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Applied Translational Medicine

Early Clinical Research in Mental Health: Working with the US TURNS Consortium

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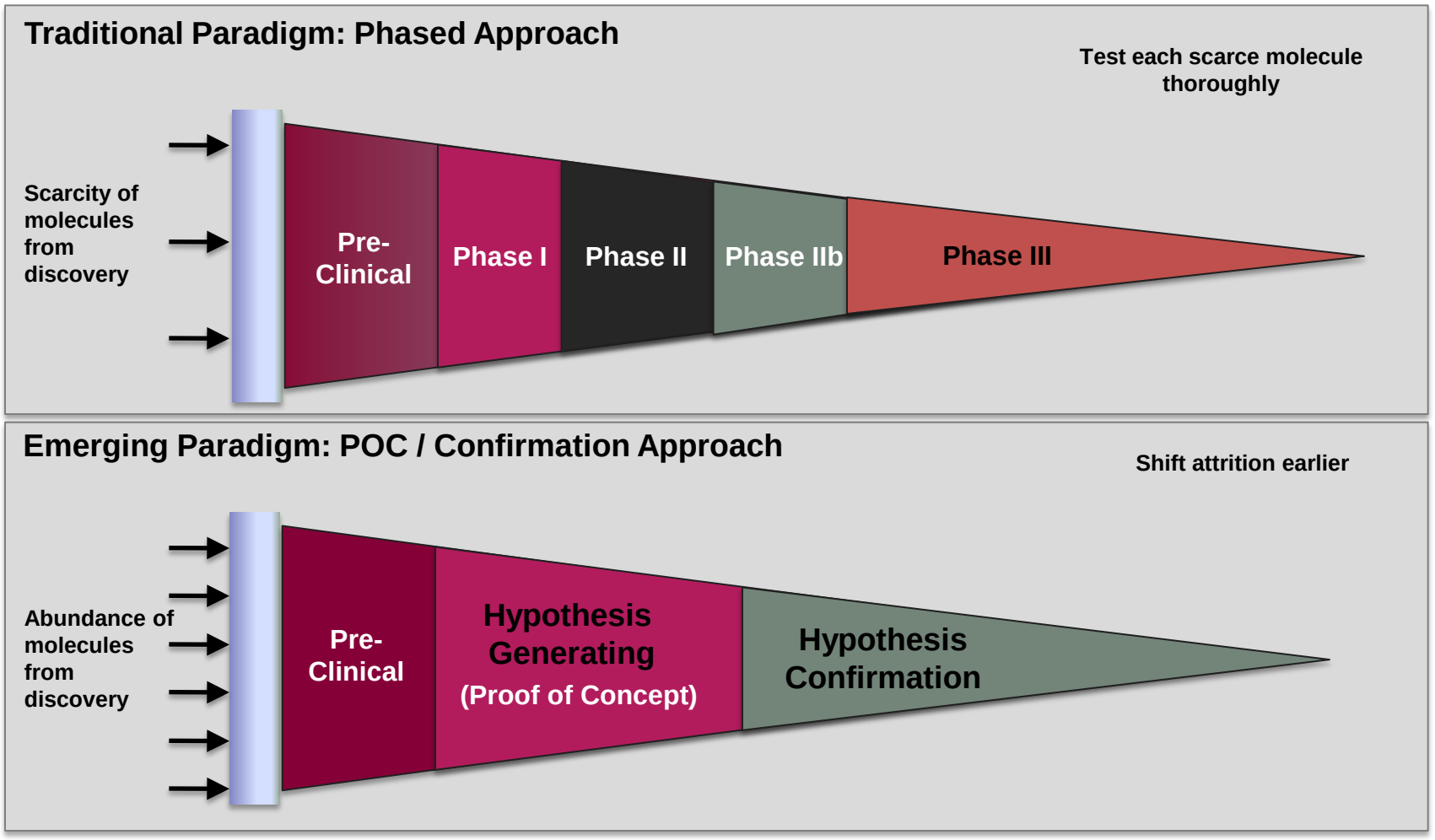
Clinical Development is Evolving



Adapted from: William Blair & Company, (Bain and Company) Covance Investors Overview June 16, 2010

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Why patients in early clinical research?

- Cost to get a drug to market
  - Estimated at $1.2 billion (!)
  - Cost of failure (less than 1 success for every 10 tries?)
- Time to get to market
  - 12 to 15 years
  - Patent clock ticking…
- Late-stage failures
  - Many high-profile drugs failing in Phase III up from 30% in 2011 to 35% in 2012
  - In 2012 alone, BMS-094 (hepC) is estimated to have cost $1.7 billion; Bapineuzumab (Pfizer, J&J, AD), Dalcetrapib (Roche, cholesterol)

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Elements of Early Clinical Research

- Primary objective
  - Safety
  - Pharmacokinetics (drug exposure)
- Secondary-Exploratory objective
  - Efficacy

- No or limited potential for clinical benefit

Challenges with patients

- More difficult to recruit
  - Early clinical research: no potential benefit, motivation to participate?
- Can be more fragile population
  - Concomitant medications:
    Potential for drug-drug interactions
  - Disease progression
  - Adverse events related to disease

Example of a US Clinical Research Consortium

What is TURNS?

- Created in 2004
- $9 US million, 4 year contract
- National Institute of Mental Health (NIMH)
- The project directed by Stephen R. Marder, MD at UCLA
- Seven academic institutions
- Core resources (trial & data management, stats, site coordination, scientific operations)

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The TURNS mission

- The NIMH approach is built on the assumption that progress in developing new treatments will require collaboration between the best academic, government, and industry scientists
- TURNS is one component of a multipronged NIMH effort to stimulate academic and industry sponsored research focused on cognitive deficits in schizophrenia.

TURNS objectives

- Developed a tool to measure cognitive impairment in schizophrenia
  - Measurement and Treatment Research for Cognition in Schizophrenia (MATRICS)
- Fund and run multiple, exploratory Phase 2a studies
  - Grant application from academia and industry (large or small companies)
  - PIs from each institution
  - Clinical conduct at TURNS institutions

Davunetide in Schizophrenia Cognitive Impairment

- Randomized, double blind, placebo controlled
- 60 patients clinically stable, on any anti-psychotic medication
- Placebo, 5 mg QD or 15 mg BID for 12 weeks
- 7 US sites
- TURNS / NIMH funded
- Clinical endpoints: safety, cognition, function
- Clinicaltrials.gov NCT00505765
- Magnetic Resonance Imaging (MRI) Sub-study

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Key Inclusion Criteria

- Men and women between 18 and 60 years of age (inclusive) with a DSM-IV/DSM-IV-TR diagnosis of schizophrenia
- On stable dose of second generation antipsychotic
- Performance less than the maximum cutoff for one MCCB tests

Characteristic	Placebo (N=22)		Davunetide 5 mg (N=20)		Davunetide 15 mg BID (N=21)	
	Mean	SD	Mean	SD	Mean	SD
Age, years	41.4	10.4	43.2	10.5	45.2	8.2
Education, years	12.1	2.7	12.6	2.2	12.4	2.7
WTAR reading score	26.1	13.1	32.0	13.7	28.6	11.4

Demographics and Safety

	Placebo		Davunetide 5 mg		Davunetide 15 mg BID	
	n	%	n	%	n	%
Female	8	36.4	7	35.0	7	33.3
Antipsychotic Medication:						
Aripipiprazole	4	18.2	6	30.0	5	23.8
Depot fluphenazine	2	9.1	2	10.0	1	4.8
Depot haloperidol	1	4.6	0	0.0	0	0.0
Olanzapine	4	18.2	6	30.0	7	33.3
Paliperidone	3	13.6	1	5.0	0	0.0
Quetiapine	1	4.6	3	15.0	2	9.5
Risperidone*	6	27.3	1	5.0	4	19.0
Ziprasidone	1	4.6	1	5.0	2	9.5

Safety

- Well tolerated
- Good compliance
- Transient nasal irritation in all groups
- No effect on extrapyramidal symptoms

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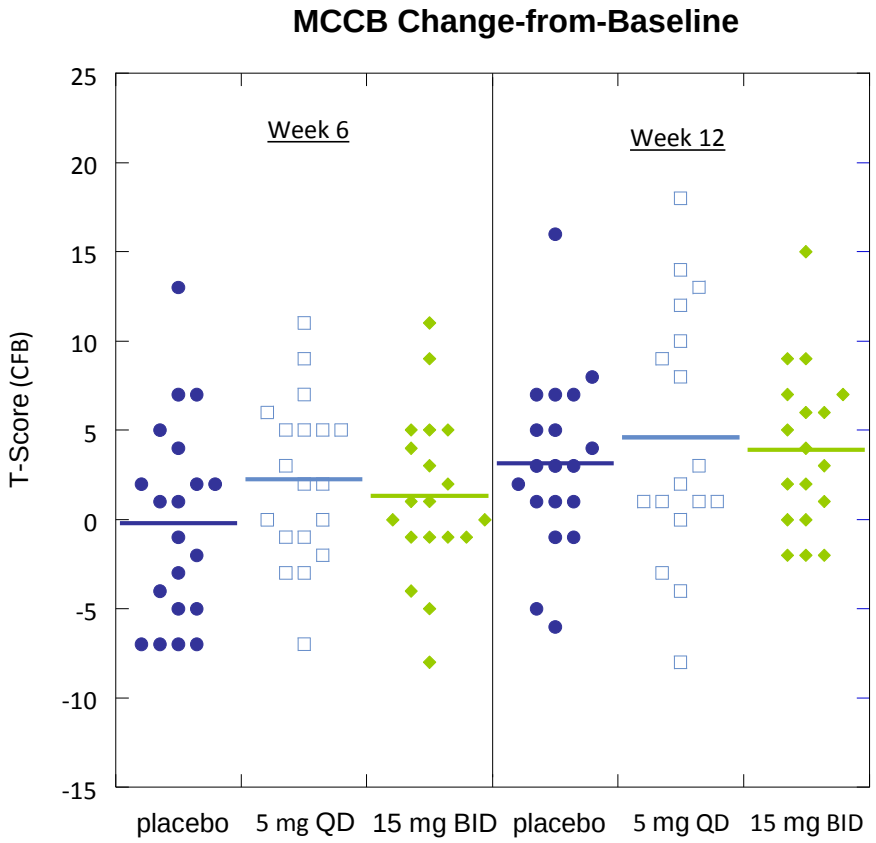
MATRICS Composite Score

- MATRICS Domains
- Attention/Vigilance
- Reasoning/Problem solving
- Social Cognition
- Visual Learning
- Verbal Learning
- Working Memory
- Processing Speed



Mixed Model ANCOVA

- 5 mg vs placebo: p=0.174 (Week 6)

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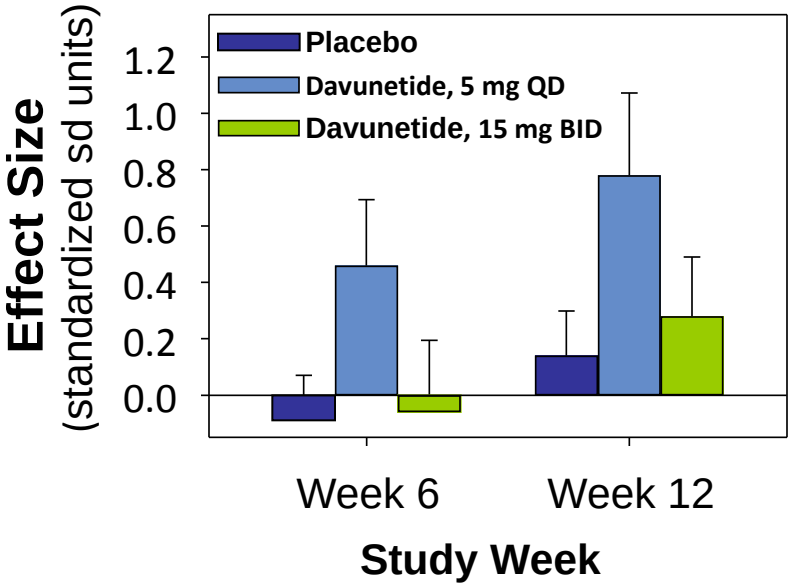
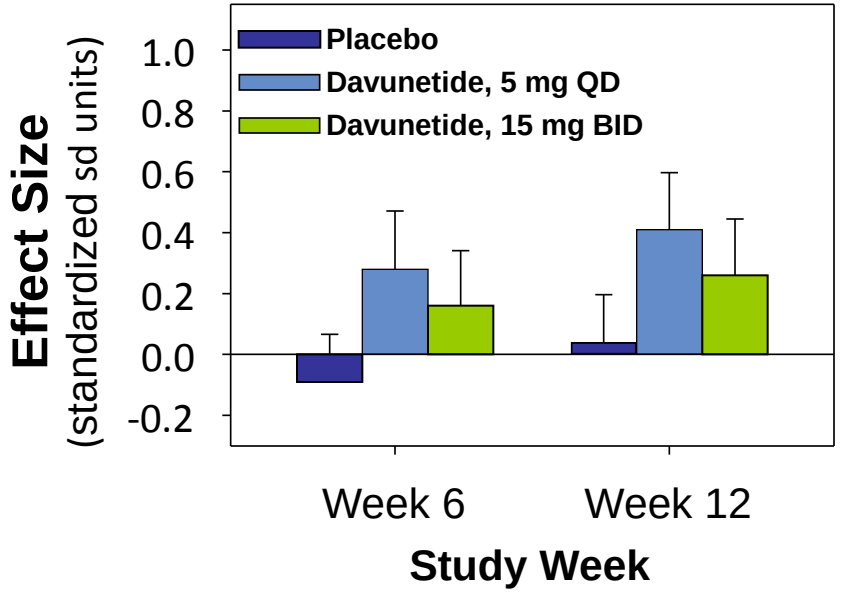
MATRICS Sub-Domain Scores

Visual Learning



Working Memory (Letter-Number Sequencing)



Conclusions

- Moderate (0.5 SD) to large (0.8 SD) treatment effect, although not statistically significant
- Visual Learning and Working Memory, same domains that improved in aMCI study

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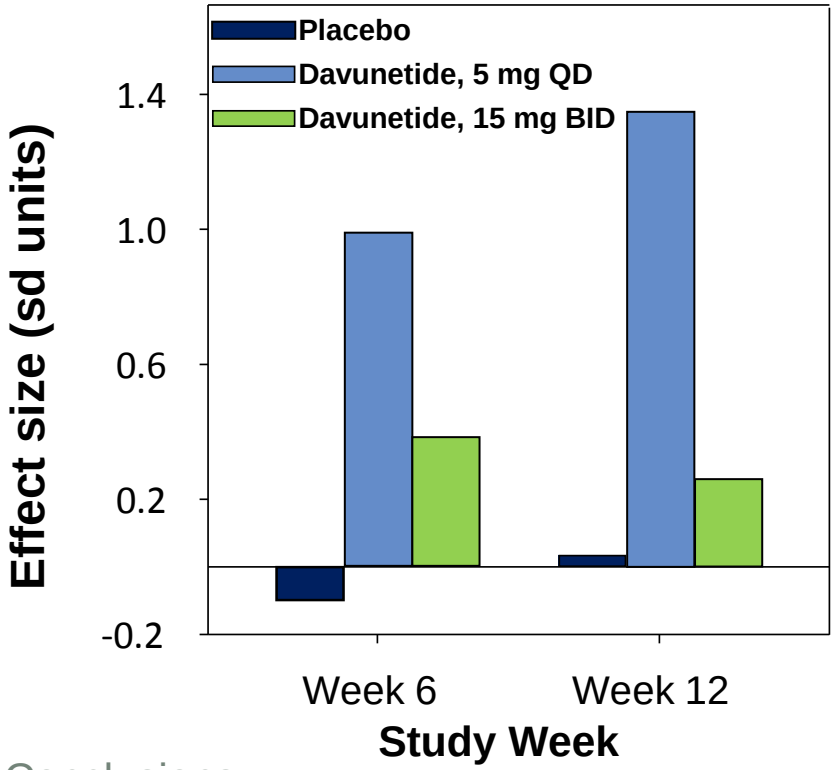
UCSD Performance-based Skills Assessment (UPSA)

- Measure of functional capacity to manage everyday tasks:
  - Household chores
  - Communication
  - Finance
  - Transportation
  - Planning recreational activities
  - Medication management

UCSD Performance-Based Skills Assessment



ANCOVA (corrected for baseline)

Effect	F	p
Treatment	3.26	0.048
Week	0.91	0.35
Treatment x week	0.17	0.85

Conclusions

- 5 mg BL was lower than placebo, ANCOVA should correct but still possibility of regression to mean
- Large (>0.8 SD) treatment effect size, should constitute a clinically meaningful change—something a family member would notice

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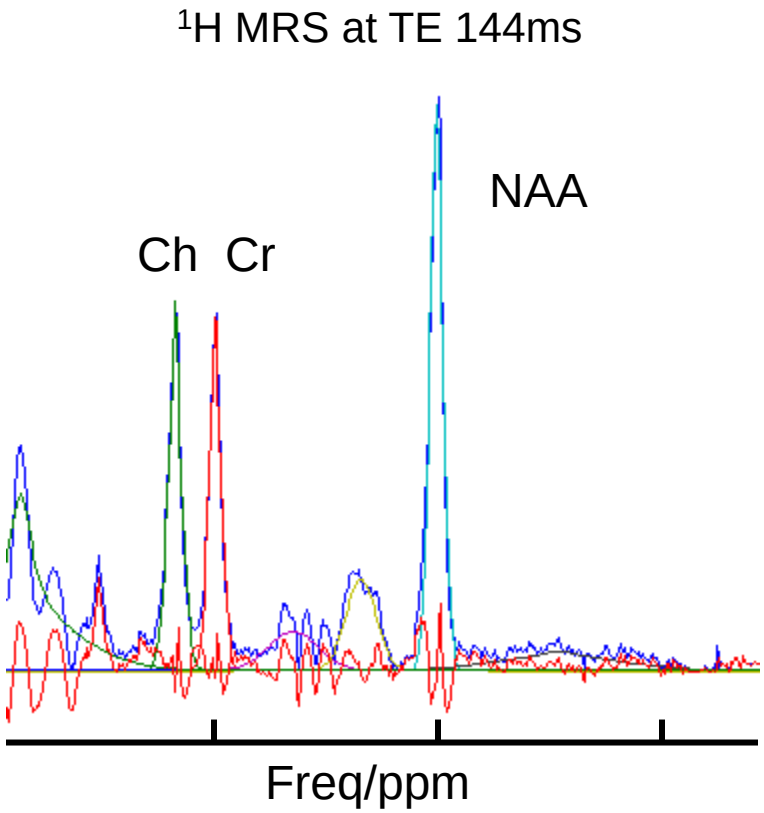
Exploratory Imaging Biomarker

Magnetic Resonance Spectroscopy

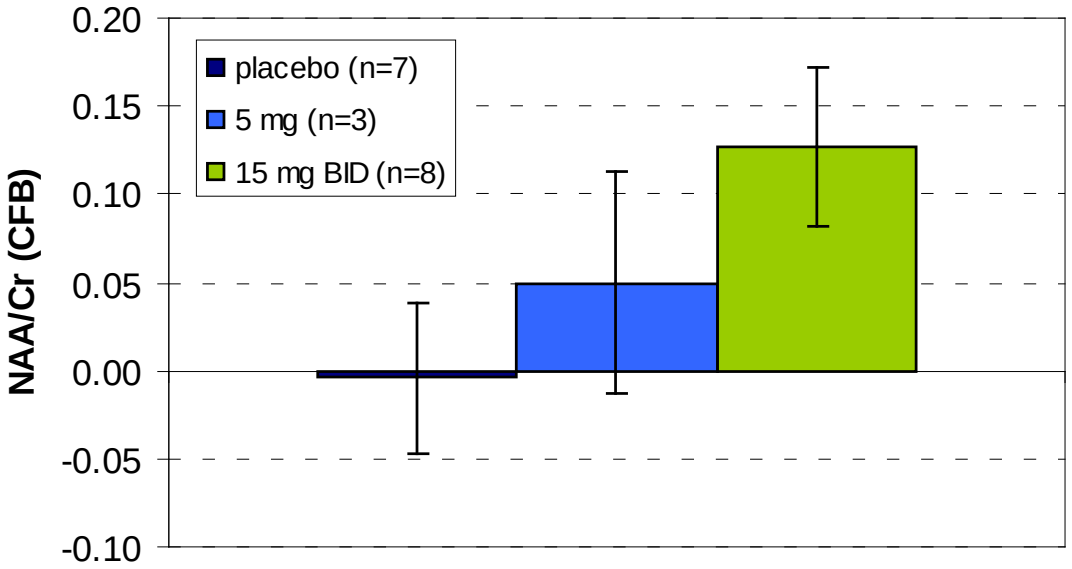
Hypothesis

Davunetide can increase the metabolic integrity as measured by the NAA/Cr ratio compared to baseline

- NAA (N-acetyl-aspartate): a marker of neuronal integrity and function
- Cr (creatine): a marker of energy metabolism
- Ch (choline): a marker of membrane density and integrity



MRI Sub-study - NAA/Cr Change-from-baseline



Wilcoxon non-parametric Exact Test

p=0.07

15mg BID vs placebo

- Non-parametric analysis shows strong trend towards significant treatment effect versus placebo
- Statistically significant increase in NAA levels found in patients treated with *davunetide* relative to baseline (p=0.017)
  - Placebo was showed no change (p=0.928)

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Lessons Learned (Sponsor's perspective)

- Partnering and collaboration key to scientific success!
- Access to leading schizophrenia KOLs
- Subdomains of MATRICS may be informative
- Imaging biomarkers (like MRS) in early clinical research can be valuable
  - Can gain mechanistic information on drug action
  - Technical challenges with multi-site data acquisition and integration

TURNS

TURNS
Treatment Units for Research on Neurocognition and Schizophrenia

TURNS TEAM

- PRINCIPAL INVESTIGATOR
  - Stephen R. Marder, M.D.
- NIMH
  - Ellen Stover, Ph.D.
- TRIALS MANAGEMENT UNIT
  - Robert W. Buchanan, M.D.
  - M. Patricia Ball, R.N.,C.,M.S.
- SCIENTIFIC OPERATIONS UNIT
  - Jeffrey L. Lieberman, M.D.
  - Marlene Carlson
- DATA MANAGEMENT
  - James Robinson, Ph.D.
- STATISTICS
  - Robert McMahon, Ph.D.
- SITE COORDINATION
  - Robert Kern, Ph.D.
- COLUMBIA UNIVERSITY
  - Jeffrey L. Lieberman, M.D., PI
  - Fred Jarskog, M.D.
- HARVARD UNIVERSITY
  - Donald Goff, M.D., PI
  - Raquelle Mesholam-Gately, Ph.D.
- NATHAN KLINE INSTITUTE
  - Daniel Javitt, M.D., PI
  - Karen Nolan, Ph.D.
- DUKE UNIVERSITY
  - Joseph McEvoy, M.D., Co-PI
  - Richard Keefe, Ph.D., Co-PI
- WASHINGTON UNIVERSITY
  - Deanna Barch, Ph.D., PI
  - John Csernansky, M.D., prev PI
- MARYLAND PSYCHIATRIC RESEARCH CENTER
  - Robert W. Buchanan, M.D., PI
  - James Gold, Ph.D.
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Effect of the neuroprotective peptide davunetide (AL-108) on cognition and functional capacity in schizophrenia
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Effects of davunetide on N-acetylaspartate and choline in dorsolateral prefrontal cortex in patients with schizophrenia. Neuropsychopharmacology. 2013 Jun;38(7):1245-52

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Questions?

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