Differentiating schizoaffective and bipolar disorder: a dimensional approach

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Disclosures

- I have received grants/research support, consulting fees and honoraria within the last three years from BMS, Desitin, Eli Lilly, Gedeon Richter, Hoffmann-La Roche, Lundbeck, Otsuka, and Servier.

- Research grants: NHS National Institute for Health Research/Medical Research Council UK.

- Neither I nor any member of my family have shares in any pharmaceutical company or could benefit financially from increases or decreases in the sales of any psychotropic medication.

During this presentation, some medication may be mentioned which are off-label and not or not yet licensed for the specified indication!! The content of the talk represents solely the opinion of the speaker, not of the sponsor.
SCZ and BD means impairment at multiple levels—and we assume SAD, too.
The polymorphic course of Schizoaffective Disorder

Marneros et al. 1995.
Dimensional view of Schizoaffective Disorder (SAD) vs Bipolar Disorder (BD)

- Genes
- Brain morphology and Function
- Symptomatology
- Outcome
Dimension

SAD AND GENES
Bipolar and schizophrenia are not so different.....

Variance accounted for by genetic, shared environmental, and non-shared environmental effects for schizophrenia and bipolar disorder.

Lichtenstein et al, Lancet 2009
Genetics of bipolar disorder - 9/12 overlap with SCZ candidate genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
</tr>
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<tbody>
<tr>
<td>DISC1</td>
<td>1q42.1</td>
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<tr>
<td>DAT</td>
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<tr>
<td>DRD1</td>
<td>5q35.1</td>
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<td>DTNBP1 (Dysbindin)</td>
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<td>NRG1 (Neuregulin1)</td>
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<tr>
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<tr>
<td>MAO-A</td>
<td>Xp11</td>
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</table>

Genetic Associations found in at least three studies in bipolar patients

Grunze 2014
Psychosis in Mania: Hot spots 2p11-q14 and 13q21-33?

LOD Scores Across Chromosome 13 with Baseline and Covariate Values in Broad Bipolar Disorder Model

Shaded region represents previously found overlap regions between schizophrenia and bipolar disorder (27), and arrow shows location of the G72/G30 gene. Location in cM is based on the Marshfield Map.

Psychosis in Mania: Hot spots 2p11-q14 and 13q21-33?

LOD Scores Across Chromosome 2 with Baseline and Covariate Values in Narrow Bipolar Disorder Model

Shaded region represents findings from a schizophrenia meta-analysis (37). Location in cM is based on the Marshfield Map

Mood-incongruent psychotic features showed evidence of a more severe course, familial aggregation, and suggestive linkage to two chromosomal regions previously implicated in major mental illness susceptibility.

AGE AT ONSET OF PSYCHOSIS

- Schizophrenic (SCH) (n=148) Age: 27.7 years
- Bipolar SAF (n=56) Age: 29.0 years
- Bipolar AFF (n=30) Age: 31.1 years
- Unipolar SAF (n=45) Age: 32.2 years
- Unipolar AFF (n=76) Age: 38.1 years

Marneros et al, 1995
Common morphological findings in SCZ and BD

- Decreased prefrontal cortex (PFC) neuronal size
- Reduced ACC neuronal density
- Reduced PFC and hippocampal synaptic and dendrite markers
- Glial cell reduction
- The limited studies in SAD show a similar pattern

Kempf et al, 2005
fMRI in SAD: Reversible frontal hypoactivation during schizomaniac episode

N-back working memory test. Hypo-activations observed during the schizomaniac episode as compared with clinical remission (whole-brain paired t-test). Graph shows mean blood oxygenation level-dependent (BOLD) response in the ROIs during the acute phase and clinical remission in schizomaniac patients ($n = 12$).

Madre et al, 2014
Failure of de-activation observed in patients with schizoaffective disorder during clinical remission as compared to matched healthy controls during session B. Chart shows mean blood oxygenation level-dependent (BOLD) response in the ROIs during clinical remission in patients ($n = 22$) and in healthy controls ($n = 22$).

Madre et al, 2014
Failure of de-activation in the medial frontal cortex in SAD, more pronounced in the schizodepressed than in the schizomanic patients group.

Similar failure of de-activation during cognitive task performance has been found in SCZ and BD.

Evidence of dysfunction in the default mode network, a series of interconnected brain regions which are metabolically active at rest but whose activity diminishes while the brain performs a wide range of cognitive tasks.

May relate to attention and memory deficits as well as executive dysfunction in SAD.

Madre et al, 2014
SYNDROMAL DIMENSIONS OF SAD
“Schizoaffective disorder is a prototypic boundary condition that epitomizes the pitfalls of the current categorical classification system.”

Malhi et al, Bipolar Disorders 2008
The categorial approach

HEALTHY

Schizophrenia

BIPOLAR
The categorial approach
Addition of severity dimension

PSYCHOSIS

HEALTHY

MOOD
DYSREGULATION

Schizophrenia

BIPOLAR I

BIPOLAR II

Cyclothymia

Schizoaffective

Schizotypal Dis.

Addition of severity dimension
A dimensional approach

PSYCHOSIS

HEALTHY

MOOD DYSREGULATION

Schizotypal Dis.

BIPOLAR II

Cyclothymia

BIPOLAR I

Schizophrenia

A dimensional approach
Continuous distribution of the frequency of psychotic symptoms in a representative population samples

Distribution of the frequency of psychotic symptoms in the EDSP Study sample (cumulated incidence at t3: n = 451 from a total of 2,547 probands), Number of “psychotic” symptoms from CIDI

Prevalence of psychotic symptoms in Bipolar I disorder (n = 352)

Keck et al, Comprehensive Psychiatry 2003; 44: 263-269
During the turn of the last century it was well accepted that all psychotic symptoms arise from mood dysregulation (Specht 1905).

Kraepelin defined instability (and unpredictability) of symptomatology as a common unifying principle of severe mental illness, with (more or less) steady intellectual decline being the only difference between MD illness and Dementia praecox.

Emil Kraepelin (1856-1927)

Paranoide Psychosis
Psychotic mood disorders causing paranoid delusions

PSYCHOTIC DEPRESSION
Paranoid self-blaming about previous “sins”
Deserve punishment

PSYCHOTIC MANIA
Paranoid delusions of grandiosity, wealth, being special etc.
Willing to defend grandiosity no matter what the cost

PARANOID PSYCHOSIS
Arising from psychotic mood disorder

Lake, CR: Hypothesis: grandiosity and guilt cause paranoia; paranoid schizophrenia is a psychotic mood disorder; a review. Schizophr Bulletin 2008, 34, 1151-1162
Combining dimensional and categorial representations of psychopathology

OUTCOME IN PATIENTS WITH SAD
Potential targets in a recovery approach

- Persistent negative symptoms
- Persistent positive symptoms
- Persistent affective symptoms
- Persistent affective symptoms
- Persistent Cognitive dysfunction
- Persistent side effects
DISABILITY ASSESSMENT SCHEDULE: DISABILITY PROFILE (WHO/DAS)

Score-mean value

1 2 3 4 5 6

Item No. (Section 1, Communicating and understanding)

Schizophrenic Disorders

Schizoaffective Disorders

Affective Disorders

Marneros et al, 1995
Poor functional recovery associated with psychosis

Percentage of Patients With First-Episode Psychotic Affective Disorders Who Reached Syndromal (N=199) and Functional (N=181) Recovery Within 6 and 24 Months After First Lifetime Hospitalization

Memory Impairment in BD, SAD and SCZ

Differences in Wechsler Memory Scale (WMS) composite scores of patient groups and healthy controls (HC). BD, Bipolar disorder; SADM, schizoaffective disorder, mania; SZ, schizophrenia. •, Represents individual outliers.

Amann et al 2012
Impaired executive function in BD, SAD and SCZ

Differences in Behavioral Assessment of the Dysexecutive Syndrome (BADS) standardized profile scores of patient groups and healthy controls (HC). BD, Bipolar disorder; SADM, schizoaffective disorder, mania; SZ, schizophrenia. •, Represents individual outliers.

Amann et al 2012
Summary

- SAD have a polymorphic course, and depending on its characteristics they may be closer to BD or SCZ within an affective psychotic spectrum.
- SAD with a bipolar, mostly schizomanic course exhibit fMRI and cognitive features which resemble more those of BD than SCZ.