NEW METHODS OF CLASSIFICATION IN PSYCHOSIS: APPLYING A PRECISION MEDICINE MODEL

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Current Diagnostic Classifications

[Image: DSM-5 book cover with a diagram showing a spectrum from severe depression to severe mania.]
Categorical Diagnostic Overlap and within Disorder Heterogeneity
The intent is to generate classifications stemming from behavioral neuroscience.

“Probably the most accurate description of RDoC is *convergent science*—bringing together many levels of analysis to ensure the right person gets the right treatment at the right time.”
EMPIRICAL CLASSIFICATION OF PSYCHOTIC PATIENTS USING NEUROCOGNITIVE PROFILES

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Cognition in BD and SZ

Burdick et al. 2011

^p<0.05; *p<0.01; **p<0.001
Functional Heterogeneity in BD
Cognitive Heterogeneity in BD

Reichenberg et al. 2009; Bora et al. 2010
Classifying Subjects Based upon Neurocognitive Profiles?

- Hierarchical cluster analyses to test for the presence of discrete cognitive subgroups
  - Optimal number of clusters is relatively objective
  - Provides an empirical test of heterogeneity

- Euthymic BD subjects completed a comprehensive battery of clinical, dx, and cognitive tasks
Empirical evidence for discrete neurocognitive subgroups in bipolar disorder: clinical implications

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---Healthy Controls---

**All p-values < 0.01**
3 Cognitive Subgroups Exist

![Graph showing 3 cognitive subgroups exist.](image-url)
Cognitively Intact Subgroup

- 32% of total sample
- No impairments
- Superior social cognition
- No pressing need for intervention

![Graph showing T-scores for various cognitive domains with a line labeled BPD Intact (n=43).]
Selectively Impaired Subgroup

- 28% of total sample
- Moderate impairments
- Intact visual learning and reasoning
- Treatment potentially warranted - domain specific
Globally Impaired Subgroup

- 40% of total sample
- Significant impairments on all domains
- Severe/Profound deficits in 4/7 domains
Globally Impaired Subgroup

- 40% of total sample
- Significant impairments on all domains
- Severe/Profound deficits in 4/7 domains
- Comparable to matched SZ sample
- Treatment most obviously warranted
Functional Implications

![Bar chart showing mean scores for BPD Global, BPD Selective, and BPD Intact. The chart indicates a significant difference (*) between BPD Global and BPD Selective.]
Are There Predictors of Subgroup?

**NO:** Age; sex; race; current mood sx; Psychosis hx; BD subtype; AAO; Illness duration; Medication class

**YES:** Premorbid IQ; Total medication load; #episodes
Episode Effects

- # Manias
- # Depressions
- Total # Episodes

BPD Global
BPD Selective
BPD Intact

* indicates statistical significance.
Cognitive Effects of Repeated Episodes

Hellvin et al. 2012
## Staging Models/Neuroprogression

<table>
<thead>
<tr>
<th>Stage</th>
<th>Berk et al. (14, 15)</th>
<th>Kapczinski et al. (16)</th>
<th>Post (19)</th>
<th>Cosci and Fava (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Increased risk of mood disorder</td>
<td>At risk, positive family history, mood or anxiety symptoms</td>
<td>Vulnerability</td>
<td>Mild or non-specific symptoms/prodromal phase</td>
</tr>
<tr>
<td>1a</td>
<td>Mild or non-specific symptom</td>
<td>Well-defined periods of euthymia without symptoms</td>
<td></td>
<td>Cyclothymia</td>
</tr>
<tr>
<td>1b</td>
<td>Prodromal features (ultra-high risk)</td>
<td>Inter episodic symptoms related to comorbidities</td>
<td>Well-interval</td>
<td>Acute manifestations of major depression or mania/hypomania</td>
</tr>
<tr>
<td>2</td>
<td>First threshold episode</td>
<td>Marked impairment in cognition or functioning</td>
<td>Prodrome</td>
<td>Residual symptoms with cognitive and functional impairment despite treatment</td>
</tr>
<tr>
<td>3a</td>
<td>Recurrence of subthreshold mood symptoms</td>
<td>Unable to live autonomously due to impairment</td>
<td>Illness onset</td>
<td>Acute episodes despite treatment</td>
</tr>
<tr>
<td>3b</td>
<td>First threshold relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>Multiple relapses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Persistent unremitting illness</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Figure 1. Mean Total Functioning Assessment Short Test (FAST) Scores in Patients in Distinct Stages and Healthy Controls*

<table>
<thead>
<tr>
<th>Marker</th>
<th>Early stage</th>
<th>Late stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDNF (76, 82)</td>
<td>≈</td>
<td>↓↓</td>
</tr>
<tr>
<td>TNF α (76)</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>IL-6 (76)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>IL-10 (76)</td>
<td>↑</td>
<td>≈</td>
</tr>
</tbody>
</table>

*Kapczinski et al. ISBD Staging Task Force 2014*
- Cytokines are a group of small, short-lived proteins released by one cell to regulate the function of another cell.

- Best known for roles in immune system’s defense against disease but more recent focus on their role in neurodevelopment/neurogenesis.
Inflammation/Immune Hypothesis

Maternal immune activation secondary to:
- Infection: influenza, T. gondii, genital/reproductive
- Autoimmune disorders

Symptomatic exacerbations

Abnormalities of:
- Behavior (e.g., hyperlocomotion)
- Psychophysiology (e.g., ↓long term potentiation, ↓pre-pulse inhibition)
- Neurochemistry
  - ↑Dopamine
  - ↓Parvalbumin+ interneurons
- Cognition (e.g., spatial memory, avoidance learning)

Increased brain & peripheral cytokines (Interleukin-6; tumor necrosis factor-α)

Cytokine release
- Interleukin-6
- Interleukin-8
- Tumor necrosis factor-α
- Other cytokines

Aberrant fetal programming?

Humans
- Neuroinflammation
- ↓Hippocampal volume
- Cognitive symptoms (e.g., ↓executive function) of schizophrenia
- Positive symptoms
- Negative symptoms

Girgis et al. 2014
# Biomarkers of Cognition in BD

<table>
<thead>
<tr>
<th>Feature</th>
<th>Impaired (n=26)</th>
<th>Intact (n=14)</th>
<th>Stat/p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49</td>
<td>42</td>
<td>t=.8; p=.43</td>
</tr>
<tr>
<td>%Female</td>
<td>39%</td>
<td>50%</td>
<td>Chi²=.5; p=.48</td>
</tr>
<tr>
<td>Age at Onset</td>
<td>23</td>
<td>20</td>
<td>t=1.0; p=.34</td>
</tr>
<tr>
<td>#Mania</td>
<td>13</td>
<td>8</td>
<td>t=1.1; p=.28</td>
</tr>
<tr>
<td>#Depression</td>
<td>12</td>
<td>13</td>
<td>t=.2; p=.88</td>
</tr>
<tr>
<td>HAMD</td>
<td>8</td>
<td>6</td>
<td>t=.3; p=.80</td>
</tr>
<tr>
<td>YMRS</td>
<td>3</td>
<td>2</td>
<td>t=1.1; p=.26</td>
</tr>
<tr>
<td>Medication #</td>
<td>1.4</td>
<td>1.6</td>
<td>t=.6; p=.56</td>
</tr>
<tr>
<td>%Psychotic</td>
<td>50%</td>
<td>50%</td>
<td>Chi²=0.0; p=1.0</td>
</tr>
</tbody>
</table>

Multiplex assay – plasma = *peripheral*
41 targets; pro-inflammatory; growth factors; chemokines
HIMC Human 41-Plex Luminex Plate

sCD40L, VEGF, TNF-β, TNF-α, TGF-α, RANTES, PDGF-AB/BB, PDGF-AA, MIP-1β, MIP-1α, MDC (CCL22), MCP-3, MCP-1, IP-10, IL-17, IL-15, IL-13, IL-12 (p70), IL-12 (p40), IL-10, IL-9, IL-8, IL-7, IL-6, IL-5, IL-4, IL-3, IL-2, IL-1ra, IL-1β, IL-1α, IFN-γ, IFN-α2, GRO, GM-CSF, G-CSF, Fractalkine, Flt-3 ligand, FGF-2, Eotaxin, EGF…and BDNF
Cognitive Grouping

all p-values < 0.01 except verbal memory (n.s.)
Cognitive Group: *Pro*-Inflammatory Markers

- Log transformed values; all p-values < 0.05
- None correlated with medication
Counterintuitive or Oversimplified?

- Collective findings indicate that the net effect of the inflammatory response is determined by a delicate balance between pro- and anti-inflammatory cytokines.

- Perturbations in this equilibrium can drive the host defense immune response either towards healing or towards chronic inflammation.

- A number of anti-inflammatory cytokines have been acknowledged in literature and these include IL-1ra, IL-4, **IL-6**, IL-10, IL-11, IL-13, TGF-β
Biological Interactions and Ratios

Cognitively impaired subgroup has a much lower ratio than Intact group
Cognitive Group: *Anti*-Inflammatory Markers

- Log transformed values
- Directionally consistent
- Trend-level
- None correlated with medication
Cognitive Group: Growth Factors

Log transformed values; p-values < 0.01
None correlated with medication
Vascular Endothelial Growth Factor

- VEGF Inhibitors used for cancer tx cause cognitive impairment
- VEGF ligands might improve cognition
  - Animal models of stroke/TBI
    - Improves cognition
    - Enhances neurogenesis in hippocampus
Conclusions

- Cognitive dysfunction is a dimensional trait that crosses dx boundaries and can be used to classify subjects based upon brain function.

- Clinical correlates and potential biomarkers of impairment are largely unknown.
  - Need to identify inflammatory profiles – empirically derived subtypes or ‘biotypes’ – can be statistically derived but biological information is critical.

- Classification approaches based upon empirically derived, neurobiologically-relevant traits may allow for the identification of novel targets, moving us closer to the goal of personalized treatment.
Acknowledgements
Cognitive Clusters Across Psychoses

---Healthy Controls---

All p-values < 0.01

SZ/SZAff/BD (n=382)
Cognitive Clusters Across Psychoses

The chart illustrates the T-score distribution across different cognitive domains (ProcSpeed, Attention, WorkMem, VerbLearn, VisLearn, Reasoning, SocialCog) for three groups: Global Severe (n=109), Global Moderate (n=212), and Intact Mild (n=61). The line graphs show the trend for each group across these domains. The X-axis represents the cognitive domains, and the Y-axis represents the T-scores.
DSM-IV Diagnosis by Cluster

- Non-Affective
- Affective

Percent

Global Severe
Global Moderate
Intact Mild