Autism and Psychosis

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Case Examples

History of ASD and Psychosis
- Diagnostic criteria and DSM
- Childhood onset schizophrenia
- Psychosis prodrome

Research Findings
- Clinical overlap
- Genetics and neurobiology

Clinical Implications
- Differential Diagnosis
- Treatment Implications
TALK OUTLINE

- **Case Examples**
- **History of ASD and Psychosis**
  - Diagnostic criteria and DSM
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“Josh”: 14yo M

- Family history of both autism and schizophrenia
- History of language delay and delayed echolalia, current formal speech and atypical intonation on exam
- Limited range of facial expressions, gestures on exam
- No friendships, difficulties with reciprocal interactions
- History of restricted interests (trains, certain videos), also at present (history, weapons)

Now also presenting with:

- Visual hallucinations (shadows of aliens)
- Paranoid ideation (being poisoned, being video taped)
- Disorganized thinking, particularly in high affect situations
"Kyle": 17yo M

- History of early language delays, but no stereotyped language or echolalia on exam
- Difficulties with conversation
- Social skills deficits, social withdrawal
  - Worsening beginning in 4th grade
- Sensory sensitivities (irritated by noises and smells)

Now presenting with:

- Decline in self-care
- Paranoia about people staring at him, foods being poisoned
- History of visual hallucinations at age 16
- Frequent violent, graphic nightmares
- Increasing agitation and irritability
Per DSM: Is it one OR the other?

But... might it be both?
  - Can ASD and Schizophrenia be comorbid?
  - Can schizophrenia masquerade as ASD in early childhood?
  - Might symptom patterns that are called “autism” actually be caused by another underlying problem?
  - Does ASD make one more susceptible to a psychotic process?
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EUGEN BLUELER

- 1911: Dementia Praecox -> the “schizophrenias”
- Physical disease characterized by exacerbations and declines
- Major symptoms, “4 A’s”
  - flattened Affect
  - Autism
  - impaired Association of ideas
  - Ambivalence
1943: Early infantile autism
- **Autistic** aloneness
- Insistence on sameness
- Speech disturbances, such as echolalia
- Large heads, clumsy gait, excellent rote memory

Differentiated from schizophrenia by onset of social withdrawal
295.8 Schizophrenia, childhood type

This category is for cases in which schizophrenic symptoms appear before puberty. The condition may be manifested by autistic, atypical and withdrawn behavior; failure to develop identity separate from the mother's; and general unevenness, gross immaturity and inadequacy of development. These developmental defects may result in mental retardation, which should also be diagnosed.

Autism does not have its own category
1971: Studies in the Childhood Psychoses

Three groups of psychoses in childhood, distinguished by age of onset:
- Under 3 years (Kanner)
- 3-5 years
- Over 5 years (adult schizophrenia)
Both disorders are schizophrenias

Both disorders have the word “autism” at their core

There is no separate diagnosis for autism until Infantile Autism appears in the DSM-III in 1980
Infantile Autism

A. Onset before 30 months of age

B. Pervasive lack of responsiveness to other people (autism)

C. Gross deficits in language development

D. If speech is present, peculiar speech patterns such as immediate and delayed echolalia, metaphorical language, pronominal reversal
E. Bizarre responses to various aspects of the environment, e.g., resistance to change, peculiar interest in or attachments to animate or inanimate objects.

F. Absence of delusions, hallucinations, loosening of associations, and incoherence as in Schizophrenia.
Prior to DSM-III: Autism Subsumed within Schizophrenia

After 1980: Autism and Schizophrenia Separate

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Psychosis and autism as diametrical disorders of the social brain

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Autistic Children Who Become Schizophrenic

Leonora K. Petty, MD; Edward M. Ornitz, MD; John D. Michelman, MD; Emory G. Zimmerman, MD, PhD

Infantile autism and schizophrenia have been regarded as unrelated and distinct disorders. There is, however, some evidence in the literature that supports a relationship between the two disorders in that there may be a subgroup of autistic children in whom schizophrenia develops. The diagnostic criteria used in the literature to describe infantile autism and schizophrenia in childhood has not been uniform. The three cases in this report, diagnosed on the basis of current criteria and detailed clinical descriptions, clearly point to an initial diagnosis of infantile autism followed by the development of schizophrenia.

(Arch Gen Psychiatry 1984;41:129-135)
CASE 1.—Early History.—The patient was the full-term product of an uneventful pregnancy and delivery. There were no neonatal complications or congenital anomalies. The family history revealed no major psychiatric syndromes, mental retardation, or neurological disease, except for a neuromuscular defect in the patient’s otherwise normal, one-year-younger sister (bilateral ptosis and epicant hus inversus).

His parents remembered him as “very good, passive, and easy” during the first six months. Breast-feeding was unsuccessful; however, he sucked well at the bottle. At the age of 8 months, he sat with support in a playpen and was responsive, affectionate, and interested in rattles and the crib mobile. His pediatrician noted “not talking much” and “trouble sleeping.” The parents recalled adequate “eye contact” at the age of 1 year, but remembered that “he did not point.” He stroked textured surfaces, e.g., wood and wall coverings, repetitively. He said “bye bye” and “mama” at the age of 18 months.

At the age of 24 months, his vocabulary had not increased. He “pulled at hands to move the hand to pick up an object” rather than communicating in other ways. His pediatrician noted “short attention span; excessive anger, spitting.”

At the age of 33 months, the pediatrician noted that the child did not speak and seemed to be extremely withdrawn, “tuning out.”

At the age of 38 months, a formal audiological evaluation gave normal findings. At the age of 44 months, on enrollment in a therapeutic nursery school, he was described as having limited eye contact and being quite withdrawn. His vocabulary consisted of about 15 words. He lined objects in straight rows and would not touch any item that was slightly sticky, e.g., cupcakes, cake, or paste. He touched objects gingerly at their outer edges. On initial testing, the Merrill-Palmer IQ was 73. After three months of intensive therapy, the IQ was 81. Test subscales showed wide scatter, with the highest success at the 60- to 65-month level (picture puzzle). At the age of 54 months, a Denver Developmental Screening Test showed the following:

Gross Motor—fails all tests for age; Fine Motor—fails most tests for age; language—comprehension was age level, expressive language was below age level, quantity of words below level and quality of speech far below normal; Personal-Social—interactions with peers almost non-existent. Very short attention span, then gets hung up on one activity.

At the age of 60 months, in an aphasia class, he appeared more alert and aware of others. By the age of 66 months, he had a “reading vocabulary” at grade level, i.e., comprehension was severely limited, and he was restricted, literal, and concrete in his thinking.

There was a developmental “spurt” manifested by word recognition and spelling at second-grade level, at the age of 66 months, although comprehension was severely limited. Motor milestones were slightly delayed but progressed in an orderly fashion.

By 36 months of age, the patient had demonstrated sufficient autistic behavior to diagnose infantile autism (Table 1). Such behavior was evident before 30 months of age and persisted past the age of 60 months.
Middle Childhood Years.—At 7 years of age, the patient began to vomit each night at bedtime. A workup was noncontributory, and the pediatrician diagnosed “psychosomatic hyperemesis.” By the age of 8 years, the initial progress in the aphasis class declined and his behavior deteriorated. Decreased attention span, conversation punctuated by irrelevant comments, and emotional lability were observed. After three weeks of trifluoperazine hydrochloride (Stelazine) therapy, his teacher reported a “truly increased attention to solitary tasks; still a loner.”

At the age of 9 years, the trifluoperazine therapy was discontinued, and his pediatrician reported “deteriorating behavior” and reappearance of regurgitation. By 10 years of age, the parents sought psychiatric help. Episodic vomiting reappeared, behavior deteriorated, and he was mumbled to himself incoherently. During psychiatric examination by one of us (E.M.O.), there was intermittent hand flapping, finger wiggling, and whole-body rhythmic movement. Eye contact was fleeting. He spoke with nasal tone that did not convey adequate emotion. Speech was literal, with lack of content, but no loose associations. He told the examiner that he heard “parrotlike voices,” and he saw bizarre, inappropriate details in the Rorschach test. He showed severe deficits in social judgment.

For the next two years, the patient was seen weekly by one of us (J.D.M.), and trifluoperazine therapy was reinstituted. He expressed concern that he was losing control. Loose associations developed. The patient learned to refer to them as “extra thoughts.” At times they were bizarre and delusional, such as “smelling a creamy feeling” or “worrying about this decade.” Other whispers and mumblings reflected age-appropriate interests contaminated by bizarre associations, such as “wanting to kiss a girl with racial feelings.” Much of his thought content, however, consisted of names of television shows, advertisement jingles, key phrases from movies, lists of words that rhymed, literal puns, and word games such as “dafynitions” (“understand . . . to stand under . . . to understand!”).

Adolescence.—At the age of 12 years, the patient was hospitalized for control of increasingly bizarre behavior and progressive deterioration in daily routines, including “increased insomnia.” The mental status examination on admission showed fleeting eye contact, physical agitation, and frequent hand flapping. There was much resistance and occasional noncompliance. Mood was flat; depression and suicidal feelings were denied. Thoughts included delusions of being controlled by life-threatening “witch craftery . . . the fearful force.” There were hallucinations of “hearing voices,” including commands. Much of the patient’s language was incomprehensible because of mumbled subvocalizations and loose associations, eg, “I like the hospital all right . . . stupid, stupid, stupid . . . (whisper and giggling) what is a slapshot?” The patient was fully oriented, with excellent memory and ability to calculate.

Results of physical and neurological examinations, routine blood and urine tests, routine chest roentgenography, EEG, and hearing and vision evaluations were within normal limits. On the revised Wechsler Intelligence Scale for Children (WISC-R) verbal IQ was 91, performance IQ was 68, and full-scale IQ was 78.

Table 2 summarizes the documentation for the diagnostic criteria for schizophrenia. The requirements for chronicity were also met. Auditory “running commentary” and two-voice hallucinations were described during the four months prior to hospital admission (when he was not taking antipsychotic medication). During hospitalization, he was again given medication. Although other schizophrenic symptoms persisted, within two weeks of initiating treatment with thiothixene hydrochloride (Navane; to 22 mg/day), the patient said, “The voices have gone away now.” At the six-month follow-up examination, the patient denied “hearing voices,” although incoherent muttering and whispering were observed.
WHISPERS OF OVERLAP: PSYCHOSIS PRODROME

- Acute: Mild/moderate Alterations in perception, cognition, language, will, initiative, motor function, energy level, stress tolerance
  - Social isolation
  - Negative symptoms of schizophrenia
  - Depression, anxiety
  - Difficulty with concentration, attention
  - Attenuated positive symptoms

- Further back
  - Language and other milestone delays
  - Atypical motor functioning
  - Attention problems
  - Social difficulties
Schizophrenia diagnosed under 13

In 97 children with COS at NIMH, 29% had a PDD diagnosis
  - Additional 39% had other developmental delays, including with language and with motor skills

In the broader COS cohort, for any given DSM-IV ASD symptom, 16-58% of children met criteria
  - Social impairment: 100% had 1; 78% had 2+
  - Communication impairment: 84% had 1; 53% had 2+
  - RRBs: 74% had 1; 37% had 2+
  - Overall: 58% had impairment in all three categories; 100% had impairment in at least two
  - Least common overlapping symptoms were pronoun reversal, impaired non-verbal communication, deficits in imaginative play
WHISPERS OF OVERLAP: CHILDHOOD ONSET SCHIZOPHRENIA
Prior to DSM-III: Autism Subsumed within Schizophrenia

After 1980: Autism and Schizophrenia Separate

Newer Conceptualization: Overlapping Disorders

**ASD**
- Stereotyped Language
- Restricted Interests
- Motor Mannerisms
- Onset under age of 5
- Limited medication effects on core symptoms

**SZ**
- Hallucinations
- Delusions
- Onset typically early adulthood
- Responds to anti-psychotics

Shared genetic contributions?  Shared underlying neurobiology?
HISTORICAL JOURNEY OF ASD AND SCHIZOPHRENIA

ASD

SZ
HISTORICAL JOURNEY OF ASD AND SCHIZOPHRENIA

ASD

SZ
HISTORICAL JOURNEY OF ASD AND SCHIZOPHRENIA
HISTORICAL JOURNEY OF ASD AND SCHIZOPHRENIA

ASD

SZ

seaver autism center for research & treatment at mount sinai
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COMMON CLINICAL RESEARCH FINDINGS

- Social
  - Theory of mind deficits
  - Face, affect, emotion, voice recognition deficits

- Sensory
  - Heightened sensory perception
  - Atypical local/global visual processing

- Cognitive
  - Impaired attention, processing speed, working memory
  - Difficulty with set-shifting, executive dysfunction
## OVERLAPPING DIAGNOSES

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number</th>
<th>Diagnosis</th>
<th>Age (years)</th>
<th>Psychotic Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tantam (1991)</td>
<td>85</td>
<td>ASD</td>
<td>Adult</td>
<td>21% psychosis 4% SCZ</td>
</tr>
<tr>
<td>Tantam (1988)</td>
<td>60</td>
<td>Autism, 46</td>
<td>16–65, mean 24</td>
<td>12% psychosis</td>
</tr>
<tr>
<td>Wing (1981)</td>
<td>18</td>
<td>ASD</td>
<td>16+</td>
<td>50% SCZ spectrum</td>
</tr>
<tr>
<td>Szatmari et al. (1989)</td>
<td>16</td>
<td>Autism, IQ &gt;68</td>
<td>Mean 26</td>
<td>25% hallucinations</td>
</tr>
<tr>
<td>Konstantareas &amp; Hewitt (2001)</td>
<td>14</td>
<td>Autism, high functioning</td>
<td>17–33, mean 25, males</td>
<td>50% SCZ</td>
</tr>
</tbody>
</table>
Psychosis symptoms and conversion in clinical-high risk (CHR), with and without premorbid ASD diagnosis

<table>
<thead>
<tr>
<th></th>
<th>CHR/ASD+</th>
<th>CHR/ASD-</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOPS positive sx</td>
<td>12.12 (3.57)</td>
<td>11.91 (3.82)</td>
</tr>
<tr>
<td>SOPS negative sx</td>
<td>13.50 (4.84)</td>
<td>11.83 (6.10)</td>
</tr>
<tr>
<td>SOPS disorganization sx</td>
<td>6.08 (3.11)</td>
<td>5.13 (3.16)</td>
</tr>
<tr>
<td>SOPS general sx</td>
<td>8.65 (4.22)</td>
<td>9.18 (4.27)</td>
</tr>
</tbody>
</table>

- Social anhedonia greater in CHR/ASD+
- No symptoms less severe in CHR/ASD+

Convert 18%

Convert 17%
SELF-REPORT OF CLINICAL SYMPTOMS

- Self-report measures of ASD and schizophrenia features do not differentiate the two groups in adulthood
### CLINICAL ASSESSMENT OF SYMPTOMS: ASD

**ADOS SENSITIVITY AND SPECIFICITY**

<table>
<thead>
<tr>
<th>ADOS Classification</th>
<th>DSM Diagnosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASD (n=54)</td>
<td>Schizophrenia Spectrum (n=40)</td>
</tr>
<tr>
<td>Autism</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>ASD</td>
<td>22.2%</td>
<td>17.5%</td>
</tr>
<tr>
<td>Non-spectrum</td>
<td>27.8%</td>
<td>57.5%</td>
</tr>
</tbody>
</table>

- Sensitivity: 72.2%
- Specificity: 57.5%

- Clinician-administered measures are somewhat better at differentiating diagnosis.
- Over 40% of SZ participants met criteria for ASD on a “gold-standard” tool.
- At least 3 participants in the SZ stream also had history consistent with ASD.

Trevesan et al., in prep
Individuals with ASD displayed fewer positive symptoms of schizophrenia.

The Negative scale of the PANSS did not differentiate ASD and schizophrenia.
Process-based measures may differentiate core features that are affected within and across groups.
<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene(s)</th>
<th>Schizophrenia data</th>
<th>Autism data</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>22q11.2 (3 Mb hemizygous deletion)</td>
<td>&gt; 50</td>
<td>Many studies + 4 cases COS, COS→AOS</td>
<td>30%PDD(^{71})</td>
<td>Nonspecific risk but both increased; 71</td>
</tr>
<tr>
<td>16p11.2</td>
<td>24</td>
<td>500kb duplication in 2% of NIMH COS cohort(^{58})</td>
<td>1% of 5 autism populations have microdeletion or duplication(^{33, 48, 49})</td>
<td>COS CNVs both inherited; one case has comorbid PDD(^{58})</td>
</tr>
<tr>
<td>2p16.3</td>
<td>NRXN1</td>
<td>MZ twins concordant for COS with deletion; affected sib pair with inherited deletion(^{56, 58})</td>
<td>Deletions, disruptions, and mutations identified in several cases(^{48, 51, 52, 54, 72})</td>
<td>Growing evidence for both autism and COS; different regions of gene affected</td>
</tr>
<tr>
<td>Xq28</td>
<td>MECP2</td>
<td>1 case reported with mutation(^{73})</td>
<td>Rett's gene; autism Increased</td>
<td>Strong data for autism</td>
</tr>
<tr>
<td>1q42</td>
<td>DISC1</td>
<td>Disrupted gene identified in single large multiplex pedigree; numerous association studies(^{74})</td>
<td>Single association study with same haplotypes reported for schizophrenia(^{50})</td>
<td>Strong evidence for schizophrenia</td>
</tr>
<tr>
<td>7q35-q36.1</td>
<td>CNTNAP2</td>
<td>Deletions in 2 unrelated patients(^{75})</td>
<td>Linkage, association, and gene expression in autism(^{76, 77})</td>
<td>Growing evidence in both schizophrenia and autism</td>
</tr>
<tr>
<td>7q22.1</td>
<td>RELN</td>
<td>Decreased mRNA in postmortem brain linkage(^{70}) &amp; association with working memory(^{78, 79})</td>
<td>Many linkage, association, and functional studies(^{40, 80})</td>
<td></td>
</tr>
<tr>
<td>2p31.1</td>
<td>GAD1 (encodes GAD67)</td>
<td>10 studies show decreased GAD67 in schizophrenia postmortem brain(^{81}); 2 studies show association(^{82, 83})</td>
<td>Protein reduced in postmortem brain(^{84, 85}); multiple studies report linkage in region</td>
<td></td>
</tr>
</tbody>
</table>

COS- Childhood Onset Schizophrenia, AOS – Adult Onset Schizophrenia, CNV – Copy Number Variation, MZ –Monozygous, mRNA – messenger RNA
### Table 5: Candidate genes validated in both schizophrenia (SCZ) and autism spectrum disorder (ASD)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Grouping</th>
<th>Function</th>
<th>Other phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RELN</td>
<td>ND</td>
<td>Neuronal migration guidance matrix, polarization</td>
<td>Lissencephaly, Alzheimer's disease</td>
</tr>
<tr>
<td>DISC1</td>
<td>ND</td>
<td>Many stages of neural development, synaptic plasticity</td>
<td>Depression, bipolar disorder</td>
</tr>
<tr>
<td>FOXPA2</td>
<td>ND</td>
<td>Regulates DISC1, CTNAP2, Neural plasticity, speech</td>
<td>Developmental verbal dyspraxia</td>
</tr>
<tr>
<td>BDNF</td>
<td>ND</td>
<td>Neurotrophic factor. Regulates mTOR/AKT</td>
<td>Alzheimer's disease, Huntington's disease</td>
</tr>
<tr>
<td>MECP2</td>
<td>ND</td>
<td>Epigenetic regulator</td>
<td>Rett syndrome, PPM-X</td>
</tr>
<tr>
<td>UBE3A</td>
<td>ND</td>
<td>Epigenetic regulator</td>
<td>Angelman syndrome</td>
</tr>
<tr>
<td>MHC</td>
<td>Immune</td>
<td>Many candidate genes for AS and SCZ in large complex. Immune regulation</td>
<td>Immune</td>
</tr>
<tr>
<td>NLGN3</td>
<td>Scaffold</td>
<td>Postsynaptic stabilization and function: complexes with NRXN</td>
<td>NAD</td>
</tr>
<tr>
<td>NLGN4</td>
<td>Scaffold</td>
<td>Postsynaptic stabilization and function: complexes with NRXN</td>
<td>ID</td>
</tr>
<tr>
<td>NRXN1</td>
<td>Scaffold</td>
<td>Presynaptic stabilization and function: complexes with NLGN</td>
<td>Pitt-Hopkins phenotype</td>
</tr>
<tr>
<td>SHANK3</td>
<td>Scaffold</td>
<td>Scaffold protein in postsynaptic density of glutamatergic synapse</td>
<td>ID</td>
</tr>
<tr>
<td>NRCAM</td>
<td>Scaffold</td>
<td>Neuronal cell adhesion and axon cone growth</td>
<td>Addiction</td>
</tr>
<tr>
<td>CTNAP2</td>
<td>Scaffold</td>
<td>Cell adhesion, axonal differentiation</td>
<td>ID, Pitt-Hopkins phenotype, epilepsy, language impairment</td>
</tr>
<tr>
<td>GRIN2B</td>
<td>Scaffold</td>
<td>NMDA receptor subunit</td>
<td>ID, epilepsy</td>
</tr>
<tr>
<td>NTNG1</td>
<td>Guidance</td>
<td>Axon guidance</td>
<td>Bipolar disorder</td>
</tr>
<tr>
<td>GABRB3</td>
<td>NT</td>
<td>GABA receptor subunits</td>
<td>Bipolar disorder</td>
</tr>
<tr>
<td>GABRA5</td>
<td>NT</td>
<td>GABA receptor subunits</td>
<td>Bipolar disorder</td>
</tr>
<tr>
<td>GAD</td>
<td>NT</td>
<td>Conversion of glutamate to GABA</td>
<td>Epilepsy</td>
</tr>
<tr>
<td>CACNA1C</td>
<td>NT</td>
<td>Voltage-dependent calcium channel subunit</td>
<td>Bipolar disorder, Brugada and Timothy syndromes</td>
</tr>
<tr>
<td>SLC25A12</td>
<td>NT</td>
<td>Solute channel protein, mitochondrial membrane</td>
<td>Mitochondrial disorders</td>
</tr>
<tr>
<td>OXTR/OXT</td>
<td>NM</td>
<td>Oxytocin receptor</td>
<td>NAD</td>
</tr>
<tr>
<td>ZNF804A</td>
<td>Not known</td>
<td>Transcription regulator of PRSS16, COMT</td>
<td>Bipolar disorder</td>
</tr>
</tbody>
</table>

### Table 6: Validated copy number variants implicated in both autism spectrum disorder (ASD) and schizophrenia (SCZ)

<table>
<thead>
<tr>
<th>Region</th>
<th>Type</th>
<th>Morph</th>
<th>Validated phenotypes</th>
<th>Candidate genes in region</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q21.1</td>
<td>Del</td>
<td>Y</td>
<td>SCZ, ASD, ID, IGE, ADHD, BAD</td>
<td>NAD</td>
</tr>
<tr>
<td>1q21.1</td>
<td>Del</td>
<td>N</td>
<td>SCZ, ASD, ID, ADHD</td>
<td>NAD</td>
</tr>
<tr>
<td>2p16.3</td>
<td>Del</td>
<td>N</td>
<td>SCZ, ASD, ID, Pitt-Hopkins phenotype, IGE</td>
<td>NRXN1</td>
</tr>
<tr>
<td>3q29</td>
<td>Del</td>
<td>Y</td>
<td>SCZ, ID, BAD, ASD</td>
<td>PAK2, DLG1</td>
</tr>
<tr>
<td>3q29</td>
<td>Del</td>
<td>Y</td>
<td>SCZ, ID, ADHD</td>
<td>NAD</td>
</tr>
<tr>
<td>15q11.2</td>
<td>Del</td>
<td>Y</td>
<td>SCZ, ASD, ID, IGE, OCD, MDD</td>
<td>CYFIP1</td>
</tr>
<tr>
<td>15q11-13</td>
<td>Dup</td>
<td>Y</td>
<td>SCZ, ASD, ID, IGE, ataxia</td>
<td>GABRA5, GABRB3, GABRG3 + 17 others</td>
</tr>
<tr>
<td>15q11.3</td>
<td>Del</td>
<td>Y</td>
<td>SCZ, ASD, ID, IGE, ADHD, BAD</td>
<td>CHRNA7</td>
</tr>
<tr>
<td>16p11.2</td>
<td>Del</td>
<td>Y</td>
<td>SCZ, ASD, ID, learning disorder</td>
<td>DOC2A, ERK1</td>
</tr>
<tr>
<td>16p11.2</td>
<td>Del</td>
<td>Y</td>
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<tr>
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<td>SCZ, ASD, ID, ADHD, epilepsy (rare)</td>
<td>PRODH, COMT, DGCX6, TBX1</td>
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*Morph* indicates dysmorphism has been noted in cases.

Abbreviations: ADHD, attention deficit hyperactivity disorder; DD, developmental delay; ID, intellectual disability; IGE, immunoglobulin E; MDD, major depressive disorder; NAD, not adequately defined; OCD, obsessive-compulsive disorder.

*Guidance* indicates dendrite and axon guidance and organization.

Abbreviations: GABA, gamma-aminobutyric acid; ID, Intellectual disability; NAD, not adequately defined; ND, neurodevelopment; NLGN, neulin; NM, neuroregulation; NMDA, N-methyl-D-aspartate; NRXN, neurexin; NT, neurotransmission; PPM-X, psychosis, pyramidal signs, Parkinsonism, and macroorchidism syndrome.
NEUROBIOLOGICAL OVERLAP

- Atypical brain specialization
- Functional under-/over-connectivity
- Resting state alterations
- Excitatory/inhibitory neurotransmitter imbalance
- Predictive coding deficits
- Social brain dysfunction
- Neural inflammation
Structural Alterations of the Social Brain: A Comparison between Schizophrenia and Autism

Daniel Radeloff*1, Angela Ciaramidaro1, Michael Siniatchkin1, Daniela Hainz1, Sabine Schlitt1, Bernhard Weber2,3, Fritz Poustka1, Sven Bölte1,2, Henrik Walter3,4, Christine Margarete Freitag1

RESEARCH ARTICLE

Shared Atypical Default Mode and Salience Network Functional Connectivity between Autism and Schizophrenia

Heng Chen, Lucina Q. Uddin, Xujun Duan, Junjie Zheng, Zhiliang Long, Youxue Zhang, Xiaoran Guo, Yan Zhang, Jingping Zhao, and Huafu Chen

Published in final edited form as: Schizophr Res. 2017 May; 183: 102–109. doi:10.1016/j.schres.2017.03.009.

Diametrical relationship between gray and white matter volumes in autism spectrum disorder and schizophrenia

Serge A. Mitelman1,2, Marie-Cecile Bralet3,4,5, M. Mehmet Haznedar1,6, Eric Hollander7, Lina Shihabuddin1, Erin A. Hazlett1,6, Monte S. Buchsbaum8

Autism Spectrum Disorders and Schizophrenia: Meta-Analysis of the Neural Correlates of Social Cognition

Gisela Sugranyes1,2,3, Marinos Kyriakopoulos3,4, Richard Corrigan5, Eric Taylor1, Sophia Frangou2

Common Mechanisms of Excitatory and Inhibitory Imbalance in Schizophrenia and Autism Spectrum Disorders

R. Gao1,2 and P. Penzes1,2

Schizophrenia and Autism: Both Shared and Disorder-Specific Pathogenesis Via Perinatal Inflammation?

URS MEYER, JORAM FELDON, AND OLAF DAMMANN
NEUROBIOLOGICAL OVERLAP

- Atypical brain specialization
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**NEUROBIOLOGICAL OVERLAP**

Perinatal Inflammation

E/I Imbalance

**Figure 1**

Intensity of Perturbed Regional Computation
Complex Genetic Risk
Microcircuit Dysfunction
Hypothesized Neural System Pathology

Schizophrenia Spectrum
Autism Spectrum

Polygenic Interactions
e.g., DISC-1, SHANK3, MECP2, GAD, CNTNAP2, NLGN, NRXN1

Rare Variants
e.g., 1q21.1; 15q11.2; 16p11.2; 22q11.2; 22q13.3

Variable Baseline & Evoked Circuit Activity

Hypothesis:
Pervasively altered neural computations with some areas affected more than others (e.g. associative vs. sensory)?

Hypothesis:
Selectively altered neural computations with some areas emerging as selectively affected?

**A** Complex Genetic Risk

**B** Developmental Variability in Gene Expression

**C** Microcircuit Dysfunction

**D** Variable Baseline & Evoked Circuit Activity

**E** Hypothesized Neural System Pathology

**Foss-Feig et al., Biological Psychiatry, 2017**

Meyer et al., 2011

Seaver Autism Center for Research & Treatment at Mount Sinai
TALK OUTLINE

- Case Examples
- History of ASD and Psychosis
  - Diagnostic criteria and DSM
  - Psychosis prodrome
  - Childhood onset schizophrenia
- Research Findings
  - Clinical overlap
  - Genetics and neurobiology
- Clinical Implications
  - Differential Diagnosis
  - Treatment Implications
“Elijah”: 9yo M

- Delayed speech (words 2.5 years; sentences 4.5 years)
- No friends or interest in engaging peers
- Minimal conversation
- Limited eye contact
- Carries stuffed animal with him everywhere
- Past anxiety diagnosis related to compulsive behaviors and difficulties with changes in routine

But also:

- “Happy daydreams,” increasing in frequency
- Communication with imaginary family, increasing in intensity and interference
CASE EXAMPLE 3: BEHAVIORAL OBSERVATIONS

- Little conversation
  - Responded to questions
  - Made social overtures by making comments, but out of context
  - Monotone speech

- Persistent body rocking

- Perseverative on specific topics

- Delayed latency in verbal responses

- Inappropriate smiling while gazing to corners of the room

- Talked to self when examiner was less engaged
CASE EXAMPLE 3: ASD ASSESSMENTS

- Lifetime History (SCQ with follow up interview)
  - Delayed language with idiosyncratic use; concrete interpretation of language
  - Limited interest in and ability to form friendships, limited shared enjoyment
  - Atypical non-verbal communication (e.g., affect)
  - Unusual preoccupations, difficulty with transitions, unusual motor mannerisms

- Current Presentation (ADOS)
  - Atypical intonation; limited complex speech
  - Few descriptive gestures and flat affect
  - Failed to pick up on bids from the examiner
  - Limited imaginative play
  - Motor mannerisms
  - Excessive focus on narrow topic of interest (train set)
CASE EXAMPLE 3: PSYCHOSIS ASSESSMENTS

- Clinical Interview
  - Reported both auditory and visual hallucinations
  - Little insight into their origin

- Parent Rating (CBCL)
  - Elevated atypicality, withdrawal; deficits in social skills and adaptability

- Teacher rating (CBCL)
  - Elevated anxiety, attention problems, atypicality, withdrawal; deficits in social skills
CASE EXAMPLE 3: DIAGNOSTIC CONCLUSIONS

- Diagnoses
  - ASD
  - Psychosis NOS*

- Remaining questions:
  - Are these disorders comorbid for Elijah?
  - Might he have a variant of ASD/SZ that hovers the line between the two disorders?
  - Could early ASD traits have been a precursor for COS?
  - What about a genetic disorder?
CASE EXAMPLE 3: RECOMMENDATIONS

- Psychopharmacology
- Consider anti-psychotic medication
- Social skills training
- Individual therapy to build reality testing
- Parent education
- Environmental accommodations
- Longer-term follow up and continued differential
Consider developmental history

Consider family history

Consider change in functioning over time
  - Declines, loss of skills, change in ADLs
  - Emergence of new symptoms

Consider “positive” symptoms of each disorder
  - Motor mannerisms, stereotyped language, restricted interests
  - Delusions, disorganized thought/speech, hallucinations

Be wary of giving additional diagnoses

Also be wary of not (diagnostic overshadowing)

Remember the opposite is also sometimes true… patients can be suspected of or diagnosed with SZ when in fact it’s unidentified ASD
POSSIBLE TREATMENT GUIDELINES

- Follow over time

- Trial of antipsychotics
  - Some research that they’re effective in prodrome
  - Also approved for ASD
  - Though less effective for COS than adult SZ, response of presumed hallucinations and delusions could be informative diagnostically
    - Clozapine better than both haloperidol and olanzapine

- Psychosocial Interventions
  - Social skills training
  - Parent education and communication training
  - Individual therapy re: reality testing skills
  - Environmental accommodations
  - Cognitive remediation?
CONCLUSIONS

- There’s good evidence that, at least in some cases, there’s overlap between ASD and psychosis
- Research on this topic (either clinical or basic science) has been limited until quite recently
  - MCDD
  - RDoC
- Information on clinical course, prognosis, and best practice treatment is limited
  - More attention to this topic is needed
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Seaver Autism Center

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Collaborators

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