

Schizophrenia

Restricted/repetitive
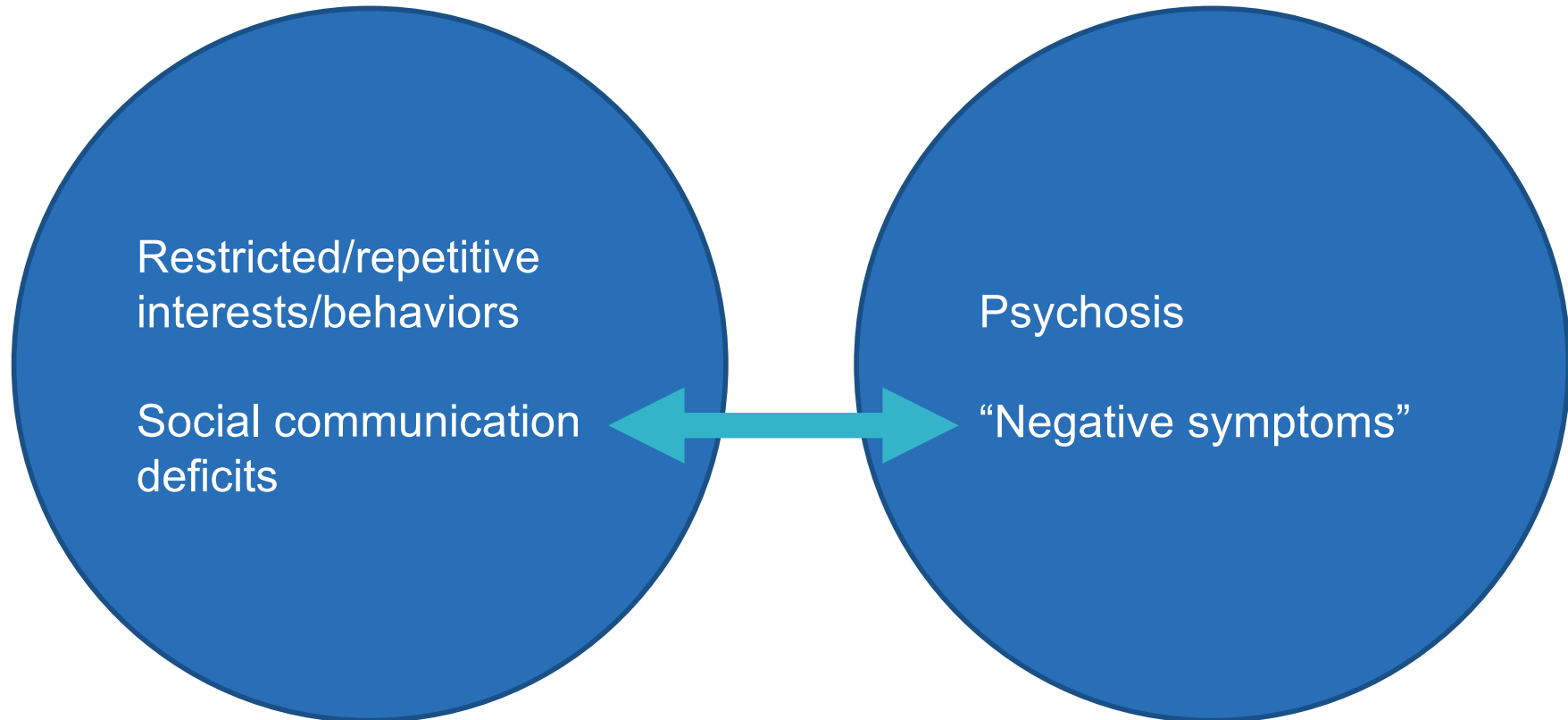interests/behaviors

Social communication
deficits

Psychosis

"Negative symptoms"

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Autism spectrum disorder

Schizophrenia

Restricted/repetitive interests/behaviors

Psychosis

Cognitive systems:
- **Language**

Social processes:
- **Social communication**
- **Perception and understanding of self**
- **Perception and understanding of others**

Autism spectrum disorder

Schizophrenia

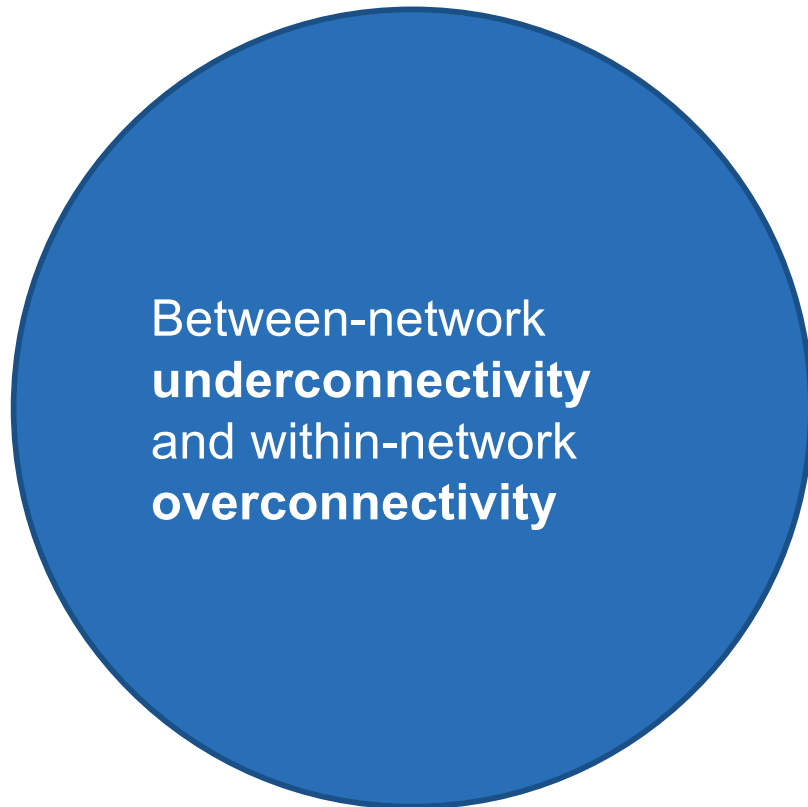Restricted/repetitive interests/behaviors

Psychosis

Cognitive systems:
- **Language**

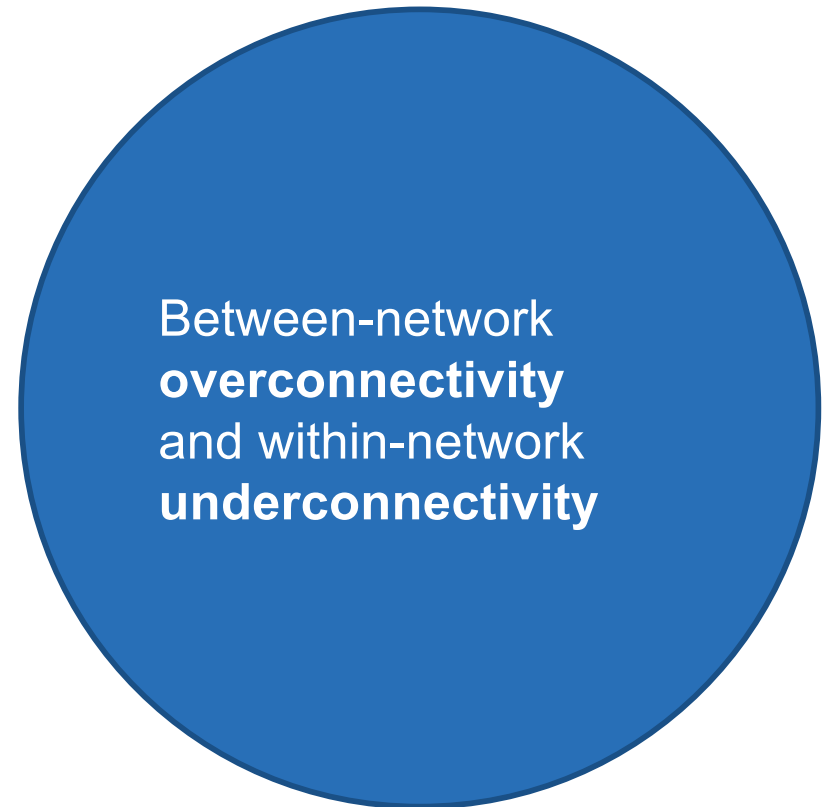Social processes:
- **Social communication**
- **Perception and understanding of self**
- **Perception and understanding of others**

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Autism spectrum disorder

Between-network **underconnectivity** and within-network **overconnectivity**

Schizophrenia

Between-network **overconnectivity** and within-network **underconnectivity**

Autism spectrum disorder

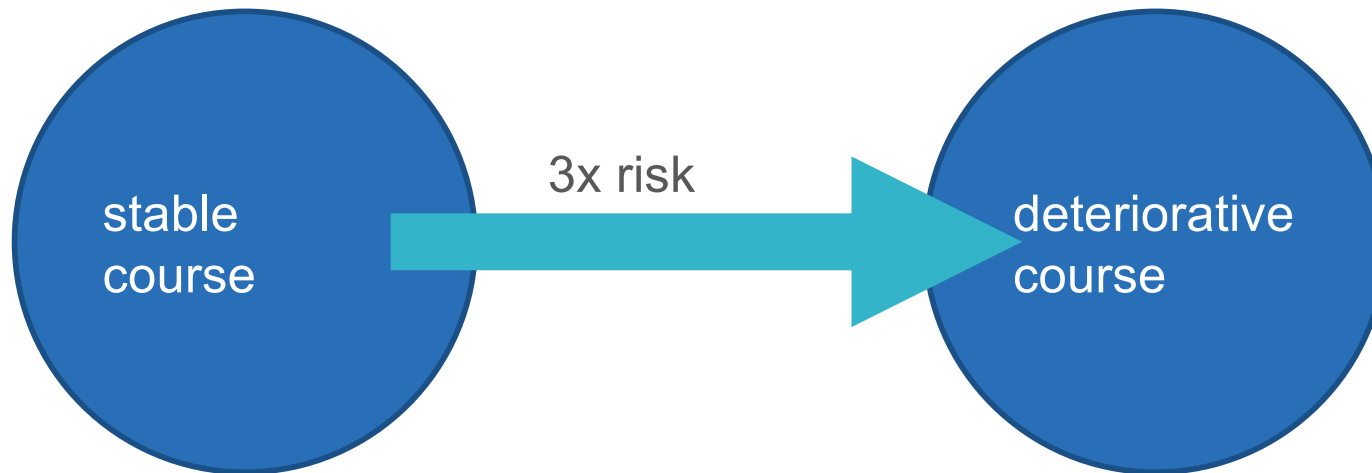Typically diagnosed in **childhood**

Typically **stable** course

Schizophrenia

Typically diagnosed in **adolescence or early adulthood**

Typically **deteriorative** course

Autism spectrum disorder

Schizophrenia

stable course

3x risk

deteriorative course

But...

Amandeep Jutla I 19 May 2019

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How can we constrain heterogeneity?

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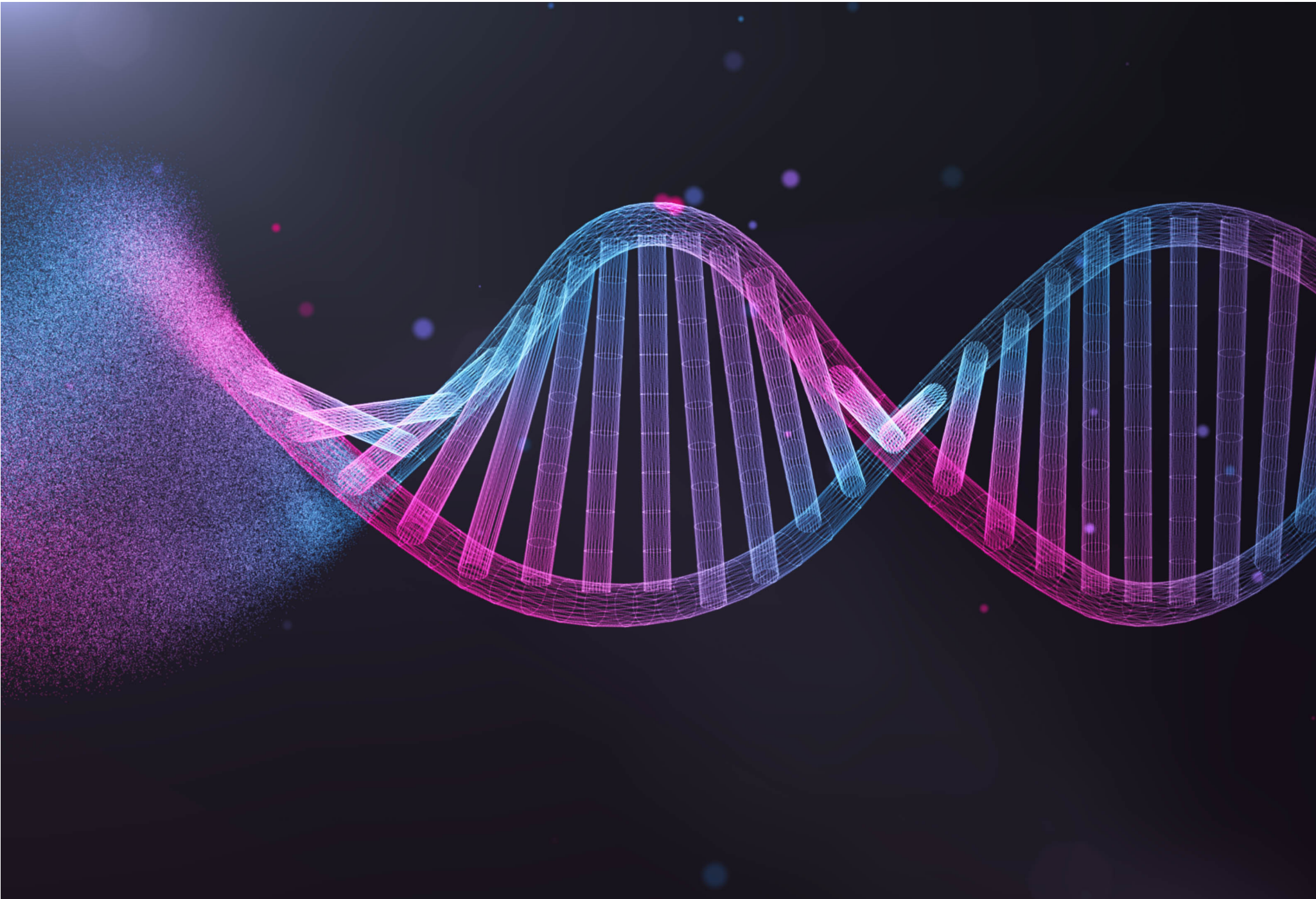
16p11.2 copy number variation

- ~25 gene region at 16p

- Prone to deletion or duplication

- Single most common genetic cause of autism

  - i.e.: 1% of autism

- Duplication, but *not* deletion, is associated with schizophrenia

Simons Variation in Individuals Project

- **546** total
  - **109** 16p11.2 duplication
  - **131** 16p11.2 deletion
  - **306** non-carrier relatives

- Phenotyping measures:
  - Behavior
  - fMRI

Looking at the behavioral data . . .

- n = 19 with likely psychotic symptoms

- Predictors:

  - **16p11.2 duplication:**

    - OR **7.44**, 95% CI 1.77 – 31.18, p = 0.006

  - **ASD diagnosis**:

    - OR **4.21**, 95% CI 1.31 – 13.56, p = 0.02

- Model adjusted for age, gender, and IQ and (with GEE) intrafamilial correlation

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Biggest limitation

- Does "likely psychotic symptoms" actually reflect psychosis?

The next step . . .

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Specific Aim 1

- Establish the clinical profile of psychosis in 16p11.2 duplication

- Hypotheses:
    - 1a: Psychosis is more common in dup than del
    - 1b: ASD is a stronger predictor in dup than del
    - 1c: ASD severity predicts psychosis in dup

Specific Aim 2

- Establish (**preliminary**) neural correlates of psychosis in 16p11.2 duplication

- Hypotheses:
  - 2a: dup**+**psychosis: ↑**intra-** and ↓**inter**-network connectivity
    - (v. noncarriers)
  - 2b: dup**+**psychosis: ↑**intra** and ↓**inter**-network connectivity
    - (v. dup-psychosis)
  - 2c: Among dup:
    - **intra**-network connectivity predicts psychosis severity
    - **inter**-network connectivity predicts ASD severity

Methods: Aim 1

- Interview all CNV carriers who either have an ASD diagnosis or have likely psychotic symptoms **(n = 36; 18 dup, 18 del)**:

  – Structured Interview for Prodromal Symptoms (SIPS)

- Between-group frequency comparisons: χ^2
- Predictors of psychosis: logistic regression models

Methods: Aim 2

- Using existing resting-state fMRI data, compare group-level correlation strength among regions of interest in the:
  - **AI** (major node of salience network)
  - **PCC** (major node of default mode network)
  - **dACC** (major node of salience network)

- Estimate models to test whether *z*-transformed AI-PCC (**inter**-network) and AI-dACC (**intra**-network) connectivity predict severity of psychosis or severity of ASD respectively.

Future work: establish generalizability of findings

- **Aim 1**
  - Prodromal psychosis clinic population at New York State Psychiatric Institute
  - Autism population at New York-Presbyterian Center for Autism and the Developing Brain
  - Simons Powering Autism Research for Knowledge (SPARK) cohort

- **Aim 2**
  - Analyze fMRI data from the Adolescent Brain Cognitive Development (ABCD) cohort

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Q&A