Cognition in Depression: Design Challenges

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Disclosures (lifetime): Maurizio Fava, MD

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Stock/Other Financial Options	Equity Holdings: Compellis; PsyBrain, Inc. Royalty/patent, other income: Patents for Sequential Parallel Comparison Design (SPCD), licensed by MGH to Pharmaceutical Product Development, LLC (PPD); and patent application for a combination of Ketamine plus Scopolamine in Major Depressive Disorder (MDD), licensed by MGH to Biohaven. Copyright for the MGH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), Symptoms of Depression Questionnaire (SDQ), and SAFER; Lippincott, Williams & Wilkins; Wolkers Kluwer; World Scientific Publishing Co. Pte.Ltd.

Critical Study Design Decisions

- Population under investigation
  - Untreated MDD
  - Treated MDD (for adjunctive study designs)
  - Remitted MDD with Residual Sxs
- Outcome measure relevance to the population
  - Sensitivity
- Comparison arm(s)
  - Placebo
  - Active Comparator
  - Both

Critical Study Population Decisions

- All Comers (With and Without Cognitive Impairment)
  - Many subjects become uninformative
- How Does One Enrich an MDD Population?
  - Subjective measures
  - Objective measures
  - Both

Objective vs Subjective Measures of Cognition

Plus - These are Objective Measures, Relatively Devoid of Biases

Performance on Standardized Cognitive Tests

Minus - The Norms are Population-Based and Do Not Reflect Premorbid Performance Levels

Self-Reported Levels of Functioning

Self-Reported Perception of One's Cognitive and Executive Function

Plus – Some of These Measures Capture the Perception of Change From Premorbid Levels

Minus – Depression and/or Anxiety May Affect the Perception of Cognitive Function

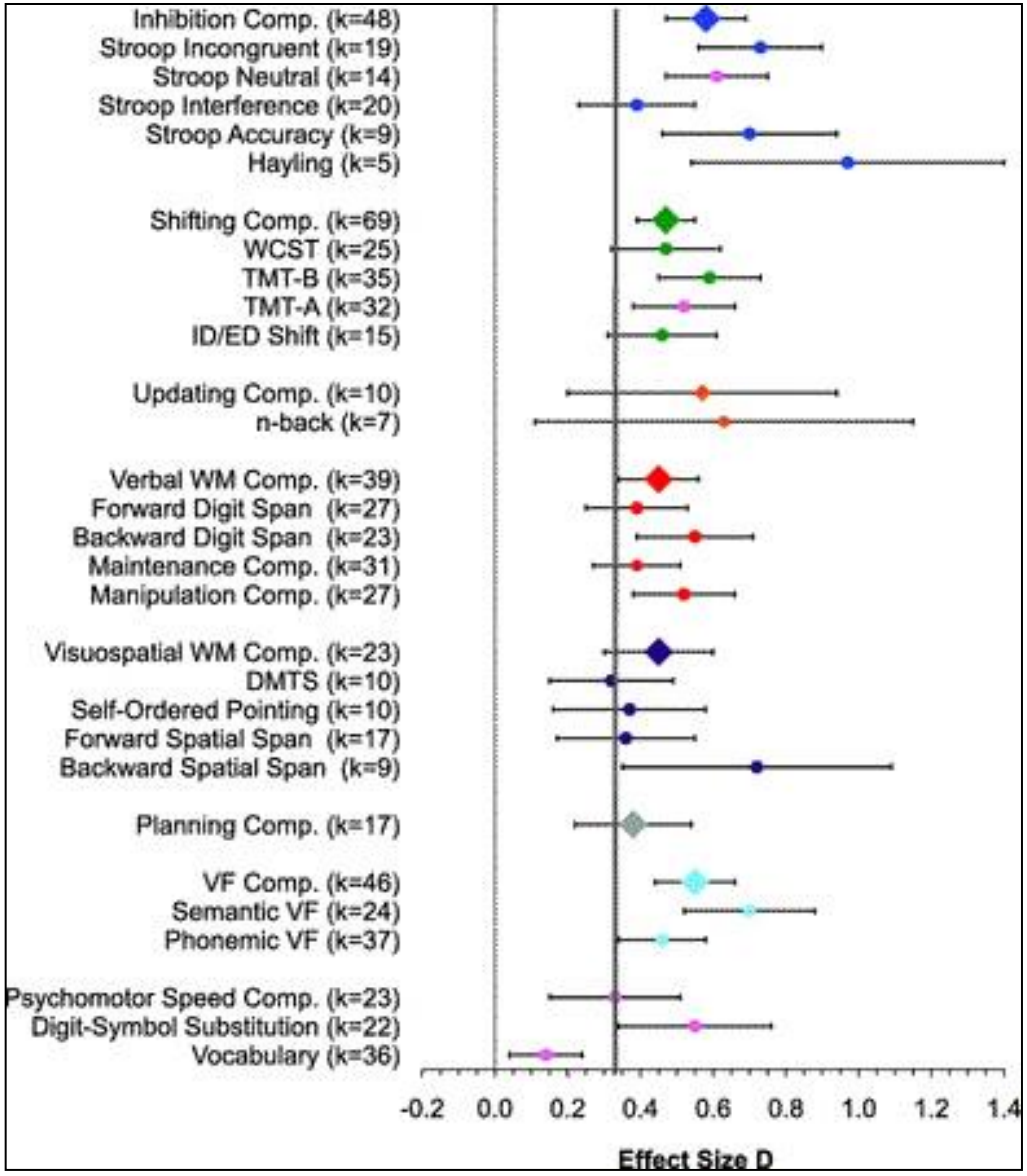
Objective Measures of Impaired Cognition in Depression

	Endogenous (20)	Neurotic (20)	Control (20)	*P* value for F test	Scheffe ($P < 0.05$)
Sum 5 AVLT Trials	40.5 (12.0)	44.0 (8.2)	55.8 (11.2)	0.0001	C > N, E
Delayed Recall	8.0 (3.5)	9.2 (4.0)	12.2 (2.9)	0.002	C > N, E
Recognition	9.2 (3.6)	9.4 (6.3)	13.4 (1.9)	0.004	C > N, E
'Forgetting'	2.3 (1.7)	2.4 (2.3)	1.5 (1.5)	0.21	
Digitspan (forward)	9.3 (2.0)	8.8 (1.7)	9.2 (1.9)	0.66	
Digitspan (back)	7.0 (2.2)	6.4 (2.1)	7.8 (2.2)	0.19	
Block design	23.9 (12.8)	29.8 (10.2)	32.1 (11.1)	0.12	
DSST	37.9 (15.0)	45.9 (12.8)	53.7 (10.6)	0.001	C > E
Trails A (secs)	50.7 (24.5)	40.9 (10.1)	35.8 (11.9)	0.02	C < E
Trails B (secs)	144 (85.1)	100.3 (70.3)	68.9 (22.5)	0.002	C < E
Verbal fluency (Words/min.)	12.8 (5.8)	13.2 (6.3)	15.8 (4.8)	0.23	

Scores for the three groups were compared by one way ANOVA. Differences between groups were located post hoc with the Scheffe test; abbreviations are, C = Control group, N = Neurotic group, E = Endogenous group.

Austin et al, Journal of Affective Disorders, 1992; 25, 21–29

Meta-Analysis of Studies Using Objective Measures of Impaired Cognition in Depression



Major Depressive Disorder Is Associated With Broad Impairments on Neuropsychological Measures of Executive Function: A Meta-Analysis and Review.
Snyder, Hannah

Psychological Bulletin. 139(1):81-132, January 2013.
DOI: 10.1037/a0028727

Figure 1 Weighted mean effect sizes for all analyses. Error bars are 95% confidence intervals. Compared to healthy control participants, patients with major depressive disorder are significantly impaired on all tasks. Executive function (EF) composite measures are indicated with diamond symbols, and individual measures within each EF component by circle symbols in the same color. Pink circles indicate non-EF comparison measures. The solid gray vertical line indicates the psychomotor speed composite score effect size: Measures for which the lower error bar (95% confidence interval) does not pass the dashed line are significantly greater than 0, and those that do not pass the solid gray line have significantly larger effect sizes than the psychomotor speed effect size. Comp. = composite score; WCST = Wisconsin Card Sorting Test; TMT-B = Trail Making Test Part B; TMT-A = Trail Making Test Part A; ID/ED = Intradimensional/Extradimensional; WM = working memory; DMTS = delayed-match-to-sample; VF = verbal fluency.

Cognition Subscale of CPFQ

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(d) How has your ability to focus/sustain attention been over the past month?					
1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent
(e) How has your ability to remember/recall information been over the past month?					
1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent
(f) How has your ability to find words been over the past month?					
1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent
(g) How has your sharpness/mental acuity been over the past month?					
1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

Fava et al, Reliability and Validity of the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire. Psychother Psychosom 2009;78:91–97

Prevalence of Subjectively-Defined Cognitive Dysfunction in MDD

TAK316

Subjective Impairment Patients scoring at least markedly impaired (≥5) on at least 2 of the 4 cognitive items in CPFQ	
CPFQ (≤moderately) NO	CPFQ (≥markedly) YES
267 (58%)	195 (42%)

Fava et al, in preparation; this is a baseline, post-hoc analysis

Differences in Depression Severity and Functioning in MDD with and without CD

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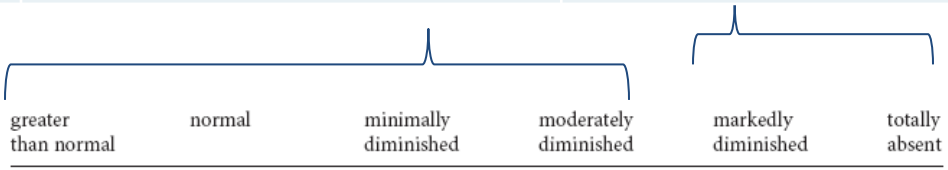
TAK316

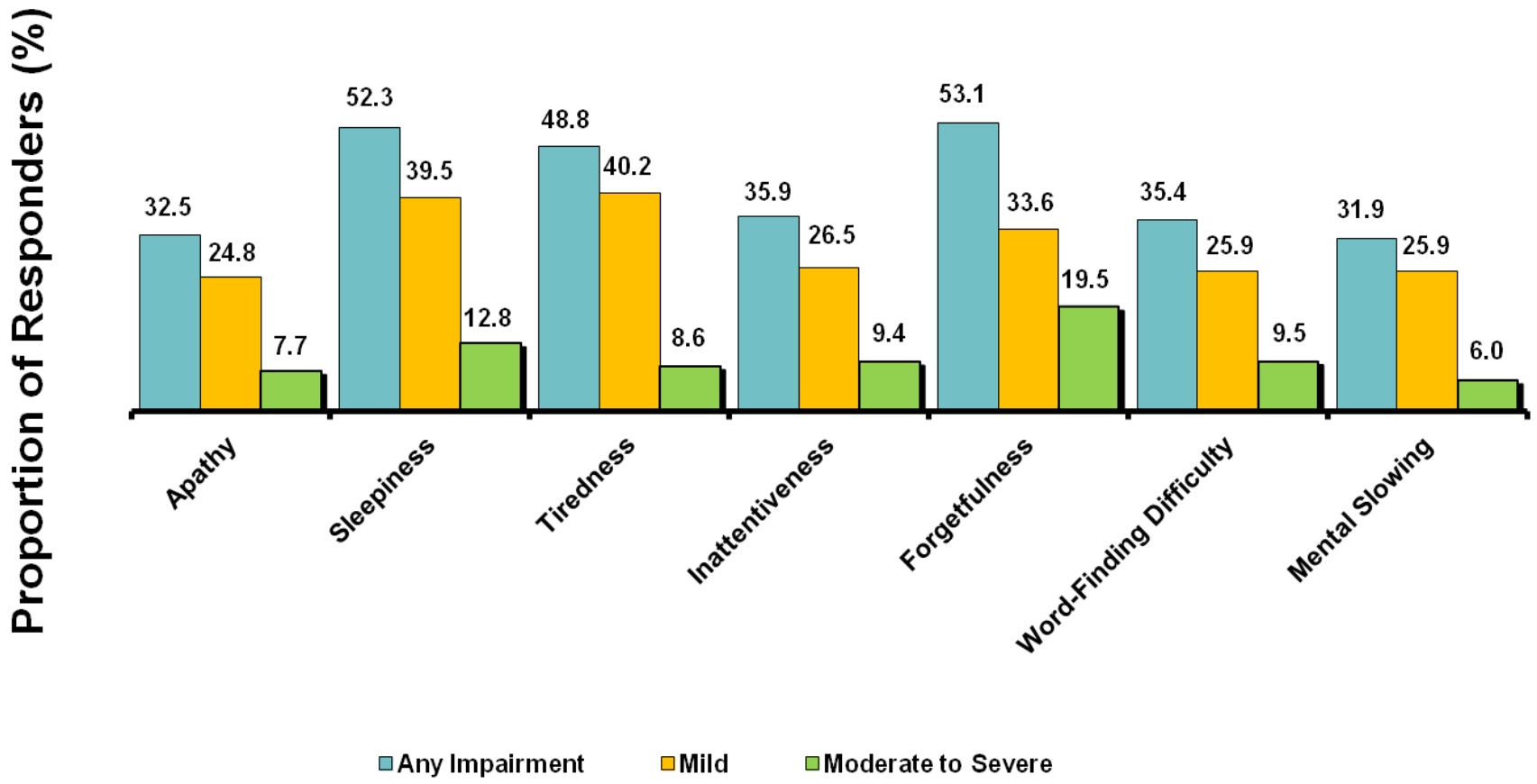
Subjectively	CPFQ (≤moderately impaired) n=267 (58%)	CPFQ (≥markedly impaired) n=195 (42%)
MADRS	31.5 ± 4.1	33.3 ± 4.3
SDS	18.2 ± 5.3 (n=169)	20.9 ± 6.2 (n=134)



Please answer all questions by *circling* the *correct answer* or the answer which seems the most *appropriate* to you (consider 'normal' the time in your life prior to the past month when you were most satisfied with your cognitive and physical functioning). Copyright: Massachusetts General Hospital.

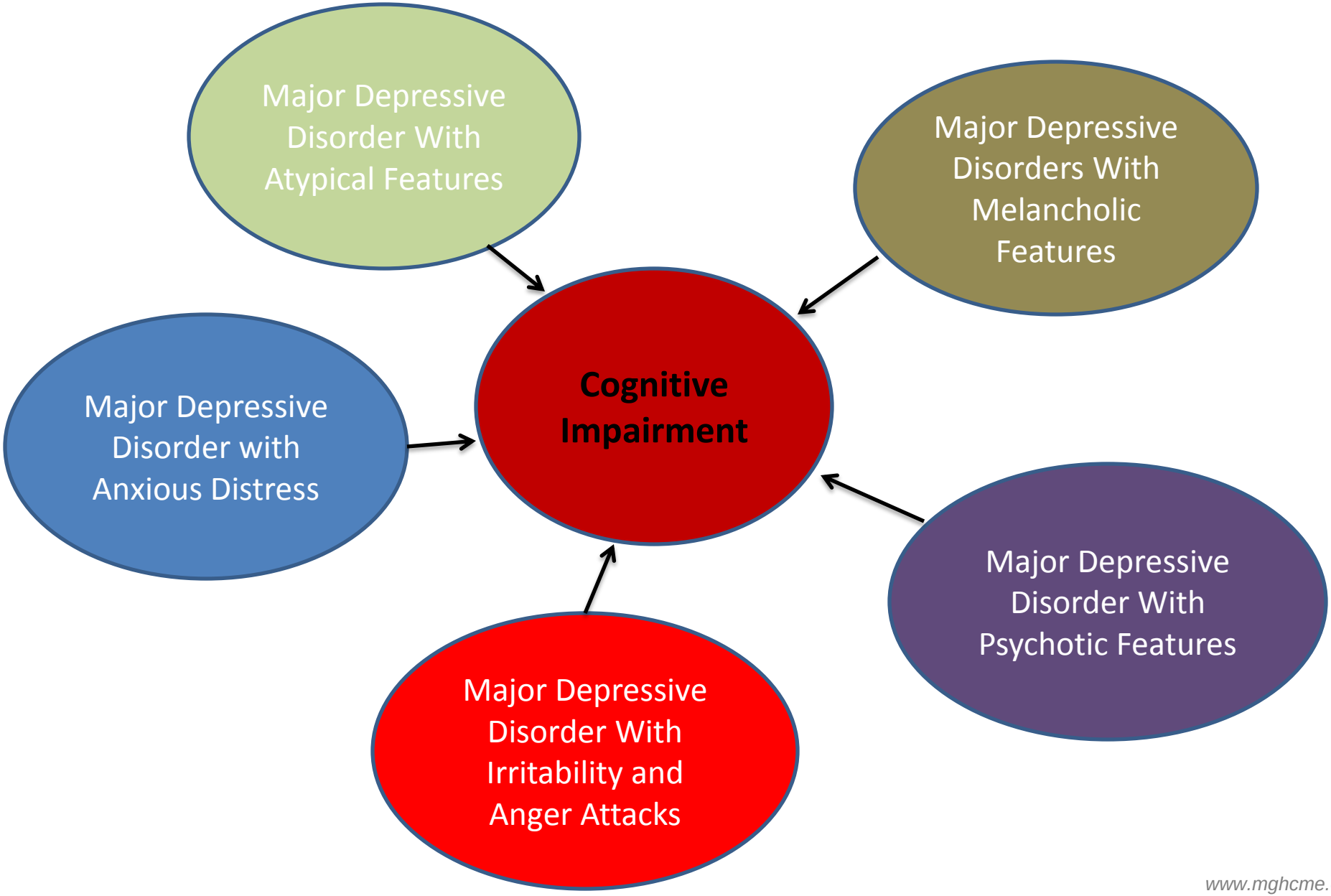
Fava et al, in preparation; this is a baseline, post-hoc analysis

Proportion of MDD Subjects with Residual Physical and Cognitive Deficits (N=117)



Fava M et al, J Clin Psych 2006; 67: 1754-1759

How Does the Heterogeneity of Depression Affect Cognition?



Relationship Between Depressive and Cognitive Symptoms in MDD

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TABLE.
Correlations Among Specific Symptoms Recorded by the HANDS and the CPFQ

CPFQ	Apathy/ Motivation	Wakefulness/ Alertness	Energy Level	Focus/Sustain Attention	Memory/ Recall	Word Finding Ability	Sharpness/ Mental Acuity
HANDS							
Fatigue	.24	.35*	.42	.32*	.45	.09	.23
Self-Blaming	.02	.01	–.04	–.09	–.04	–.02	–.03
Appetite	.11	–.12	.08	.04	–.04	.06	–.06
Sleep	–.04	–.07	.26	.09	–.12	.02	–.03
Hopelessness	.23	.13	.09	.18	.00	–.05	.09
Blue	.34*	.27	.27	.29	.04	.00	.18
Interest	.42*	.28	.29	.29	.08	.14	.24
Worthlessness	–.06	.13	.08	.04	.01	.049	.19
Suicide Thoughts	.10	.15	.09	.27	.17	.13	.11
Concentration/Making Decision	.32*	.29	.30	.52*	.29	.26	.38*

* $P<0.0007$

HANDS=Harvard Department of Psychiatry National Depression Screening Day Questionnaire; CPFQ=Cognitive and Physical Functioning Questionnaire; MGH=Massachusetts General Hospital.

Pedrelli P, Baer L, Iosifescu DV, Fava M. *CNS Spectr.* Vol 15, No 1. 2010.

What is the overlap Between Subjective and Objective Cognitive Impairment in MDD?

Distribution of MDD patients with Cognitive Dysfunction

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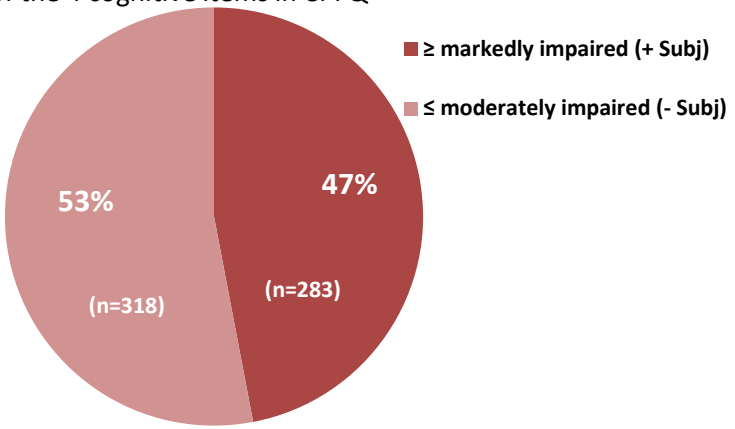
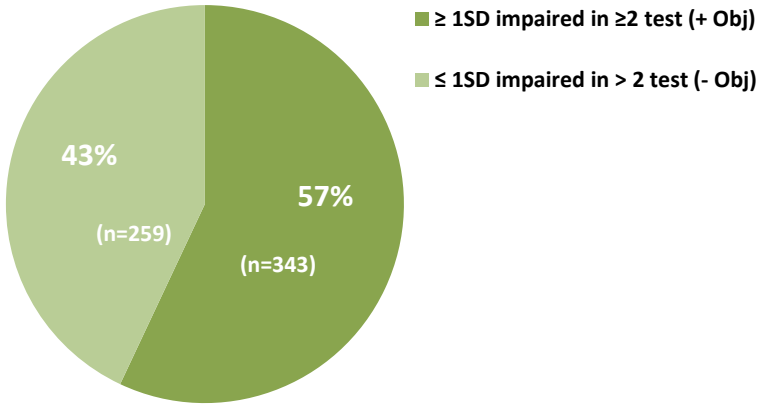
Subjective Self-reported Cognitive Dysfunction in MDD

patients scoring at least markedly impaired (≥5) on at least 2 of the 4 cognitive items in CPFQ

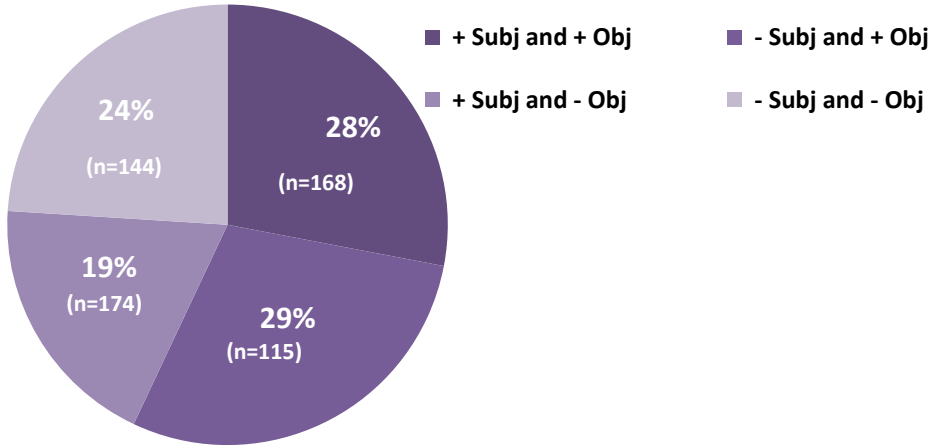


Objective Cognitive Performance Deficit in MDD

patients scoring >1 SD below norm on 2 or more of DSST, TMT-B, CRT, One-back



Subjective AND/OR Objective Cognitive Dysfunction in MDD



Fava et al, in preparation; this is a baseline, post-hoc analysis

CONNECT

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Differences in Depression Severity and Functioning in MDD with and without CD

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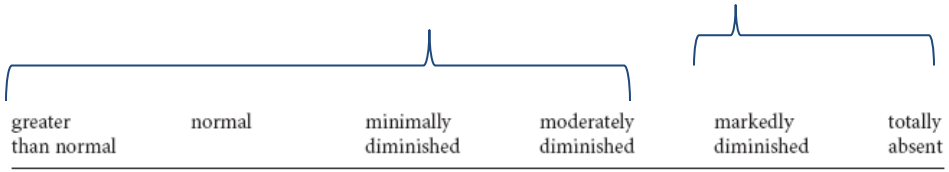
Subjectively	CPFQ (≤moderately impaired) n=318 (53%)	CPFQ (≥markedly impaired) n=283 (47%)
MADRS	30.9 ± 3.5	32.5 ± 4.0
PDQ	37.4 ± 10.5	49.2 ± 9.1
UPSA	78.5 ± 12.3	77.9 ± 12.9

Objectively	"Not/Less" impaired (<1SD) n=259 (43%)	Impaired (≥1SD) n=343 (57%)*
MADRS	31.6 ± 3.9	31.7 ± 3.8
PDQ	42.2 ± 11.3	43.5 ± 11.6
UPSA	80.6 ± 10.2	76.4 ± 13.9



Please answer all questions by *circling* the *correct answer* or the answer which seems the most *appropriate* to you (consider 'normal' the time in your life prior to the past month when you were most satisfied with your cognitive and physical functioning). Copyright: Massachusetts General Hospital.

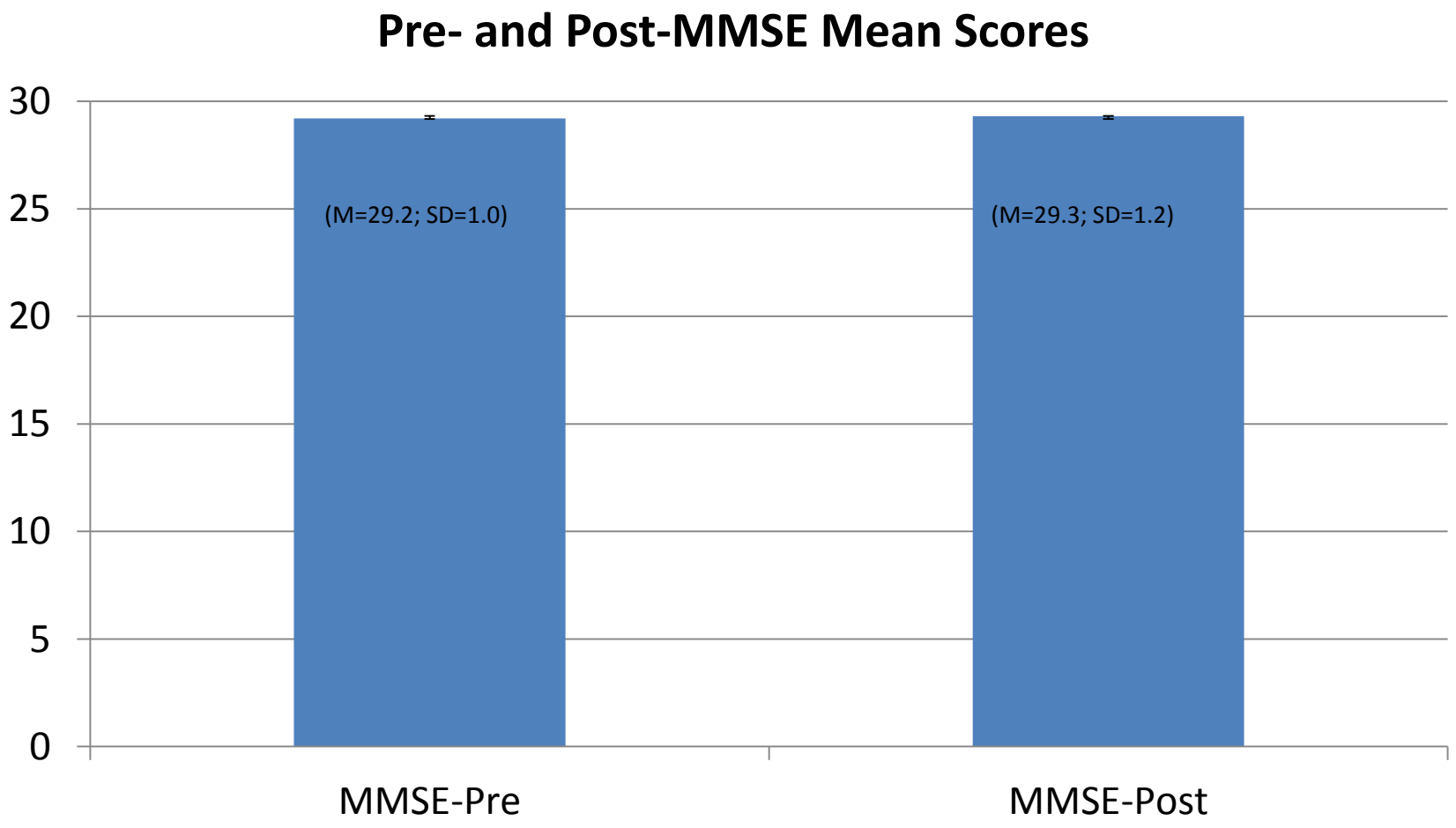
*patients scoring >1 SD below norm on 2 or more of DSST, TMT-B, CRT, One-back
(Objectively impaired)

Fava et al, in preparation; this is a baseline, post-hoc analysis

Sensitivity of Cognitive Function Measures

- The term sensitivity, when applied to therapeutics, connotes the ability of a measure or test to discriminate the effects of two treatments
  (Kellner R, Research Designs and Methods in Psychiatry - Fava M and Rosenbaum JF, eds. – Elsevier Science, 1992)
- "Flooring" and "Ceiling" effects have a markedly negative effect on the sensitivity of measures to detect treatment effects
- Most cognitive measures were developed for the assessment of severe neuropsychiatric conditions and may not be the best fit for the assessment of cognitive impairment in depression

MMSE Scores Before and After Treatment with Fluoxetine in MDD



Alpert et al, Psychother Psychosom. 1995;63(3-4):207-11

Changes in Neuropsychological Testing After Antidepressant Therapy in MDD

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Table 2

Performance of the MDD patients in the neuropsychological functional tests before and after antidepressant treatment.

	Before treatment	After treatment	*p* values	RCI corrected for practice effects
CPT				
Non-masked	3.7 ± 1.1	4.2 ± 0.9	0.052	–
Masked	2.9 ± 1.2	3.7 ± 0.8	<0.001*	0.4 ± 0.7[a]
FTT				
Dominant finger	37.5 ± 10.8	41.1 ± 12.2	0.111	–
Non-dominant finger	35.8 ± 8.5	39.9 ± 8.4	0.020*	4.2 ± 4.6
WCST				
Completed categories	1.7 ± 1.4	2.2 ± 1.8	0.027*	0.4 ± 0.5[a]
Preservative errors	15.7 ± 13.1	14.2 ± 11.9	0.981	–

MDD: major depression disorder, RCI: reliable change indices, CPT: continuous performance test, FTT: Finger-Tapping Test, WCST: Wisconsin card-sorting test.

* $p < 0.05$.

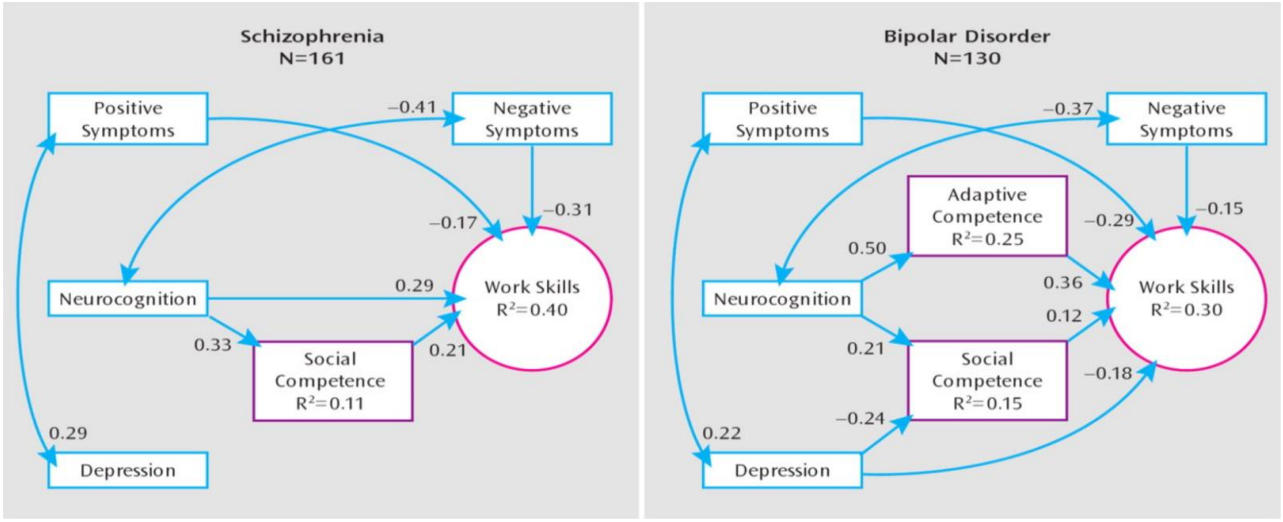
[a] Clinically significant changes.

Chang et al, Brain, Behavior, and Immunity 26 (2012) 90–95

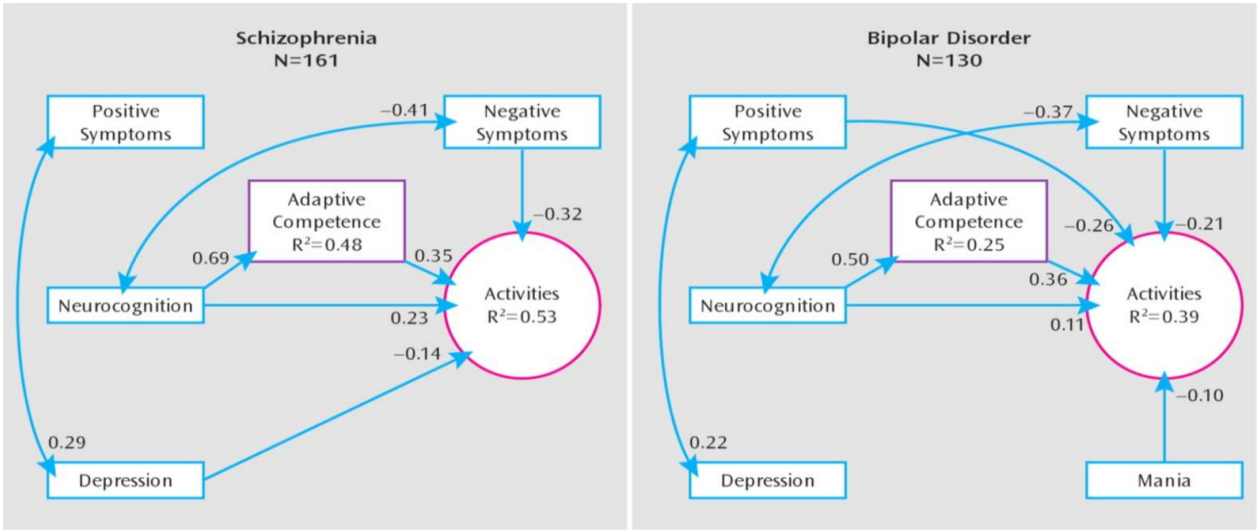
Depression and Cognitive Deficits are Independently Related to Functional Deficits in Mood Disorders

Bowie et al, Am J Psychiatry. 2010 Sep;167(9):1116-24.

a) Prediction of Work Skills



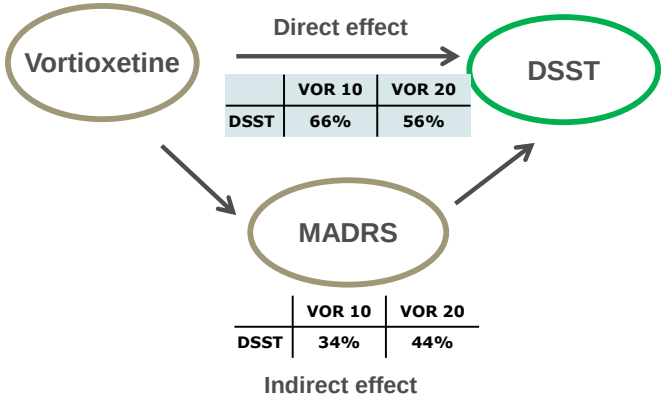
b) Prediction of Community and Household Activities



The Effects on Cognition Cannot Solely be Explained by the Improvement in Depressive Symptoms

FOCUS

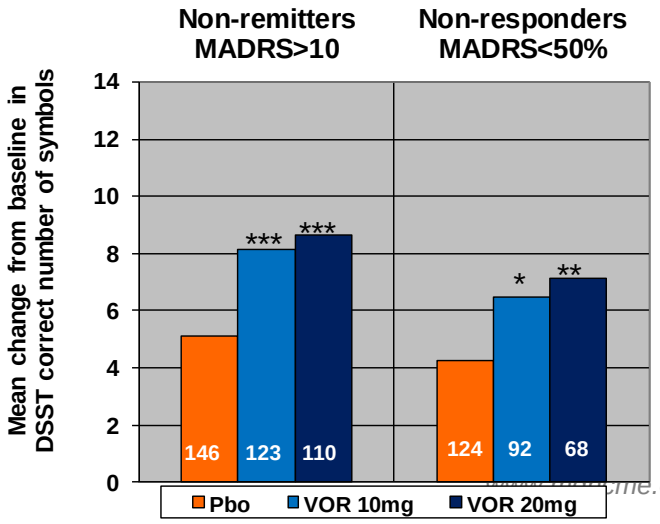
Path-analysis shows that up to two thirds of the effect on cognition can be considered as independent effect, not mediated by improvement on mood



Vortioxetine significantly improves cognitive performance even after correcting for effect on mood

Change from Baseline to Placebo (FAS, LOCF)	VOR 10mg	VOR 20mg
Effect on DSST after correcting for effect on MADRS	2.59**	2.23**

Vortioxetine significantly improves cognitive function in both non-remitters and non-responders

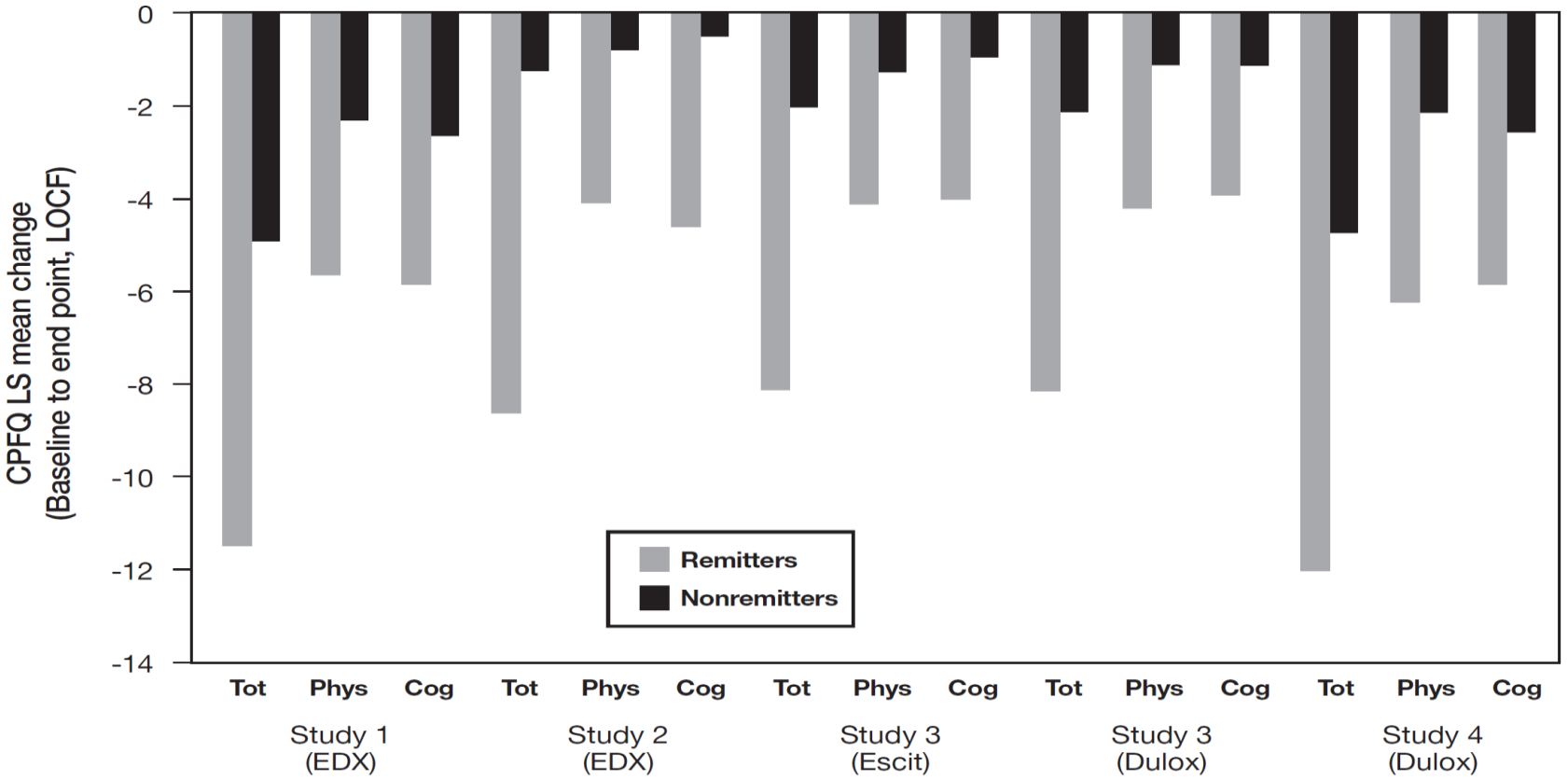


McIntyre et al.
Int J Neuropsychopharmacol 30 April 2014:1-11. Epub ahead of print

Subjective Cognitive Improvement in MDD Remitters and non-Remitters

FIGURE 1

CPFQ total, physical subscale, and cognitive subscale scores for remitters vs nonremitters



In studies 1, 2, and 3, remission was defined as a MADRS total score ≤10. In study 4, remission was defined as a HAM-D-17 total score ≤7. Only the active treatment arms are presented in this figure.

All remitter vs nonremitter differences were statistically significant ($P < .0001$).

Cog: CPFQ cognitive subscore (items 4–7); CPFQ: Cognitive and Physical Functioning Questionnaire; Dulox: duloxetine; EDX: edivoxetine; Escit: escitalopram; HAM-D-17: Hamilton Rating Scale for Depression, 17-item; LOCF: last observation carried forward; LS: least-squares; MADRS: Montgomery-Åsberg Depression Rating Scale; Phys: CPFQ physical subscore (items 1–3), Tot: CPFQ total score.

Baer et al, ANNALS OF CLINICAL PSYCHIATRY 2014;26(4):270-280

Relationship between Changes in Functioning (SDS) and Cognition (CPFQ) in MDD Patients with Residual Apathy

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- Correlation between SDS and CPFQ change in total score from baseline to endpoint in patients with MDD and residual apathy

Model	Label	Standardized Coefficient	*p*-value[a]	Ordinary Coefficient	R-square
Change in SDS total score					0.67
	Intercept	0.00	<0.001	−10.27	
	Treatment	−0.03	0.339	−0.40	
	Baseline SDS total score	−0.71	<0.001	−0.78	
	Baseline CPFQ total score	0.69	<0.001	0.84	
	Change in CPFQ total score	0.77	<0.001	0.85	

Rothschild et al, Comprehensive Psychiatry 55 (2014) 1–10;

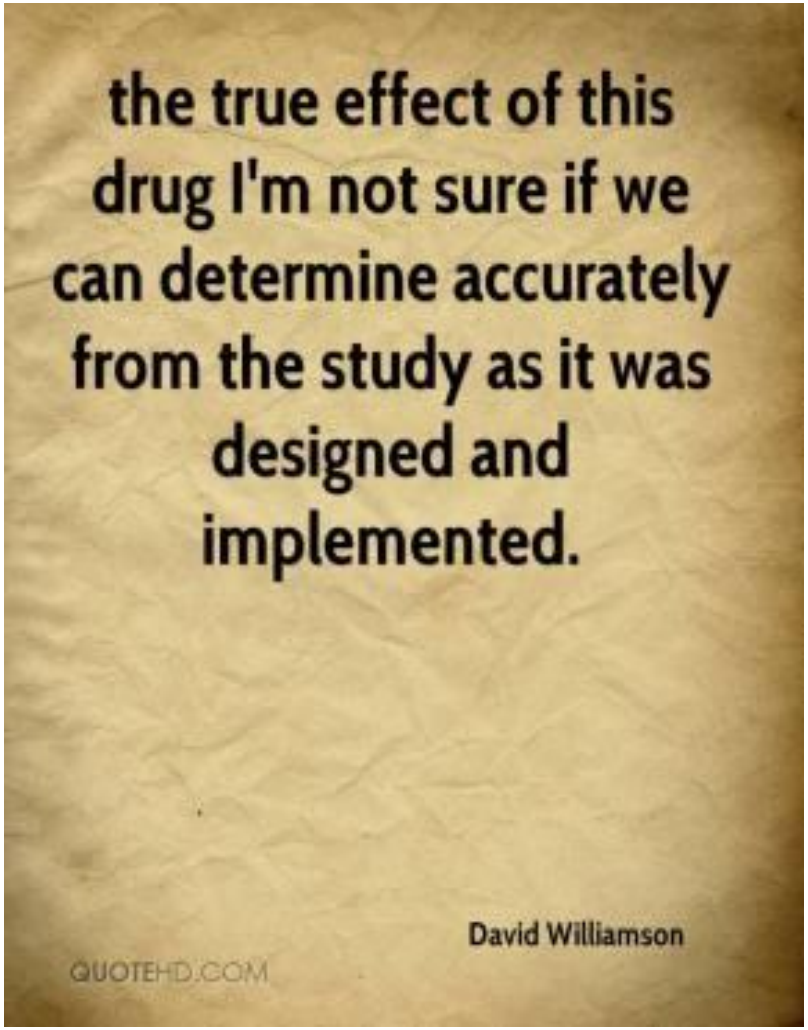
TABLE 5
Percentage of variance in SDS scores as explained by the CPFQ total score and the MADRS

Model	Study 1	Study 2	Study 3	Study 4
MADRS only, % variance	35.8%	45.6%	21.0%	23.4%
MADRS + CPFQ total score, % variance	58.0%	54.2%	40.0%	40.4%

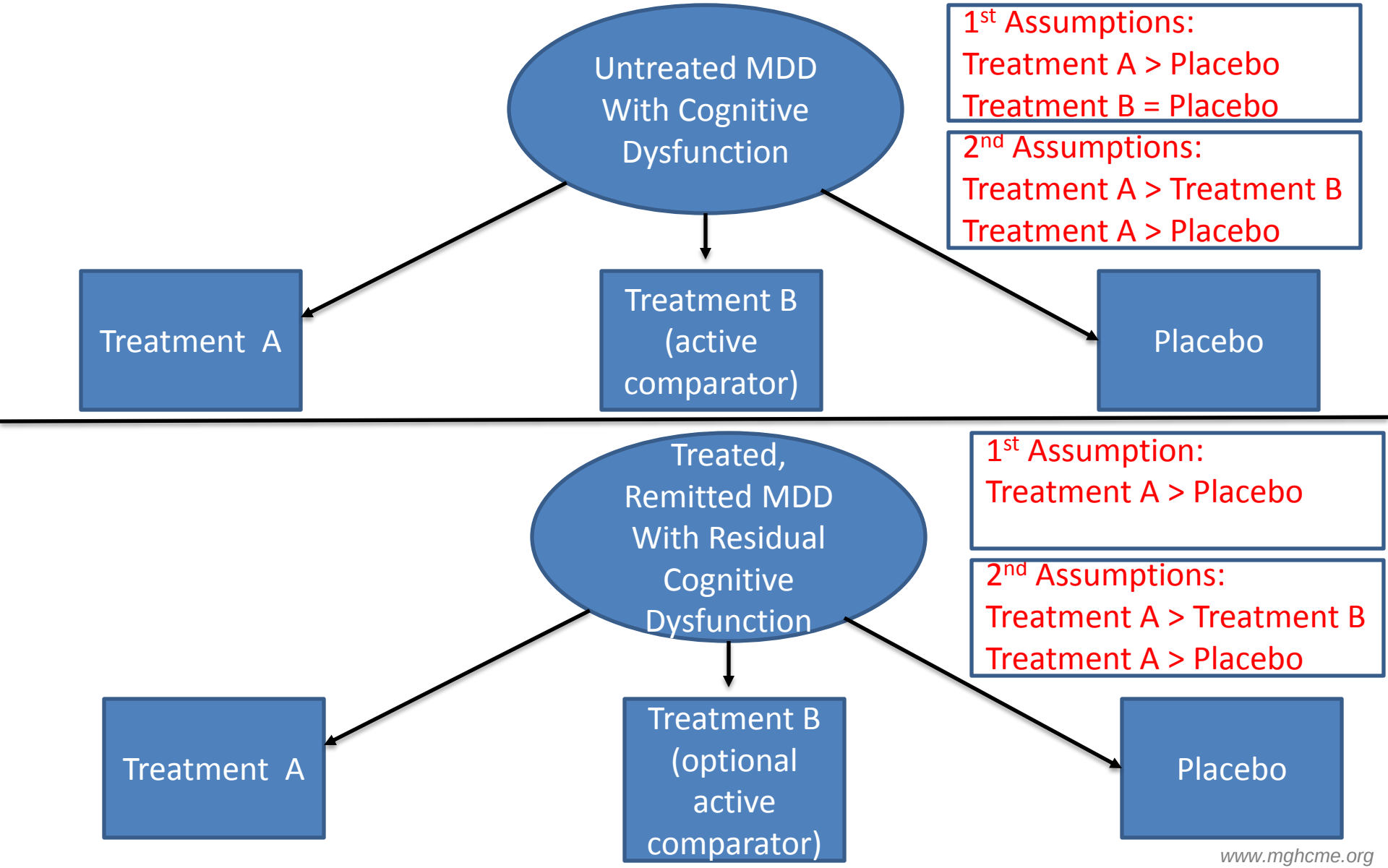
CPFQ: Cognitive and Physical Functioning Questionnaire; MADRS: Montgomery-Åsberg Depression Rating Scale, SDS: Sheehan Disability Scale.

Baer et al, ANNALS OF CLINICAL PSYCHIATRY 2014;26(4):270-280

How Do We Address Issues of Pseudospecificity in Designing a Study in MDD with Cognitive Impairment?



Study Design Options



Conclusions

- In MDD studies, critical design decisions pertain to both population and measures
- 40% to 55% of adults with MDD present with either subjective or objectively defined cognitive dysfunction
- There is only partial overlap between subjective and objective cognitive impairment in MDD
- The presence of cognition dysfunction in MDD is associated with greater illness severity and poorer functioning than MDD alone
- The heterogeneity of MDD is associated with a poor correlation between core MDD symptoms and cognitive symptoms

Conclusions (cont.)

- Depression and cognitive deficits are independently related to functional deficits in MDD
- Cognitive symptoms are reported by 30% to 40% of responders/remitters with MDD
- Changes in levels of functioning among MDD patients with residual symptoms are significantly accounted for by changes in cognitive symptoms
- Measures of cognition in MDD need to be adequately sensitive to detect therapeutic effects
- Various study design options exist, including some with and others without active comparison