Cognitive Impairment, Assessment and Treatment in Schizophrenia

Richard Keefe, PhD
Professor of Psychiatry, Neuroscience and Psychology
Duke University Medical Center

January 21, 2016
Financial Disclosures
Past 3 Years

CONSULTANT/AD BOARD/SERVICE PROVIDER
Abbvie, Akebia, Amgen, Astellas, Asubio, Avanir, AviNeuro/ChemRar, Biogen Idec, BiolineRx, Biomarin, Boehringer-Ingelheim, Eli Lilly, EnVivo/Forum, GW Pharmaceuticals, Helicon, Janssen, Lundbeck, Merck, Minerva, Mitsubishi, Neuronix, Novartis, Otsuka, Pfizer, Roche, Sanofi-Aventis, Shire, Sunovion, Takeda, Targacept

RESEARCH FUNDING
Department of Veteran’s Affairs, Feinstein Institute for Medical Research, GlaxoSmithKline, NIMH, Novartis, Psychogenics, Research Foundation for Mental Hygiene, Singapore Medical Research Council

FOUNDER OF NEUROCOG TRIALS
Providing rater training, data quality assurance and consultation to several pharmaceutical companies and other consortia

SHAREHOLDER
Sengenix

ROYALTIES
Brief Assessment of Cognition in Schizophrenia (BACS), MATRICS Consensus Cognitive Battery (MCCB), Virtual Reality Functional Capacity Assessment Tool (VRFCAT)
Diagnostic and Statistical Manual, 5th Edition (DSM-V), Description of Schizophrenia

- **A Criterion.** Characteristic symptoms: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these should include 1–3
  1. Delusions
  2. Hallucinations
  3. Disorganized speech
  4. Grossly disorganized or catatonic behavior
  5. Negative symptoms (i.e., diminished emotional expression or avolition)

- **B Criterion**
  - Social and Occupational Dysfunction

- **C Criterion**
  - Duration of 6 or more months

- **D Criterion**
  - Not due to mood d/o or schizoaffective

- **E Criterion**
  - Not due to a medical condition or substance abuse

- **F Criterion**
  - Not due autism or communication disorder

Worldwide, Schizophrenia is a leading cause of disability

Leading global causes of years of life lived with disability in 15- to 44-year-olds

1. Unipolar depressive disorders
2. Alcohol-use disorders
3. Schizophrenia
4. Iron-deficiency anemia
5. Bipolar disorder
6. Hearing loss, adult onset
7. HIV/AIDS
8. Chronic obstructive pulmonary disease
9. Osteoarthritis
10. Road traffic accidents

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 over a dozen 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
• Associated Featured Supporting Diagnosis: “Cognitive deficits in Schizophrenia are common and are strongly linked to vocational and functional impairments. These deficits can include decrements in declarative memory, working memory, language function, and other executive functions, as well as slower processing speed. Abnormalities in sensory processing and inhibitory capacity, as well as reductions in attention, are also found. Some individuals with Schizophrenia show social cognition deficits, including deficits in the ability to infer the intentions of other people (theory of mind), and may attend to and then interpret irrelevant events or stimuli as meaningful, perhaps leading to the generation of explanatory delusions. These impairments frequently persist during symptomatic remission.”
Clinician-Rated Dimensions of Psychosis
Symptom Severity: Impaired Cognition

- Not present
- Equivocal
  - Cognitive function not clearly outside the range expected for the age or SES; i.e., within 0.5 SD of mean
- Present, but mild
  - Some reduction in cognitive function; below expected for age or SES, 0.5 – 1.0 SD of mean
- Present and moderate
  - Clear reduction in cognitive function for age and SES, 1-2 SD from mean
- Present and severe
  - Severe reduction in cognitive function; below expected for age and SES, > 2 SD from mean

Severity and Profile of Cognitive Impairment in Schizophrenia at Baseline of Clinical Trial

Neurocognitive profile for drug-naive first-episode and previously treated patients

**Neuropsychological Profile (±SEM)**

ABS, abstraction-flexibility; ATT, attention-vigilance; MOT, fine manual motor functions; SEM, standard error of the mean; SPT, spatial organization; VBL, verbal intelligence and language function; VBM, verbal memory and learning; VIM, visual memory; VSM, speeded visual-motor processing and attention.

Cognitive Impairment & Positive symptoms in chronic Schizophrenia

CATIE Trial: Correlations Between Symptom Dimensions and Neurocognitive Domains

PANSS

Positive Symptoms

No relationship

Negative Symptoms

Small to medium correlations

CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; PANSS, Positive and Negative Syndrome Scale.

Figure based upon Keefe RS, et al. Neuropsychopharmacology. 2006;31(9):2033-2046.
Relationship between cognitive deficits and functional outcome

**Neurocognitive Deficits**

- Community Functioning
- Instrumental and Problem-Solving Skills
- Psychosocial Rehabilitation Programs

**Summary Scores**

- Large
- Medium
- Small

*Correlation With Outcome*

- **Verbal Memory**
- **Immediate Memory**
- **Executive Functions**
- **Attention/Vigilance**
- **Summary Scores**

**P < .0001**

Composite cognitive scores more strongly related than individual test scores

Normative Data Compared to a Schizophrenia Sample: RBANS Total Scale Score Distribution

Nearly all patients (98%) exhibit cognitive impairment relative to expected cognitive performance.
Nearly all patients (98%) exhibit cognitive impairment relative to expected cognitive performance.

98% of patients fail to reach expected levels of cognitive performance.

*Cognitive score predicted by maternal education.*

**Group**
- Patients (n = 150)
- Normal control regression line
- Controls (n = 50)

*Maternal education values jittered for clarity.*

Successful functioning relies on intact cognitive processing

<table>
<thead>
<tr>
<th>Some Representative Cognitive Domains</th>
<th>What Is It?</th>
<th>Real-World Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Attention/vigilance</strong></td>
<td>• Responding correctly to targets while not responding to distractors during a series of rapidly presented stimuli</td>
<td>• Being able to read a book or pay attention to a movie</td>
</tr>
<tr>
<td><strong>Working memory</strong></td>
<td>• Maintaining and manipulating information in mind for brief (approximately 5-20 seconds) periods of time</td>
<td>• Remembering a phone number just given to you</td>
</tr>
<tr>
<td><strong>Verbal learning and memory</strong></td>
<td>• Remembering verbal information over longer periods of time (minutes to years)</td>
<td>• Remembering the items someone told you to purchase at the supermarket</td>
</tr>
<tr>
<td><strong>Visual learning and memory</strong></td>
<td>• Remembering visual information over longer periods of time (minutes to years)</td>
<td>• Remembering where you put something in a closet</td>
</tr>
</tbody>
</table>

# Cognitive Processing

<table>
<thead>
<tr>
<th>Some Representative Cognitive Domains</th>
<th>What Is It?</th>
<th>Real-World Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reasoning and problem solving</td>
<td>• The ability to apply strategies effectively</td>
<td>• Arriving on time for work even though your bus schedule has changed</td>
</tr>
<tr>
<td>Speed of processing</td>
<td>• Responding quickly and accurately when executing relatively simple tasks</td>
<td>• Using a touch-screen computer to serve customers at a fast-food restaurant</td>
</tr>
<tr>
<td>Social cognition</td>
<td>• Effectively processing social information, such as facial expressions and emotions and the meaning of social interactions</td>
<td>• Knowing by looking at someone whether they are angry at you or not; being able to take someone else’s perspective in a conversation.</td>
</tr>
</tbody>
</table>

Penn Emotion Recognition Test 40 (ER40)
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.
Perception of emotion correlates with functional outcome

**FIG. 3.** Final model of concurrent global functional status

** Neurocognition → .56**

Social Cognition:
- Perception of Emotion → .16*
- .74

Social Competence → .97
Social Support → .30**
- .20**

Global Functional Outcome → .79

** p < .01, * p < .05, # p < .10, one-tailed
Tonal discrimination correlates with auditory emotion recognition

---

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)

Speech in Noise
• Masked Speech Tracking

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)
Demographics of Study Sample

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia</th>
<th></th>
<th>Controls</th>
<th></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>
<td>Mean</td>
<td>S.D.</td>
</tr>
<tr>
<td>Age</td>
<td>87</td>
<td>41.83</td>
<td>9.60</td>
<td>71</td>
<td>39.35</td>
<td>11.59</td>
</tr>
<tr>
<td>Education (years)</td>
<td>81</td>
<td>12.81</td>
<td>2.46</td>
<td>71</td>
<td>14.49</td>
<td>2.23</td>
</tr>
<tr>
<td>Maternal Education</td>
<td>69</td>
<td>13.13</td>
<td>2.89</td>
<td>69</td>
<td>13.58</td>
<td>2.93</td>
</tr>
<tr>
<td>Paternal Education</td>
<td>64</td>
<td>12.73</td>
<td>4.16</td>
<td>65</td>
<td>13.83</td>
<td>3.31</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></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>
<td>61.11%</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>32</td>
<td>36.78%</td>
<td></td>
<td>28</td>
<td>38.89%</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></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>
<td>40.28%</td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>51</td>
<td>58.62%</td>
<td></td>
<td>40</td>
<td>55.56%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1.15%</td>
<td></td>
<td>3</td>
<td>4.17%</td>
<td></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>Frequency Disc.</td>
<td>29.45**</td>
<td>45.37</td>
<td>.51</td>
</tr>
<tr>
<td>Intensity Disc.</td>
<td>25.17**</td>
<td>45.04</td>
<td>.66</td>
</tr>
<tr>
<td>Duration Disc.</td>
<td>24.93**</td>
<td>39.94</td>
<td>.47</td>
</tr>
<tr>
<td>Pulse-Train</td>
<td>25.25**</td>
<td>40.90</td>
<td>.49</td>
</tr>
<tr>
<td>Embedded Tone</td>
<td>20.06**</td>
<td>35.76</td>
<td>.53</td>
</tr>
<tr>
<td>Temporal Order</td>
<td>22.25</td>
<td>28.07</td>
<td>.20</td>
</tr>
<tr>
<td>Syllable Order</td>
<td>12.19**</td>
<td>24.23</td>
<td>.54</td>
</tr>
<tr>
<td>Syllable Recognition</td>
<td>31.96*</td>
<td>42.34</td>
<td>.36</td>
</tr>
<tr>
<td>Formant Disc.</td>
<td>48.02**</td>
<td>52.73</td>
<td>.48</td>
</tr>
<tr>
<td>SAM60</td>
<td>2.99**</td>
<td>2.58</td>
<td>.50</td>
</tr>
<tr>
<td>Pitch Disc. (6000 HZ)</td>
<td>5.52</td>
<td>5.00</td>
<td>.28</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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>CATS</td>
<td>78.09**</td>
<td>11.17</td>
</tr>
<tr>
<td>MAV</td>
<td>41.25**</td>
<td>5.90</td>
</tr>
<tr>
<td>Emotion Comp.</td>
<td>47.46**</td>
<td>9.72</td>
</tr>
<tr>
<td>BACS Comp.</td>
<td>33.73**</td>
<td>15.84</td>
</tr>
</tbody>
</table>

*p < .05, **p < .01
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>

*p < .05, **p < .01
Partial Correlations between basic auditory processing and emotion recognition in patients with schizophrenia (Controlling for Cognition)

<table>
<thead>
<tr>
<th></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>
<td>.31**</td>
<td>.21</td>
</tr>
<tr>
<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
Formant discrimination accounts for additional variance in emotion discrimination beyond frequency discrimination

<table>
<thead>
<tr>
<th>Variables Entered/Removed&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Dependent Variable: MAV

<sup>b</sup> All requested variables entered.

<table>
<thead>
<tr>
<th>Model Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Predictors: (Constant), Frequency Disc. Rank

<sup>b</sup> Predictors: (Constant), Frequency Disc. Rank, Total Formant Composite
Auditory Emotion Perception
Cognitive Impairment in Schizophrenia

• Generalized and severe impairment of various cognitive functions is present in patients with Schizophrenia when compared to healthy controls

• Mild to moderate cognitive impairment is evident before the onset of psychotic symptoms for individuals who have yet to convert to schizophrenia$^{1-3}$

Prodromal Cognitive Decline?

Standardized Scholastic Test Scores in 70 Students Who Later Developed Schizophrenia

- Grade 4 and 8 results represent performance on the Iowa Tests of Basic Skills; grade 11 results represent performance on the Iowa Tests of Educational Development.
- Grade 11 score significantly lower than median percentile rank (F=5.89, df=1, 45, p<0.05).
- Grade 11 score significantly lower than median percentile rank (F=7.80, df=1, 45, p<0.01). Repeated measures ANOVA revealed a significant difference in scores among the three grades (F=3.18, df=2, 107, p<0.05), with further analyses showing that the grade 11 scores were significantly lower than the scores in grade 4 (F=5.04, df=1, 45, p<0.05) and grade 8 (F=4.97, df=1, 45, p<0.05).
- Grade 11 score significantly lower than median percentile rank (F=5.63, df=1, 45, p<0.05). Repeated measures ANOVA revealed a significant difference in scores among the three grades (F=3.66, df=2, 107, p<0.03), with further analyses showing that the grade 11 scores were significantly lower than the scores in grade 8 (F=6.40, df=1, 46, p=0.01).
- Grade 11 score significantly lower than median percentile rank (F=4.77, df=1, 45, p<0.05).

Fuller et al., AJP, 2002
Neuropsychological Profiles Standardized against Healthy Controls

In regression analyses, cognitive variables did not contribute to the prediction of psychosis beyond clinical measures.

COWA, Controlled Oral Word Association; CPT-IP, Continuous Performance Test–Identical Pairs; TMT-B, Trail Making Test Part B; and WCST, Wisconsin Card Sorting Test.

Change of Cognitive Score within 1 year follow-up in 4 Groups

Keefe et al, Schiz Res, 2006
Schizophrenia may be associated with early cognitive deficits and additional decline prior to overt psychotic symptoms.

Significant differences in academic achievements as early as first grade—patients behind by 0.8 to 1.0 grade levels.

Grade equivalent scores on achievement tests by grade in patients (lower curve) and healthy volunteers (upper curve). Thin straight lines are linear regression functions of their respective data series. Error bars represent standard errors of the mean at each grade for each group.

By 12th grade, gap widens to 1.5 to 1.8 grade equivalents.

Verbal “Deficit” in Young Subjects Who Later Develop Schizophrenia

The dependence upon verbal learning throughout early education may be particularly important in the development of later cognitive skill.

Processing Speed “Lag” in Young Subjects Who Later Develop Schizophrenia

Average correlation between tests showing lag and deficit in Schizophrenia subjects who later developed Schizophrenia: $r = .61$ vs. $r = .43$ in controls ($p = .06$)
Key Questions for Future Work

• Do auditory perception deficits underlie emotion recognition deficits in people at high risk for psychosis?
• Are these impairments risk factors?
• If so, could behavioral treatment of these deficits help prevent later psychosis?
Cognitive impairment is a rate-limiting factor for successful rehabilitation and optimal functioning\(^1\)

Successful cognitive enhancement might provide a foundation for improved functioning\(^2\)

---

The MATRICS Initiative

In the absence of effective treatments, the development of medications to treat cognitive impairment is a major public health priority\(^1\)

**Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS)**

- Unique collaboration sponsored by the NIMH\(^1,2\)
- **Goal:** support the development of pharmacologic agents intended to improve cognition in Schizophrenia\(^1,3\)

---

CATIE Schizophrenia Trial Design

**Phase 1***
Double-blind, random treatment assignment

- Olanzapine 7.5-30 mg/day
- Quetiapine 200-800 mg/day
- Risperidone 1.5-6 mg/day
- Ziprasidone 40-160 mg/day**
- Perphenazine 8-32 mg/day

1460 Patients With SCZ Comorbidity Other Medications

**Phase 2**
Participants who discontinue phase 1 choose either the clozapine or the ziprasidone randomisation pathways

- Clozapine (open-label)
- Olanzapine, quetiapine, or risperidone
- Ziprasidone
- Olanzapine, quetiapine, or risperidone

No one assigned to same drug as in phase 1

**Phase 3**
Participants who discontinue phase 2 choose 1 of the following open-label treatments

- Aripiprazole
- Clozapine
- Fluphenazine decanoate
- Olanzapine
- Perphenazine
- Quetiapine
- Risperidone
- Ziprasidone

2 of the antipsychotics above

*Phase 1A: participants with tardive dyskinesia (N=231) do not get randomized to perphenazine; phase 1B: participants who fail perphenazine will be randomized to an atypical (olanzapine, quetiapine, or risperidone) before eligibility for phase 2.

**Ziprasidone added after 40% sample enrolled.

Change in Neurocognitive Composite Score After 2 Months of Treatment

N above histogram. No significant differences between treatments (p=.20). TD=tardive dyskinesia.

Change in CATIE Neurocognitive Composite Score with Donepezil or Placebo

N above histogram. Overall differences between treatments (p<.05).

Change in the Cognitive Composite Score from Baseline to 6 Months in First Episode Psychosis

In over 38 studies, cognitive remediation was found to have a significant benefit to patients with Schizophrenia.
Neuroplasticity-Based Auditory Training

FIGURE 2. Change in Cognitive Performance in Patients With Schizophrenia After 50 Hours of Computerized Auditory Training or 50 Hours of Computer Games

- **Global Cognition**
- **Speed of Processing**
- **Verbal Working Memory**
- **Verbal Learning**
- **Verbal Memory**
- **Problem Solving**
- **Nonverbal Working Memory**
- **Visual Learning**
- **Visual Memory**
- **Social Cognition**

- **Auditory training (N=29)**
- **Computer games (N=26)**

---


---

\(^a\) Significant difference between groups (p<0.01, repeated-measures ANOVA).

\(^b\) Significant difference between groups (p<0.05, repeated-measures ANOVA).

\(^c\) Nonsignificant difference between groups (p=0.10, repeated-measures ANOVA).
The learner must perform a time-order judgment task and identify each of two successive frequency modulation sweeps as either “up” (sweep on left) or “down” (sweep on right). Sweep duration and inter-stimulus interval are modified parametrically as the learner’s performance improves.
Phase 2b trial design for encenicline in Schizophrenia

319 patients in the U.S. and Europe

Subjects: Schizophrenic patients in non-acute phase and on stable dose of atypical antipsychotic drugs

Dose: 0.3 or 1 mg or placebo; QD for 12 weeks
• US, Russia, Ukraine, Serbia

Primary endpoint: Overall Cognition Index by CogState

Secondary endpoints
• MCCB Battery - MATRICS Battery of Cognition tests (U.S. patients)
• SCoRS - Clinical rating of patient function based on cognition (Interviewer total)
• PANSS - Positive and Negative Syndrome Scale Score
Encenicline in Schizophrenia: baseline demographics

Table 1: Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Encenicline 0.27 mg (n = 107)</th>
<th>Encenicline 0.9 mg (n = 105)</th>
<th>Placebo (n = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, n</td>
<td>70:37</td>
<td>75:30</td>
<td>70:35</td>
</tr>
<tr>
<td>Mean (SD) age, years</td>
<td>39.1 (9.7)</td>
<td>37.3 (10.5)</td>
<td>39.2 (9.9)</td>
</tr>
<tr>
<td>Range, years</td>
<td>21–55</td>
<td>18–55</td>
<td>20–54</td>
</tr>
<tr>
<td>Number (%) &gt; 30 years</td>
<td>80 (74.8)</td>
<td>72 (68.6)</td>
<td>79 (75.2)</td>
</tr>
<tr>
<td>Mean (SD) BMI, kg/m²</td>
<td>27.0 (4.2)</td>
<td>27.7 (4.3)</td>
<td>28.1 (4.4)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>72 (67.3)</td>
<td>64 (61.0)</td>
<td>72 (68.6)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>32 (29.9)</td>
<td>37 (35.2)</td>
<td>31 (29.5)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (2.8)</td>
<td>1 (1.0)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>3 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Smoking or tobacco use, n (%)</td>
<td>55 (51.4)</td>
<td>57 (54.3)</td>
<td>66 (62.9)</td>
</tr>
<tr>
<td>Onset ≥ 10 years, n (%)</td>
<td>63 (58.9)</td>
<td>50 (47.6)</td>
<td>63 (60.0)</td>
</tr>
<tr>
<td>Current antipsychotic, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>51 (47.7)</td>
<td>53 (50.5)</td>
<td>52 (49.5)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>22 (20.6)</td>
<td>16 (15.2)</td>
<td>22 (20.9)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>17 (15.9)</td>
<td>7 (6.7)</td>
<td>11 (10.5)</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>10 (9.3)</td>
<td>8 (7.6)</td>
<td>12 (12.4)</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>4 (3.7)</td>
<td>13 (12.4)</td>
<td>4 (3.8)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (2.8)</td>
<td>8 (7.6)</td>
<td>4 (3.8)</td>
</tr>
</tbody>
</table>

Keefe et al, Neuropsychopharmacology, 2015
Change in CogState Composite Index

Keefe et al, Neuropsychopharmacology, 2015
Change in MCCB – US Only

MCCB (LOCF)
(Adjusted Mean Change from Baseline)

Study Day
Day 44
Day 84

LSMEAN Change from Baseline
(90% CI)

MCCB (LOCF)
(Adjusted Mean Change from Baseline)

EVP-6124 0.3 mg
EVP-6124 1.0 mg
Placebo

1.0 mg vs. Placebo: P = 0.069
ES = 0.28

Keefe et al, Neuropsychopharmacology, 2015
EVP-6124-009 MCCB (Age ≤ 50)

- EVP-6124 1.0 mg vs. Placebo
  - Day 84: P-value = 0.058
  - ES = 0.48
  - Overall: P-value = 0.083
  - ES = 0.40

- EVP-6124 0.3 mg vs. Placebo
  - Day 84: P-value = 0.114
  - ES = 0.41
  - Overall: P-value = 0.169
  - ES = 0.34

Keefe et al, Neuropsychopharmacology, 2015
EVP-6124-009 MCCB

Age ≤ 45 yrs old
(N = 74)

Age ≤ 40 yrs old
(N = 48)

EVP-6124 1.0 mg vs. Placebo
Day 44: P-value = 0.237 ES = 0.34
Day 84: P-value = 0.032 ES = 0.67
Overall: P-value = 0.052 ES = 0.56

EVP-6124 0.3 mg vs. Placebo
Day 44: P-value = 0.163 ES = 0.43
Day 84: P-value = 0.043 ES = 0.67
Overall: P-value = 0.048 ES = 0.61

EVP-6124 1.0 mg vs. Placebo
Day 44: P-value = 0.106 ES = 0.58
Day 84: P-value = 0.010 ES = 1.00
Overall: P-value = 0.014 ES = 0.90

EVP-6124 0.3 mg vs. Placebo
Day 44: P-value = 0.386 ES = 0.35
Day 84: P-value = 0.136 ES = 0.63
Overall: P-value = 0.171 ES = 0.56
Schizophrenia Cognition Rating Scale (SCoRS) – All Subjects

SCoRS Total
(Adjusted Mean Change from Baseline)

0.00
-1.00
-2.00
-3.00
-4.00
-5.00
-6.00
-7.00
-8.00

LSMEAN Change from Baseline (90% CI)

Day 28
Day 56
Day 77

Study Day

1.0 mg vs. Placebo:
P = 0.011
ES = 0.36
SCoRS Total (Subjects with Informants) (Adjusted Mean Change from Baseline)

1.0 mg vs. Placebo: P = 0.003
ES = .51
## Time of Day Effects on Treatment Response Sensitivity EVP-6124

<table>
<thead>
<tr>
<th>Therapy (Battery)</th>
<th>Grouping</th>
<th>LSM Change (SE) from Baseline</th>
<th>p-Value for High-Dose vs. PBO</th>
<th>Cohen’s d for High-Dose vs. PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PBO</td>
<td>Low-Dose</td>
<td>High-Dose</td>
</tr>
<tr>
<td>EVP-6124 (MCCB)</td>
<td>All Subjects (n=139)</td>
<td>1.9</td>
<td>3.1</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>Consistent-timing (n=58)</td>
<td>1.3</td>
<td>4.1</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>Inconsistent-timing (n=81)</td>
<td>2.8</td>
<td>2.3</td>
<td>2.4</td>
</tr>
</tbody>
</table>

The table above shows the Least Squares Mean (LSM) change (with standard error) from baseline for different groupings of subjects treated with different doses of EVP-6124 (MCCB) under consistent and inconsistent timing conditions. The p-values and Cohen’s d values indicate the statistical significance and effect size of the treatment response differences between high-dose and placebo (PBO) conditions.
Future Directions

• Cognitive neuroscience measures?
  – Current versions have weak reliability, implementation challenges, and questionable relation to functional outcomes

• Cognitive remediation platforms for clinical drug trials
  – Steroid analogy

• Home web-based assessment?
  – May be promising for clinical practice but probably not for clinical trials
  – Will big data trump fraud?

• Mobile technology and wearables
  – Phone movement predicts treatment response
  – Ecological momentary assessment
Cognitive Impairment in Schizophrenia: Conclusions

- Severe in Schizophrenia
- Present in almost all patients with Schizophrenia
- Severity is associated with important functional outcomes
- Small-to-no improvements found with antipsychotic treatment
- Several pharmacologic mechanisms are being studied in clinical trials
- Cognitive remediation may have modest benefit
Acknowledgements

- **Duke**
  - Mike Kraus
  - Trina Walker
  - Ashwin Patkar

- **NeuroCog Trials**
  - Vicki Davis
  - Alexandra Atkins

- **UNC**
  - Fred Jarskog
  - Kathy Jones
  - John Gilmore

- **Carolina Behavioral Care**
  - Rob Millet