**Cognitive Impairment: Implications for Psychotherapeutic Treatment of Late Life Depression**

R. Scott Mackin, PhD  
The Over 60 Program  
Department of Psychiatry, UCSF

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**Overview/Objectives**

- What are "mild" cognitive impairments and how are they typically defined?
- How prevalent are mild cognitive impairments in late life depression?
- Why is it important to understand cognitive impairment to study interventions in LLD?
- Preliminary findings on the effects of cognitive impairment and clinical outcomes
  - Depression
  - Functional Status/Disability
Cognitive Domains

- Memory
- Language
- Attention
- Executive Functioning
- Visuospatial Processing
- Abstract Reasoning
- Speed of Information Processing

Methods of Neuropsychological Assessment

Development of Tests
Validation
Standardization

Interpretation of Scores
Normative Data
Age
Education
Practice Effects

Several Different Diagnostic Criteria for Mild Cognitive Impairments

- Benign Senescent Forgetfulness (Kral, 1962)
- Age Associated Memory Impairment (Crook et al 1986)
- Age Consistent Memory Impairment; Late Life Forgetfulness (Blackford & LaRue, 1989)
- Age Associated Cognitive Decline (Levy, 1994)
- Mild Cognitive Impairment (MCI) (Petersen et al 1995; Petersen et al, 2001)

Key Diagnostic Characteristics of Mild Cognitive Impairment

- Cognitive complaints
- Informant report of cognitive decline
- Objective evidence of cognitive impairment (usually 1.5 sd below populations norms on neuropsychological tests)
- Cognitive impairment does not significantly interfere with daily fx
- No Dementia
Mild Cognitive Impairment and Late-life Depression Frequently Co-occur

- In individuals with cognitive impairment
  - Depression occurs in 20-40% of patients (Lyketsos et al. 2002; Gabryelewicz et al. 2004)

- In individuals with Late Life Depression
  - MCI occurs in 13 to 60% of patients (Butters et al., 2004; Barnes et al., 2006)

- Co-occurrence of MCI and LLD may signal neurodegenerative processes (incipient dementia)

- LLD may cause cognitive impairments

Depression as Neuropsychiatric Symptom of Neurodegenerative Disease

Cumulative Percentage of NPI symptoms

Why is the Accurate Assessment of Cognitive Functioning Important in the Treatment of Older Adults with Psychiatric Disorders?

- Treatment adherence
- Impact of Cog Deficits on disability
- Cognitive impairments as phenotypic markers of treatment resistant depression/tx selection
  - Focus on Vascular Depression and Executive Dysfunction
Examples of Impact of Cognitive Impairment on Treatment Adherence

- Medication tx
  - Taking medicine as prescribed
  - Attending medical appts

- Psychotherapy
  - Remembering prior sessions
  - Processing language in session
  - Problem solving skills, mental flexibility

Cognitive Impairments Contribute to Disability Independent of Depression Severity

Executive Dysfunction associated with increased fx impairment independent of LLD severity (Steffens, Hays et al. 1999; Cahn-Weiner, Malloy et al. 2000; Lockwood, Alexopoulos et al. 2000; Kiosses; Kiosses and Alexopoulos 2005)

Memory impairment shows relationship to fx impairment independent of LLD severity (Gallo, Rebok et al. 2003; Burdick, Rosenblatt et al. 2005; Tuokko, Morris et al. 2005)

Implications:
1) Specific types of cognitive impairment are independent contributors to disability in older depressed adults.
2) Effects of cog impairment on disability/QOL should be evaluated in evaluation of tx outcomes

Evaluating Cognitive Functioning and Associated Disability is Crucial for Evaluating Treatment Outcomes for LLD

Neurodegenerative Disease

Cognitive Impairments

Disability

Depression

ED as phenotypic Marker of Tx Resistant Depression: Focus on “Vascular Depression” as a Distinct Subtype of LLD

- Etiology = small-vessel vascular changes in fronto-subcortical regions (Alexopoulos et al. 1997; Alexopoulos, 2003)
- Atypical presentation = late onset
- Medical comorbidities (HTN, CAD, DM, etc)
- Cognitive correlates = executive dysfunction
- Prognosis = poor (med tx response, greater disability)
**Depression + MCI (Executive Dysfunction)**

- Decreased treatment response to conventional pharmacological treatments (Alexopoulos et al., 2000; Alexopoulos & Kalayam, 2000; Kalayam & Alexopoulos, 1999)
- Psychotherapy treatments modified to accommodate cognitive impairment have improved outcomes (Alexopolous et al, 2003)

**Growing Evidence Supporting Psychotherapy for Individuals with LLD and ED**

- Mixed-effects models:
  - Time, p<0.0001
  - Tx, p=0.07
  - Time x tx, p=0.12, ES=0.35
- Post, PST > ST, p<0.01
- 75% PST vs. 22% ST remitted, p<0.01

**Abnormal Stroop Scores are Associated with Low Remission of LLD in Citalopram Trial (daily dose of 40 mg for 8 weeks)**

Remission rates in 112 elderly patients with major depression with high and low scores (Median Split) on the Stroop Color-Word Test.

**Focus on Vascular Depression May Obscure Potential Role of Other Etiologies with Regard to Tx Resistant Depression**

- AD = Alzheimer’s Dementia
- VaD = vascular dementia
- DLB = dementia with Lewy bodies
- FTD = frontotemporal dementia

Reflects difficulties diagnosing overlapping dementia; only estimations of prevalence can be made.

**Irreversible dementias (%)**

- AD
- VaD
- DLB
- FTD
- Other

Guttman R et al., Arch Fam Med. 1999;8:347-353.
Neuropsychological Profile for Alzheimer’s Disease

- **Memory**: “Encoding deficit”, rapid decay, recognition poor, intrusion errors
- **Language**: WFD; semantic paraphasic errors
- **Executive Dysfunction**: Yes
- **Visual Spatial Impairment**: Yes
- **Onset**: Insidious
- **Progression**: Gradual
- **Depression**: Common

Won’t Cognitive Impairments be Easy to Recognize?

Will the MMSE Help Identify Cognitive Impairment?

Cognitive Predictors of Psychotherapeutic Outcomes in Late Life Depression

Preliminary Findings

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Cognitive Predictors of Positive Psychotherapy Outcomes

- Supplement to a larger randomized clinical trial of PST vs. Supportive Psychotherapy for individuals with ED (COPE D Project)
- 12 weekly psychotherapy sessions
- Weekly assessments of depression severity and disability
- Comprehensive neuropsychological assessments (baseline, week 12, week 36)

Inclusion Criteria

- Age: 60 years and older
- Diagnosis: Major depression, unipolar (SCID)
- Severity of depression: HAMD>19
- Evidence of Executive Dysfunction
  - Dementia Rating Scale Initiation/Perseveration or Stroop Color-Word < 1.5 sd below the mean of normal elders
- Not taking antidepressants

Exclusion Criteria

- Acute suicide risk, i.e. intent or plan to attempt suicide in near future.
- Axis I psychiatric disorder other than unipolar major depression.
- Evidence of Dementia (MMSE <25)
- Severe acute medical illness
- Use of medication known to cause depression, e.g., reserpine, alpha-methyl-dopa, steroids.
- Currently in individual psychotherapy.
- Aphasia, sensory problems, and non-English speakers.

Methods-Neuropsychological Assessment

- Use of age/edu corrected scores
- Cognitive Domains Index Scores
  - Memory
  - Executive functioning
  - Visuospatial processing
  - Language
  - Attention/Working Memory
  - Abstract Reasoning
  - Speed of Information Processing
Neuropsychological Battery

**MEMORY:**
- Logical Memory-WMS-III, Hopkins Verbal Learning Test, Brief Visuospatial Memory Test

**EXECUTIVE FUNCTIONING:**
- Wisconsin Card Sorting Test, Stroop Color Word Test, Delis Kaplan Card Sorting*, Trail Making Test Part B

**LANGUAGE:**
- Boston Naming Test

**VISUOSPATIAL:**
- Motor Free Visuospatial Test; Judgment of Line Orientation

**ATTENTION/WORKING MEMORY:**
- WAIS-Digit Span & Letter Number Sequencing

**SPEED OF INFORMATION PROCESSING**
- Symbol Digit Modalities Test; Trail Making Test Part A

**ABSTRACT REASONING:**
- WAIS-Similarities; Matrix Reasoning

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Calculating Cognitive Domain Index Scores

\[ \text{Cognitive Domain Index Score} = \frac{S_{\text{Test1}} + S_{\text{Test2}} + S_{\text{Test3}}}{3} \]

- Scaled Scores Corrected for Age/Education

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Study Timeline

**Aim 1:** Evaluate impact of baseline cognitive impairments on treatment outcomes

**Aim 2:** Evaluate cognitive improvements following tx

- Baseline Cognitive/Disability Evaluation
- Weekly psychotherapy
- Week 12
- Week 36
- Patient Evaluated for Depression
- Week 12
- Week 36

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Baseline Characteristics (n=32)

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>59%</td>
</tr>
<tr>
<td>Late Onset Depression</td>
<td>52%</td>
</tr>
<tr>
<td>Age</td>
<td>Mean: 72.3, SD: 6.9</td>
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<tr>
<td>Education</td>
<td>Mean: 15.8, SD: 2.6</td>
</tr>
<tr>
<td>Hamilton Depression**</td>
<td>Mean: 22.5, SD: 2.2</td>
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<tr>
<td>Disability-SF36 Physical Health</td>
<td>Mean: 39.8, SD: 11.4</td>
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<tr>
<td>Disability-SF36 Mental Health*</td>
<td>Mean: 33.6, SD: 9.1</td>
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</tbody>
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* p < .05 ** p < .001
How We Defined Cognitive Impairment

Cognitive domain score < 16th percentile

Cumulative Number of Cognitive Deficits at Baseline For Treatment Group (n=32)

Evaluating Cognitive Fx in Relation to Tx Outcomes

- "Positive Response": 50% reduction in HAM D sx
- Severity of Symptoms:
  - Weekly HAM D scores
Positive Response Rates

Depression Severity Scores for Executive Dysfunction Impaired Individuals (n=29)
(During 12 Weeks of Psychotherapy)

Depression Severity Scores for Delayed Recall Memory Impaired Individuals (n=29)
(During 12 Weeks of Psychotherapy)

Depression Severity Scores for Memory and Language Impaired Individuals (n=29)
(During 12 Weeks of Psychotherapy)
Summary

- Cognitive impairments in late Life depression are common and heterogeneous
- Evaluating cognitive functioning is crucial in evaluating psychotherapeutic treatment outcomes
- Preliminary data suggests that patterns of cognitive impairment may confer stronger effects on clinical outcomes than individual types of cognitive impairment
- Cognitive impairment has significant influence on disability in LLD

Example of a Brief Neuropsychological Screening Battery

- **Mental Status**: Mini Mental Status Exam (MMSE)
- **Memory**: California Verbal Learning Test (CVLT) Short Form
- **Attention/Information Processing Speed**: WAIS III Digit Span; Digit Symbol Modalities (oral version)
- **Executive Functioning**: Stroop; Trail Making Test Part B
- **Abstract Reasoning**: WAIS III Similarities
- **Language**: Boston Naming Test (15 item)
The UCSF Over-60 Research Team

- Patricia Areán, Ph.D.
- Liat Ayalon, Ph.D.
- Rebecca Crabb, Ph.D.
- Joyce Chu, Ph.D.
- Nicole Duffy, MA
- Alex Elite-Marcandonatou, LCSW
- Erin Gillung, BA
- Amber Gum, PhD
- Christa Hogan, Psy.D.
- Terri Huh, Ph.D.
- Maura McLane, MFT
- R. Scott Mackin, Ph.D.
- Craig Nelson, M.D.
- Peder Wolff, LCSW

When to Refer for Neuropsychological Evaluation

- As an adjunct to a diagnostic workup
- To establish a baseline
- To evaluate early dementia
- To evaluate competency, independence, safety issues
- To provide recommendations for psychosocial interventions

Incidence of Cognitive Impairment for Tx and Control Groups (N=67)

Depression Severity Scores for Language Impaired Individuals (n=28)
(During 12 Weeks of Psychotherapy)
Language Impairment: Post-treatment QOL/Functional Status

Language impaired
Intact language

Mental Component Score of SF36

Norm

Baseline 3 month

P<.05