New Developments in the Assessment and Treatment of Cognition and Functional Disability

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Disclosures

• In the past year, Dr. Harvey has served as a consultant to:
  – Boeheringer-Ingelheim, Forum Pharma, Genentech, Otsuka America, Roche, Sanofi, Sunovion, and Takeda Pharma
Functional Outcome and Treatments Offered

Percentage of Patients with Clinical Remission Living Independently

Data from Hegarty et al., 1994; Am J Psychiatry
The First Episode Paradox: Treatment of Primary Symptoms as a Poor Predictor of Disability Reduction

- 90% of first episode schizophrenia patients experience remission at the end of one year of treatment
- At 5 year follow-up 18% recover
- 95% relapse at least once
- Figures in Bipolar disorder are:
  - 98% remission rate
  - 40% recovery rate

Robinson et al., 2004; Tohen et al., 2003
Psychosis and Brain Volume Changes During the First 5 Years of Schizophrenia


N = 48
Successive Relapses Prolonged Time to Remission

Successive Episodes

3-Episode Group (n=6)

First episode: 4.0
Second episode: 7.0
Third episode: 24.3

Successive Relapses Prolonged Time to Remission

Median Time to Remission (Weeks)

Cognitive Functioning in Schizophrenia

- Cognitive impairment is ubiquitous, profound, and disabling
- It shows up early and stays late
- It limits potential vocational and residential success and creates loneliness and isolation
- And now, we may be able to treat it
Prediction of Community Activities

Neg Sx → SSPA: -.47*
Processing Speed → SSPA: .34*
Verbal Memory → SSPA: .50*
Working Memory → SSPA: .41*
Executive Functioning → SSPA: .43*

SSPA → UPSA: .40*
UPSA → Community Activities: .38*

R² = 0.48

*p < .01
Google Search for “Brain training”

- About 177,000,000 results (0.19 seconds).
- Sure seems popular
- More than me:
- About 148,000 results (0.13 seconds)
- It Must work, I saw it on the Internet:
- **BrainPro® Official Site**
  www.scilearn.com/BrainPro
  Up To A 2 Year Gain In 3 Months
  Backed By 240 Research Studies
- Results of a Pub Med search:
- Your search for *BrainPro* retrieved no results.
- Must be unpublished research studies
Cognitive Remediation and Cognitive Enhancement

• Clinically relevant and a critical research question

• This presentation tries to separate clinical treatment delivery from remaining research questions

• We use results from rehabilitation approaches to evaluate issues for pharmacological cognitive enhancement
The Treatment Imperative


- Marder SR, Fenton W. Measurement and treatment research to improve cognition in schizophrenia: NIMH MATRICS initiative to support the development of agents for improving cognition in schizophrenia. Schizophr Res 2004; 72:5-9.

But, who was there first?


The first message

- Cognition is critical
- Clinical Stability is a pre-requisite
- Treatment efforts are underway
What About Other Conditions, like Bipolar Disorder?

- Disability is common and substantial in bipolar illness
- Cognitive impairment may be more significant than previously believed
Rates of Real-World Functional Milestones in Schizophrenia and Bipolar Disorder

From Huxley and Baldessarini, 2007; Leung et al., 2008
Outcome in the McLean Study

Tohen et al., 2003
Performance of First Episode Patients Compared to Normative Standards

From Reichenberg et al., 2009
UPSA B Scores as a Function of Residential Status

Note: Diagnostic effect: $F = 0.66$, $p = .417$; Mausbach et al., 2010
Schizophrenia
N=161

Bipolar
N=130

Bowie et al., 2010
The second message

• From a cognitive and functional perspective, bipolar disorder and schizophrenia may be more similar than different

• Let’s not quibble about a diagnosis:
  – Schizoaffective; Bipolar II; Bipolar NOS

• The functional implications of cognitive impairments are consistent
Features of the Cognitive Enhancement Research Design

- Use of a consensus-derived cognitive battery
  - The MATRICS Consensus Cognitive Battery
- Use of a co-primary outcomes measure
  - Either a performance-based assessment of functional skills or a structured interview
- Enrollment of clinically stable patients
  - To rule out “pseudospecificity”
- Long trial duration

Buchanan et al., 2005, 2010
Cognitive Remediation Results

• Recent cognitive remediation results have been more promising than old results
  – Over 10 different studies with different methods have found persistent functional gains
  – Computerized systems simplify delivery
• May be an interesting “background” intervention to add to potential pharmacological cognitive enhancers
• All effective interventions share characteristics
  – Dynamic difficulty titration
  – Feedback on performance
  – Computerized delivery
Cognitive Remediation and Direct Functional Gains

• All patients receiving supported employment services
  Randomized trial
  – COG Pack + SE vs. SE alone

• Outcomes included
  – Cognitive change
  – Employment Outcomes
Relative Employment Outcomes: Remediation vs. Control

% improvement

1 year Difference (%)  3 year Difference (%)

Income
Time Worked

McGurk et al., 2007
Other Supported Employment Results

Sample 1
- CRT+WT
- WT

Sample 2
- CRT+SE
- SE

HOURS WORKED

Active Intervention | Follow-up
Intake | 6 Months | 12 Months

Quarters
1st | 2nd | 3rd | 4th | 5th | 6th | 7th | 8th

Wexler and Bell, 2005
Other evidence of Persistence

- One year follow-up after two years of treatment, early course patients (Eack et al., 2010)

![Graph showing the One-Year Durability of the Effects of Cognitive Enhancement Therapy or Enriched Supportive Therapy on Social Adjustment](image-url)
BDNF Levels and cognitive remediation

Figure 1. Serum brain-derived neurotrophic factor (BDNF) levels (ng/mL) in schizophrenia subjects participating in 50 hours of computerized auditory training (AT) versus subjects participating in 50 hours of computer games (CG). By post-training (Week 10), the AT subgroup’s serum BDNF level was comparable to that of age-, sex-, and education-matched healthy comparison subjects (HC: M31.88, SD9.90; AT: M32.23, SD15.10; CG: M23.97 SD 11.21). S. Vinogradov et al. BIOL PSYCHIATRY 2009
Meta Analysis of Functional Benefits of Cog Rem

• Large-scale Meta-analysis (Wykes et al., 2011)
• Several critical findings for cognition and functioning
  – Strategic > Repetition
  – Better with Psychosocial Intervention
  – No symptom effects

Christopher R. Bowie, Ph.D.
Susan R. McGurk, Ph.D.
Brent Mausbach, Ph.D.
Thomas L. Patterson, Ph.D.
Philip D. Harvey, Ph.D.

Objective: Cognitive remediation is an efficacious treatment for schizophrenia and, when used within broader psycho-social treatments, improves transfer to real-world behavior change. The authors examined whether cognitive remediation effectively generalizes to functional competence and real-world functioning as a standalone treatment and when combined with a functional skills treatment.

Method: Outpatients with schizophrenia (N=107) were randomly assigned to receive cognitive remediation, functional adaptation skills training, or combined treatment, with cognitive remediation preceding functional skills training. Clinical symptoms, neurocognition, social competence, functional competence, and case-manager-rated real-world behavior were assessed at baseline, at end of treatment, and at a 12-week durability assessment.

Results: Neurocognition improved, with durable effects, after cognitive remediation but not after functional skills training. Social competence improved both with functional skills training and with combined treatment but not with cognitive remediation alone. Improvements in functional competence were greater and more durable with combined treatment. Cognitive remediation alone did not produce significant improvements in real-world behavior, but when combined with functional skills training, statistically significant improvements from baseline to end of treatment and follow-up were observed in community or household activities and work skills. Number-needed-to-treat analyses suggest that as few as three cases are required for treatment to induce a meaningful improvement in functional skills.

Conclusions: In a short intervention, cognitive remediation produced robust improvements in neurocognition. Generalization to functional competence and real-world behavior was more likely when supplemental skills training and cognitive remediation were combined.

(Am J Psychiatry 2012; 169:710–718)
Outcomes of the Study: End of Treatment

Effect Size (Cohen’s d)

- COG REM
- FAST
- Both

- NP
- UPSA
- SLOF
Can you do it at home?

- Study of first episode patients with psychosis
- Home based CRT vs. inactive control condition
  - 60 participants and randomized to active and 60 randomized to inactive
  - 70% adherence rate in each condition
Neuroplasticity-Based Auditory Training Via Laptop Computer Improves Cognition in Young Individuals With Recent Onset Schizophrenia

Melissa Fisher¹,², Rachel Loewy¹, Cameron Carter³, Ashley Lee¹, J. Daniel Ragland³, Tara Niendam³, Danielle Schlosser¹, Lien Pham³, Tara Miskovich³, and Sophia Vinogradov*¹,²

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Cognitive Benefits
But...

- There were no concurrent functional gains
- Psychosocial interventions may be needed
UCLA Study of Cognitive Remediation after a First Psychotic Episode
(Nuechterlein et al, ICOSR, 2013)

• 12-month randomized controlled trial with first-episode schizophrenia patients at the UCLA Aftercare Research Program
• Patients received Individual Placement and Support to provide a context of active work rehabilitation
• Randomly assigned to cognitive remediation or healthy behavior training after stabilization
• Randomized to long-acting medications or oral antipsychotics
Correlations between Antipsychotic Medication Adherence and MCCB Gains in First-Episode Schizophrenia

**MCCB Gain in 6 Mo.**

<table>
<thead>
<tr>
<th>MCCB Gain in 6 Mo.</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Composite*</td>
<td>0.35</td>
</tr>
<tr>
<td>Working Memory*</td>
<td>0.25</td>
</tr>
<tr>
<td>Visual Lrng*</td>
<td>0.20</td>
</tr>
<tr>
<td>Social Cognition</td>
<td>0.15</td>
</tr>
</tbody>
</table>

* * p < .05
MCCB Overall Composite Score Covarying for Medication Adherence and Finishing Full 1-Year Protocol (n = 46)

Group X Time interaction, p = .025
Cognitive Training Leads to Better Work/School Role Functioning in 12 Months of Treatment (n = 53)

Group X Time interaction, \( p = .03 \)
# Pharmacological Studies to date

<table>
<thead>
<tr>
<th>General pharmacological domain</th>
<th>Specific compounds</th>
<th>Specific actions of the compounds</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinergic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscarinic</td>
<td>Donepezil</td>
<td>Acetylcholinesterase Inhibition</td>
<td>N</td>
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<tr>
<td></td>
<td>Galantamine</td>
<td>Acetylcholinesterase Inhibition</td>
<td>N</td>
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<tr>
<td></td>
<td>Rivastigmine</td>
<td>Acetylcholinesterase Inhibition</td>
<td>N</td>
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<tr>
<td>Nicotinic</td>
<td>DMX-B</td>
<td>alpha-7 partial agonist</td>
<td>N</td>
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<tr>
<td></td>
<td>AZD3480</td>
<td>alpha4-beta2 agonist</td>
<td>N</td>
</tr>
<tr>
<td>Glutamatergic</td>
<td>Glycine</td>
<td>NMDA co-transmitter</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>d-cyloserine</td>
<td>NMDA glycine site partial agonist</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>CX-516</td>
<td>AMPA-Kine (allosteric modulator)</td>
<td>N</td>
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<tr>
<td></td>
<td>Lamotrigine</td>
<td>Glutamate release regulation</td>
<td>+/-</td>
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<tr>
<td>Noradrenergic</td>
<td>Guanfacine</td>
<td>Alpha-2 agonist</td>
<td>+/-</td>
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<tr>
<td></td>
<td>Atomoxetine</td>
<td>Transport inhibitor</td>
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<tr>
<td>Gamma-aminobutyric Acid</td>
<td>Flumazenil</td>
<td>GABA-A antagonist</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>MK-0777</td>
<td>GABA-A&lt;sub&gt;23&lt;/sub&gt; antagonist</td>
<td>N</td>
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<tr>
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<td>Tandospirone</td>
<td>5-HT&lt;sub&gt;1a&lt;/sub&gt; Partial Agonist</td>
<td>+/-</td>
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<tr>
<td></td>
<td>Buspirone</td>
<td>5-HT&lt;sub&gt;1a&lt;/sub&gt; Partial Agonist</td>
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<tr>
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<td>COMT Inhibitor</td>
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<tr>
<td>Stimulant</td>
<td>Amphetamine</td>
<td>monoamine agonist and transport inhibitor</td>
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</tr>
<tr>
<td>Alertness Agents</td>
<td>Modafinil</td>
<td>unknown</td>
<td>+/-</td>
</tr>
</tbody>
</table>
The Third message

- CRT and related interventions are quite promising
- Not many off the shelf medications seem to work
- Cholinesterase inhibitors seem worst
- Psychosocial interventions seem necessary in most case
Phase 2b Study in Stably Treated Schizophrenic Subjects (EVP-6124-009)

• Trial
  – Schizophrenic patients (n=319) stably treated with second generation atypical antipsychotic drugs except Clozapine
  – Parallel, double-blind design: placebo, 0.3, 1 mg/day for 12 weeks
  – Trial conducted in the US and Eastern Europe (Ukraine, Serbia, Russia)

• Efficacy Measures
  • MCCB Battery- MATRICS Battery of Cognition tests (US patients only due to language availability)
  • SCoRS (I)- Clinical rating of patient function based on cognition
  • PANSS- Positive and Negative Syndrome Score
    – Overall PANSS
    – Positive Symptom Score
    – Negative Symptom Score
SCoRS (Visits with Informant Present)

![Graph showing the change in SCoRS Interviewer Total (Subjects with Informants) over study days.](Image)

- **1 mg vs. placebo:**
  - P = 0.003
  - ES = .51

**Legend:**
- EVP-6124 0.3 mg
- EVP-6124 1.0 mg
- Placebo
EVP-6124-009: MCCB (US patients only)

Age ≤ 45 yrs old
(N = 74)

Age ≤ 40 yrs old
(N = 48)

EVP-6124 1 mg vs. Placebo
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 84: P-value = 0.043  ES = 0.67
Overall: P-value = 0.048  ES = 0.61

EVP-6124 1 mg vs. Placebo
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 84: P-value = 0.136  ES = 0.63
Overall: P-value = 0.171  ES = 0.56
Lurasidone Effects on Cognition in Patients With Schizophrenia

- New atypical antipsychotic
- Minimal weight gain effects
- Active at several potentially important receptor sites

Randomized Comparative Trial

CogState computerized cognitive battery:
- Baseline
- Week 6
- Week 19
- Week 32

**Double-Blind Acute Phase**
- Lurasidone 80 mg/d
- Lurasidone 160 mg/d
- Placebo
- Quetiapine XR 600 mg/d

**Double-Blind Extension Phase**
- Lurasidone 40-160 mg/d
- Lurasidone 40-160 mg/d
- Quetiapine XR 200-800 mg/d

6 weeks
- Double-Blind Acute Phase

12 months
- Double-Blind Extension Phase

Effect of Lurasidone on CogState Composite Score: Change in Z-Scores at Week 6

- **Lurasidone 160 mg/day (n=65)**: Change in Z-Score = 0.50, *P*=0.038 (ES=0.37)
- **Lurasidone 80 mg/day (n=72)**: Change in Z-Score = 0.05
- **Quetiapine XR (n=67)**: Change in Z-Score = -0.24, *P*=0.018 (ES=0.41)
- **Placebo (n=63)**: Change in Z-Score = -0.16

Effect of Lurasidone 40-160 mg/d on CogState Composite Score: LS Mean Change in Z-Scores at Weeks 19 and 32

- **Week 19 (Month 6 of Extension)**
  - LUR-LUR: 0.71 (ES=0.35), P=0.058
  - PBO-LUR: 0.14
  - QXR-QXR: 0.11

- **Week 32 (Month 6 of Extension)**
  - LUR-LUR: 1.19 (ES=0.57), P=0.004
  - PBO-LUR: 0.77
  - QXR-QXR: 0.12

Sample sizes:
- LUR-LUR: n=97
- PBO-LUR: n=34
- QXR-QXR: n=41
- LUR-LUR: n=81
- PBO-LUR: n=28
- QXR-QXR: n=37
Change from Baseline in Epworth Sleepiness Scale

LS Mean Change From Baseline (LOCF)

Lurasidone 160mg/d  n=116
Lurasidone 80mg/d  n=119
Quetiapine XR 600 mg/d  n=112
Placebo  n=114

Improvement

** p < 0.01
Specific Mediators

- Quetiapine XR caused significant sleepiness in this trial
- Quetiapine has previously been shown to have adverse effects on cognition compared with risperidone
What about Everyday Practice?

• Who gets treatment?
• What do they not get?
Survey of APA Practice Research Network: Schizophrenia Treatments

The last message

- New treatments improve cognition and functioning
- We just need patients to get access to them
University of Miami opens South Florida’s First Brain Fitness Pavilion

March 6, 2014

The Department of Psychiatry and Behavioral Sciences, in collaboration with the Center on Aging at the University of Miami Miller School of Medicine, opens South Florida’s first Brain Fitness Pavilion.

The Pavilion, directed by Dr. Philip D. Harvey and Dr. Sara J. Craja, faculty at the University of Miami Miller School of Medicine, offers state-of-the-art, comprehensive cognitive programs, including neuropsychological assessments, assessments of everyday living skills and a customized brain fitness training program especially tailored for YOU.

Administered by trained and certified healthcare professionals, the brain fitness training program will help improve memory, concentration, attention, and mental speed. BrainHQ, an online brain training program designed by Posit Science and the only cognitive remediation intervention being considered by the FDA for clearance as a medical device, will be used at the Pavilion.

Your personalized program, which involves performing structured exercises such as remembering words and sorting objects, includes two 45-minute sessions a week at the Pavilion, as well as home exercises.

Call us now for an appointment and fee schedule

Phone Number: (305) 355-9080

Location: 1695 NW 9th Ave, Suite 3202, Miami FL 33136

Established by a generous gift from the Gaddis Family Foundation of Fort Lauderdale, FL