



**HOPE FOR DEPRESSION**  
RESEARCH FOUNDATION

- Lecture: *"New Directions for the Integration of Psychotherapy and Pharmacotherapy in the Treatment of Depression"*
- Event: Banbury Seminar: Neurobiology of Depression:  
From Molecules to Mood  
New York - March 22-25, 2009
- Speaker: Harold W. Koenigsberg  
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Mount Sinai School of Medicine and  
James J. Peters VA Medical Center

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## New Directions for the Integration of Psychotherapy and Pharmacotherapy in the Treatment of Depression

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### Psychotherapies Used to Treat Depression

- Cognitive-Behavioral Therapy (CBT)
- Interpersonal Psychotherapy of Depression (IPT)
- Psychodynamic Psychotherapy
  - (meta-analysis: Leichsenring et al, Archives Gen Psych, 2004)
  - (Bond, Curr Opinion Psychiat 2006)
- Supportive Psychotherapy

### Combined Psychotherapy & Pharmacotherapy

- Combination generally more effective than either alone
- Additive Effect
  - Two modalities targeting same symptoms
  - Each modality targets different symptoms
  - Improved compliance
- New Directions Informed by Neurobiological Advances

## Learning-based Psychotherapies

### Extinction Learning and D-Cycloserine

- D-Cycloserine – a partial NMDA agonist at the glycine site
- Enhances extinction learning in animal models ( $d = 1.19$ ) [Meta-analysis: Norberg, Crystal & Tolin, Biol Psychiatry 2008]
- Most effective when administered close to the time of exposure/extinction

### Extinction Learning and D-Cycloserine

- Application to Psychotherapy ( $d = .60$ )
  - Virtual reality exposure Rx of fear of heights (Ressler et al 2004)
  - Exposure Rx of Social Anxiety Disorder (Hoffman et al 2006)
  - Exposure Rx of Panic Disorder (Tolin et al 2007)
  - Obsessive-Compulsive Disorder (Kushner et al 2007; Wilhelm et al 2008)
- A role in the treatment of depression ?
  - 6-week DCS augmentation pharmacotherapy for treatment resistant depression – One small study not encouraging (Heresco-Levy et al 2006)
  - Possibility in Enhancing Behavioral Therapy of Depression
    - Seligman (1975) – exposure to an escape contingency can reverse learned helplessness

## Psychodynamic Psychotherapies

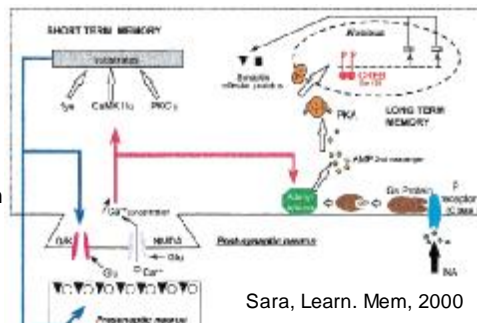
The forte of psychodynamic psychotherapy is the highly specific retrieval (reactivation) of pathogenic memories

## Memory and Depression

- Memories (either conscious or unconscious) may contribute to depression
  - Memories of trauma, loss, regrets, guilt evoking situations
  - Past or present
- Memory retrieval is altered in depression (Barnhofer et al 2002; Watkins & Teasdale 2001)
  - Ruminative
  - Overgeneralized
- Can we intervene in a way to affect memory?

“... memories are highly malleable and dynamic, even the very strong ones that may control our daily lives”  
C. Alberini, Cell Mol Life Sci 2006

- Dynamics of memory
  - Acquisition (NMDA receptor; CaMKII)
  - Consolidation (requires protein synthesis, post-learning reactivation of NMDAR)
  - Storage
  - Retrieval (labile)
  - Reconsolidation

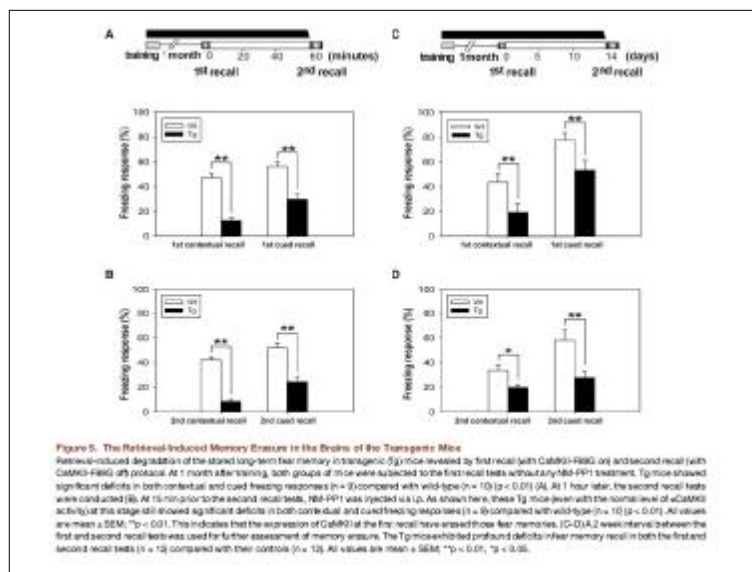


Neuron 60, 353-366, 2008

## Inducible and Selective Erasure of Memories in the Mouse Brain via Chemical-Genetic Manipulation

Xiaohua Cao,<sup>1,2</sup> Haimin Wang,<sup>2,3</sup> Ding Mei,<sup>2,4</sup> Shuming An,<sup>1</sup> Liang Yin,<sup>1</sup> L. Philip Wang,<sup>2</sup> and Jie Z. Tsien<sup>2,5\*</sup>  
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<sup>3</sup>These authors contributed equally to this work.

- Used a chemical genetic technique which allowed them to rapidly manipulate the activity of  $\alpha$ CaMKII in transgenic mice (over expressing it and then selectively inhibiting it when desired with the molecule NM-PP1)
- Memory tasks: 1) Contextual Fear Conditioning, 2) Cued Fear Conditioning, 3) Object Recognition
- Long-term memories (one month) which are retrieved when  $\alpha$ CaMKII activity is high are erased – i.e. they can not be retrieved later even when  $\alpha$ CaMKII activity is back to normal
- This erasure is specific for the memory that was retrieved at the time the  $\alpha$ CaMKII activity was elevated



### Can selective erasure of memory ever be a therapeutic tool?

- Can such selective memory erasure be therapeutic?
  - Would it ever be therapeutic to erase episodic memory? Trauma? PTSD? Depression?
  - Can context or cued fear memory be erased while leaving episodic memories intact?
- It is possible to selectively erase specific long-term memories
- This requires reactivation of the memory and treatment (e.g. to alter  $\alpha$ CaMKII activity) at the time the memory is reactivated
- Psychodynamic psychotherapy provides a systematic approach to selectively reactivate psychologically relevant memories

Are we on the threshold of a paradigm shift in the integration of psychotherapy and pharmacotherapy?

- Classical Model: Medication to treat disorders/symptoms
- A Different Paradigm
  - Psychotherapy and Pharmacotherapy Combined to Facilitate the Alteration of Underlying Neurobiological Processes
    - D-Cycloserine facilitating extinction learning
    - Psychodynamic psychotherapy to selectively engage personally relevant circuits for neuroplastic change.
- In this model medication is used not to directly treat symptoms but to enhance the psychotherapeutic process.
  - à Medication Facilitated Psychotherapy