

Neurobehavioral Correlates of Mood Disorder



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Objectives

- **Provide background concerning neurobiological correlates of major depression**
- **Describe neuropsychological dysfunction in major depression** ■
- **Delineate factors that moderate cognitive dysfunction in major depression**
- **Illustrate contributions of neuropsychological impairment to functional outcomes in major depression**

Depression and Brain Function

- **Mayberg (2003)**
 - “It is now generally understood that depression is unlikely the result of a single brain region. Instead, it can be conceptualized as a multidimensional, systems-level disorder affecting discrete, but functionally integrated pathways.”
- **What regions are implicated?**

Depression and Brain Function

- **Functional Abnormalities**

- In untreated depression:

- » Frontal hypoactivation; dorsolateral, ventral, and orbital

- » Abnormal but variable activation: cingulate, basal-ganglia, and thalamic

- In treated depression:

- » Normalization of regional abnormalities, regardless of treatment modality

- **Structural Abnormalities**

- e.g., volume loss in hippocampus; ventral and medial frontal lobes; basal-ganglia

Implications

- **Such abnormalities may serve as neural substrates for deficits involving:**
 - Executive function
 - Memory ■
 - Speed of information processing
 - Working memory
 - Psychomotor speed
- **But....**
 - What is the proof?

Neuropsychological Deficit in Major Depressive Episodes

- **Impairment appears to be:**
 - **Common**
 - » Numerous studies report the presence of cognitive deficits in major depressive disorder (cf. Burt et al., 1995; Christensen et al., 1997; Kindermann & Brown, 1997; Meiel, 1997)
 - **Broad**
 - » Executive function, memory, attention, speed of information processing, visuo-spatial perception, psychomotor speed (cf. Basso & Bornstein, 1999; Franke et al., 1993; Heaton & Crowley, 1981; Martin et al., 1991; Sackeim et al., 1992; Massman et al., 1992; Yozawitz, 1986)
 - **Chronic**
 - » Patients in euthymic periods demonstrate cognitive impairment (cf. Kessing, 1998)

Who Has These Difficulties?

- **Inpatients**
- **Elderly Depressed with Pre-Morbid Psychiatric Histories**
- **Elderly Depressed with Neurological Disease**
 - e.g., **Multi-Infarct, Neurodegenerative Diseases**

But Who Else?

Individuals with Recurrent Depressive Episodes

- **Recurrent depression is associated with:**
 - poorer prognosis
 - more severe depression
 - poorer treatment outcomes
 - Greater presence of cerebral abnormalities outlined by Mayberg
- **These characteristics may reflect greater cerebral dysfunction in patients with recurrent depression than patients with single episodes**
- **Such dysfunction may be reflected by poorer neuropsychological function**

Method

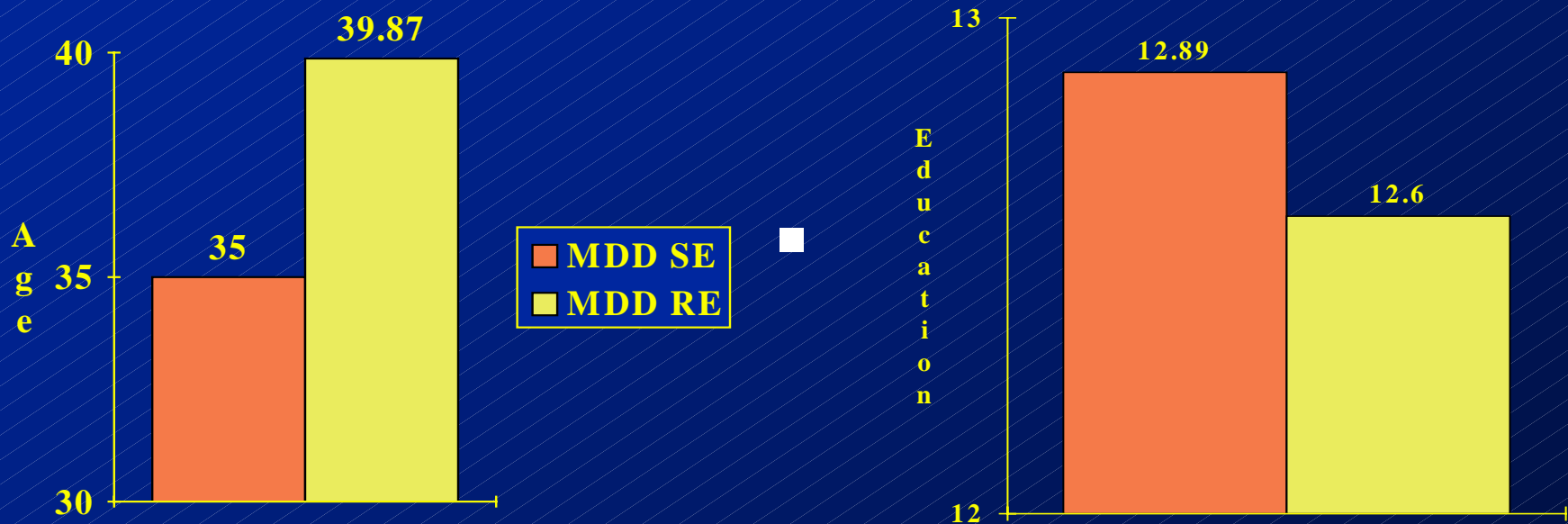
- Subjects

- 19 MDD Single Episode/53 MDD Recurrent
- Screened for neurologic disease/CHI >60 minutes
- Examined during inpatient admission
- Diagnoses made by attending physician in teaching hospital

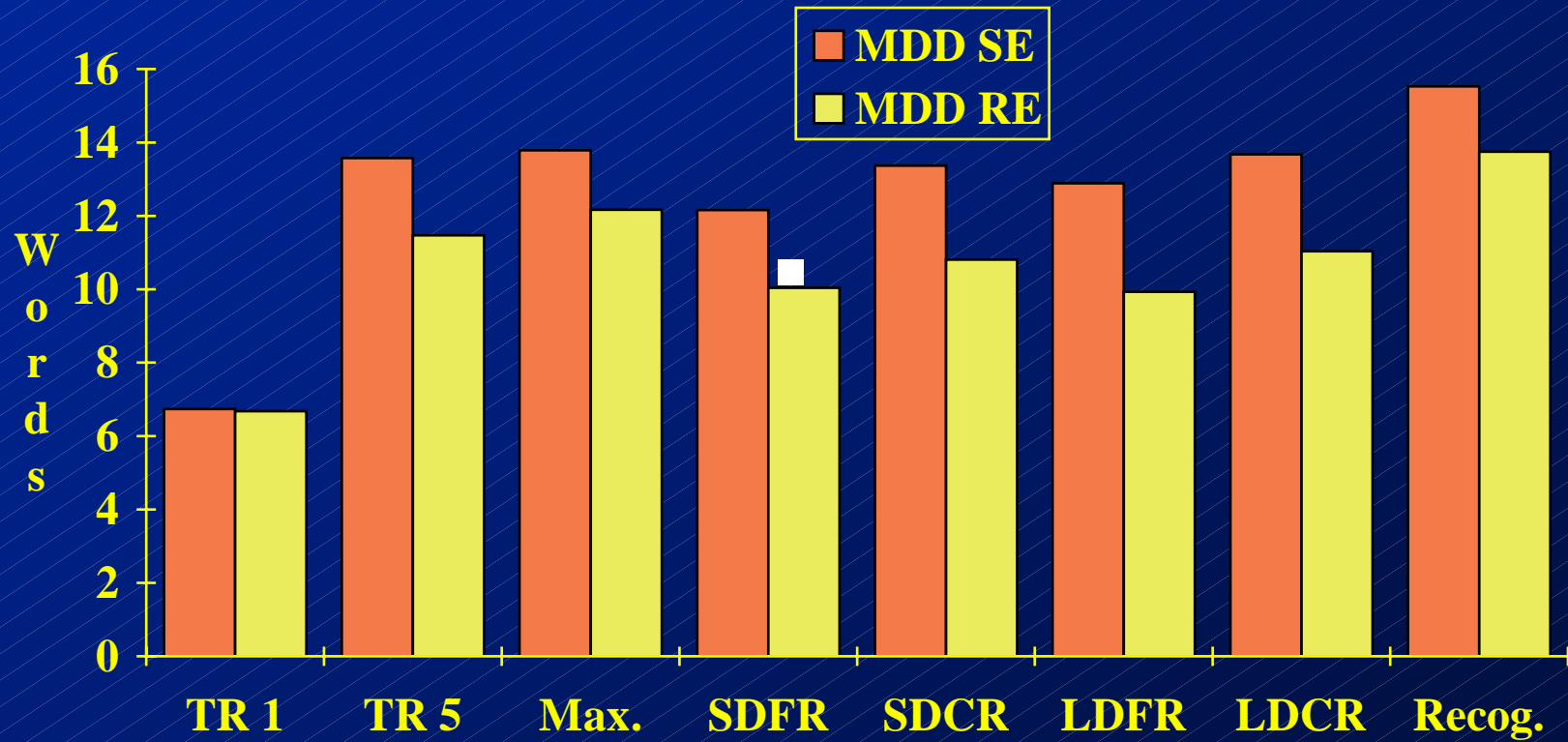
- Measures

- WAIS-R--Vocabulary/Block Design
- WMS-R--Logical Memory/Visual Reproduction/Digit & Visual Spans
- CVLT
- Trails A & B
- JLO/COWAT
- Grooved Pegboard Test
- MMPI-2

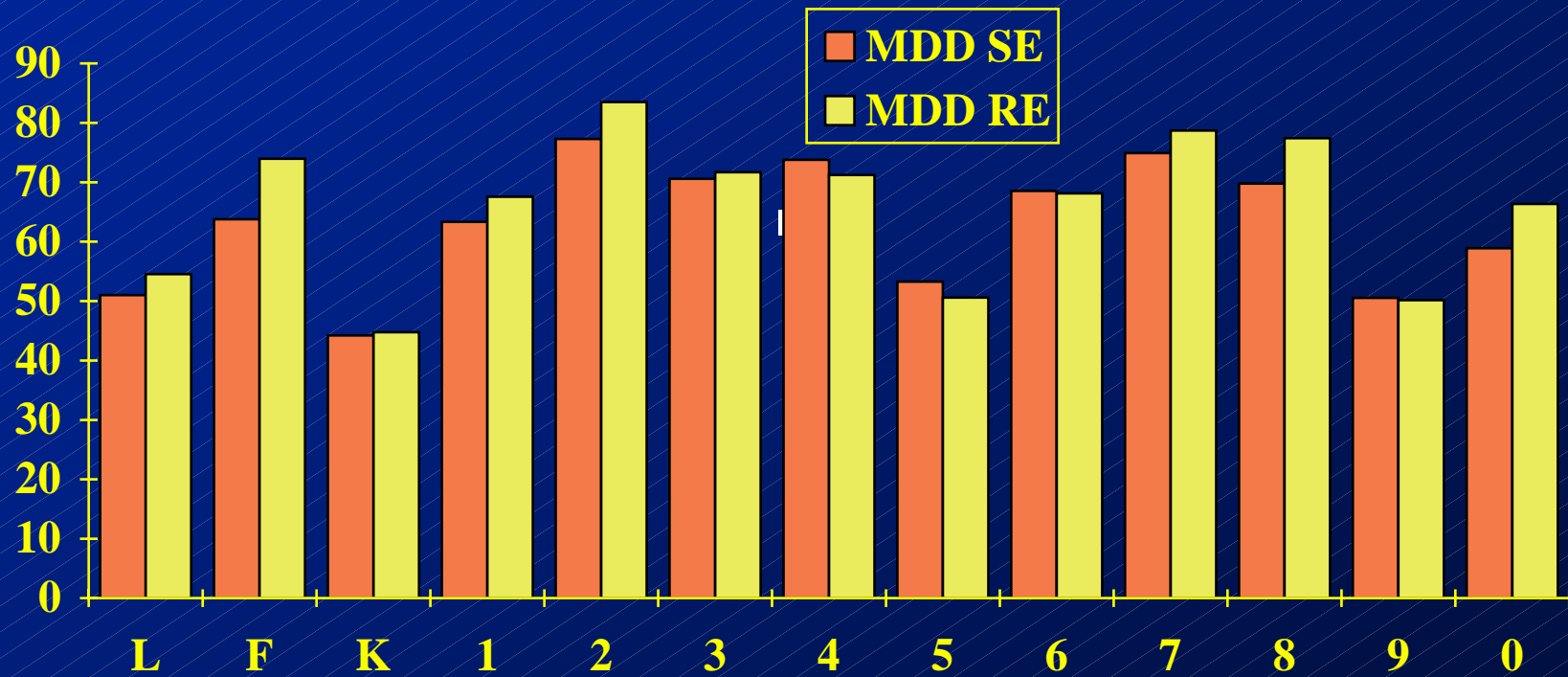
Mean Age and Education Levels for MDD SE and RE Groups



CVLT Scores of MDD Groups



MMPI-2 Scores of MDD Groups



Results

- **On CVLT**
 - **MDD SE had better acquisition, retention, and retrieval**
- **MDD SE also had better attention span and visual memory**
- **No differences on measures of psychomotor speed or speed of information processing**

Conclusions

- **Recurrent MDD is associated with greater deficits in new learning than is MDD-Single Episode**
- **Relative performances are not due to pre-morbid ability, severity of depression, or other demographic factors**
- **Data suggest that MDD-Recurrent is associated with a mild decrease in function from pre-morbid levels**
 - Consistent with “Kindling” hypothesis of Post
 - Consistent with imaging data of Shelline suggesting greater hippocampal abnormalities in people with chronic recurrent depression
- **May explain previous inconsistencies in studies of MDD and neuropsychological function**

DSM-IV Melancholic Features

- **Features:**
 - **Marked Anhedonia**
 - **Affective Non-Reactivity**
 - **Diurnal Variation**
 - **Motor Retardation or Agitation** ■
 - **Anorexia/Weight Loss**
 - **Excessive Guilt**
- **Correspond with:**
 - **Endogenous Onset**
 - **Dexamethasone Non-Suppression**
 - **Hyperadrenocorticism**
 - **Decreased REM Latency**
 - **Abnormal Asymmetry on Dichotic Listening Tests**

Neural Substrates of Melancholic Features

- Psychomotor retardation is similar to Parkinson's and Huntington's Diseases
- Neural models of depression imply that melancholic features especially involve cingulate and frontal dysfunction

CORE—A Measure of Melancholia

- **Sign Based Clinician Rating of Melancholic Features**

1) Non-Interactiveness	10) Facial Apprehension
2) Facial Immobility	11) Delay in Verbal Response
3) Postural Slumping	12) Decreased Length of Verbal Response
4) Non-Reactivity	13) Inattentiveness
5) Facial Agitation	14) Body Immobility
6) Motor Agitation	15) Poverty of Associations
7) Slowed Movement	16) Verbal Stereotypy
8) Delay in Motor Response	17) Impaired Spontaneity of Speech
9) Slowed Speech Rate	18) Stereotyped Movements

CORE Correlates

- **Dexamethasone Non-Suppression**
- **Older age of onset**
- **Severity of depressive symptoms**
- **Decreased rates of full remission**
- **Greater likelihood of bipolar disorder**
- **Frequency of psychotic features**
- **Slower reaction times**
- **Poor new-learning**
- **Perseverative errors on the WCST**

CORE Implications

- **Melancholic features may correspond with cognitive impairment in depression.**
- **Thus, the present study**
 - **Cross-validation and extension of preliminary findings concerning CORE and neuropsychological function**

Method

- Subjects

- 55 depressed inpatients
 - » 41 unipolar depression (8 with psychotic features)
 - » 14 bipolar I depression (2 with psychotic features)
- 24 control subjects
- Screened for neurologic disease/CHI > 5 minutes
- Examined during inpatient admission
- Diagnoses made with SCID-IV by attending physician in teaching hospital

- Measures

- Executive
 - » Trails A & B, COWAT, Figural Fluency
- New-Learning
 - » CVLT, WMS-III Logical Memory & Faces
- Working Memory/Attention
 - » WMS-III Letter Number, Spatial Span
- Motor Speed
 - » Grooved Pegboard Test
- Emotional Distress
 - » MMPI-2

Demographics

	<u>Age</u>	<u>Education</u>	<u>Sex</u>	<u>Ethnicity</u>
Patients	36.27 (11.14)	12.78 ■ (2.58)	35F/20M	13C/1B/2AmIn
Controls	29.04 (9.18)	15.08 (1.64)	24F/0M	47C/6B/2AmIn/1As

Mean Scores of Patients and Controls

<u>Measure</u>	<u>Controls</u>	<u>Patients</u>
COWAT	36.89	41.86
TMT A	24.72	33.61
TMT B	59.45 ■	95.50
FFT-Unique Designs	46.95	44.11
CVLT Total T-Score	47.31	30.47
CVLT Short Delay Free	-.18	-1.81
CVLT Short Delay Cued	-.31	-1.58
CVLT Long Delay Free	-.31	-2.02
CVLT Long Delay Cued	-.37	-2.08
CVLT Recognition	-.31	-1.29

Mean Scores of Patients and Controls

<u>Measure</u>	<u>Controls</u>	<u>Patients</u>
Logical Memory I	12.45	9.17
Logical Memory II	12.77	9.35
Faces I	11.72 ■	9.06
Faces II	11.68	9.50
Letter Number	12.09	9.53
Spatial Span Forward	10.55	8.29
Spatial Span Backward	10.91	8.62
Grooved Pegboard-Dom	60.14	90.30
Grooved Pegboard-Non	70.14	98.23
Impaired Scores	1.18	3.93

Mean MMPI-2 Clinical Scales of Patients and Controls

<u>Measure</u>	<u>Controls</u>	<u>Patients</u>
1 HS	56.08	66.18
2 D	49.83	72.23
3 HY	56.71 ■	67.10
4 PD	55.50	63.87
6 PA	53.62	69.85
7 PT	52.04	68.23
8 SC	52.33	71.18
9 MA	50.08	54.87

GLM--Multivariate Analysis of Neuropsychological Measures

<u>Effect</u>	<u>Hotellings T²</u>	<u>P-Value</u>
Age	1.68	.09
Sex	1.99 ■	.04
Education	1.52	.13
CORE	2.23	.02
MMPI-2 Sum	2.14	.02

Univariate Analyses of Executive Function Measures

<u>Measure</u>	<u>Effect</u>	<u>Semi-Partial</u>
COWAT	Sex	.02
	CORE	-.29**
	MMPI-2 Sum	-.02
TMT-A & B	Sex	ns
	CORE	ns
	MMPI-2 Sum	ns
FFT-Unique Designs	Sex	-.03
	CORE	-.27**
	MMPI-2 Sum	.02

Univariate Analyses of Memory Measures-CVLT

<u>Measure</u>	<u>Effect</u>	<u>Semi-Partial</u>
Total T-Score	Sex	-.06
	CORE	-.26*
	MMPI-2 Sum	-.07
Short Delay Free	Sex	-.20
	CORE	-.30**
	MMPI-2 Sum	.09
Short Delay Cued	Sex	-.14
	CORE	-.35***
	MMPI-2 Sum	.09

Univariate Analyses of Memory Measures-CVLT

<u>Measure</u>	<u>Effect</u>	<u>Semi-Partial</u>
Long Delay Free	Sex	-.01
	CORE	-.24*
	MMPI-2 Sum	-.08
Long Delay Cued	Sex	-.18
	CORE	-.32**
	MMPI-2 Sum	.07
Recognition	Sex	ns
	CORE	ns
	MMPI-2 Sum	ns

Univariate Analyses of Memory Measures-Logical Memory

<u>Measure</u>	<u>Effect</u>	<u>Semi-Partial</u>
Logical Memory I	Sex	-.21*
	CORE	-.37***
	MMPI-2 Sum	.14
Logical Memory II	Sex	-.32**
	CORE	-.32**
	MMPI-2 Sum	.20

Univariate Analyses of Memory Measures-Faces

<u>Measure</u>	<u>Effect</u>	<u>Semi-Partial</u>
Faces I	Sex	-.22*
	CORE	-.22*
	MMPI-2 Sum	.20
Faces II	Sex	-.09
	CORE	-.22*
	MMPI-2 Sum	.14

Univariate Analyses of Working Memory

<u>Measure</u>	<u>Effect</u>	<u>Semi-Partial</u>
Letter Number	Sex	-.04
	CORE	-.29**
	MMPI-2 Sum	.07
Spatial Span Forward	Sex	-.07
	CORE	-.24*
	MMPI-2 Sum	-.01
Spatial Span Backward	Sex	ns
	CORE	ns
	MMPI-2 Sum	ns

Univariate Analyses of Psychomotor Speed

<u>Measure</u>	<u>Effect</u>	<u>Semi-Partial</u>
Grooved Pegboard-Dom	Sex	-.002
	CORE	.28**
	MMPI-2 Sum	-.09
Grooved Pegboard-Non	Sex	-.06
	CORE	.35**
	MMPI-2 Sum	-.08

Univariate Analyses of Impaired Scores

<u>Measure</u>	<u>Effect</u>	<u>Semi-Partial</u>
Impaired Scores	Sex	.14
	CORE	.36***
	MMPI-2 Sum	-.16

Results

- **Total CORE score accounted for significant variance on measures of:**
 - Executive function
 - Attention and working memory
 - New-learning
 - Psychomotor speed ■
 - Overall impairment
- **Gender and Severity of Emotional Distress failed to do so**
- **Melancholia had moderately sized effects on neuropsychological test scores**

Conclusions

- **Melancholia accounts for diminished neuropsychological test scores regardless of depressive severity**
 - This is unlikely due to multicollinearity
 - Tolerances were no less than .94
- **Melancholia predicts neuropsychological impairment during major depressive episodes**
- **Deficits associated with melancholia seem to invoke diffuse dysfunction, as the pattern of poor neuropsychological performance was broad**

Implications

- **Melancholia may predict greater impairment in activities of daily living**
- **Melancholia may correspond with worse treatment outcomes** ■

Implications

- **Neuropsychological impairment is not a generic feature of major depression**
 - It corresponds with clinical correlates of illness
 - These clinical characteristics are phenotypic manifestations of underlying neural substrates.
- **Parker: Melancholic symptoms reflect dysfunction involving basal ganglia and medial and orbital frontal structures**
- **The present data support this hypothesis**
 - Deficits were observed on measures of executive function, working memory, and motor slowing
- **But, melancholic symptoms also corresponded with decreased new learning**

Functional Outcomes in Major Depressive Disorder

- **MDD is associated with reduced quality of life, activities of daily living**
 - Saarijarvie et al. (2002)
 - » Impairment in physical function, pain, fatigue, social relationships, and activities of daily living
- **Reductions in functional outcomes occur:**
 - Regardless of medical illness
 - Early in the disease
- **Work is also impaired**
 - Hawthorne et al. (2003)

Functional Outcomes in Major Depressive Disorder

- **Reductions in functional outcomes appear chronic**
 - **Angermeyer et al. (2002)**
 - » **Remitted depressives functioned more effectively than those with residual symptoms over 7 months**
 - **All patients continued to report poor ability to manage daily affairs and more health complaints**
 - **Goethe & Fischer (1995)**
 - » **Assessed functional outcomes with SIP over 12 months**
 - » **Communication and bodily care improved**
 - » **Emotional symptoms, alertness, recreational activities, socialization, and work performance were unchanged and impaired**

What Accounts for Functional Impairment in Major Depressive Disorder?

- **Depressive Severity**
 - **Bonicatto et al. (2001)**
 - » **15 month assessment of depressed patients**
 - » **Poor functional outcomes remained**
 - These were correlated with depressive severity
 - **McCall et al. (1999)**
 - » **Increasing depression and older age predicted worse outcomes**

What About Neuropsychological Impairment?

- **Neuropsychological impairment is common in major depression**
- **Neuropsychological impairment predicts poor functional outcomes in other mental illnesses (e.g., schizophrenia)**
- **Perhaps such impairment might predict poor functional outcomes in major depression**

An Initial Study

- **McCall & Dunn (2003)**
 - Administered MMSE and self-report measures of ADLs to people with major depressive disorder
 - MMSE had a modest relationship with ADL
- **But what if....**
 - A broader or more sensitive battery of tests was administered
 - Perhaps a more discrete relationship between neuropsychological function and functional outcomes may be observed.
- **Thus, the present study**

Method

- **Subjects**
 - 35 inpatients with major depression (29 non-psychotic)
 - 24 control subjects
 - Screened for neurologic disease/LOC > 5 minutes
 - Examined during inpatient admission
 - Diagnoses made with the use of SCIDs and patient history by attending physician in teaching hospital
- **Neuropsychological Measures**
 - Executive Function
 - » Trails A & B/Figural Fluency Test/COWAT
 - New Learning
 - » CVLT/Logical Memory/Faces
 - Attention-Concentration
 - » Spatial Span/Letter Number Sequencing
 - Motor
 - » Grooved Pegboard Test
 - MMPI-2

Method

- **SF-36**
 - **Physical Functioning**
 - » (limited ability to perform physical activities including bathing or dressing)
 - **Role-Physical**
 - » (problems with work or daily activities due to physical problems)
 - **Bodily Pain**
 - **General Health (physical health)**
 - **Vitality (fatigue)**
 - **Social Functioning**
 - » (capacity for normal social activities)
 - **Role-Emotional**
 - » (problems with work or other daily activities due to emotional problems)
 - **Mental Health**
 - » (constant feelings of nervousness and depression)

Demographics

	<u>Age</u>	<u>Education</u>	<u>Sex</u>	<u>Ethnicity</u>	<u>Employment</u>	<u>Self-Supporting</u>
Controls	29.04	15.08	24 Female	21C/1B/1AsAm	24 Employed	24 Yes
Patients	35.54	12.97	20F/15M	28C/6B/1AmIn	20 Employed/15 Unemployed	18 Yes/17 No

Neuropsychological Performance

	Controls	Patients
COWAT	41.92	37.31
TMT A/TMT B	24.37/57.92	35.20/100.35
FFT-Unique/Error	46.90/44.64	43.10/50.50
CVLT Total	46.83	33.23
LM1/LM2	12.33/12.67	9.71/9.86
Faces1/Faces2	11.67/11.63	9.34/9.60
SSF/SSB	10.42/11.04	8.26/8.63
LN Seq	12.04	9.32
GPT Dom/Non	60.25/68.83	91.26/102.71
MMPI AVG	52.32	66.21
Impaired Scores	1.12	4.54

SF-36 Scores

	Controls	Patients
Physical Functioning	87.71	75.71
Role Physical	90.63	36.43
Bodily Pain	22.08	36.57
General Health	56.25	55.43
Social Functioning	52.08	51.79
Role Emotional	79.17	12.38
Mental Health	67.33	50.97

Regression Analyses

<u>Functional Outcomes</u>	<u>Impairment</u>	<u>MMPI2</u>	<u>Age</u>	<u>Educ</u>
SF-36 Physical Functioning	-0.09	-0.20	0.01	**0.37
SF-36 Role Physical	-0.22	*-0.34	-0.09	0.13
SF-36 Bodily Pain	-0.07	**0.30	0.18	-0.27
SF-36 General Health	-0.07	**0.44	-0.10	-0.20
SF-36 Vitality	-0.12	*0.31	0.24	*0.35
SF-36 Social Functioning	** -0.38	0.12	-0.28	-0.27
SF-36 Role Emotional	*-0.29	** -0.41	-0.02	0.15
SF-36 Mental Health	** -0.40	-0.09	0.15	0.14
Employed?	** -0.39	** -0.30	-0.20	0.14
Self-supporting?	** -0.37	-0.14	-0.14	*0.26

Conclusions

- **Consistent with previous research, emotional distress predicts functional impairment in MDD**
 - **Significant prediction was obtained for:**
 - » **Role Physical**
 - » **Bodily Pain** ■
 - » **General Health**
 - » **Vitality**
 - » **Role Emotional**
 - » **Employment Status**

Conclusions

- **Extending previous findings, neuropsychological impairment predicted functional outcomes**
 - **Significant prediction was obtained for:**
 - » **Social Functioning**
 - » **Role Emotional** ■
 - » **Mental Health**
 - » **Employment Status**
 - » **Self-Supporting**

Implications

- **Clinicians should assess and treat neuropsychological deficits in MDD**
- **Results of neuropsychological examinations could be used to tailor treatment plans and rehabilitation efforts**

Models of Competent Treatment Decisions & Consent

- Appelbaum & Grisso's Model of Consent
 1. Understanding
 2. Appreciation of consequences
 3. Rational and logical decision-making
 4. Expressing a choice
- Each of these 4 capacities may be affected by cognitive impairment or emotional duress (Appelbaum & Grisso, 1995, Marson, 2001)
- Neuropsychological Model of Consent Competency (Marson et al., 1999)

Depression and Informed Consent

- Depressed *outpatients* do not appear to differ from controls in their ability to provide informed consent (Appelbaum et al., 1999; Stiles et al., 2001)
- Little is known about the ability to depressed patients receiving *inpatient* treatment ■
- Meta-analyses suggest that neuropsychological impairment occurs more commonly in inpatients than in outpatients
 - Executive function
 - Retrieval of new-learning
 - Inattention

Hypotheses

- Cognitively impaired depressed inpatients differ from controls and unimpaired inpatients in their ability to provide informed consent
- Cueing and recognition recall will enhance understanding of consent information
- Executive functioning deficits will best predict the inability to provide consent

Methods

- Participants
 - 31 Depressed Inpatients
 - 27 Controls
- Exclusion Criteria
 - Age 18-65
 - English as native language
 - Developmental disability
 - Hx of neurological disorder
 - LOC in past 6 months or life-time LOC > 5 minutes
 - Substance abuse (controls only)

Measures

- **Diagnostic interview**
 - SCID-I
- **Depression Screen**
 - CMDI
- **Cognitive Measures**
 - WAIS-III Digit Span (backward span cumulative percentage)
 - CVLT-II (standard score of trials 1-5 total)
 - WCST (perseverative errors)
- **Consent Measure**
 - Understanding Treatment Disclosures Scale (Appelbaum & Grisso, 1995)
 - » Free Recall
 - » Cued Recall
 - » Recognition

Impairment Groups

Group	N	Age M (SD)	Education* M (SD)
Controls	23	40.7 (12.1)	15.5 (2.6)
Unimpaired Depressed	16	35.8 (11.0)	12.9 (1.8)
Impaired Depressed	15	40.5 (11.6)	11.9 (1.9)

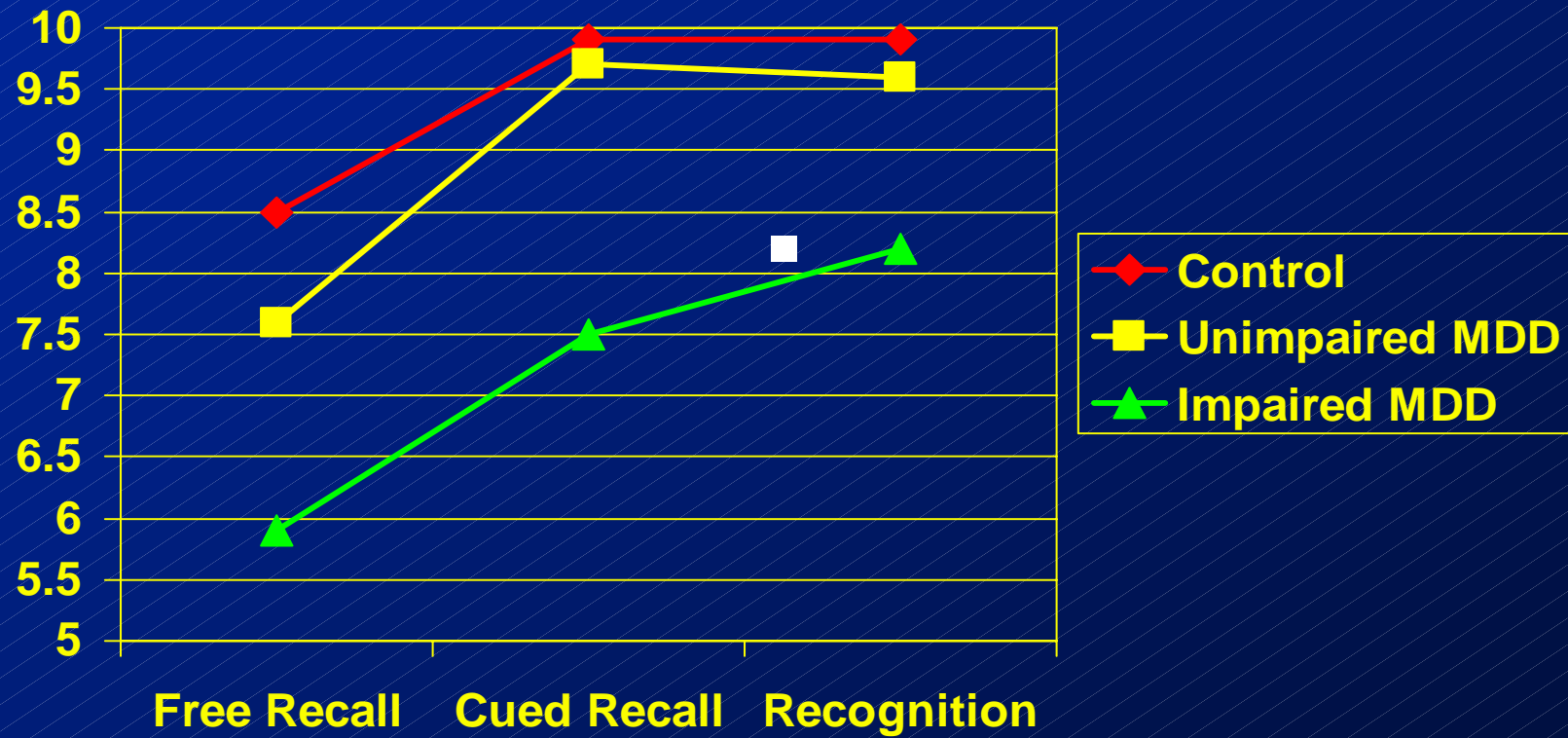
* p<.05

Impairment Group Performance

	Digit Span M (SD)	WCST M (SD)	CVLT-II M (SD)	CMDI M (SD)
Controls	43.4 (31.3)	■ 6.1 (2.4)	61.1 (9.7)	60.8* (3.3)
Unimpaired MDD	60.5 (24.7)	9.1 (3.5)	48.9* (10.4)	106.2 (15.6)
Impaired MDD	89.2* (15.1)	19.9* (9.1)	35.4* (11.2)	108.5 (12.5)

* p<.05

UTD Performance



Regression Analysis: CVLT-II

	Semi-partial correlation	Significance level
Free Recall	.48 ■	p<.05
Cued Recall	.37	p<.05
Recognition	.39	p<.05

Conclusions

- Some depressed inpatients experience cognitive impairment that impedes their ability to understand information presented during informed consent
- Cueing and recognition recall can enhance the ability of cognitively impaired inpatients to provide consent
- Memory impairment (CVLT-II performance) was the best predictor of the inability to understand consent material
- Given that some depressed inpatients may be at risk, these individuals should be carefully screened for cognitive impairment in order to assure that these individuals are being treated in an ethical manner