Predicting Psychosis with an Aim Toward Prevention

December 14, 2017

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Professor of Psychiatry, Neuroscience and Psychology
Duke University Medical Center
Financial Disclosures

Past 3 Years

Consultant/Ad Board/Service Provider:
Abbvie, Acadia, Akebia, Akili, Alkermes, Astellas, Asubio, Avanir, AviNeuro/ChemRar, Axovant, Biogen, BiolineRx, Biomarin, **Boehringer-Ingelheim**, Cerecor, CoMentis, FORUM, Global Medical Education (GME), GW Pharmaceuticals, Intracellular Therapeutics, Janssen, Lundbeck, MedScape, Merck, Minerva Neurosciences Inc., Mitsubishi, Moscow Research Institute of Psychiatry, Neuralstem, Neuronix, Novartis, NY State Office of Mental Health, Otsuka, Pfizer, Reviva, Roche, Sanofi, Shire, Sunovion, Takeda, Targacept, University of Moscow, University of Texas Southwest Medical Center, and WebMD

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Royalties:
Brief Assessment of Cognition in Schizophrenia (BACS), Virtual Reality Functional Capacity Assessment Tool (VRFCAT)
People with Schizophrenia in the United States rarely marry or find jobs and may end up homeless at some point

- Schizophrenia affects about 1% of the general population\(^1\)
- There are 23 medications approved to treat Schizophrenia\(^2\) (*primarily targeting positive symptoms*)
- And yet, functional outcomes remain exceedingly poor in this population

In a 2012 study of milestone achievements, only 19% had ever achieved all 3 milestones (marriage, employment and financial responsibility)\(^6\)

\(^{1}\)http://www.nimh.nih.gov/health/topics/schizophrenia/index.shtml
\(^{2}\)http://www.nami.org
\(^{4}\)http://www.nami.org
Severity and Profile of Cognitive Impairment in Schizophrenia at Baseline of Clinical Trial

Keefe et al, Schiz Res, 2011
Relationship Between Cognitive Deficits and Functional Outcome

Penn Emotion Recognition Test 40 (ER40)

Happy
Sad
Anger
Fear
No Emotion
Auditory emotion recognition is impaired in Schizophrenia

**FIG. 1.** Between-Groups Analysis of Emotion Identification

*P < .05, between-group t test. Dotted line represents chance performance level (16.6%). Error bars reflect standard error of the mean.

Tonal Discrimination Correlates with Auditory Emotion Recognition

Leitman et al. Getting the Cue: Sensory Contributions to Auditory Emotion Recognition Impairments in Schizophrenia
Emotion is Conveyed in the Acoustic Properties of Speech

- Level, range and contour of fundamental frequency
- Vocal amplitude
- Temporal phenomenon (tempo and pausing)
- Formant locations

Speech Formants

• Speech formants are peaks in the sound spectrum caused by the morphology of the oral tract.

• Vowel formant frequencies, particularly the first and second formants, change systematically with emotion\(^1\) and healthy individuals are capable of identifying emotional valence after very little exposure to a vowel sound segment (150 ms)\(^2\).

An extensive study of basic auditory deficits in Schizophrenia and their relationship to emotion identification deficits has not yet been performed. We hypothesize that:

- Vowel formant frequency discrimination is impaired in individuals with Schizophrenia.
- Impairment in basic auditory perception is strongly correlated with emotion processing. Chief among these impairments is vowel formant discrimination.
Test Battery:
Test of Basic Auditory Capabilities (TBAC)

- Pitch Discrimination
- Intensity Discrimination
- Duration Discrimination
- Pulse Train
- Embedded Tone
- Temporal Order
- Syllable Sequence
- Non-word Recognition

**FIG. 2.** Factor loadings for each of the 19 TBAC-E subtests

Subtests are grouped according to the factor on which they have the highest loading and ordered within each factor according to the magnitude of the primary loading on that factor.
Test Battery: Additional basic auditory processing tests

- Formant Discrimination
- Sinusoidal Amplitude Modulation Detection (SAM 60 HZ)
- Pitch Discrimination 6000 HZ
Test Battery: Outcome Measures

Emotion Recognition
- Comprehensive Affective Testing System (CATS)
- Montreal Affective Voices (MAV)

Cognition and Functional Capacity
- Brief Assessment of Cognition in Schizophrenia (BACS)
- UCSD Performance-based Skills Assessment (UPSA)

Symptoms
- Positive and Negative Syndrome Scale (PANSS)
- Psychotic Symptom Rating Scales (PSYRATS)
Current State of the Science in Auditory Perception

Fear | Happiness | Disgust | Sadness | Surprised
--- | --- | --- | --- | ---
Anger | CATS Anger | CATS Fear | CATS Happy | CATS Sad
## Demographics of Study Sample

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia</th>
<th>Controls</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>S.D.</td>
<td>N</td>
</tr>
<tr>
<td>Age</td>
<td>87</td>
<td>41.83</td>
<td>9.60</td>
<td>71</td>
</tr>
<tr>
<td>Education (years)</td>
<td>81</td>
<td>12.81</td>
<td>2.46</td>
<td>71</td>
</tr>
<tr>
<td>Maternal Education</td>
<td>69</td>
<td>13.13</td>
<td>2.89</td>
<td>69</td>
</tr>
<tr>
<td>Paternal Education</td>
<td>64</td>
<td>12.73</td>
<td>4.16</td>
<td>65</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>55</td>
<td>63.22%</td>
<td></td>
<td>44</td>
</tr>
<tr>
<td>Female</td>
<td>32</td>
<td>36.78%</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>35</td>
<td>40.23%</td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>African-American</td>
<td>51</td>
<td>58.62%</td>
<td></td>
<td>40</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1.15%</td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>
Schizophrenia Patients are Impaired on Several Basic Auditory Skills

<table>
<thead>
<tr>
<th>Measure</th>
<th>Schizophrenia</th>
<th>Controls</th>
<th>Cohen's d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Frequency Disc.</td>
<td>29.45**</td>
<td>30.33</td>
<td>45.37</td>
</tr>
<tr>
<td>Intensity Disc.</td>
<td>25.17**</td>
<td>29.70</td>
<td>45.04</td>
</tr>
<tr>
<td>Duration Disc.</td>
<td>24.93**</td>
<td>29.92</td>
<td>39.94</td>
</tr>
<tr>
<td>Pulse-Train</td>
<td>25.25**</td>
<td>30.17</td>
<td>40.90</td>
</tr>
<tr>
<td>Embedded Tone</td>
<td>20.06**</td>
<td>28.16</td>
<td>35.76</td>
</tr>
<tr>
<td>Temporal Order</td>
<td>22.25</td>
<td>28.19</td>
<td>28.07</td>
</tr>
<tr>
<td>Syllable Order</td>
<td>12.19**</td>
<td>16.67</td>
<td>24.23</td>
</tr>
<tr>
<td>Syllable Recognition</td>
<td>31.96*</td>
<td>27.82</td>
<td>42.34</td>
</tr>
<tr>
<td>Formant Disc.</td>
<td>48.02**</td>
<td>9.59</td>
<td>52.73</td>
</tr>
<tr>
<td>SAM60</td>
<td>2.99**</td>
<td>0.86</td>
<td>2.58</td>
</tr>
<tr>
<td>Pitch Disc. (6000 HZ)</td>
<td>5.52</td>
<td>1.88</td>
<td>5.00</td>
</tr>
</tbody>
</table>

*p < .05, **p < .01
## Group Means on Emotion Recognition and Cognition Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Schizophrenia</th>
<th>Controls</th>
<th>Cohen's d</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATS</td>
<td>78.09**</td>
<td>83.59</td>
<td>.49</td>
</tr>
<tr>
<td>MAV</td>
<td>41.25**</td>
<td>44.57</td>
<td>.58</td>
</tr>
<tr>
<td>Emotion Comp.</td>
<td>47.46**</td>
<td>53.10</td>
<td>.59</td>
</tr>
<tr>
<td>BACS Comp.</td>
<td>33.73**</td>
<td>43.77</td>
<td>.65</td>
</tr>
</tbody>
</table>

CATS = Comprehensive Affect Testing System, MAV = Montreal Affective Voices. BACS, Brief Assessment of Cognition in Schizophrenia
Correlations between basic auditory processing and emotion recognition in patients with schizophrenia

<table>
<thead>
<tr>
<th></th>
<th>CATS</th>
<th>MAV</th>
<th>BACS SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency Disc.</td>
<td>.47**</td>
<td>.37**</td>
<td>.45**</td>
</tr>
<tr>
<td>Intensity Disc.</td>
<td>.46**</td>
<td>.34**</td>
<td>.49**</td>
</tr>
<tr>
<td>Duration Disc.</td>
<td>.44**</td>
<td>.38**</td>
<td>.29*</td>
</tr>
<tr>
<td>Pulse-Train Disc.</td>
<td>.38**</td>
<td>.28*</td>
<td>.27*</td>
</tr>
<tr>
<td>Embedded Tone</td>
<td>.42**</td>
<td>.40**</td>
<td>.37**</td>
</tr>
<tr>
<td>Temporal Order</td>
<td>.42**</td>
<td>.33**</td>
<td>.32**</td>
</tr>
<tr>
<td>Syllable Order</td>
<td>.33**</td>
<td>.28*</td>
<td>.31**</td>
</tr>
<tr>
<td>Syllable Recognition</td>
<td>.49**</td>
<td>.46**</td>
<td>.45**</td>
</tr>
<tr>
<td>Formant Disc.</td>
<td>.47**</td>
<td>.44**</td>
<td>.33**</td>
</tr>
<tr>
<td>SAM60</td>
<td>-.52**</td>
<td>-.45**</td>
<td>-.31**</td>
</tr>
<tr>
<td>Pitch Discrim 6000 HZ</td>
<td>-.38**</td>
<td>-.28*</td>
<td>-.31*</td>
</tr>
</tbody>
</table>

CATS = Comprehensive Affect Testing System, MAV = Montreal Affective Voices. BACS, Brief Assessment of Cognition in Schizophrenia
Basic Auditory Perception Impairment Explains Significant Variance in Emotion Recognition Deficits in Patients with Schizophrenia

- All correlations are controlled for general cognitive impairment
- The highlighted measures were significantly different between controls and patients
- The pattern of results suggests that the inability of patients with schizophrenia to understand how others feel is driven by an impairment of the frequency following response (FFR), otherwise known as phase-locking, the way that the human brain efficiently processes key auditory information
- These relationships are currently being studied in individuals at high risk for psychosis at Duke clinics
- R01 funding is being pursued to identify the circuitry abnormalities that drive these FFR impairments

<table>
<thead>
<tr>
<th>Measure</th>
<th>CATS</th>
<th>MAV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency Disc.</td>
<td>.33**</td>
<td>.26*</td>
</tr>
<tr>
<td>Intensity Disc.</td>
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<td>.21</td>
</tr>
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<td>Duration Disc.</td>
<td>.36**</td>
<td>.31**</td>
</tr>
<tr>
<td>Pulse-Train Disc.</td>
<td>.30**</td>
<td>.21</td>
</tr>
<tr>
<td>Embedded Tone</td>
<td>.30**</td>
<td>.31**</td>
</tr>
<tr>
<td>Temporal Order</td>
<td>.32**</td>
<td>.25*</td>
</tr>
<tr>
<td>Syllable Order</td>
<td>.22</td>
<td>.19</td>
</tr>
<tr>
<td>Syllable Recognition</td>
<td>.36**</td>
<td>.37**</td>
</tr>
<tr>
<td>Formant Disc.</td>
<td>.39**</td>
<td>.36**</td>
</tr>
<tr>
<td>SAM60</td>
<td>-.44**</td>
<td>-.38**</td>
</tr>
<tr>
<td>Pitch Discrim 6000 HZ</td>
<td>-.29*</td>
<td>-.19</td>
</tr>
</tbody>
</table>

*p < .05; **p < .01; CATS, Comprehensive Affective Testing System; MAV, Montreal Affective Voices, SAM, Sinusoidal Amplitude Modulation
Formant discrimination accounts for additional variance in emotion discrimination beyond frequency discrimination

Variables Entered/Removed\textsuperscript{a}

<table>
<thead>
<tr>
<th>Model</th>
<th>Variables Entered</th>
<th>Variables Removed</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Frequency Disc. Rank\textsuperscript{b}</td>
<td></td>
<td>Enter</td>
</tr>
<tr>
<td>2</td>
<td>Total Formant Composite\textsuperscript{b}</td>
<td></td>
<td>Enter</td>
</tr>
</tbody>
</table>

a. Dependent Variable: MAV\textsubscript{b}.
b. All requested variables entered.

Model Summary

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>Std. Error of the Estimate</th>
<th>R Square Change</th>
<th>F Change</th>
<th>df1</th>
<th>df2</th>
<th>Sig. F Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>.267\textsuperscript{b}</td>
<td>.135</td>
<td>.124</td>
<td>5.5447</td>
<td>.135</td>
<td>12.004</td>
<td>1</td>
<td>77</td>
<td>.001</td>
</tr>
<tr>
<td>2</td>
<td>.454\textsuperscript{b}</td>
<td>.206</td>
<td>.185</td>
<td>5.3468</td>
<td>.071</td>
<td>6.806</td>
<td>1</td>
<td>76</td>
<td>.011</td>
</tr>
</tbody>
</table>

a. Predictors: (Constant), Frequency Disc. Rank
b. Predictors: (Constant), Frequency Disc. Rank, Total Formant Composite
Auditory Emotion Perception as measured by the INTONATION Test

INTONATION = IdeNTification Of autheNtic AudiTory emotION
## Emotion Recognition Batteries

<table>
<thead>
<tr>
<th>Battery</th>
<th>Schizophrenia (N=25)</th>
<th>Control (N=16)</th>
<th>p</th>
<th>Cohen's d</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATS</td>
<td>79.42 (12.38)</td>
<td>85.12 (7.42)</td>
<td>0.073</td>
<td>0.56</td>
</tr>
<tr>
<td>MAV</td>
<td>42.32 (4.78)</td>
<td>45 (3.76)</td>
<td>0.065</td>
<td>0.62</td>
</tr>
<tr>
<td>INTONATION Pilot</td>
<td>72.6 (9.71)</td>
<td>81.5 (8.86)</td>
<td>0.005</td>
<td>0.96</td>
</tr>
<tr>
<td>INTONATION Pruned</td>
<td>65.24 (9.38)</td>
<td>75.06 (7.36)</td>
<td>0.001</td>
<td>1.16</td>
</tr>
</tbody>
</table>

CATS = Comprehensive Affect Testing System  
MAV = Montreal Affective Voices  
INTONATION =IdeNTification Of authenTic AudiTory emotION
Frequency Following Response (FFR) Deficits in Schizophrenia and those at Risk?

Courtesy Nina Kraus Lab:  http://www.brainvolts.northwestern.edu/demonstration.php
Key Questions

• **How do we predict who will develop psychosis?**

• Can auditory emotion perception contribute to prediction of psychosis? New Duke study of those at risk for psychosis is underway with the outcome measures described.

• Are auditory emotion perception deficits and FFR deficits a manifestation of the underlying neural circuitry changes that lead to psychosis?

• Can we develop treatments that target auditory emotion perception as a preventative measure?

• Are there currently approved treatments to prevent psychosis? No. New Phase 2 clinical trial at Duke tests the efficacy and safety for a phosphodiesterase 9 inhibitor as prevention.
Diagnosis of Attenuated Psychotic Syndrome (APS)

Defined by the presence of recent attenuated positive symptoms of sufficient severity and frequency.

To meet criteria for an attenuated symptom, a patient must at some point have rated level “3”, “4”, or “5” on at least one of the P1-P5 Positive Symptom items of the SOPS (“severity criterion”):

- P1. Unusual Thought Content/Delusional Ideas
- P2. Suspiciousness/Persecutory Ideas
- P3. Grandiosity
- P4. Perceptual Abnormalities/Hallucinations
- P5. Disorganized Communication

The symptom(s) must have occurred at the then-current intensity level at an average frequency of at least once per week in the past month (“frequency criterion”), and must not have been likely due to another disorder (“attribution criterion”).
Meta-analysis of Cognitive Impairment in High-risk

Neurocognitive profiles of individual tasks in high-risk individuals (n = 1188) compared with controls (n = 1029). Error bars represent 95% CI. C indicates number of controls; CPT, Continuous Performance Test (d prime); CVLT, California Verbal Learning Test; HR, number of high-risk individuals; LNS, Letter Number Sequencing; RAVLT, Rey Auditory Verbal Learning Test; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; VF, Verbal Fluency; VRI, Visual Reproduction Index (WMS visual reproduction and Rey complex figures); WCST, Wisconsin Card Sorting Test (perseverative errors); and WMS, Wechsler Memory Scale (verbal recall). Working memory is shown in green, verbal memory in blue, visual memory in violet, attention in orange, processing speed in yellow, verbal fluency in gray, and executive functions in red.

### TABLE 2. Statistics for Individual Predictor Variables in the Multivariate Cox Proportional Hazards Regression Analysis of Conversion to Psychosis*

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Multivariate Model</th>
<th>C-Index^b</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95% CI</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>Modified SIPS items P1 + P2</td>
<td>2.1</td>
<td>1.6–2.7</td>
<td>&lt;0.001</td>
<td>0.092</td>
</tr>
<tr>
<td>Decline in social functioning (Global Functioning: Social scale)</td>
<td>1.3</td>
<td>1.1–1.5</td>
<td>0.01</td>
<td>0.014</td>
</tr>
<tr>
<td>Hopkins Verbal Learning Test–Revised, trials 1–3 summed</td>
<td>0.8</td>
<td>0.6–0.9</td>
<td>0.05</td>
<td>0.007</td>
</tr>
<tr>
<td>BACS symbol coding, raw score (number completed)</td>
<td>0.8</td>
<td>0.5–1.1</td>
<td>0.10</td>
<td>0.006</td>
</tr>
<tr>
<td>Age</td>
<td>0.7</td>
<td>0.5–1.1</td>
<td>0.09</td>
<td>0.004</td>
</tr>
<tr>
<td>Stressful life events</td>
<td>1.2</td>
<td>0.9–1.6</td>
<td>0.21</td>
<td>0.001</td>
</tr>
<tr>
<td>Family history of psychosis</td>
<td>1.2</td>
<td>0.7–2.1</td>
<td>0.55</td>
<td>0.000</td>
</tr>
<tr>
<td>Traumas</td>
<td>1.0</td>
<td>0.8–1.3</td>
<td>0.99</td>
<td>−0.004</td>
</tr>
</tbody>
</table>

*a BACS=Brief Assessment of Cognition in Schizophrenia; SIPS=Structured Interview for Prodromal Syndromes.

^b Harrell’s C-index (equivalent to the area under the receiver operating characteristic curve) was used to quantify the discrimination ability for separating converters and nonconverters. The C-index for the overall model was 0.714.

^c The base model included only the modified SIPS P1 + P2 score; the C-index for the base model was 0.666.

Cannon et al, AJP, 2016
2-Year Probability of Conversion to Psychosis

Risk 12.4%

This calculator was based on a Cox proportional hazards regression model that was developed from a cohort consisting 596 clinical high risk participants from the second phase of the North American Prodrome Longitudinal Study (NAPLS)

http://riskcalc.org:3838/napls/
Predicted Linear Mixed Model Trajectories in Healthy Controls, Remitters, Non-Remitters and Converters in Singapore

Individual lines represent each cognitive test administered to participants in the overall cognitive battery

384 healthy controls
84 remitters
84 non-remitters
17 converters

Lam et al, submitted.
Cognitive Changes Over 2 Years Best Predict Diagnosis in APS Patients

Group*Time Interaction (F=14.301, p < 0.00001, df=2, eta²=.054)

Lam et al, submitted.
Key Questions

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• Are there currently approved treatments to prevent psychosis? No. New Phase 2 clinical trial at Duke tests the efficacy and safety for a phosphodiesterase 9 inhibitor as prevention.
Inclusion Criteria for Perception, Emotion and Neurocognition Study (PENS)

- Male or female between 15 and 30 years old.
- Understand and sign an informed consent (or assent for minors) document in English.
- Meet Attenuated Psychosis Syndrome (APS) diagnostic criteria
- Rate 3 or higher on either P1 (unusual thoughts) or P2 (suspiciousness)
Addressing Clinical Needs of Patients in PENS

Patients who are sent to us by a clinician and who meet criteria for Attenuated Psychosis Syndrome (APS) will be referred back to the clinician with a set of recommendations. Those recommendations will include:

A brief report for the clinician, including a description of the specific symptoms observed or reported by the patient, their relevance for long term prognosis and psychosis risk, recommendations for treating APS symptoms, and how the symptoms were discussed with the patient;

Participation in a cost-free 3-session psychoeducational program specified for those diagnosed with Attenuated Psychosis Syndrome; and Options for additional clinical services, such as the OASIS Clinic at UNC.
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<thead>
<tr>
<th>Source</th>
<th>HR Inclusion Criteria</th>
<th>Focused Treatment</th>
<th>Contrast Group</th>
<th>DI, mo</th>
<th>NNT at 1 y (Mean (95% CI))</th>
<th>Transition at 1 y (Focused vs Contrast)</th>
<th>Meta-analysis</th>
<th>RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGorry et al., 2002a</td>
<td>CAARMS</td>
<td>Risperidone, 1-2 mg + CBT + NBI (n=31)</td>
<td>NBI (n=28)</td>
<td>6</td>
<td>4 (2.1-18.3)</td>
<td>19.3 vs 35.7, NS</td>
<td>0.541 (0.225-1.297)</td>
<td>.17</td>
<td></td>
</tr>
<tr>
<td>Morrison et al., 2004b</td>
<td>CAARMS based</td>
<td>CT (n=37)</td>
<td>Monitoring (n=23)</td>
<td>6</td>
<td>5 (2.3-63.8)</td>
<td>5.7 vs 21.7, NS</td>
<td>0.263 (0.057-1.205)</td>
<td>.09</td>
<td></td>
</tr>
<tr>
<td>McGlashan et al., 2006</td>
<td>SIPS</td>
<td>Olanzapine, 5-15 mg (n=31)</td>
<td>Placebo (n=29)</td>
<td>12</td>
<td>5 (2.3-inf)</td>
<td>16.1 vs 37.9, NS</td>
<td>0.425 (0.169-1.075)</td>
<td>.07</td>
<td></td>
</tr>
<tr>
<td>Amminger et al., 2010</td>
<td>CAARMS</td>
<td>ω-3 PUFA, 1.2 g (n=41)</td>
<td>Placebo (n=40)</td>
<td>3</td>
<td>5 (2.6-13.7)</td>
<td>4.8 vs 27.5, Sig</td>
<td>0.175 (0.041-0.746)</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Yung et al., 2011</td>
<td>CAARMS</td>
<td>Risperidone, 0.5-2 mg + CT (n=43)</td>
<td>CT + placebo (n=44)</td>
<td>6</td>
<td>NA</td>
<td>4.7 vs 9.1 vs 7.1, NS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.516 (0.100-2.659)</td>
<td>.43</td>
<td></td>
</tr>
<tr>
<td>Addington et al., 2011</td>
<td>SIPS</td>
<td>CBT (n=27)</td>
<td>ST (n=24)</td>
<td>6</td>
<td>8 (3.7-inf)</td>
<td>0 vs 12.5, NS</td>
<td>0.128 (0.007-2.350)</td>
<td>.17</td>
<td></td>
</tr>
<tr>
<td>Barchdol et al., 2012</td>
<td>EIPS</td>
<td>IPI (n=63)</td>
<td>SC (n=65)</td>
<td>12</td>
<td>8 (4.2-27.3)</td>
<td>3 vs 16.9, Sig</td>
<td>0.178 (0.039-0.799)</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Overall&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.335 (0.219-0.575)</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CAARMS, Comprehensive Assessment of At-Risk Mental State; CBT, cognitive behavior therapy; CT, cognitive therapy; DI, duration of intervention; EIPS, early initial prodromal state (COPER or first-degree relatives with psychosis plus functional decline); HR, clinical high risk; inf, infinite; IPI, integrated psychological intervention (CT, social skills, psychoeducation for family, and cognitive remediation); NA, not assessed; NBI, needs-based intervention; NNT, number needed to treat; NS, nonsignificant differences between focused treatment and contrast group; PUFA, polyunsaturated fatty acid; RR, risk ratio; SC, supportive counseling; Sig, significant; SIPS, Structured Interview for Prodromal Symptoms; ST, supportive therapy.

<sup>a</sup>See also Phillips et al.<sup>14d</sup>

<sup>b</sup>See also Morrison et al.<sup>14d</sup> Additional evidence suggests that preventing the start of cannabis use or stopping already started use may diminish the risk of a psychotic disorder.<sup>14d</sup>

<sup>c</sup>Six-month results.

<sup>d</sup>Random effects models applied, Q=3.590, P=.732, I²=0.

Not replicated in larger clinical trial, where the conversion to psychosis rate was about 10% over one year.

Conclusion that ω-3 PUFAs are not effective under conditions where good quality, evidence-based psychosocial treatment is available.
Survival of ultra high risk patients receiving cognitive-behavioral therapy (dotted line; N=98; mean number of sessions=10) and treatment as usual (solid line; N=103) during 18-month follow-up. Log rank test, $X^2 (1) = 5.575$, $P = .03$.

Evidence of a Biological MOA: Link of the glutamatergic system and plasticity to schizophrenia and APS

Reorganization of synapses occurs extensively during postnatal brain development until young adulthood; one of the major changes is reorganization of glutamatergic synapses in which the NMDA receptor plays a key role.1

‘Synaptic pruning’, in which synapses are reorganized into more efficient configurations and weak connections are being eliminated, also involves glutamatergic synapses2 and might be associated with activated microglia and neuroinflammation.

One hypothesis of schizophrenia genesis includes ‘faulty’ over-pruning later during adolescence3,4 which is consistent with a decrease in NMDA receptor density reported in postmortem brain from patients with schizophrenia5

Link of the glutamatergic system and plasticity to schizophrenia and APS

Synaptic over-pruning (i.e. elimination of important as well as less-relevant synaptic connections related to NMDA receptor function) during synaptic reorganization of the brain in adolescence is a hypothesized candidate pathogenic mechanism underlying transition from clinical high-risk (CHR) states to frank psychosis.

Link of the glutamatergic system and plasticity to schizophrenia and its prodrome (CHR)

- Synapses are strengthened with experience via mechanisms of synaptic plasticity, including NMDA receptor–dependent signalling and long-term potentiation (LTP)
- Imaging (faster gray matter decline) and electrophysiological data (reduced mismatch negativity, an NMDA receptor–dependent paradigm of event-related potentials linked to neural plasticity) from the NAPLS cohort study seem to confirm the association of these findings with a higher risk of transition to psychosis, consistent with the over-pruning hypothesis
Biological insights from 108 schizophrenia-associated genetic loci.


Manhattan plot of the discovery genome-wide association meta-analysis of 49 case control samples (34,241 cases and 45,604 controls) and 3 family based association studies (1,235 parent affected-offspring trios). The x axis is chromosomal position and the y axis is the significance (−log_{10} P; 2-tailed) of association derived by logistic regression. The red line shows the genome-wide significance level (5 × 10^{-8}). SNPs in green are in linkage disequilibrium with the index SNPs (diamonds) which represent independent genome-wide significant associations.
MHC complex

• The MHC-schizophrenia association arises in part from many structurally diverse alleles of the complement component 4 (C4) genes.

• These alleles generated widely varying levels of C4A and C4B expression in the brain, with each common C4 allele associating with schizophrenia in proportion to its tendency to generate greater expression of C4A.

• Human C4 protein localized to neuronal synapses, dendrites, axons, and cell bodies.

• In mice, C4 mediated synapse elimination during postnatal development.

• These results implicate excessive complement activity in the development of schizophrenia and may help explain the reduced numbers of synapses in the brains of individuals with schizophrenia.

PDE9 inhibition increases neurite outgrowth and synapse formation in hippocampal neurons

Medical and pharmacological rationale: Conclusion

• CHR / APS subjects exhibit a deficit in glutamatergic/NMDA receptor function and synaptic plasticity, markers of which are associated with higher risk of transition to psychosis (e.g. NAPLS cohort study outcome)

• The glutamatergic/NMDA receptor dysfunctions and plasticity deficits are hypothesised to be caused by synaptic over-pruning during synaptic reorganisation of the brain in adolescence (schizophrenia as neurodevelopmental disorder)

• PDE9 inhibition enhances NMDA receptor signalling, leading to strengthening of synaptic plasticity and to synapse formation

PDE9 inhibitor BI 409306 may be a rational approach for improvement or even normalization of these dysfunctional processes in CHR subjects, which may ultimately lead to the delay or even prevention of first episode psychosis
## 1289.6 Signal Frequency of Serious AEs

<table>
<thead>
<tr>
<th>N (%)</th>
<th>BI 409306 10 mg (N=87)</th>
<th>BI 409306 25 mg (N=85)</th>
<th>BI 409306 50 mg (N=85)</th>
<th>BI 409306 100 mg (N=86)</th>
<th>Placebo (N=173)</th>
<th>Total (N=516)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any SAE</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>10 (5.8)</td>
<td>10 (1.9)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>8 (4.6)</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>5 (2.9)</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (1.7)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Empyema</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Ischaemic cardiomyopathy</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Hypertensive crisis</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

AE, adverse event; SAE, serious adverse event
A phase II randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of orally administered phosphodiesterase inhibitor (PDE9) during a 52-week treatment period as an early intervention in patients with attenuated psychosis syndrome.

• N=300
• Randomization 1:1
• Stratification is by NAPLS risk score and baseline use of antipsychotic medication
Inclusion Criteria

1. Meet diagnostic criteria for attenuated psychosis syndrome as defined in DSM-5 and determined by SIPS administered at screening after review of the videotaped SIPS interview.

2. NAPLS risk calculator score ≥ 0.20 at screening, indicative of a group aggregate risk of greater than 35% of conversion to psychosis.

3. Age ≥16 and ≤ 30 years at the time of consent/assent.

4. Male or female patients willing to use highly effective methods of contraception.

   Signed and dated written informed consent/assent.

5. Patients may be enrolled if they are currently taking antipsychotic medication. If a patient discontinues an antipsychotic medication, they can be randomized two weeks after discontinuation.
Other Treatments – Brief Supportive Psychoeducation

All patients will receive a Brief Supportive Psychoeducation session at Visits 2, 4, 6, and EOT

• Educate patients and family members
  o APS symptoms
  o Clinical trial program
  o Risk and protective factors for APS
  o Impact of stress on symptoms
  o Importance of medication adherence

• Will also evaluate the patient’s and family’s needs, develop a symptom reduction plan, and make referrals for community services as required
Acknowledgements

Duke
• Mike Kraus
• Trina Walker
• Ashwin Patkar
• Lin Sikich
• John Curry

UNC
• Fred Jarskog
• Kathy Jones
• John Gilmore
• Diana Perkins

Carolina Behavioral Care
• Rob Millet

Boehringer Ingelheim
• Michael Sand
• Kristen Daniels

NeuroCog Trials
• Caren Gadigian
• JJ Riley
If you have a patient who may meet Attenuated Psychosis Syndrome (APS) Criteria, and is interested in receiving specific treatment or participating in research or a clinical trial, Please contact us:

Richard.keefe@duke.edu

Michael.Kraus@duke.edu