

ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI

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****Keynote Address****

“A Roadmap for Innovation in Psychiatry”

**Innovations in Psychiatry Symposium
Advances in Understanding and Treating Depression**

February 1, 2013

Big Problems that Need Answers

The function of genes contributing to the vulnerability to most psychiatric disorders have not been identified and relatedly, modifiable environmental and behavioral risk factors have not been precisely determined. A clinically relevant understanding of gene-environment interactions is needed.

There is no diagnostic system for psychiatric disorders based upon etiology or pathophysiology that adequately predicts illness course and response to therapy.

Identification of new molecular targets for drug development for psychiatric disorders has been inadequate.

There has been little recent innovation in the development of new and novel psychosocial therapies.

Preventative measures for subjects at high risk for psychiatric disorders are needed.

Barriers to care and disparities in diagnosis and health care delivery remain and need to be remedied.

CNS Drug Development. Part I: The Early Period of CNS Drugs

<i>Drug</i>	<i>Class</i>	<i>Decade of discovery</i>
Amphetamine	stimulant	1880s ¹
Cocaine	analgesic/stimulant	1850s ²
Chlorpromazine	antipsychotic	1950s ³
Diazepam	anti-anxiety	1950s ^{4,5}
Imipramine	antidepressant	1950s ⁶
Isocarboxazid	antidepressant	1950s ⁷
Lithium	mood stabilizer	1940s ⁸
Morphine	analgesic	2100 BC ⁹
Phenobarbital	anticonvulsant	1930s ¹⁰
Reserpine	antipsychotic	1950s ^{11,12}

TABLE 1. Early drugs that targeted the central nervous system

CNS Drug Development. Part I: The Early Period of CNS Drugs

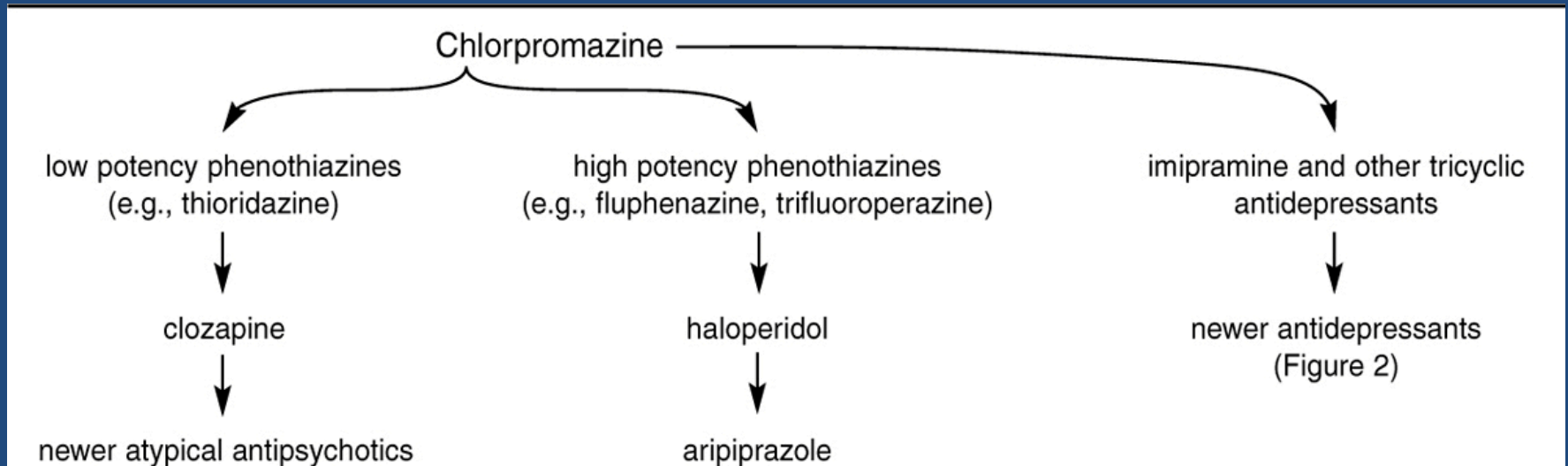


FIGURE 1. Drug development based on chlorpromazine

CNS Drug Development. Part I: The Early Period of CNS Drugs

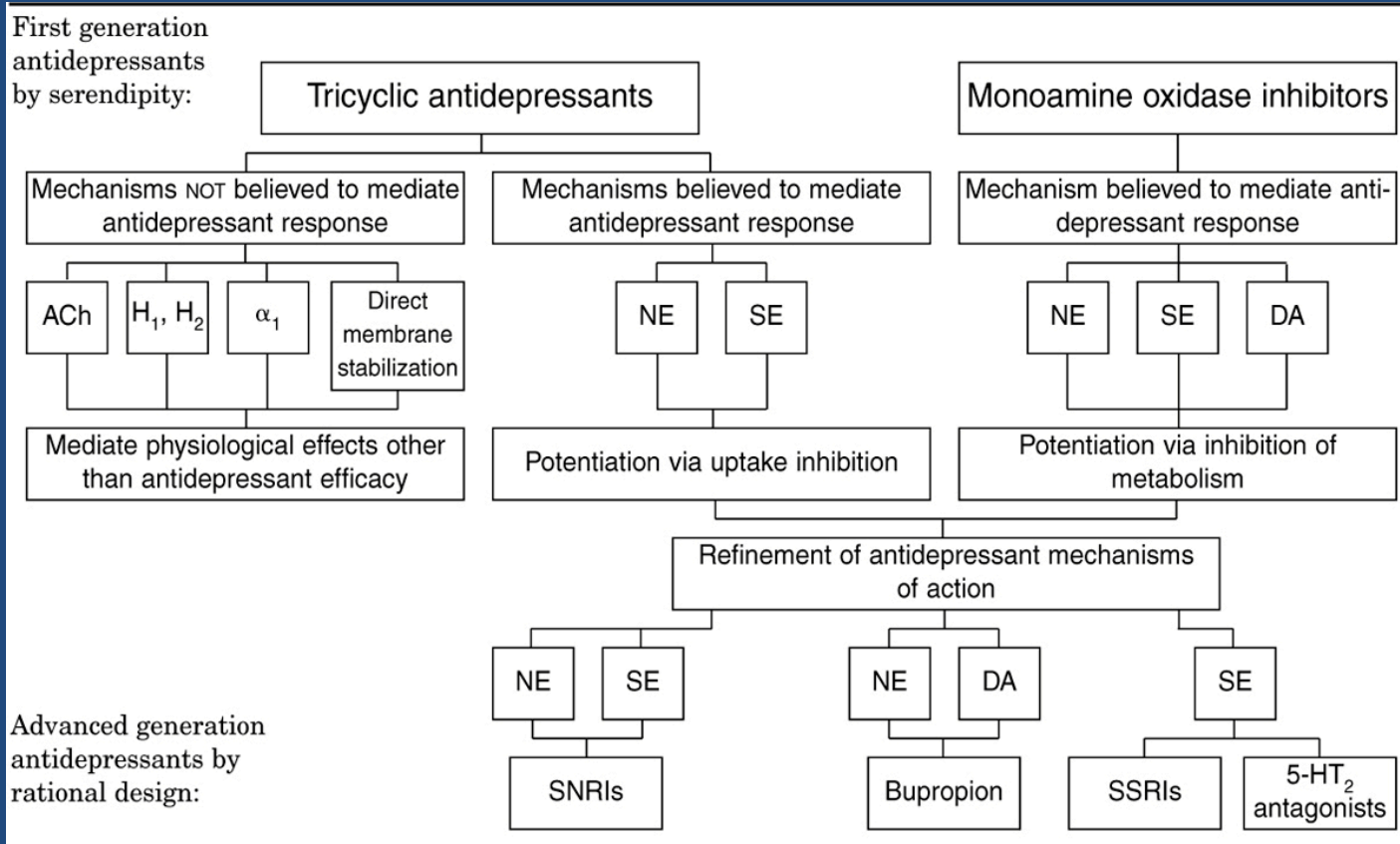


FIGURE 2. Evolution of antidepressants.

Legend:

Ach, acetylcholine;
 H, histamine;
 [alpha]1, alpha-1 adrenergic;
 NE, norepinephrine;
 SE and 5-HT, serotonin;
 DA, dopamine;
 SNRI, serotonin-norepinephrine reuptake inhibitor;
 SSRI, selective serotonin reuptake inhibitor.

Reproduced with permission from Preskorn 1996.

Legend: ACh = acetylcholine; H = histamine; α₁ = alpha-1 adrenergic; NE = norepinephrine; SE and 5-HT = serotonin; DA = dopamine; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

Reproduced with permission from Preskorn 1996²⁷

Static Clinical Targets Limit New Drug Development

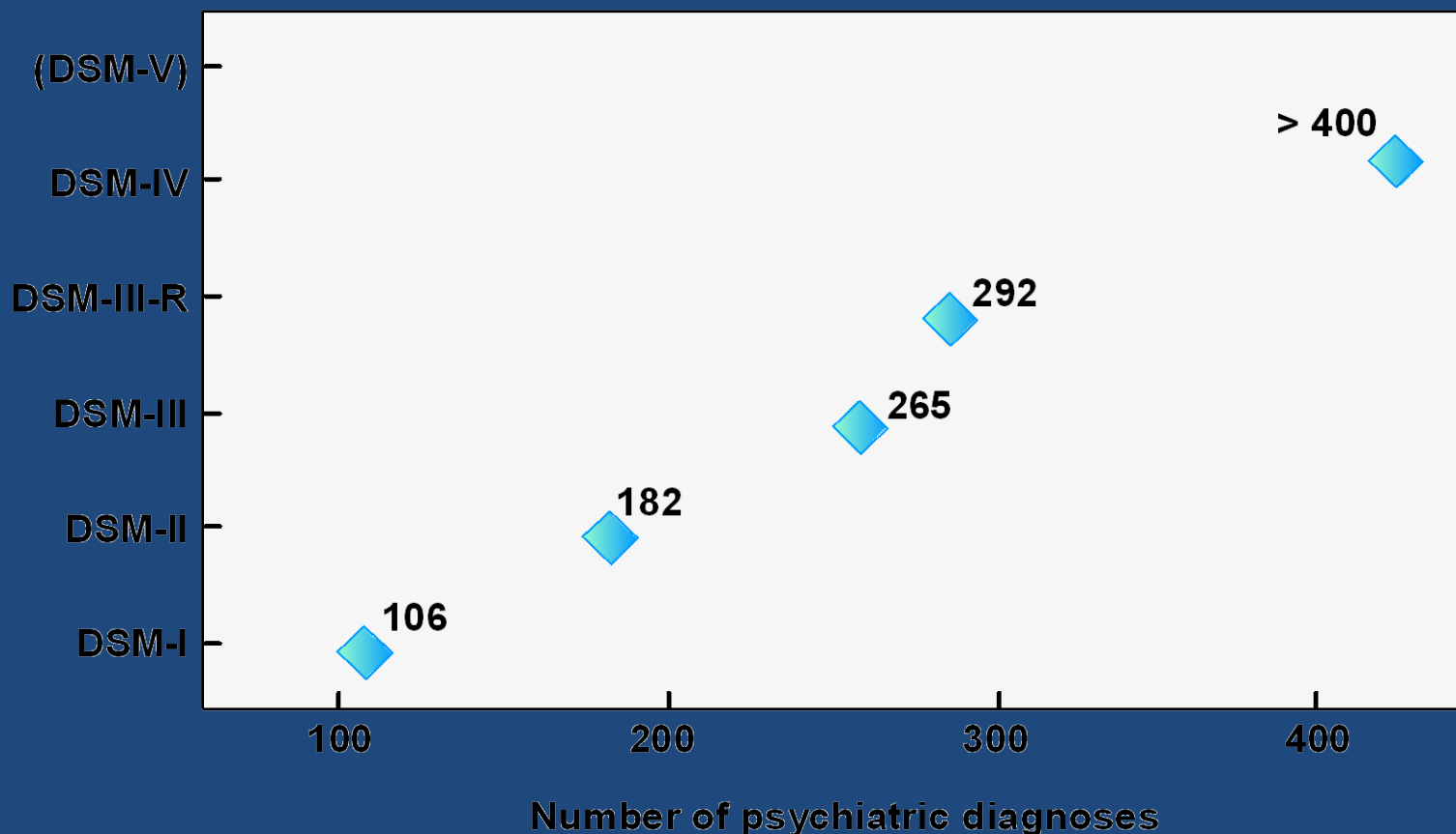
DSM IV syndromes represent our current clinical targets

Medicines treat symptoms, not DSM diagnoses

Psychopharmacology needs new clinical targets closer to pathophysiology

Each new edition of the American Psychiatric Association released Diagnostic Statistical Manual (DSM) offered an increased number of diagnostic categories

Each new edition of the American Psychiatric Association released Diagnostic Statistical Manual (DSM) offered an increased number of diagnostic categories



The Initial Field Trials of DSM-5: New Blooms and Old Thorns

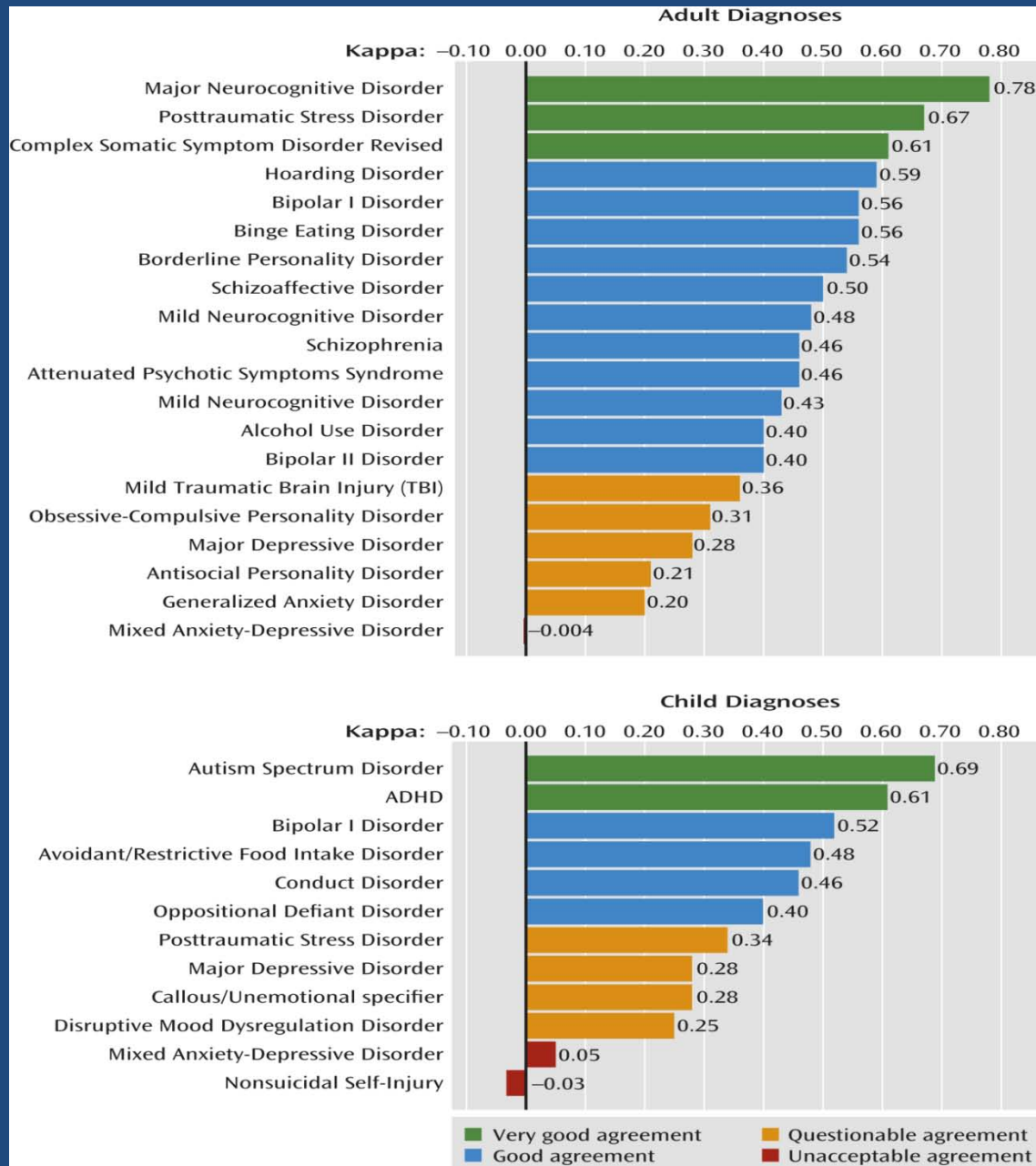


FIGURE 1. Interrater Reliability of Diagnoses From the Initial DSM-5 Field Trials. Some of the kappa statistics did not pass the criterion of a standard error less than 0.1. They are included here for illustrative purposes. See the field trial reports for further details (3–5).

Am J Psychiatry 2013;170:1-5. 10.1176

A New Diagnostic System

GENOTYPE

Identification of disease/symptom related genes

Identification of resiliency/protective genes

Identification of genes related to therapeutic responses and side effects to specific psychotropic drugs

NEUROBIOLOGICAL PHENOTYPE

Identification of intermediate phenotypes (neuroimaging, cognitive function, emotional regulation) related genotype

Relates to targeted pharmacotherapy

BEHAVIORAL PHENOTYPE

The range and frequency of expressed behaviors associated with genotype, neurobiological phenotype, and environment

Relates to targeted therapies

ENVIRONMENTAL MODIFIERS OR PRECIPITANTS

Environmental factors which alter the behavioral and neurobiological phenotype

THERAPEUTIC TARGETS AND RESPONSE

Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders

RDoC classification rests on three assumptions.

- **First, the RDoC framework conceptualizes mental illnesses as brain disorders. In contrast to neurological disorders with identifiable lesions, mental disorders can be addressed as disorders of brain circuits.**
- **Second, RDoC classification assumes that the dysfunction in neural circuits can be identified with the tools of clinical neuroscience, including electrophysiology, functional neuroimaging, and new methods for quantifying connections *in vivo*.**
- **Third, the RDoC framework assumes that data from genetics and clinical neuroscience will yield biosignatures that will augment clinical symptoms and signs for clinical management.**

Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it?

Patients with mental disorders show many biological abnormalities which distinguish them from normal volunteers; however, few of these have led to tests with clinical utility. Several reasons contribute to this delay: **lack of a biological 'gold standard' definition of psychiatric illnesses; a profusion of statistically significant, but minimally differentiating, biological findings; 'approximate replications' of these findings in a way that neither confirms nor refutes them; and a focus on comparing prototypical patients to healthy controls which generates differentiations with limited clinical applicability. Overcoming these hurdles will require a new approach.** Rather than seek biomedical tests that can 'diagnose' DSM-defined disorders, **the field should focus on identifying biologically homogenous subtypes that cut across phenotypic diagnosis--thereby sidestepping the issue of a gold standard.** To ensure clinical relevance and applicability, the field needs to focus on clinically meaningful differences between relevant clinical populations, rather than hypothesis-rejection versus normal controls. Validating these new biomarker-defined subtypes will require longitudinal studies with standardized measures which can be shared and compared across studies--thereby overcoming the problem of significance chasing and approximate replications. Such biological tests, and the subtypes they define, will provide a natural basis for a 'stratified psychiatry' that will improve clinical outcomes across conventional diagnostic boundaries.

Anatomical Brain Images Alone Can Accurately Diagnose Chronic Neuropsychiatric Illnesses

Objective: Diagnoses using imaging-based measures alone offer the hope of improving the accuracy of clinical diagnosis, thereby reducing the costs associated with incorrect treatments. Previous attempts to use brain imaging for diagnosis, however, have had only limited success in diagnosing patients who are independent of the samples used to derive the diagnostic algorithms. We aimed to develop a classification algorithm that can accurately diagnose chronic, well-characterized neuropsychiatric illness in single individuals, given the availability of sufficiently precise delineations of brain regions across several neural systems in anatomical MR images of the brain.

Methods: We have developed an automated method to diagnose individuals as having one of various neuropsychiatric illnesses using only anatomical MRI scans. The method employs a semi-supervised learning algorithm that discovers natural groupings of brains based on the spatial patterns of variation in the morphology of the cerebral cortex and other brain regions. We used split-half and leave-one-out cross-validation analyses in large MRI datasets to assess the reproducibility and diagnostic accuracy of those groupings.

Results: In MRI datasets from persons with Attention-Deficit/Hyperactivity Disorder, Schizophrenia, Tourette Syndrome, Bipolar Disorder, or persons at high or low familial risk for Major Depressive Disorder, our method discriminated with high specificity and nearly perfect sensitivity the brains of persons who had one specific neuropsychiatric disorder from the brains of healthy participants and the brains of persons who had a different neuropsychiatric disorder.

Conclusions: Although the classification algorithm presupposes the availability of precisely delineated brain regions, our findings suggest that patterns of morphological variation across brain surfaces, extracted from MRI scans alone, can successfully diagnose the presence of chronic neuropsychiatric disorders. Extensions of these methods are likely to provide biomarkers that will aid in identifying biological subtypes of those disorders, predicting disease course, and individualizing treatments for a wide range of neuropsychiatric illnesses.

Anatomical Brain Images Alone Can Accurately Diagnose Chronic Neuropsychiatric Illnesses

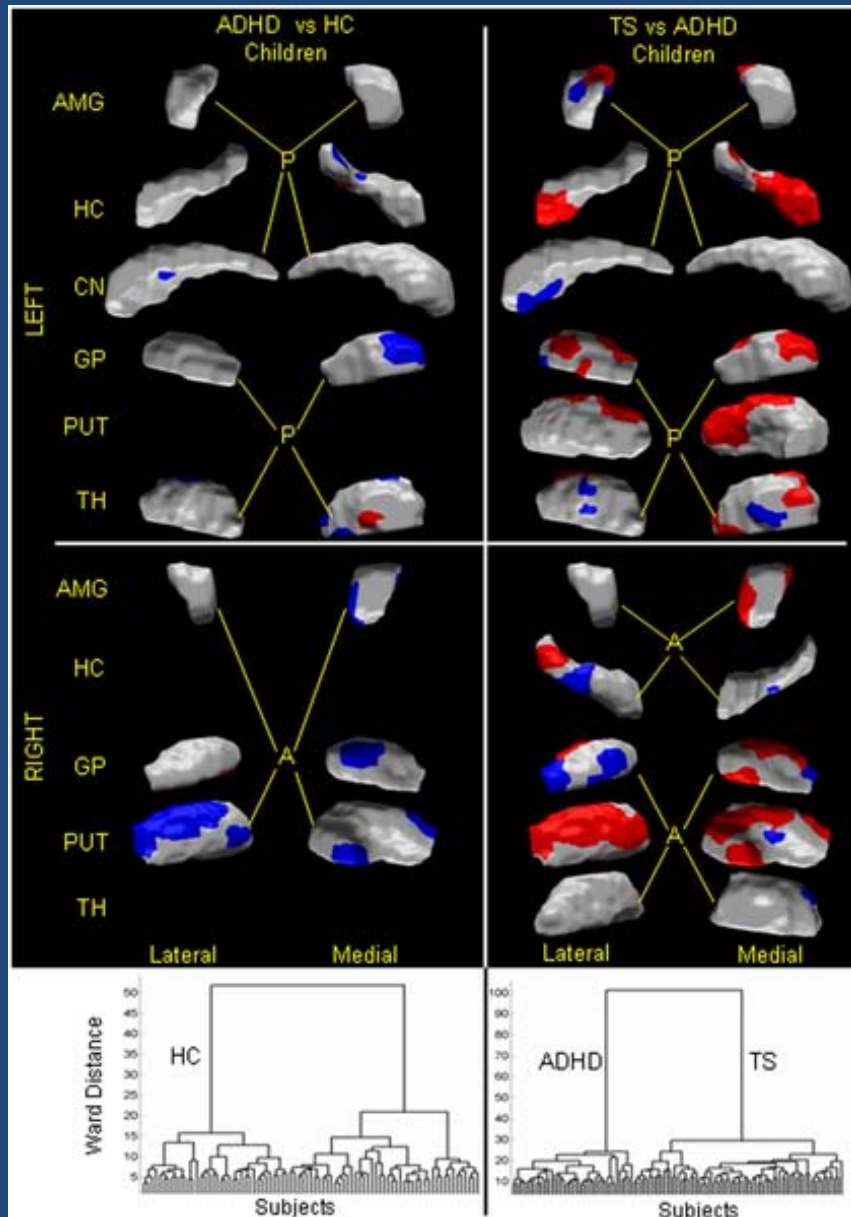


Figure 7. Classifying a child as healthy or with ADHD, or as having either TS or ADHD. The sensitivity and specificity were: 93.6% and 89.5%, respectively, for classifying a child as an ADHD child; and 99.83% and 99.5%, respectively, for classifying a child as having either ADHD or TS.

PLoS One. 2012;7(12):e50698. doi: 10.1371/journal.pone.0050698. Epub 2012 Dec 7.

Anatomical Brain Images Alone Can Accurately Diagnose Chronic Neuropsychiatric Illnesses

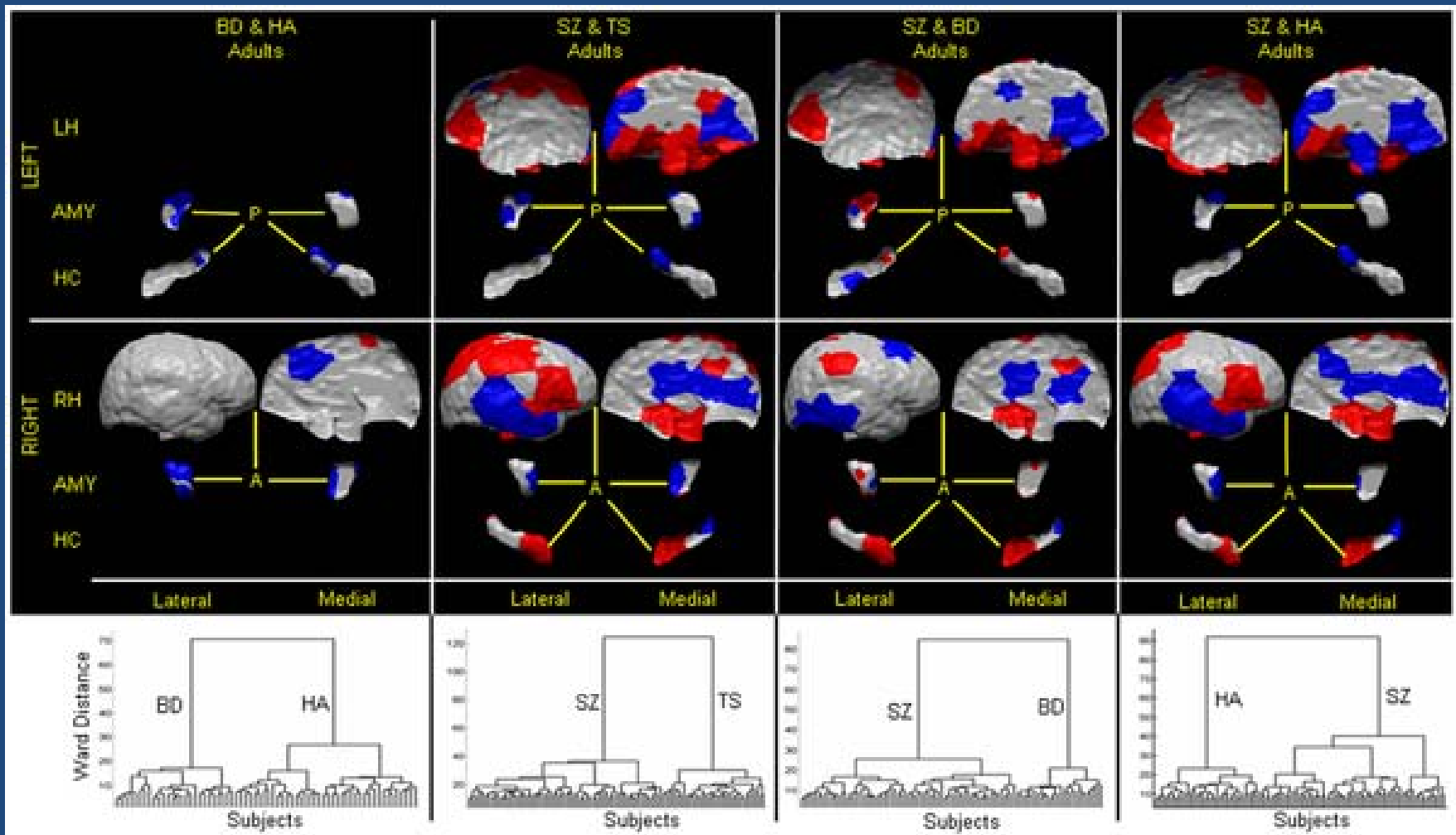


Figure 8. Classifying an adult as healthy or with disorder, or between two neuropsychiatric illness. The sensitivity and specificity were (1) 100% and 96.4%, respectively, for classifying a participant as a BD adult, (2) 100% for classifying an adult as TS or SZ adult, (3) 100% for classifying an adult as BD or SZ adult, and (4) 93.1% and 94.5%, respectively, for classifying a participant as SZ adult.

Anatomical Brain Images Alone Can Accurately Diagnose Chronic Neuropsychiatric Illnesses

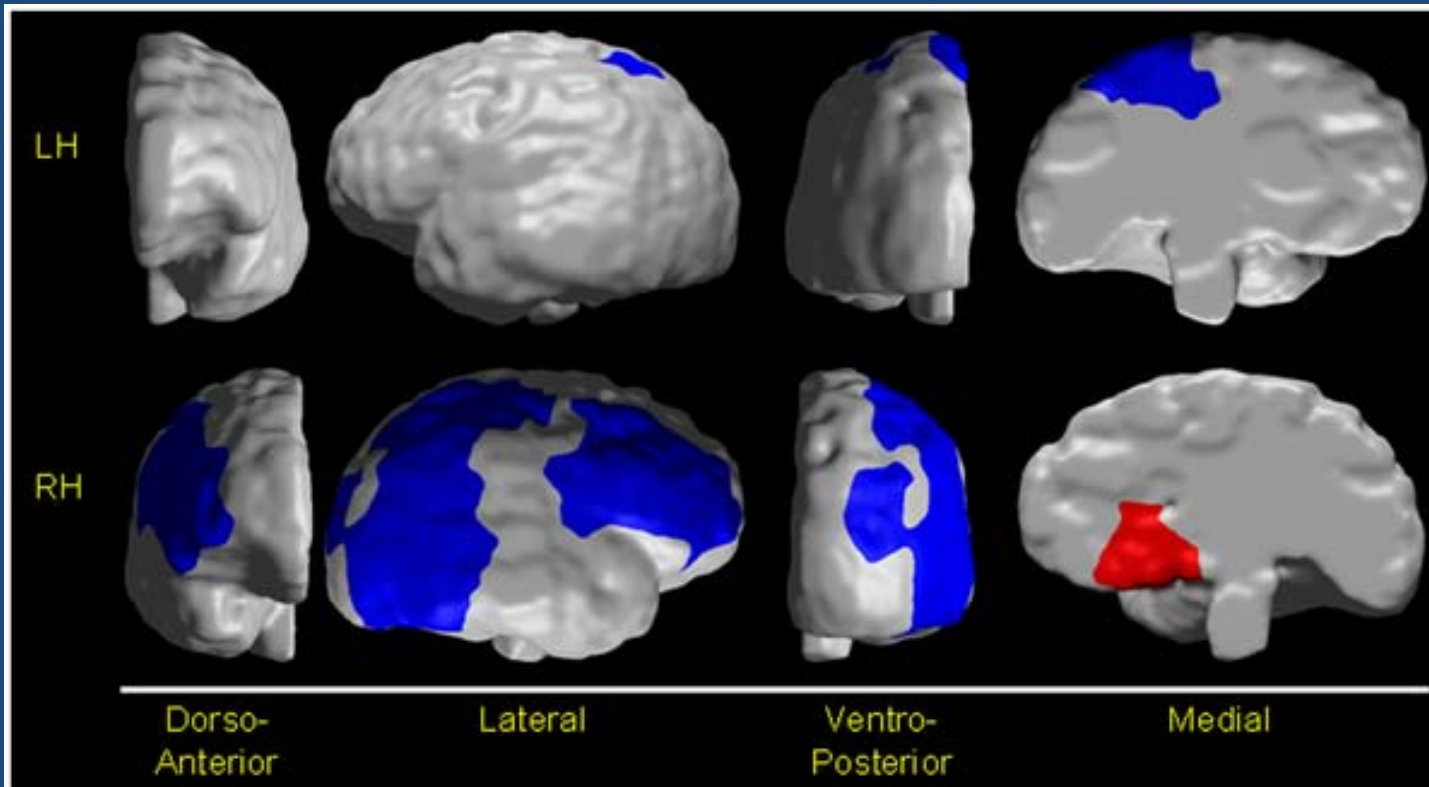
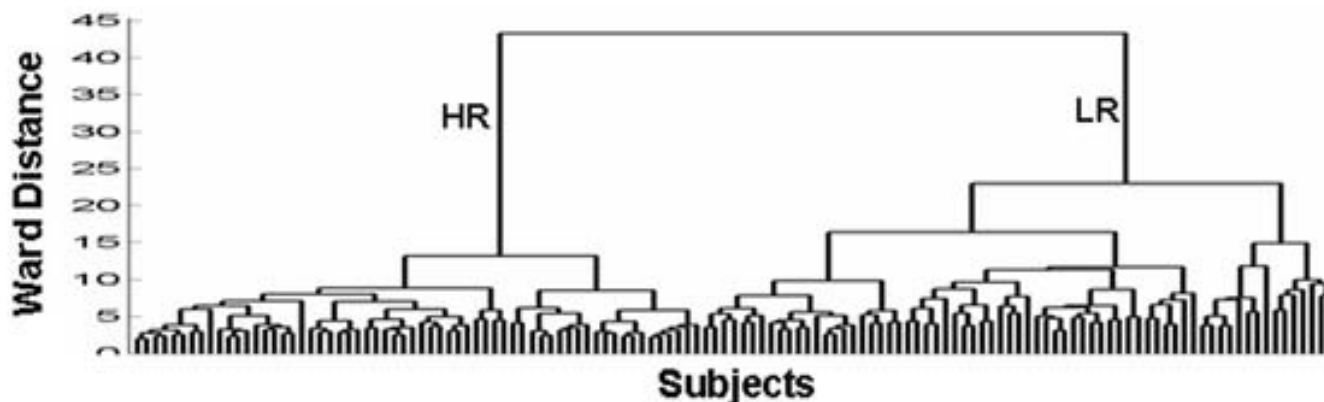


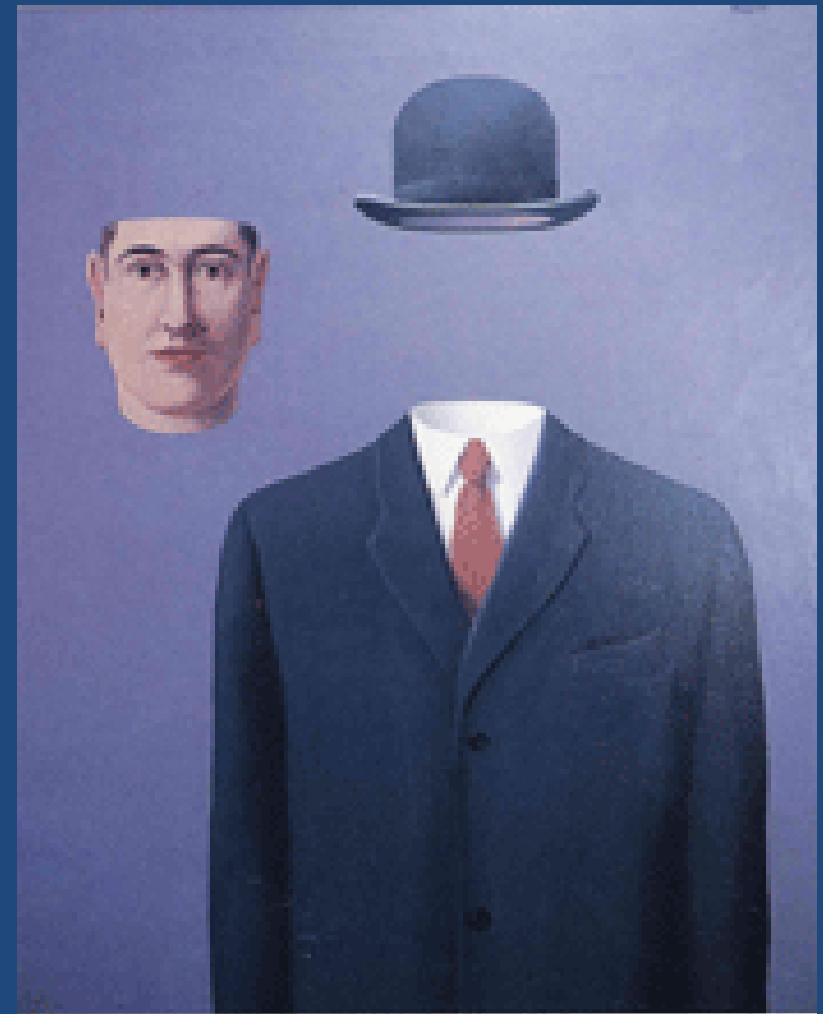
Figure 10. Classifying an individual as high or low familial risk for MDD. The sensitivity and the specificity for classifying an individual as HR were 81% and 71%, respectively.



PLoS One.
2012;7(12):e50698. doi:
10.1371/journal.pone.00
50698. Epub 2012 Dec 7.

Revolution Stalled

Drug discovery is at a near standstill for treating psychiatric disorders such as schizophrenia, bipolar disorder, depression, and common forms of autism. Despite high prevalence and unmet medical need, major pharmaceutical companies are deemphasizing or exiting psychiatry, thus removing significant capacity from efforts to discover new medicines. In this Commentary, I develop a view of what has gone wrong scientifically and ask what can be done to address this parlous situation.



Terrible thing to waste. Pharma has removed psychiatric diseases from its body of drug discovery projects. Geneticists might help reverse the trend. [The Pilgrim by René Magritte. 1966]

Revolution Stalled

Refocusing Translational Psychiatry

- **Move beyond most current animal models of psychiatric disease.**
- **Move beyond overly simplistic pathophysiological hypotheses**
- **Potential innovation**
 - **Use IPS from patients to derive neurons as disease models**
 - **Optogenetics to activate and inhibit neural circuits in real time and observe behavioral changes**
 - **Use of genetic and epigenetic studies to identify pathways in involved disease pathogenesis**
- **Models that can identify compelling molecular mechanisms of disease (rather than misleading animal behavioral models)**

Next-Generation Treatments for Mental Disorders

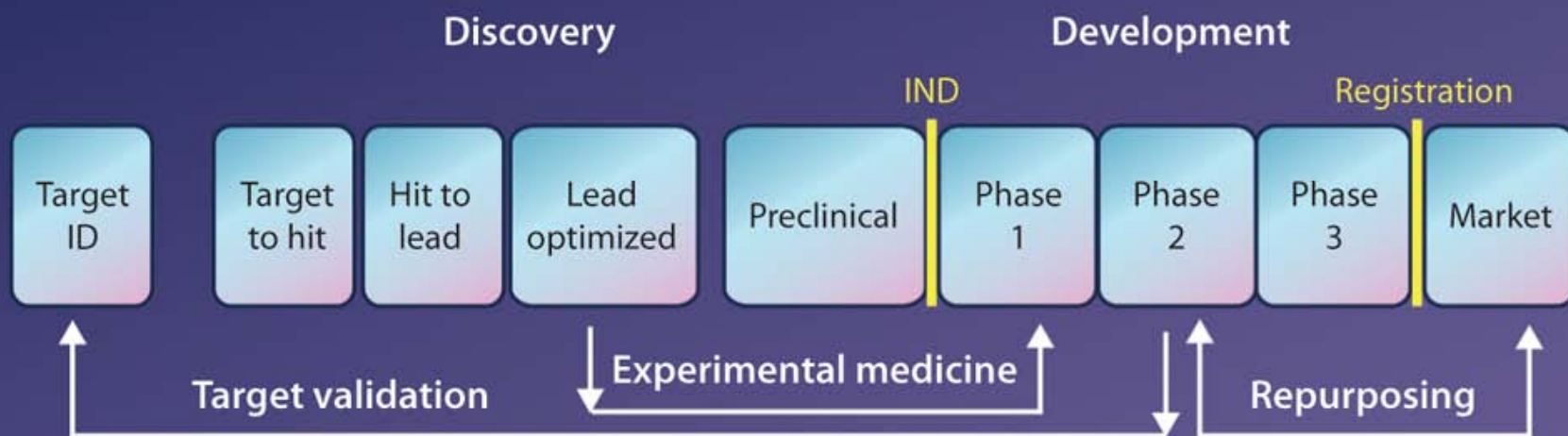


Fig. 2. Pipeline of medication development. The canonical pipeline for medication development is not working for mental disorders. A new strategy focusing on target validation, experimental medicine, and repurposing is required. Target validation tests whether a compound engages the presumed target and if that mechanism of action is involved in the disease. The experimental medicine approach leads quickly into patients to determine if a lead compound target is effective. In this new construct for drug development, the drug is a probe, the focus is on the target, and success can be defined by “fast fail.” Drug repurposing is an even faster way forward by identifying new beneficial effects of approved medications.

Next-Generation Treatments for Mental Disorders

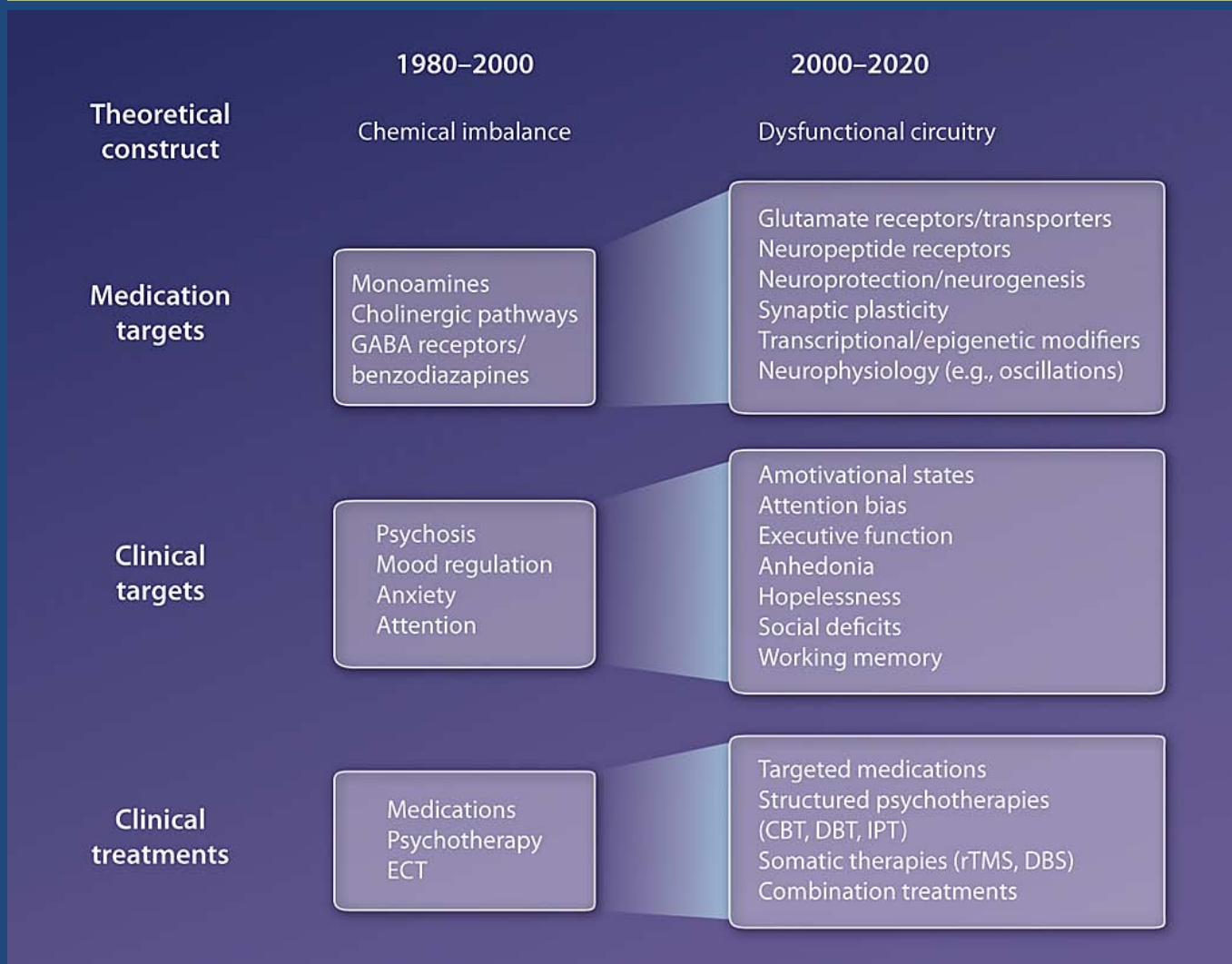


Fig. 3. New opportunities for treatment development. The enormous expansion of the medication portfolio for mental disorders between 1980 and 2000 was limited to a relatively narrow space of biology. Over the past decade, a new focus on the genetics and neurobiology of these disorders has generated a range of new targets for next-generation treatments. In addition, the broad categories of symptoms (analogous to fever or pain) are giving way to more targeted clinical symptoms that cut across current diagnostic bins (e.g., anhedonia and social deficits). And the limited options for treatments is expanding to include targeted behavioral interventions disseminated via new media, innovative somatic treatments based on identified circuit dysfunction, and strategic combinations (such as cognitive enhancers to improve the impact of cognitive behavior therapy). ECT, electroconvulsive therapy; CBT, cognitive behavioral therapy; DBT, dialectical behavior therapy; IPT, interpersonal behavior therapy; rTMS, transcranial magnetic stimulation; DBS, deep brain stimulation.

Next-Generation Treatments for Mental Disorders

Table 1. R & D pipeline in three new areas for psychiatric medications

New strategies	Discovery targets	Treatment targets in development	Clinical trials
Rapid-acting antidepressants	Trophic factors: (BDNF, FGF2) Neuritin P11 MIF	NR2B antagonist: (AZD6765), phase 2 Ketamine, phase 2 Muscarinic receptor antagonist: (scopolamine), phase 2	NCT01482221 NCT01627782, NCT01558063 , NCT00768430 NCT01613820 NCT00369915
Prosocial Drugs (Autism, Fragile X syndrome)	Synaptic proteins: (Shank3, CNTNAP2, Neuroigin 2,3, Neurexin 1)	GABA _A agonists: (STX207), phase 3 mGluR5 antagonists: (AFQ056), phase 2 (RO4917523), phase 2 (RO5028442), phase 1 (STX107), phase 1 Oxytocin receptor agonist: (Carbetocin), phase 2a Vasopressin V1A rec. antagonist: (RG7314), phase 1 1	NCT01282268 http://clinicaltrials.gov/ct2/results?term=AFO056+fragile+x NCT01517698 NCT01474278 NCT00965432 http://kyalinbio.com/products.html http://www.roche.com/research_and_development/pipeline/roche_pharma_pipeline.htm?ta=%25&Phase=%25&submit=Show+pipeline
Cognitive enhancers (Schizophrenia)	Ion channels: (KCNH2, CACNA1C) NRG1-ErbB4/DISC ligands: (PI3 Kinase, mTOR inhibitors) Epigenetic modifiers: (HDAC2 siRNA) miR-137	GlyT1 inhibitor: (AMG747), phase 2 (RO4917838), phase 3 α 7 nicotinic agonists: (ABT126), phase 2 (AQW051), phase 2 (DMXB-A), phase 2 (EVP6124), phase 1 (TC5619), phase 2 H3 antagonists: (CEP26401), phase 1 AMPA Positive Allosteric Modulators: (PF4958242), phase 1 1	NCT01568229, NCT01568216 NCT01192906, NCT01192880 , NCT01192867 , NCT01235559 , NCT01235520 , NCT01235585 NCT01655680 NCT01163227 NCT00100165 NCT00968851 NCT01488929 http://www.ncbi.nlm.nih.gov/pubmed/21634396 NCT01511510, NCT01365338

Sci Transl Med 10 October 2012; Vol. 4, Issue 155, p. 155ps19

Support for Involvement of Glutamate Decarboxylase 1 and Neuropeptide Y in Anxiety Susceptibility

Genetic mapping efforts have identified putative susceptibility genes for human anxiety disorders. The most intensively studied genes are involved in neurotransmitter metabolism and signaling or stress response. In addition, neuropeptides and targets of anxiolytics have been examined. It has become apparent that gene-environment interactions may explain individual variation in stress resilience and predisposition to mental disorders. We aimed to replicate previous genetic findings in 16 putative anxiety susceptibility genes and further test whether they modulate the risk for developing an anxiety disorder in adulthood after childhood stress exposure. We tested 93 single-nucleotide polymorphisms (SNPs) for genetic association to anxiety disorders in the Finnish population-based Health 2000 sample (282 cases and 575 matched controls). In addition, we examined by logistic regression modeling whether the SNP genotypes modified the effect of the number of self-reported childhood adversities on anxiety disorder risk. The most significant evidence for association was observed in glutamate decarboxylase 1 (GAD1) with phobias ($P = 0.0005$). A subsequent meta-analysis ($N = 1985$) incorporating previously published findings supported involvement of a single GAD1 risk haplotype in determining susceptibility to a broad range of internalizing disorders ($P = 0.0009$). **We additionally found that SNPs and haplotypes in neuropeptide Y (NPY) modified the effect of childhood adversities on anxiety susceptibility ($P = 0.003$).** In conclusion, we provide further support for involvement of mainly GAD1, but also NPY in determining predisposition to anxiety disorders.

Emotion Processing, Major Depression, and Functional Genetic Variation of Neuropeptide Y

Among healthy individuals, negatively valenced words activated the medial prefrontal cortex. Activation within this region was inversely related to genotype-predicted NPY expression ($P = .03$). Whole-brain regression of responses to negative words showed that the rostral anterior cingulate cortex activated in the low-expression group and deactivated in the high-expression group ($P < .05$). During the stress challenge, individuals with low-expression NPY genotypes reported more negative affective experience before and after pain ($P = .002$). Low-expression NPY genotypes were overrepresented in subjects with MDD after controlling for age and sex ($P = .004$). Population stratification did not account for the results.

These findings support a model in which NPY genetic variation predisposes certain individuals to low NPY expression, thereby increasing neural responsivity to negative stimuli within key affective circuit elements, including the medial prefrontal and anterior cingulate cortices. These genetically influenced neural response patterns appear to mediate risk for some forms of MDD.

Emotion Processing, Major Depression, and Functional Genetic Variation of Neuropeptide Y

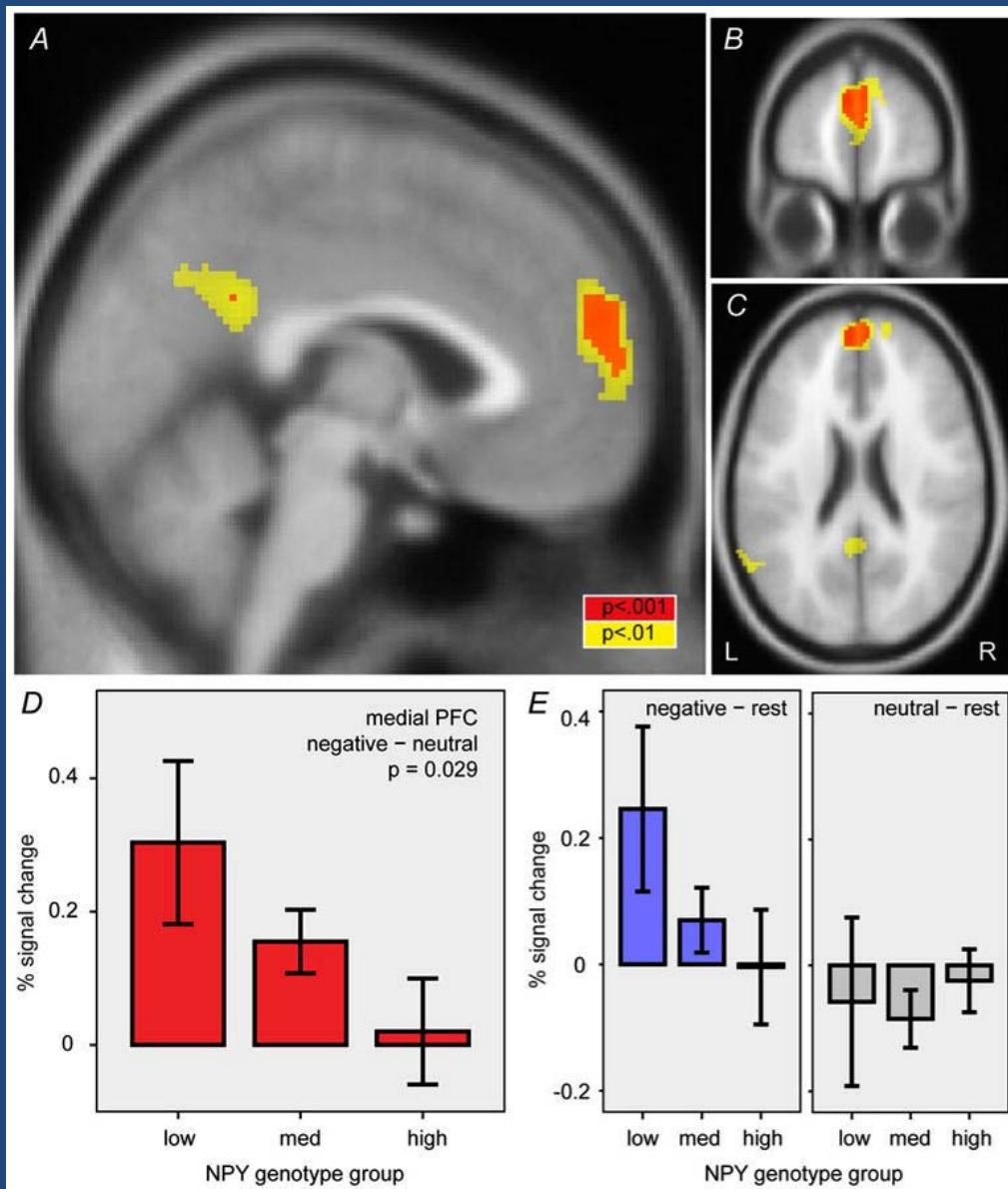


Figure 1. Effect of NPY genotype on medial PFC responses to negative words. Task effect in medial PFC with the negative–neutral word contrast is shown in three sections: (A) sagittal at $x = -2$, (B) coronal at $y = 56$, and (C) horizontal at $z = 22$. Red and yellow areas indicate uncorrected 2-sided $p < 0.001$ and 0.01 , respectively. This cluster was extracted as a region of interest to test for effect of NPY genotype. (D) Effect of NPY genotype group on percent signal change in the medial PFC region of interest shown in A–C ($p = 0.029$, ordinal regression). (E) Percent signal change for negative–rest and neutral–rest contrasts. Error bars, mean \pm standard error. L, left. R, right.

Arch Gen Psychiatry. 2011 February;68(2):158-166.

Emotion Processing, Major Depression, and Functional Genetic Variation of Neuropeptide Y

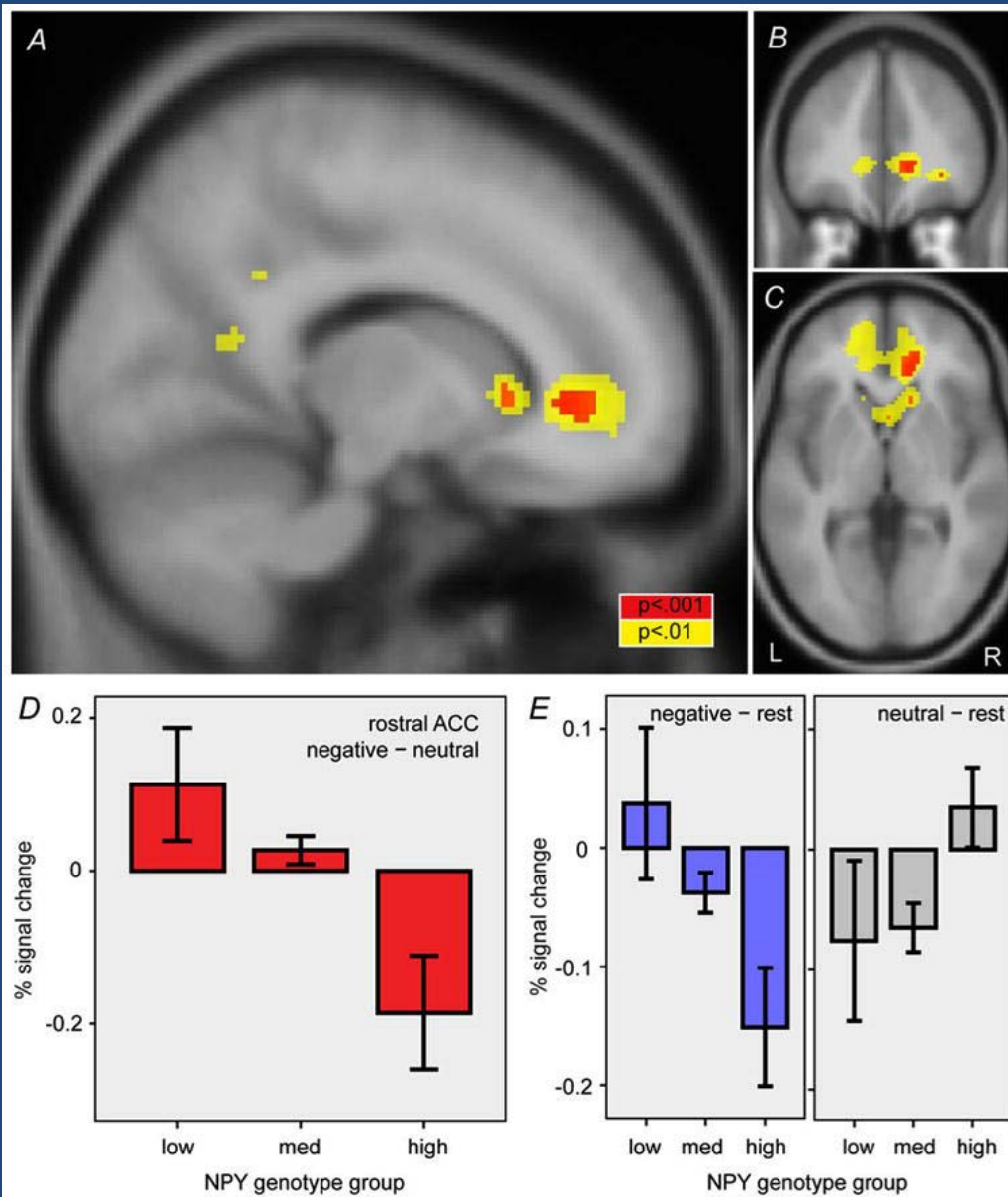


Figure 2. Effect of NPY genotype on rostral ACC responses to negative words. Effect of NPY genotype in right rostral ACC with the negative-neutral word contrast is shown in three sections: (A) parasagittal at x = 14, (B) coronal at y = 38, and (C) horizontal at z = 0. Red and yellow areas indicate uncorrected 2-sided p < 0.001 and 0.01, respectively. (D) Effect of NPY genotype group on percent signal change in the rostral ACC region identified in A-C. (E) Percent signal change for negative-rest and neutral-rest contrasts. Error bars, mean \pm standard error. L, left. R, right.

Arch Gen Psychiatry. 2011 February;68(2):158-166

Harnessing Neuroplasticity for Clinical Applications

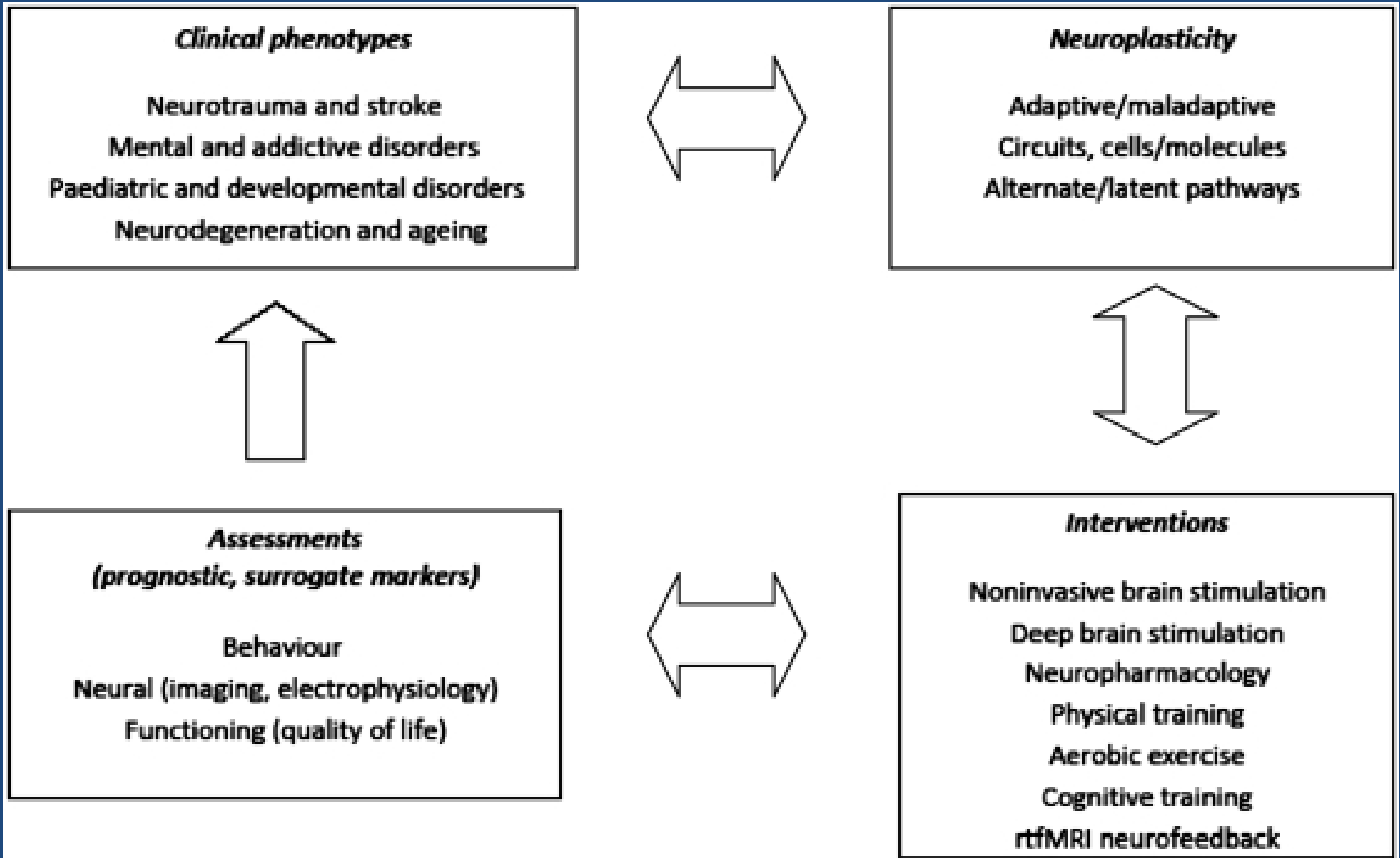


Figure 1. Conceptual overview of the relationship between clinical phenotypes, neuroplasticity, therapeutic interventions and assessment of function.

Attention Bias Modification Treatment: A Meta-Analysis Toward the Establishment of Novel Treatment for Anxiety

BACKGROUND: Attention Bias Modification Treatment (ABMT) is a newly emerging, promising treatment for anxiety disorders. Although recent randomized control trials (RCTs) suggest that ABMT reduces anxiety, therapeutic effects have not been summarized quantitatively.

CONCLUSIONS: Attention Bias Modification Treatment shows promise as a novel treatment for anxiety. Additional RCTs are needed to fully evaluate the degree to which these findings replicate and apply to patients. Future work should consider the precise role for ABMT in the broader anxiety-disorder therapeutic armamentarium.

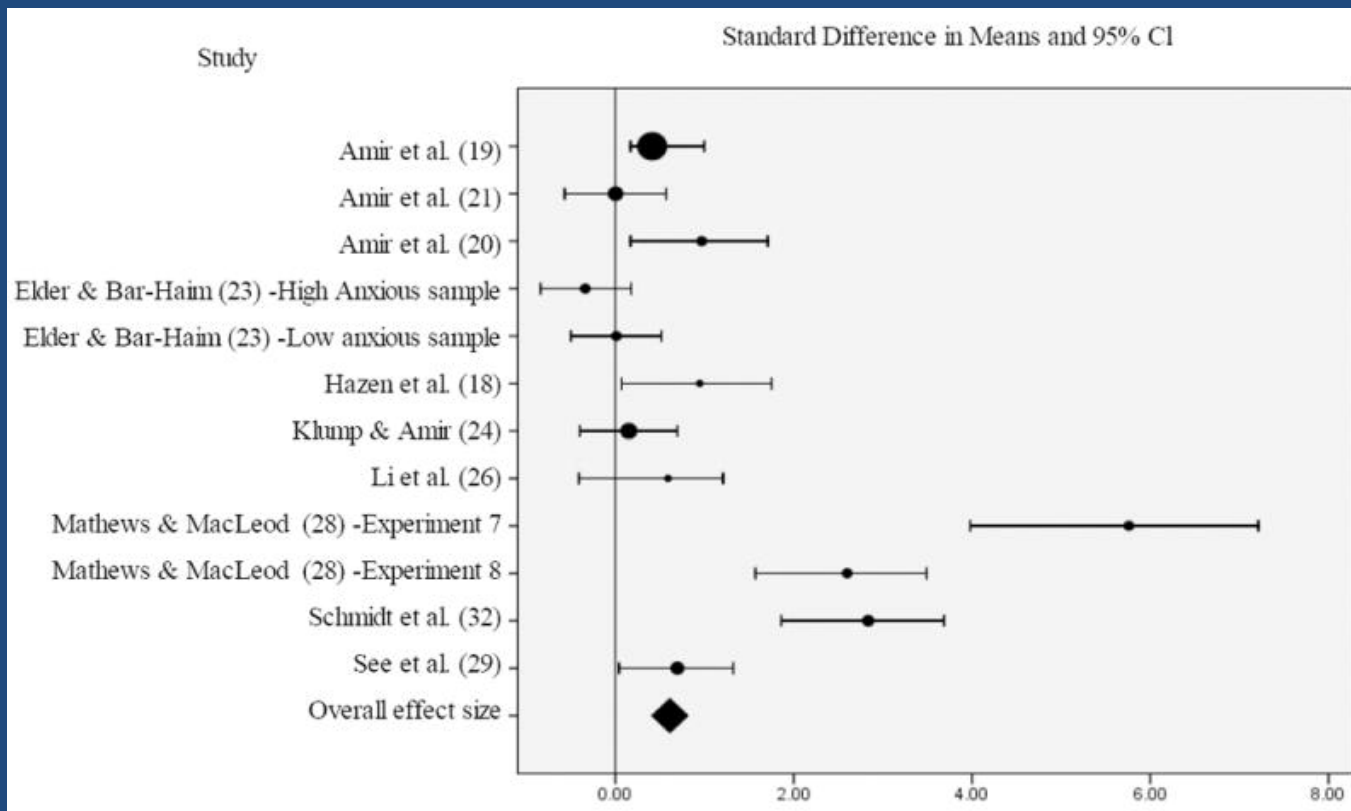


Figure 2. Size of round circle reflects sample size. CI, confidence interval.

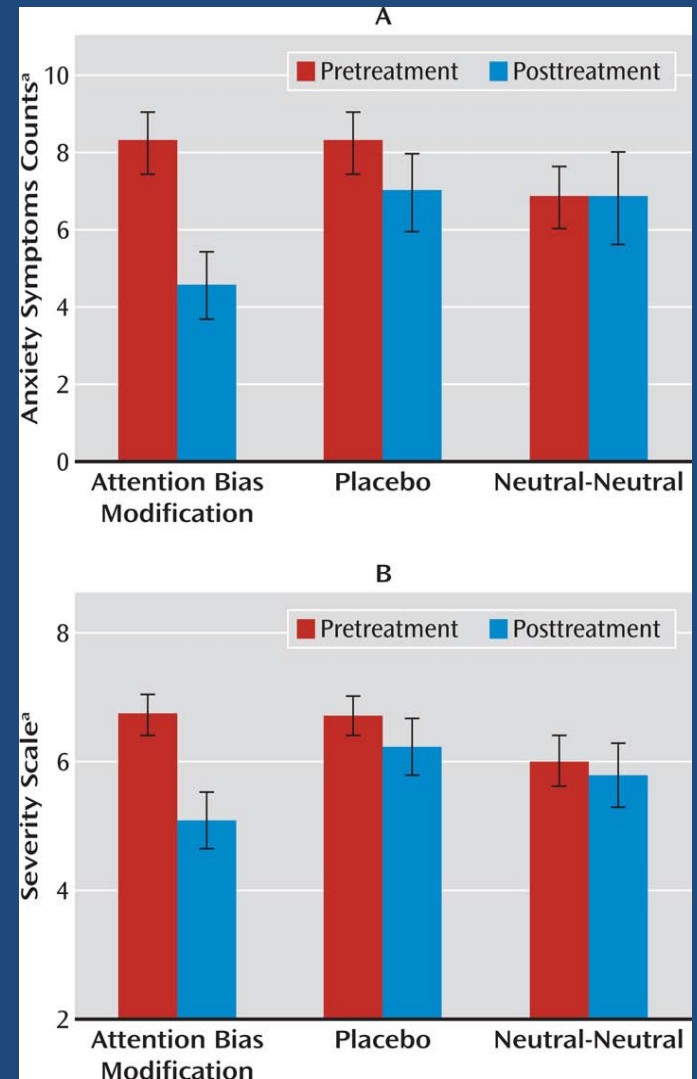
Attention Bias Modification Treatment for Pediatric Anxiety Disorders: A Randomized Control Trial

OBJECTIVE: While attention bias modification (ABM) is a promising novel treatment for anxiety disorders, clinical trial data remain restricted to adults. The authors examined whether ABM induces greater reductions in pediatric anxiety symptoms and symptom severity than multiple control training interventions.

METHOD: From a target sample of 186 treatment-seeking children at a hospital-based child anxiety clinic, 40 patients with an ongoing anxiety disorder who met all inclusion criteria were enrolled in the study. Children were randomly assigned to one of three conditions: **ABM designed to shift attention away from threat; placebo attention training using stimuli identical to those in the ABM condition; and placebo attention training using only neutral stimuli.** All participants completed four weekly 480-trial sessions (1,920 total trials). Before and after the attention training sessions, children's clinical status was determined via semistructured interviews and questionnaires. Reduction in the number of anxiety symptoms and their severity was compared across the three groups.

RESULTS: Change in the number of anxiety symptoms and their severity differed across the three conditions. This reflected significant reductions in the number of anxiety symptoms and symptom severity in the ABM condition but not in the placebo attention training or placebo-neutral condition.

CONCLUSIONS: ABM, compared with two control conditions, reduces pediatric anxiety symptoms and severity. Further study of efficacy and underlying mechanisms is warranted.



^a Per the Anxiety Disorders Interview Schedule for DSM-IV–Child and Parent versions.

Cognitive Interventions Targeting Brain Plasticity in the Prodromal and Early Phases of Schizophrenia

Table 2 Cognitive training programs to target impaired cognition in clinical high-risk and recent-onset schizophrenia

Phase of illness	Study and sample size	Cognitive function target and type of training	Cognitive training treatment intensity	Effects ^a
Clinical high risk	Rauchensteiner et al. (2011); N = 26	Target: attention, memory, and executive functioning Training: computerized cognitive training (CogPack)	10 hours over a maximum of 4 weeks	Improvement in verbal memory and 3 out of 8 CogPack exercises
	Bechdolf et al. (2012); N = 128	Target: concentration, attention, vigilance, and memory Training: computerized cognitive training (CogPack), individual cognitive-behavioral therapy, group skills training, and multifamily psychoeducation	12 sessions over 12 months	Lower rate of conversion to psychosis at 12- and 24-month follow-up
Recent-onset schizophrenia	Wykes et al. (2007); N = 40	Target: memory, complex planning, and problem solving Training: paper/pencil tasks with the guidance of a therapist	40 hours, 3 times per week over 3 months	Improvement in problem solving
	Ueland & Rund (2004, 2005); N = 24	Target: cognitive differentiation, memory, social perception, and attention including SPAN Training: paper/pencil tasks and practice on cognitive measures (e.g., SPAN) with the guidance of a teacher or therapist	30 hours, 2-3 times per week over 12 weeks	Improvement in SPAN task at 1-year follow up
	Eack et al. (2009); N = 58	Target: attention, memory, problem solving, and social cognition Training: computerized cognitive training (CogRehab) and social cognitive group exercises	60 hours, 1 time per week over 1-2 years	Improvement in neurocognition, social cognition, cognitive style, social adjustment, symptoms, and competitive employment
	Hansen et al. (2012); N = 62	Target: global and social functioning Training: compensatory training (e.g., schedules, schemes and signs to solve concrete problems related to daily life) along with assertive community treatment (ACT)	12 sessions, 1 session every 2 weeks over 6 months	None
	Vinogradov (2012); N = 80	Target: auditory processing and verbal memory functions Training: computerized cognitive training (BFP) of lower-level auditory processes and auditory/verbal working memory	40 hours, 5 times per week over 8 weeks	Improvement in global cognition, verbal learning and memory, problem solving

^A Significant improvement in cognitive training subjects relative to control subjects. BFP, Brain Fitness Program; SPAN, Span of Apprehension Task.

^aSignificant improvement in cognitive training subjects relative to control subjects. BFP, Brain Fitness Program; SPAN, Span of Apprehension Task.

Cognitive Training Interventions

Cognitive training, or “Brain Training,” has recently begun to gain a popular following.



Taking advantage of brain plasticity, cognitive training exercises aim to enhance intelligence via global domains of cognitive function: memory, attention, processing speed, etc.

An Example: Training to Enhance Fluid Intelligence

- **Fluid intelligence refers to the ability to reason and solve new problems. It is a critical component of IQ.**
- **Jaeggi and colleagues (2008, PNAS) showed that training on one component of fluid intelligence (working memory) transferred to improvement in independent tests of fluid intelligence.**

Extending the Neural Network Hypothesis to Develop Interventions for Major Depressive Disorder

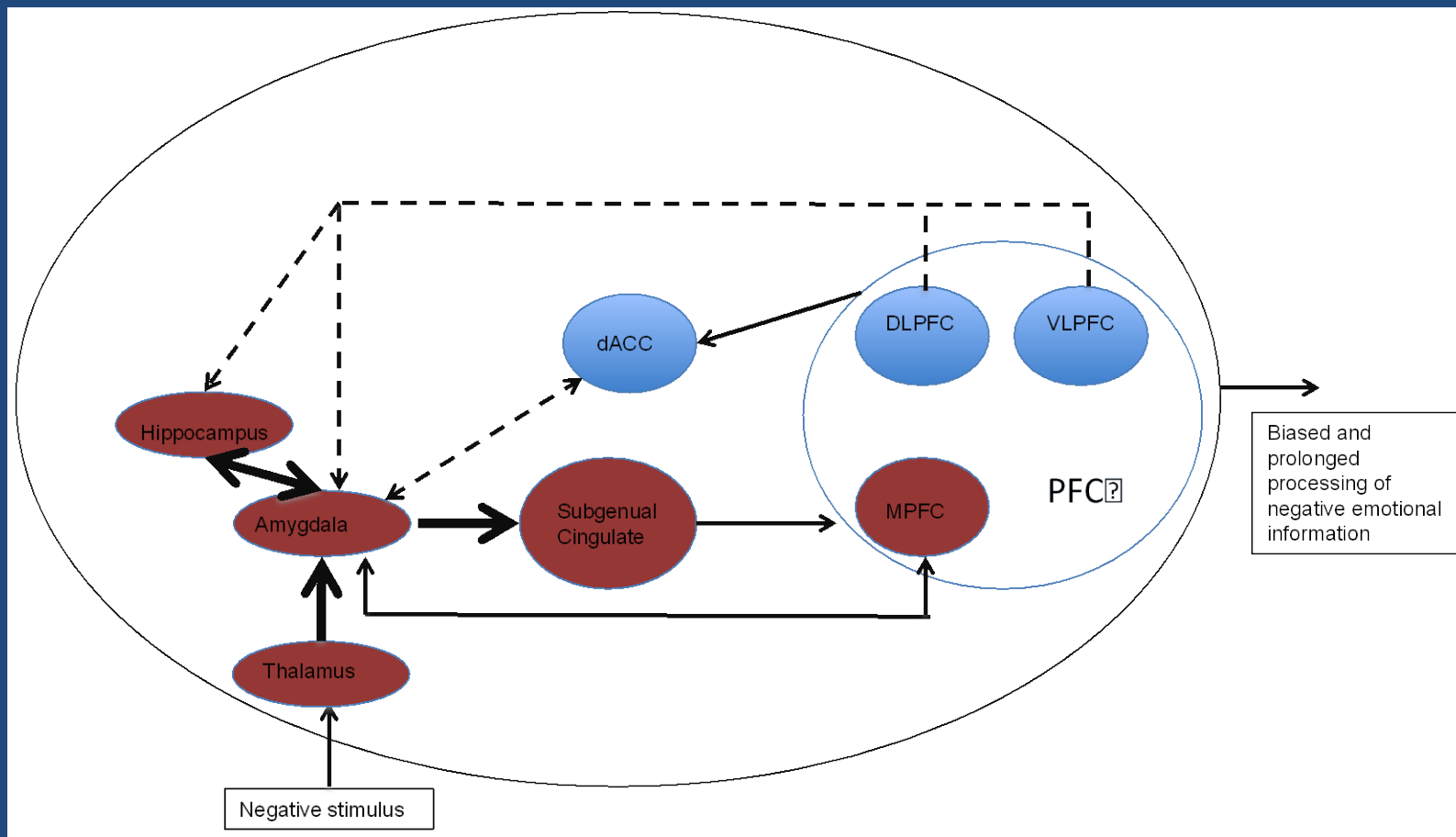
- **Knowledge of the neural network abnormalities implicated in MDD could highlight targets for cognitive training interventions.**

Five Steps for Developing a Cognitive Training Intervention:

- **Identify the underlying neural network abnormality to address.**
- **Determine the components of the network that are most amenable to target with a cognitive training intervention.**
- **Identify a cognitive activity/task that taps into these components.**
- **Devise a training regimen using the task in a repeated, progressively challenging manner.**
- **Evaluate the effects on MDD symptoms and on neural network function.**

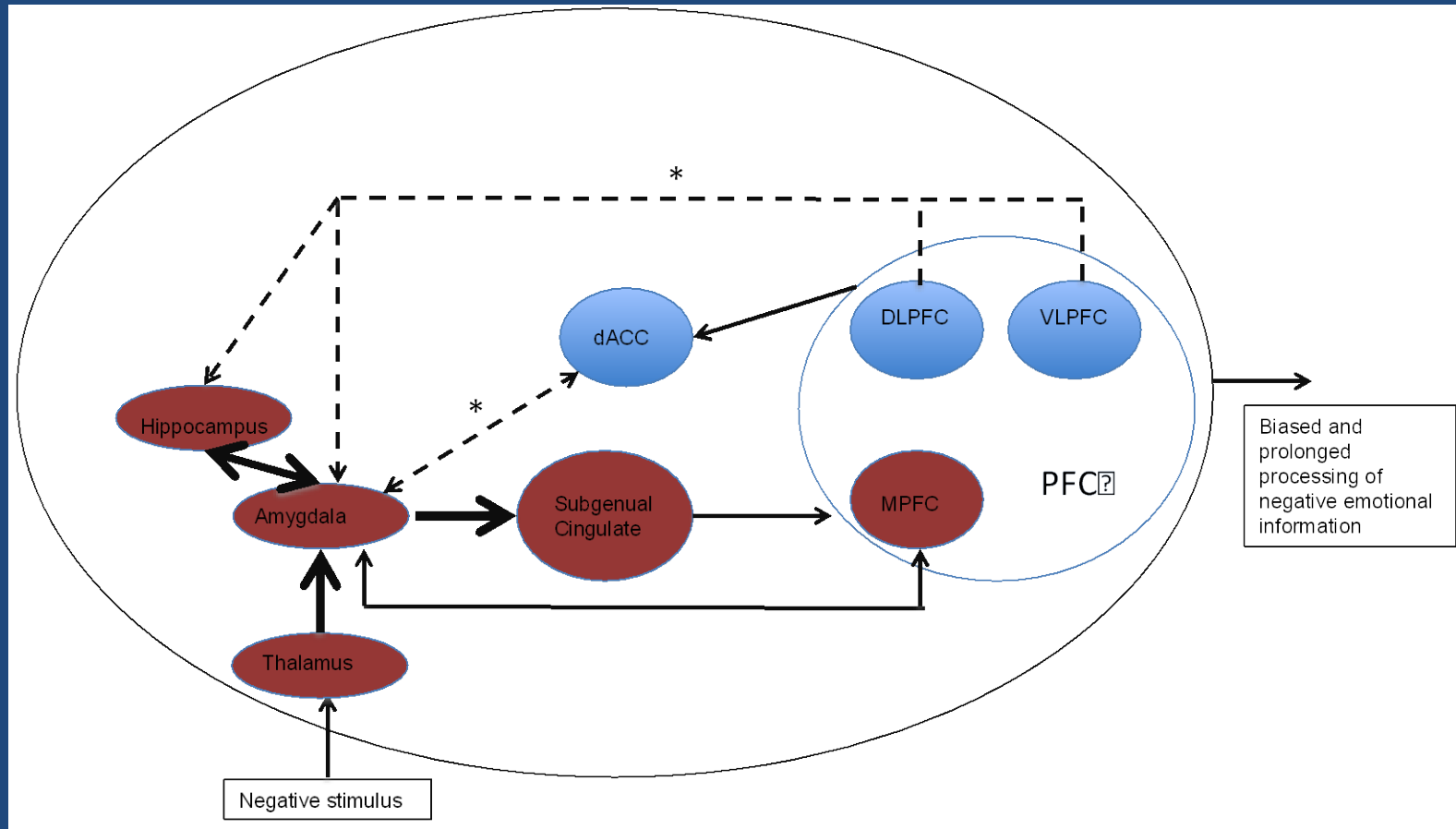
Step 1: Identify the underlying neural network abnormality to address

A putative cognitive neurobiological model of biased and prolonged processing of negative information in MDD.



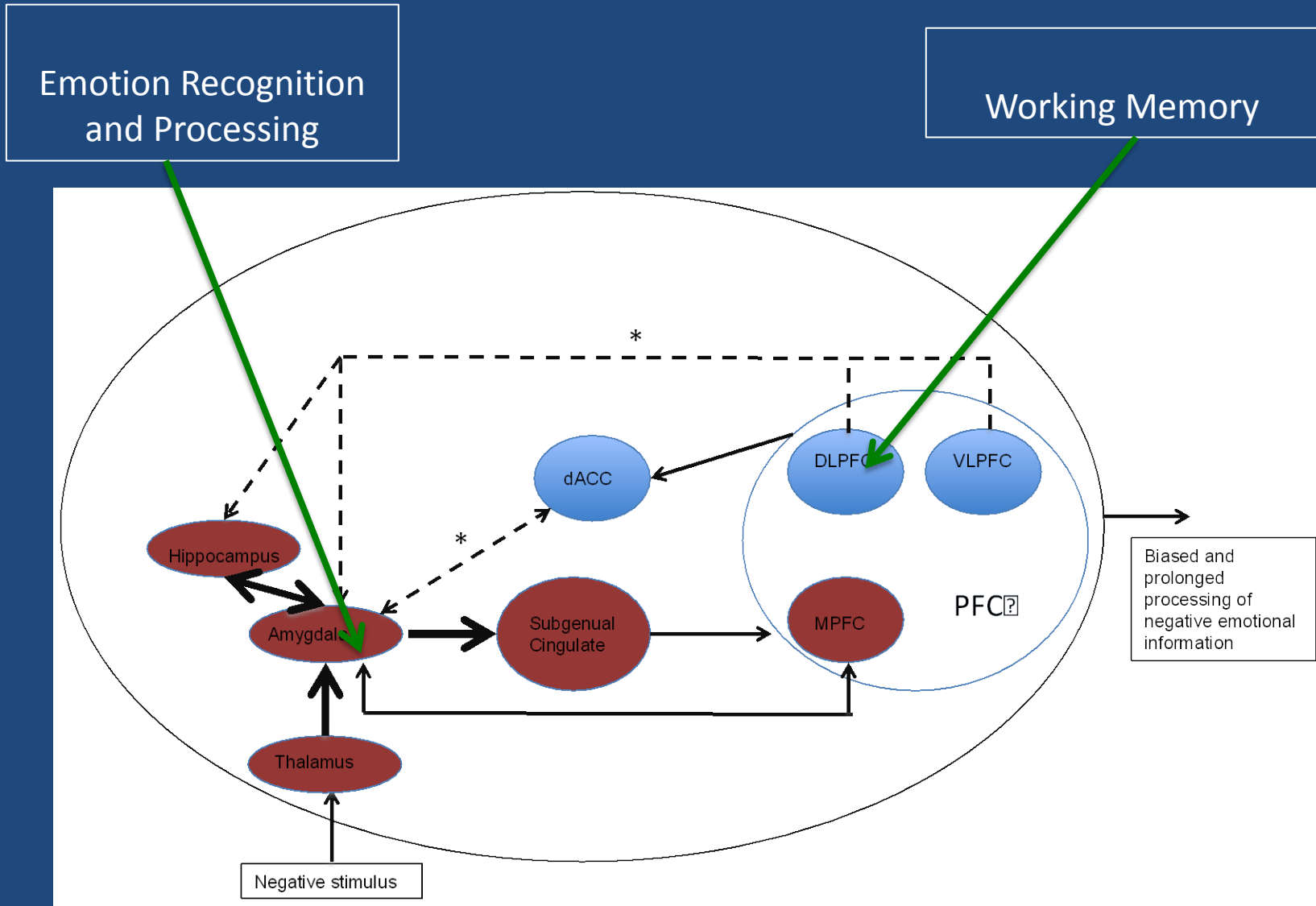
Red= hyperactive; Blue= hypoactive. Thicker arrows represent a stronger signal between regions. Solid arrows (showing intact associations) and dashed arrows (showing attenuated associations) represent functional connections. PFC= prefrontal cortex; MPFC= medial PFC; DLPFC= dorsolateral PFC; VLPFC= ventrolateral PFC; dACC= dorsal anterior cingulate cortex.

Step 2: Determine the components of the network that are most amenable to target with a cognitive training intervention.



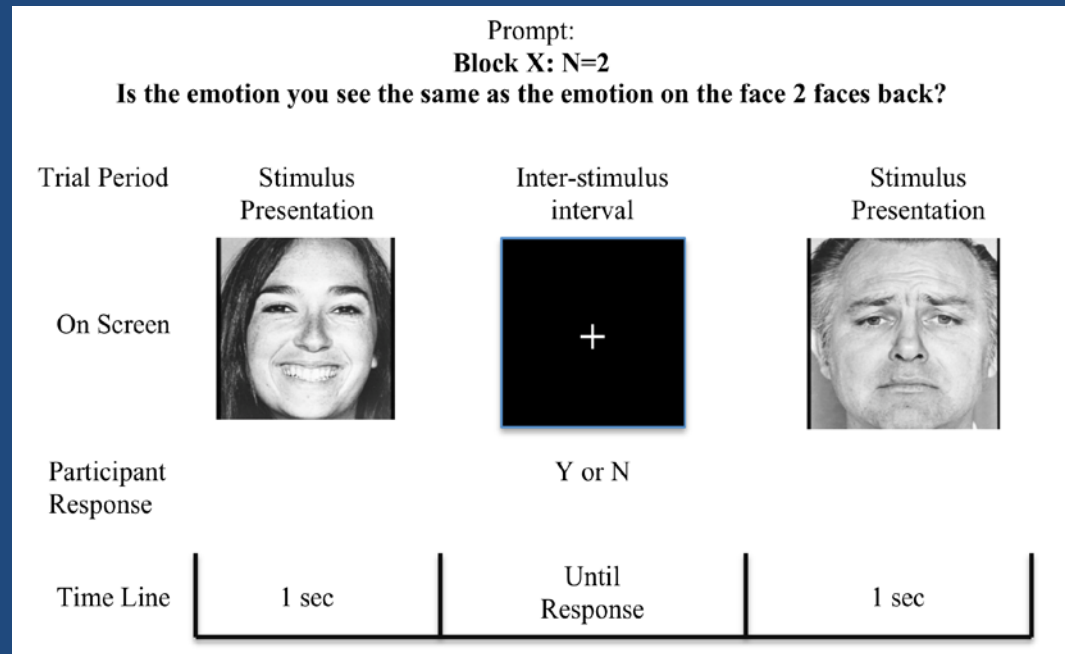
Stars indicate functional connectivity abnormalities between PFC regions and limbic system associated with impaired cognitive control for emotional information in MDD, and represent targets for cognitive training interventions.

Step 3: Identify a cognitive activity/task that taps into these components

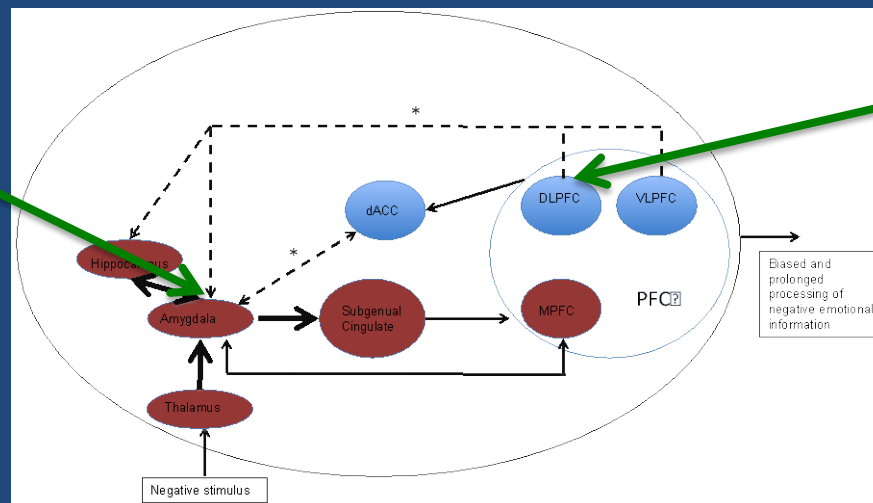


The Emotional Faces Memory Task (EFMT)

- Progressively challenging n-back working memory task.
- Adapted from Jaeggi et al. (2008, PNAS) to include emotional faces as stimuli.

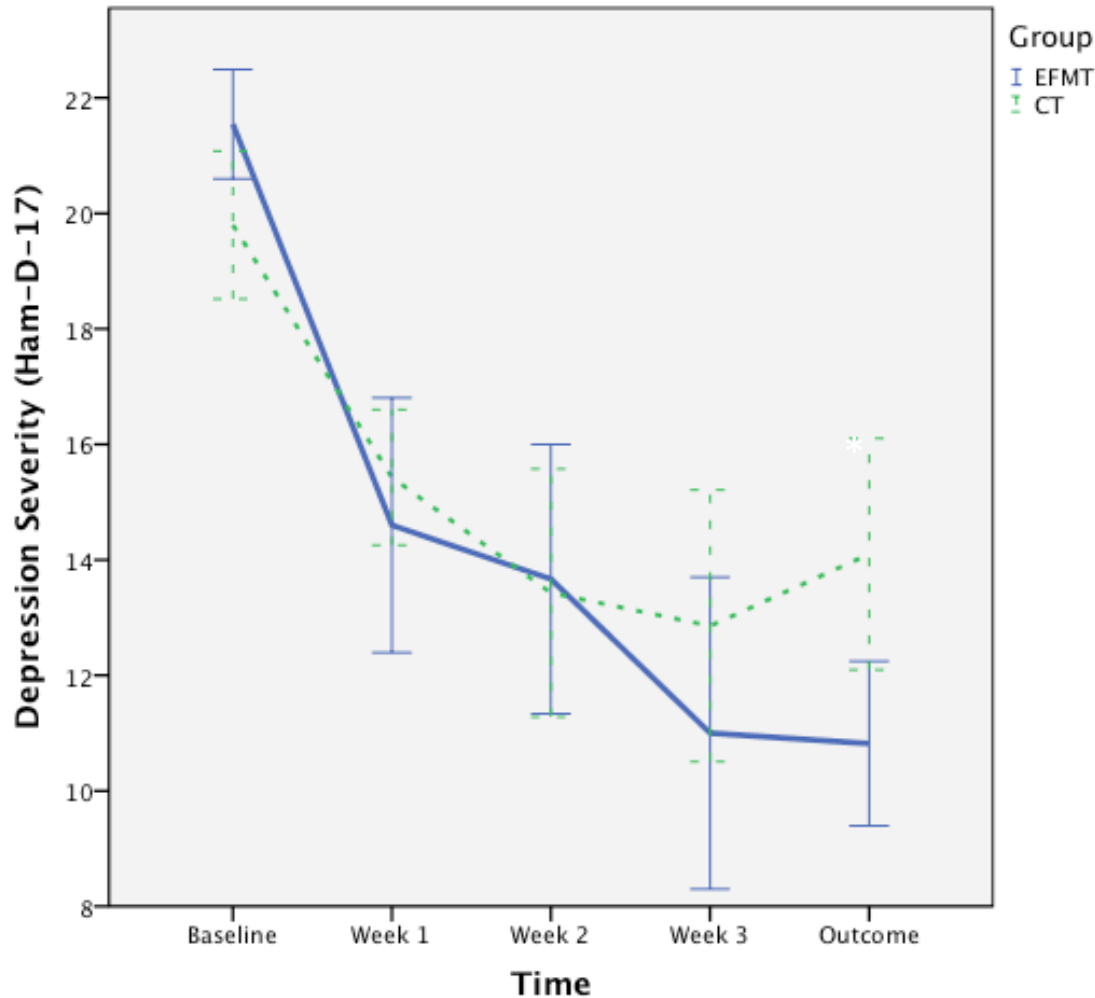


Emotion Recognition and Processing



Working Memory

Effects on Depression Symptoms



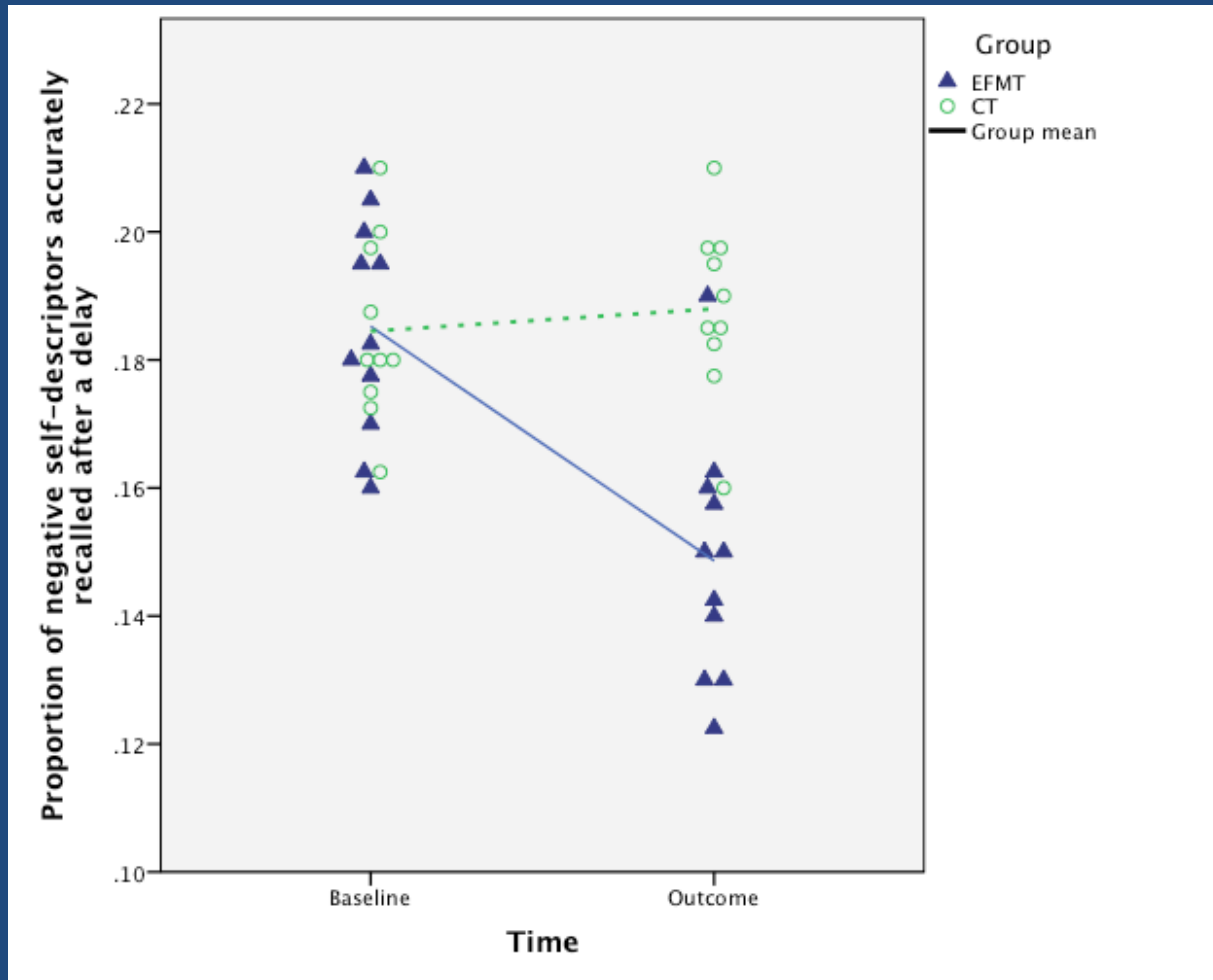
Repeated measures analysis of Ham-D change (group x time [baseline-outcome]): $F(1,19) = 5.605, p = .029, d = 0.82$.

Mean Ham-D change:
EFMT = -10.64
CT = -5.7

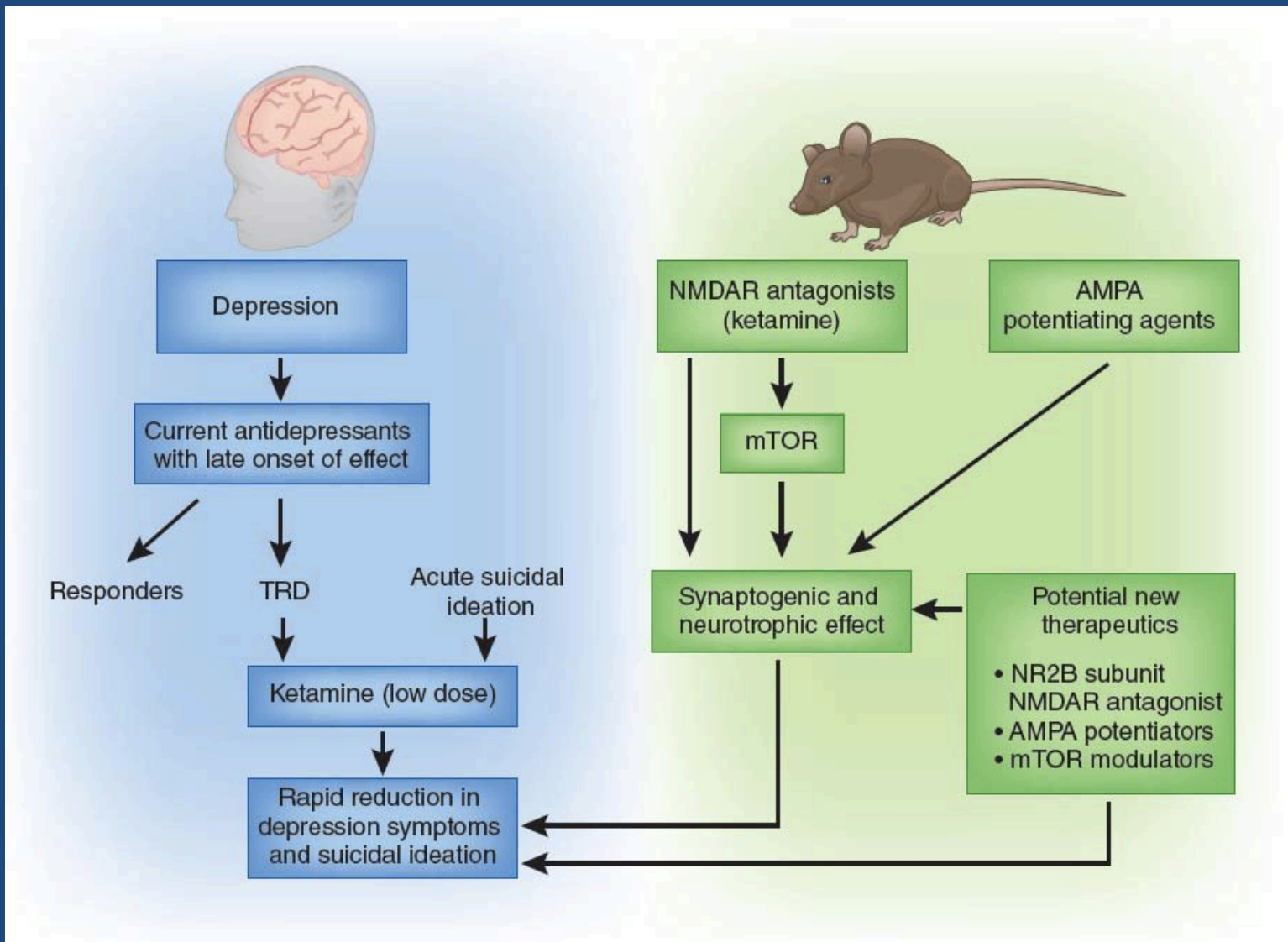
6/11 EFMT responders (>50% reduction in Ham-D)

Effects on Cognitive Biases: SRIP

- After training, the EFMT group accurately recalled more positive self-descriptors ($d= .31$) and fewer negative self-descriptors ($d= .66$).
- The CT group accurately recalled more positive self-descriptors ($d= .27$) and the same amount of negative self-descriptors ($d= .09$).

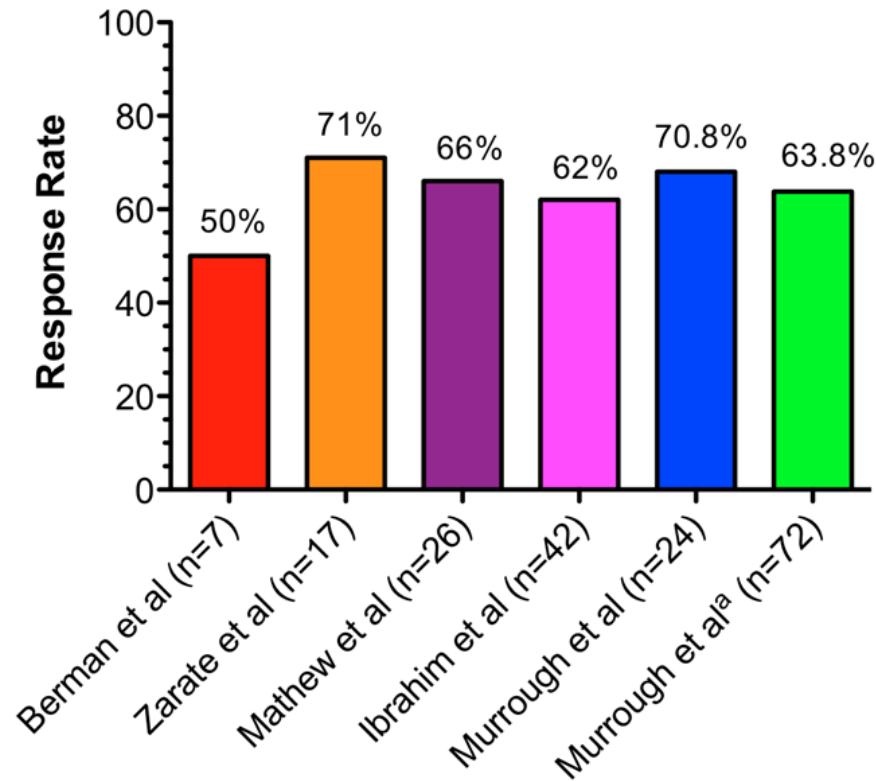


The Translational Research Potential of Ketamine for Depression: New Avenues of Drug Discovery



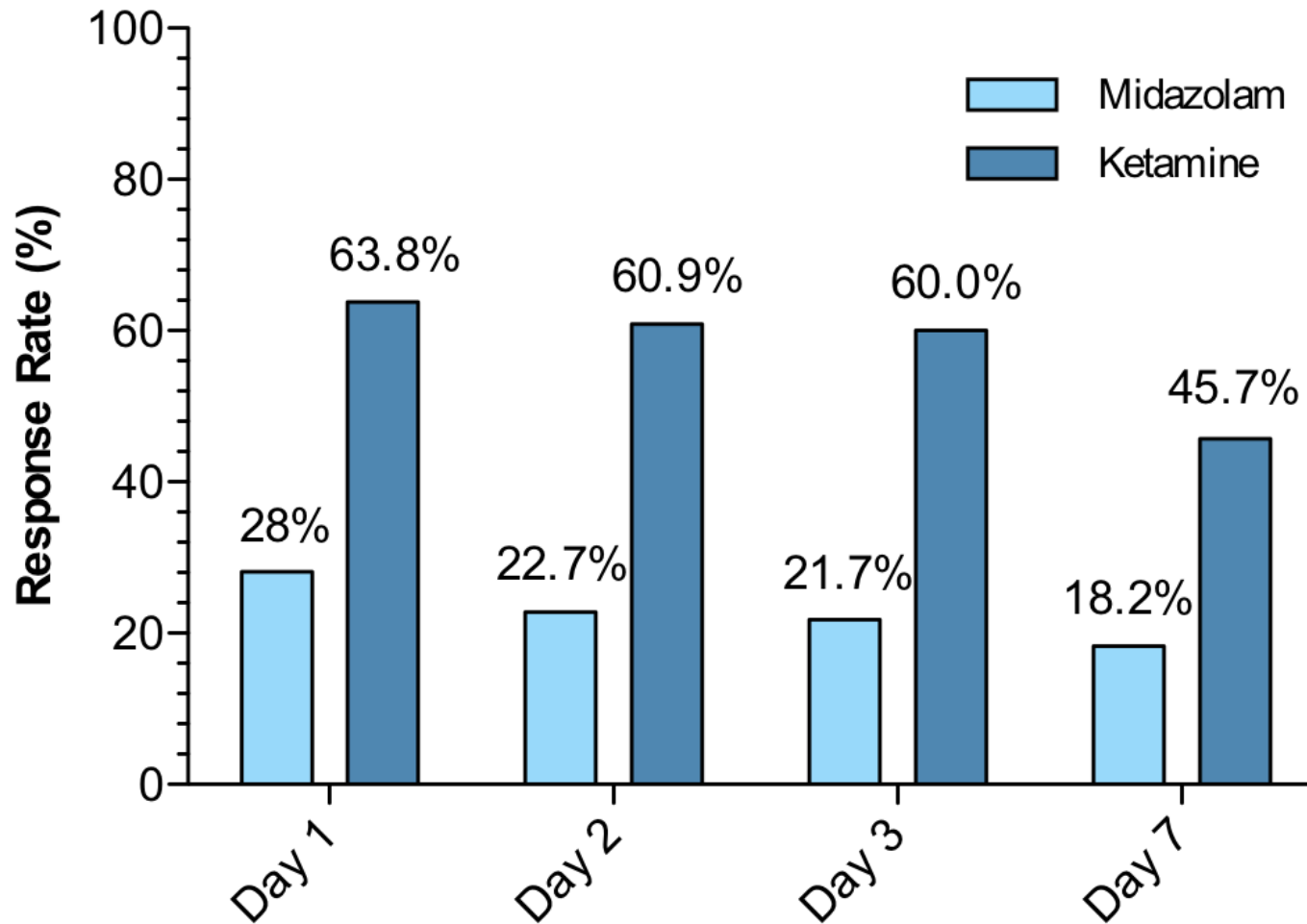
Summary of Acute Response Rates in Ketamine Depression Studies

Figure 1. Response Rates Following Acute Treatment With Ketamine in Major Depression

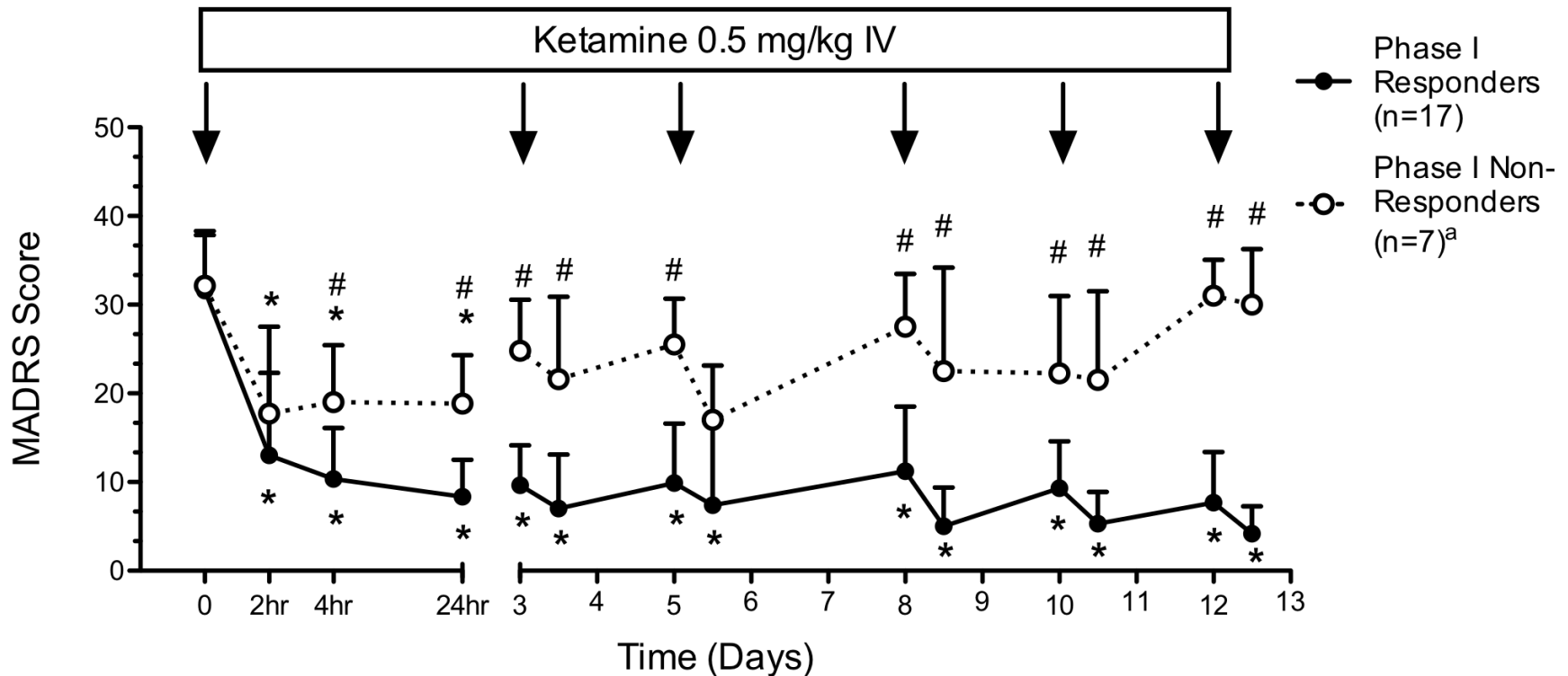


Response rates represent maximal reported rate within 72 hours of a single infusion. See text for full citations; citations represent published studies except Murrough et al^a is data in preparation based on the recently completed study funded by NIMH R01MH081870-01A2 (PI: Mathew).

Antidepressant Response Rates Over Time in Clinical Trial of Ketamine Compared to Midazolam

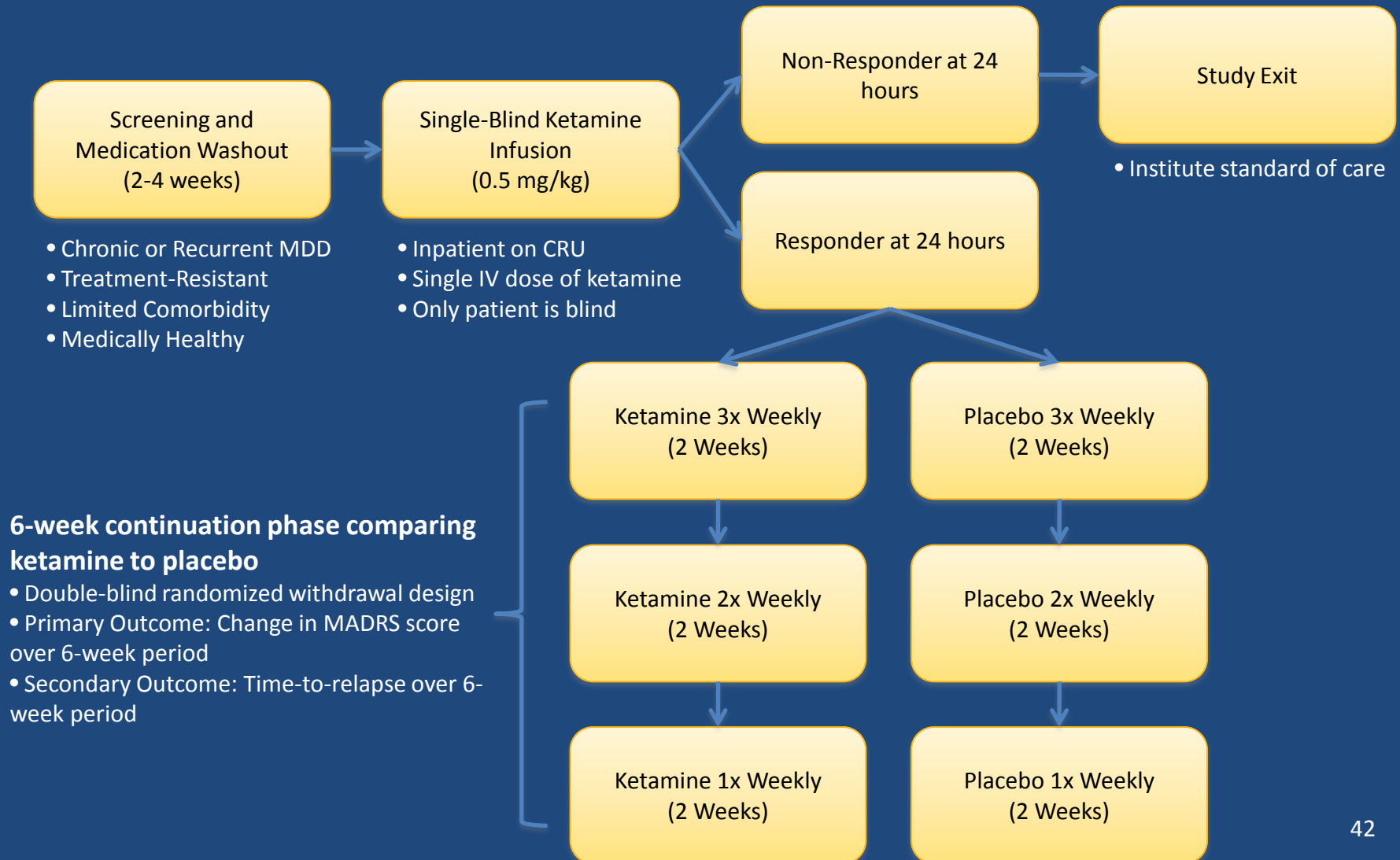


Antidepressant Efficacy of Repeated Administrations of Ketamine Over Two Weeks in Patients with Treatment-Resistant Depression



Murrough et al, Biological Psychiatry 2012

Proposed Placebo-Controlled Ketamine Maintenance Design



Basic and Clinical Neuroscience: A Foundation for Discovery

