Translational Medicine:

Using Systems of Differential Equations to Identify Patterns in Symptom Remission in Response to Treatment

Knowledge Recovery

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Overview

Why we did this work - to explore the utility of computational methods in medicine

How we did it - used differential equations (“neural networks”) to model recovery and compared recovery of two different antidepressant treatments

What we found - recovery patterns for the two treatments were different - the order and timing of improvement of symptoms were different

What we think it means -

- Improved treatment selection
- Reduced costs
- Reduced suffering, possibly saving lives.

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Depression is a BIG problem

Characterized by persistent and pathological sadness, dejection, and melancholy

Prevalence (US)

- 6% year (18 million)
- 16% experience it in their lifetime

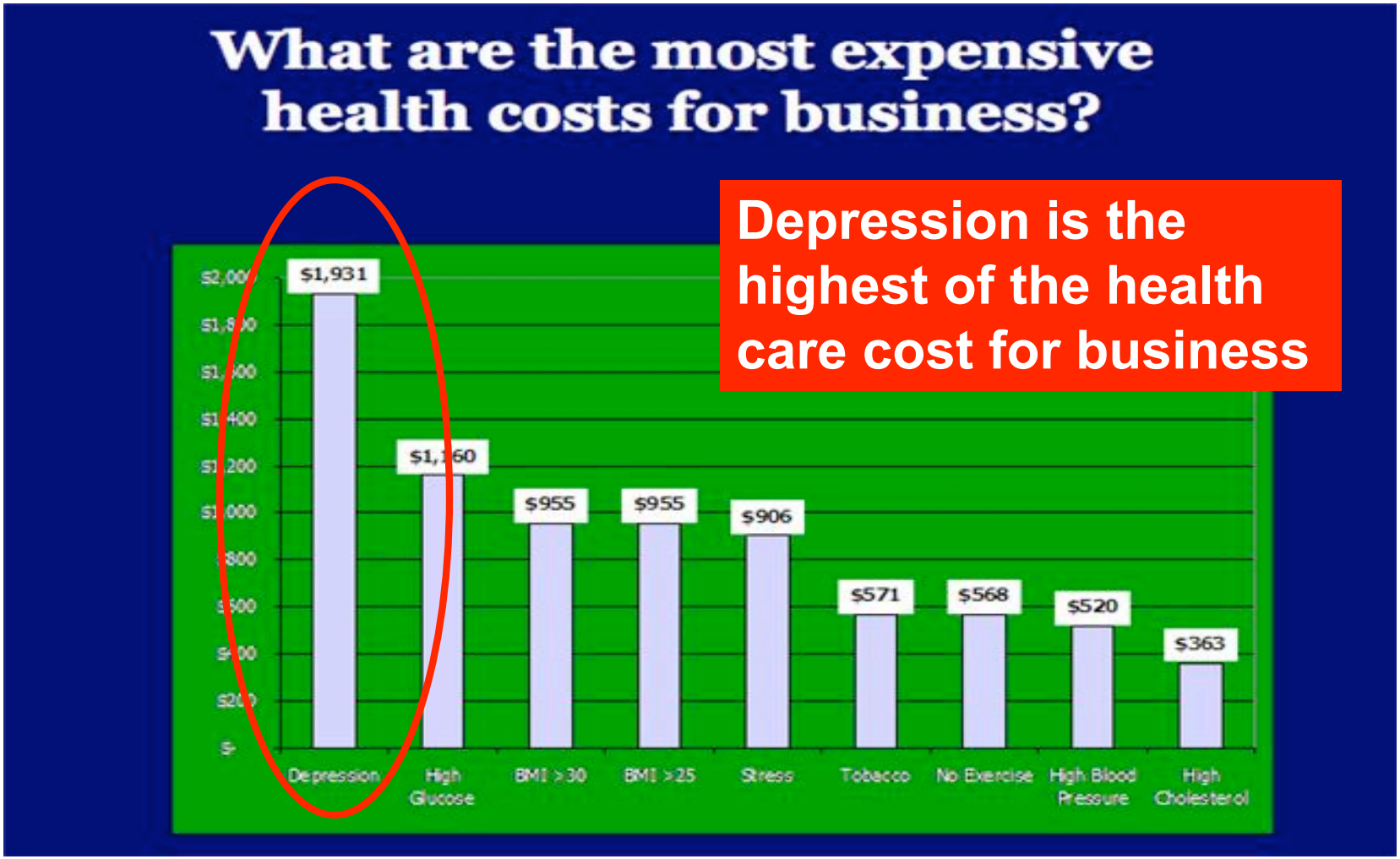
Cost

- 44 Billion (1990)

Potential Impact

- 1% Improvement would mean 180, 000 people helped
- 1% Improvement would mean 440 million in savings

The Economic Burden of Depression



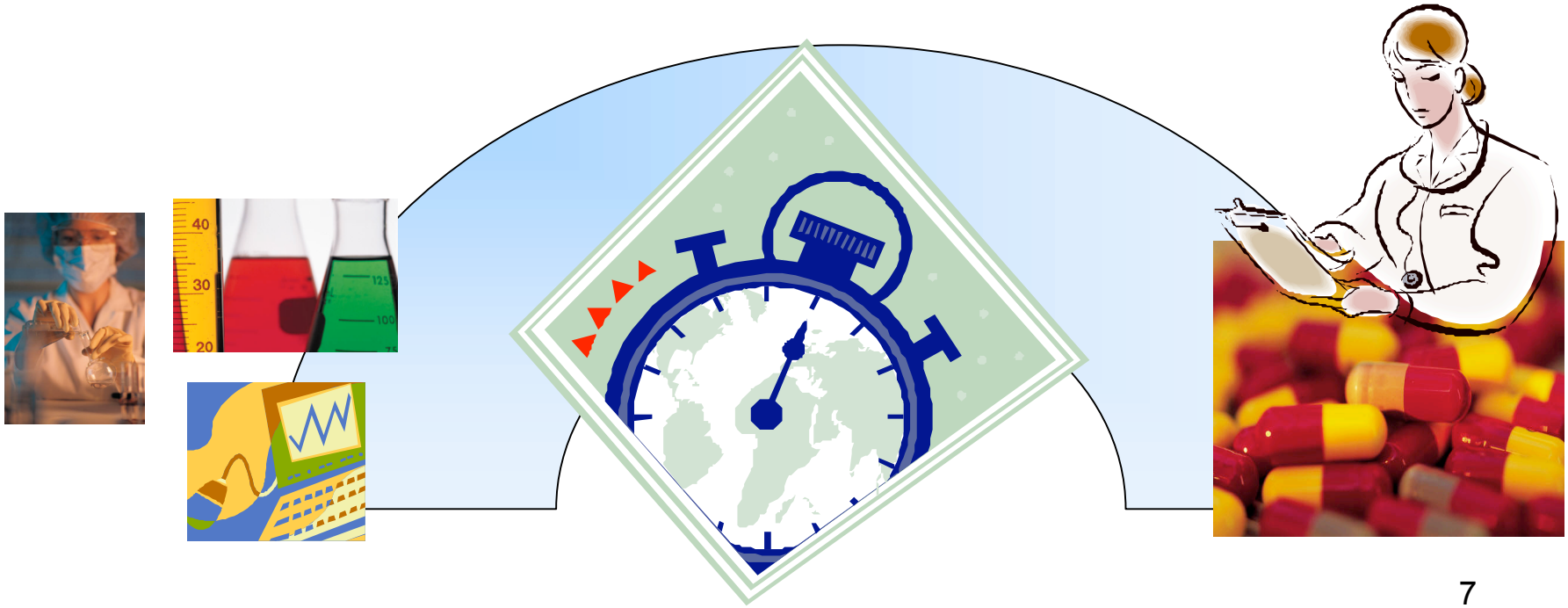
http://www.preventingdepression.com/costs.htm

Source: The Healthy Thinking Initiative

The Economic Burden of Depression

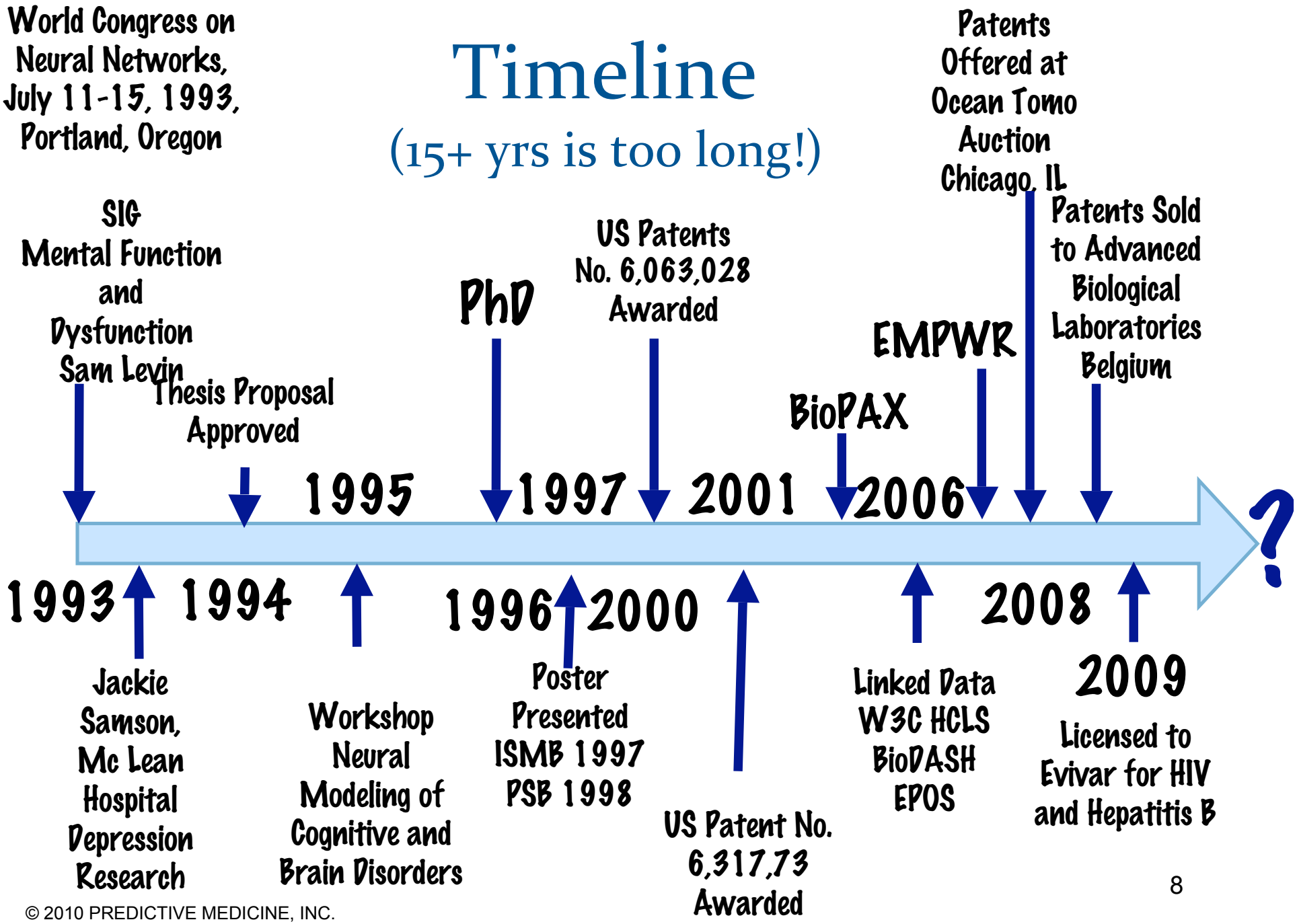
Translational Medicine

- Rapid transformation of laboratory findings into clinically focused applications
- ‘From bench (computer) to bedside (psychiatrists couch) and back’



Timeline

(15+ yrs is too long!)



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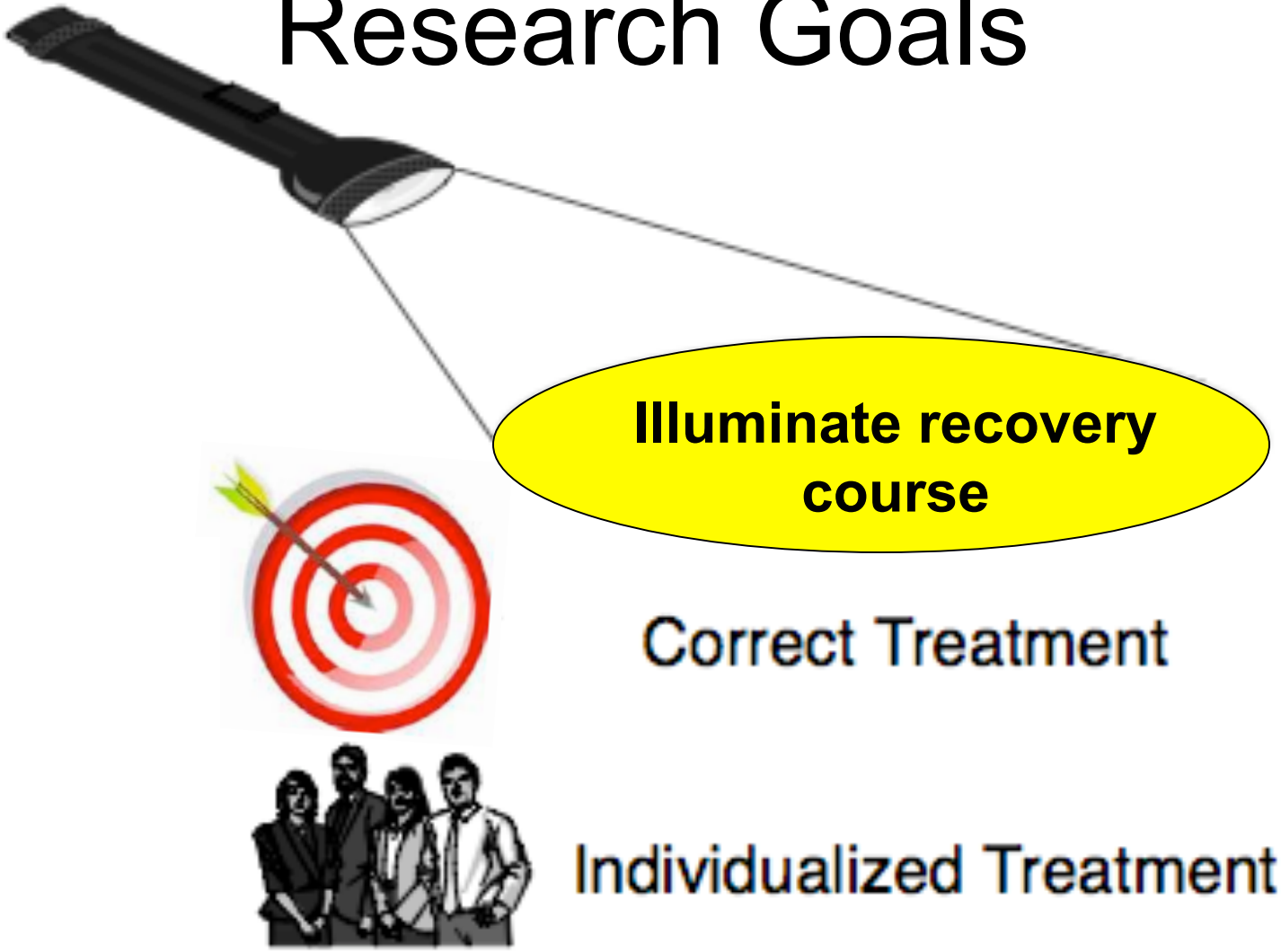
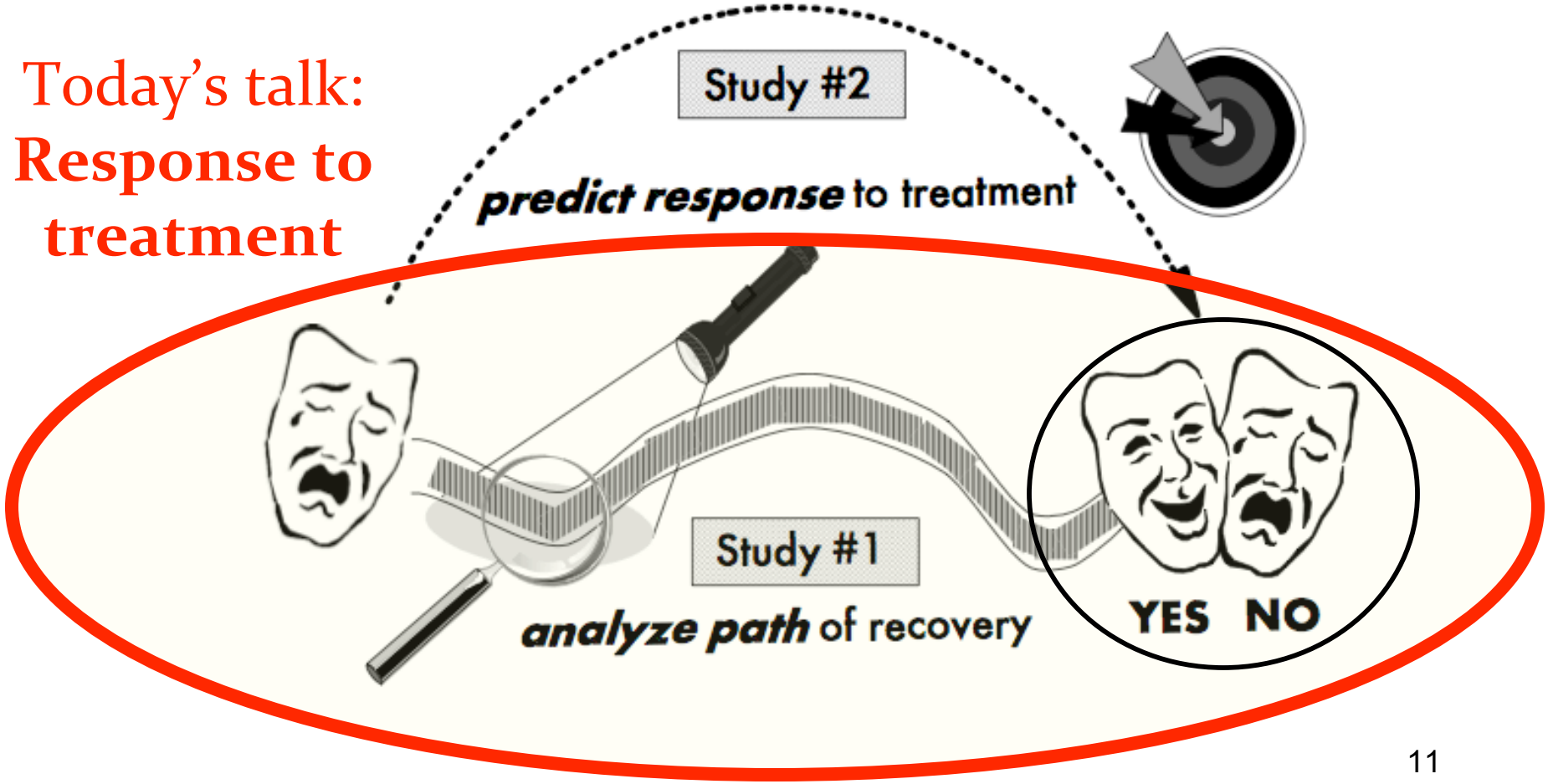
Research Goals



Treatment Response Study

Today's talk:
Response to treatment



Background

Characteristics

- Clinical Depression (Major Depressive Disorder (MDD)
- Current Treatments

Measurements

- Clinical Symptom (Hamilton Scale)

Problems with current status

- MDD has no sub-diagnosis
- MDD treatment guidelines vague
- MDD treatment not specific to patients

Clinical Data

Symptom Intensity

-Hamilton Depression Rating Scale (0-4 scale)

Treatment

-Desipramine (DMI)

-Cognitive Behavioral Therapy (CBT)

Outcome

- Recovery studied
    - those patients who responded to treatment

Hamilton Scale for Depression

Example Questions

1. **DEPRESSED MOOD** (Sadness, hopeless, helpless, worthless)

_____

0= Absent
1= These feeling states indicated only on questioning
2= These feeling states spontaneously reported verbally
3= Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep
4= Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

2. **FEELINGS OF GUILT**

_____

0= Absent
1= Self reproach, feels he has let people down
2= Ideas of guilt or rumination over past errors or sinful deeds
3= Present illness is a punishment. Delusions of guilt
4= Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. **SUICIDE**

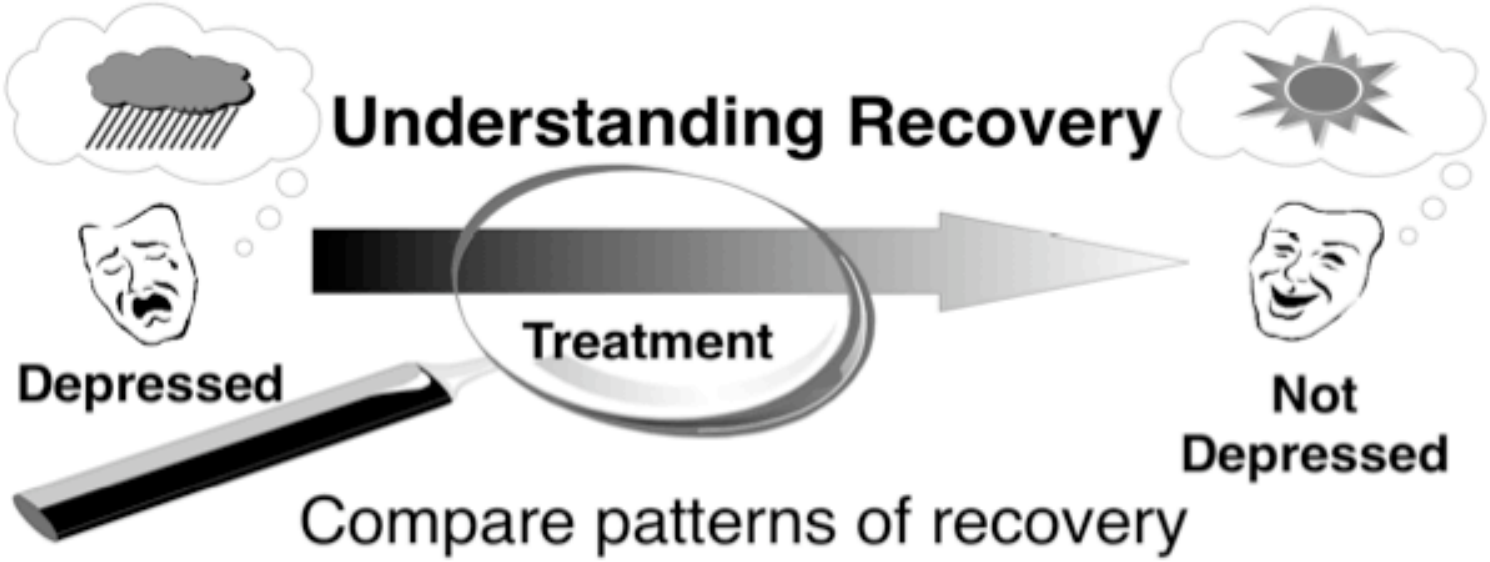
_____

0= Absent
1= Feels life is not worth living
2= Wishes he were dead or any thoughts of possible death to self
3= Suicidal ideas or gesture
4= Attempts at suicide (any serious attempt rates 4)

Modelling

Recast problem into mathematical terms

- Easier to understand
- Easier to manipulate
- Easier to analyze

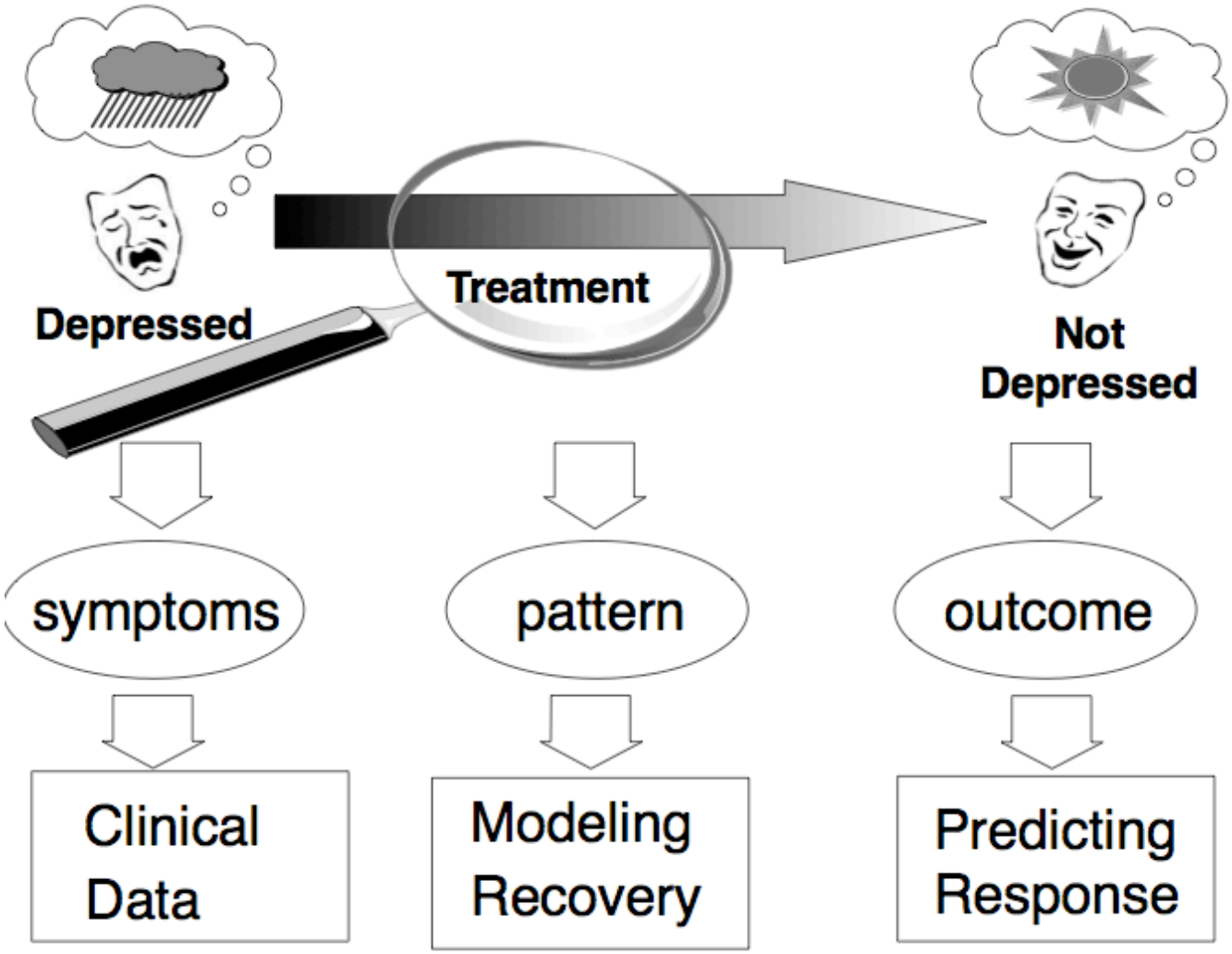


6 week	When response begins	(Latency)	Δt
7 symptoms	Indirect (between symptoms)	(Interaction Effects)	w
2 treatments	Direct (on symptoms)	(Treatment Effects)	u,v

Recast as dynamical system

Patient	Recovery pattern	(Differential Equations)	$\ddot{x}$

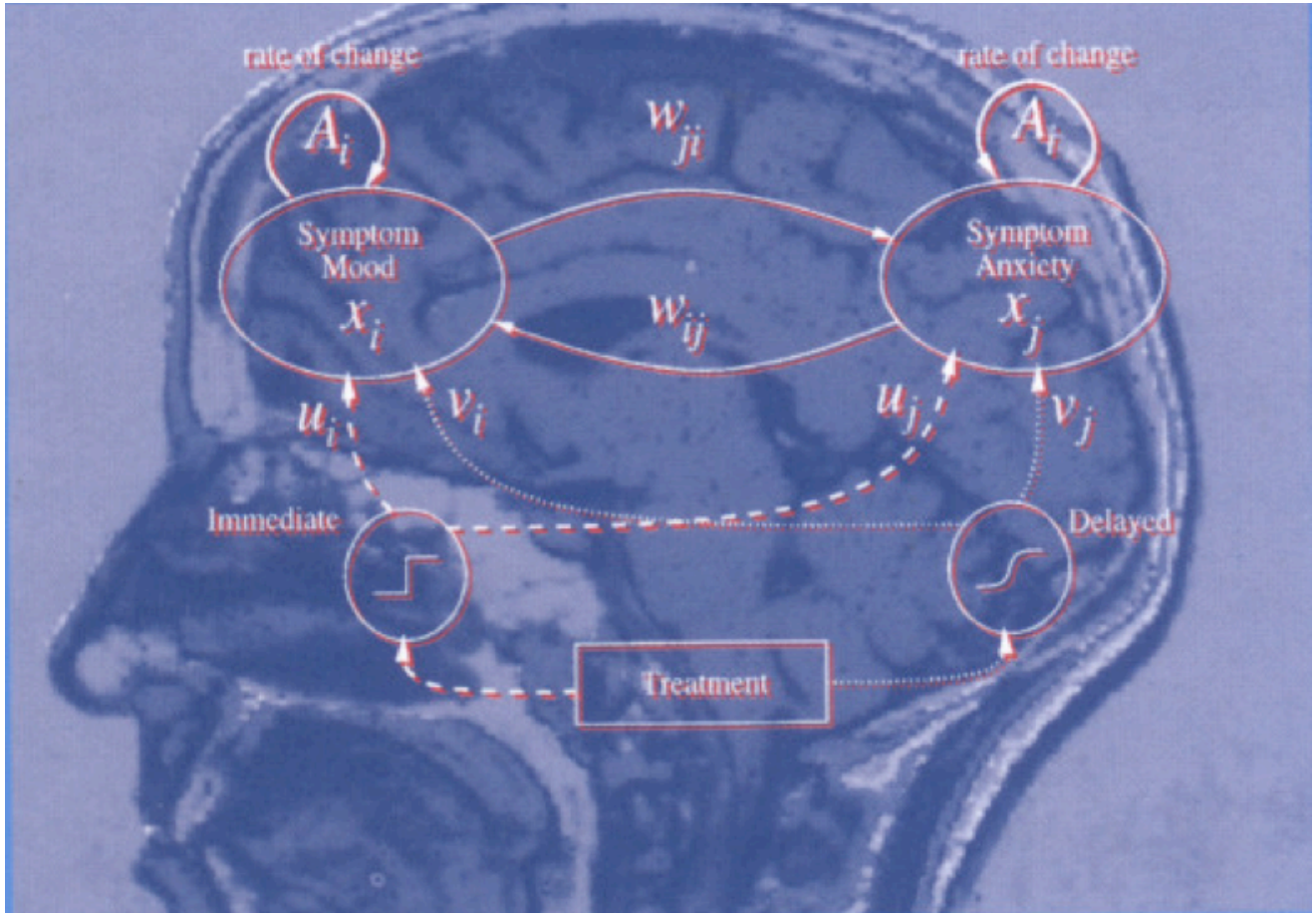
Understanding Recovery



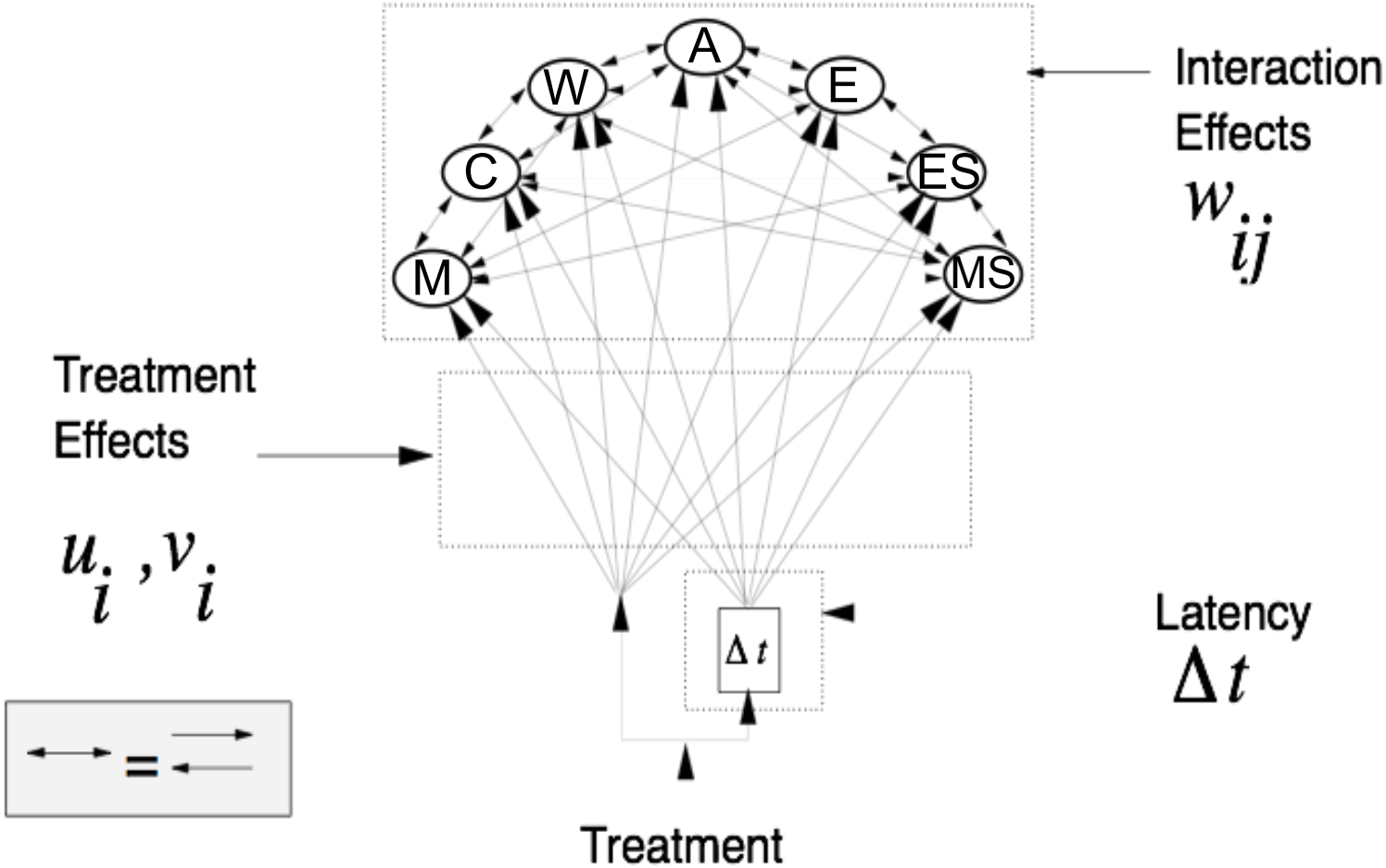
Data

• 7 Symptoms (Hamilton questionnaire values measure severity)	Physical:	Early Sleep Disturbance Mid, Late Sleep Disturbance Energy
	Performance:	Work & Interests
	Psychological:	Mood (sadness, hopelessness) Cognitions (guilt, suicidal) Anxiety
• 2 Treatments	Cognitive Behavioural Therapy (CBT) Desipramine (DMI)	
• Clinical Data	Responders = improvement >= 50% N = 6 patient each study 6 weeks = 252 data points each study	

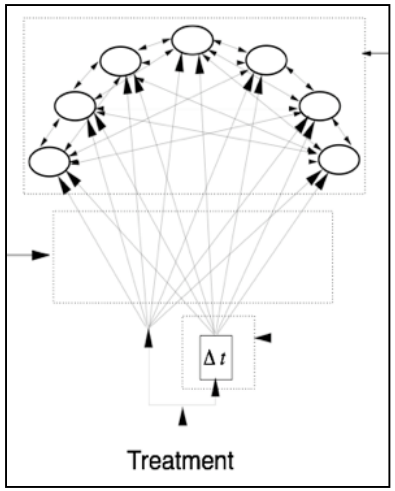
Linking Hypotheses
Symptoms and Brain Region Activity

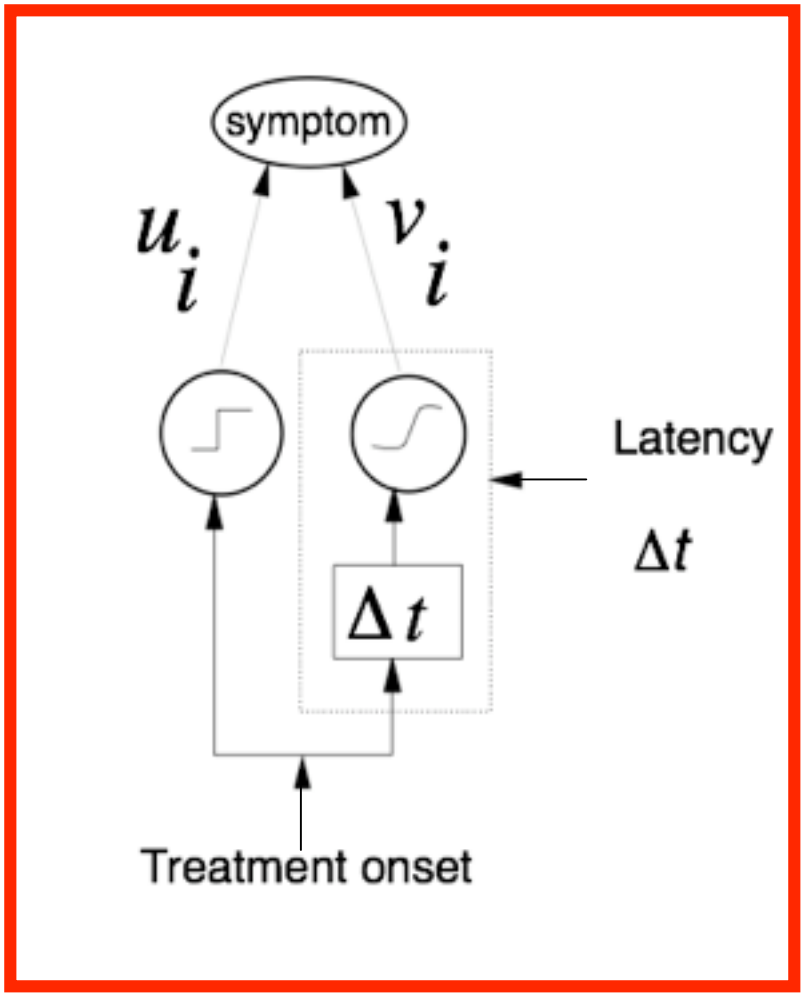


Overview
Recovery Model and Parameters



Modelling Time to Response





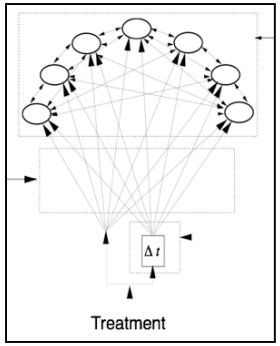
Latency
Δt

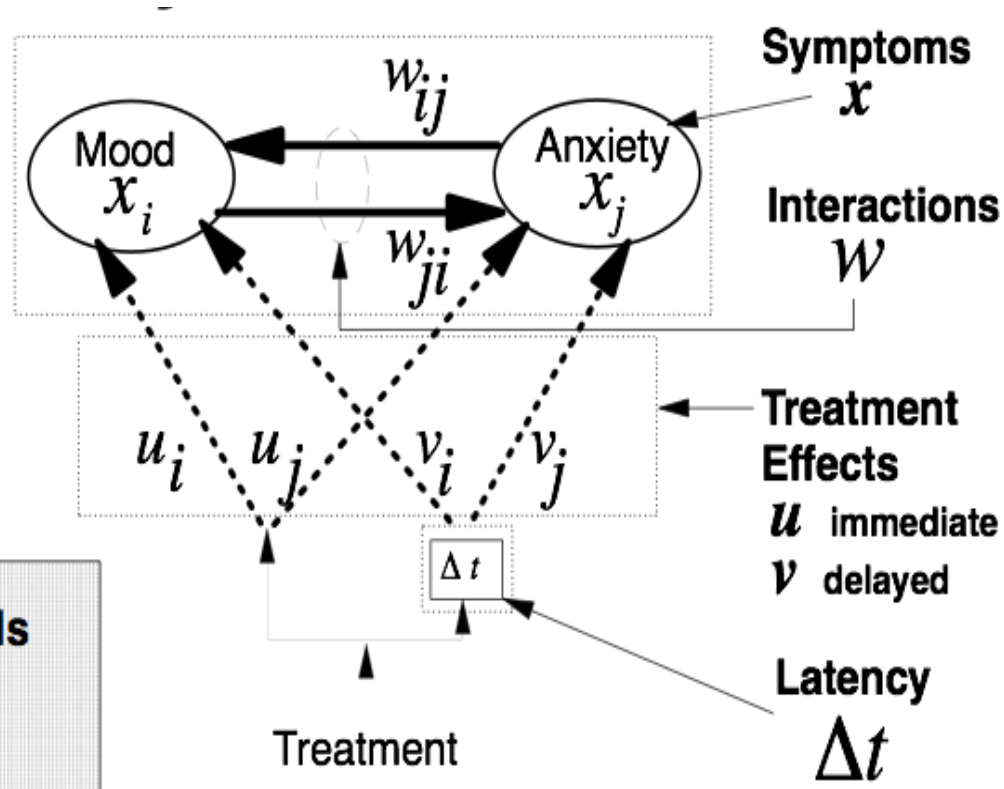
$$h(\alpha, t-\Delta t) = \frac{1}{1+e^{-\alpha(t-\Delta t)}}$$

α Rapidness of response

Δt Latency

Modelling Treatment Effects





2 Models
- **CBT**
- **DMI**

Optimized parameters specify model
Initial conditions predict patient trajectory

Recovery Model Equation

$$\ddot{x}_i = -A_i \dot{x}_i + \sum_{j=1}^{7} (x_j - B_j) w_{ij} + s(t) u_i + h(\alpha, t - \Delta t) v_i$$

Stabilizing factor

Rate of symptom change

Interactions
between symptoms

Acceleration of symptom

Symptom

Baseline

7 symptoms

Immediate effect
step function

Treatment Effects
on each symptom
(strength)

Delayed effect
sigmoid function

Steepness

Latency

Training the model

estimated

$$L = \int_0^T \sum_{ik} \left(\left(X_{ik} - \hat{X}_{ik} \right)^2 + \mu_{ik} \left(\dot{\hat{X}}_{ik} - f\left(\hat{X}_{ik} \right) \right) \right) dt + K \sum_j P_j^2$$

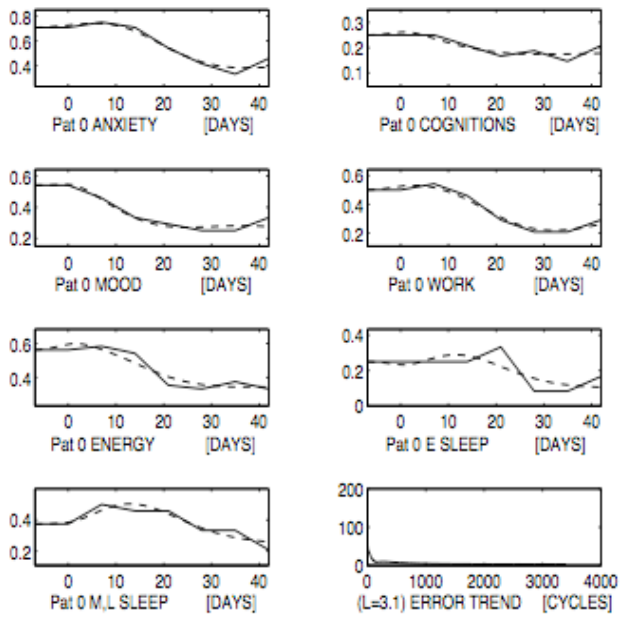
actual

L = Error term
X = data
i = symptoms
P_j = parameter
k = patients

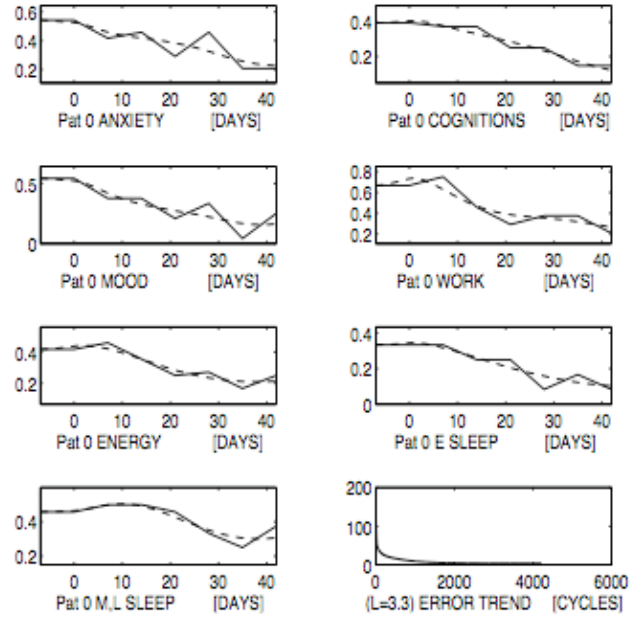
Obtain optimized parameters
- -fit patient data
- -train on time course
- -minimize error term L
- -gradient descent on parameters

Results of Training

(treatment group)



(a) Predicted and actual mean patterns of recovery (CBT)



(b) Predicted and actual mean patterns of recovery (DMI)

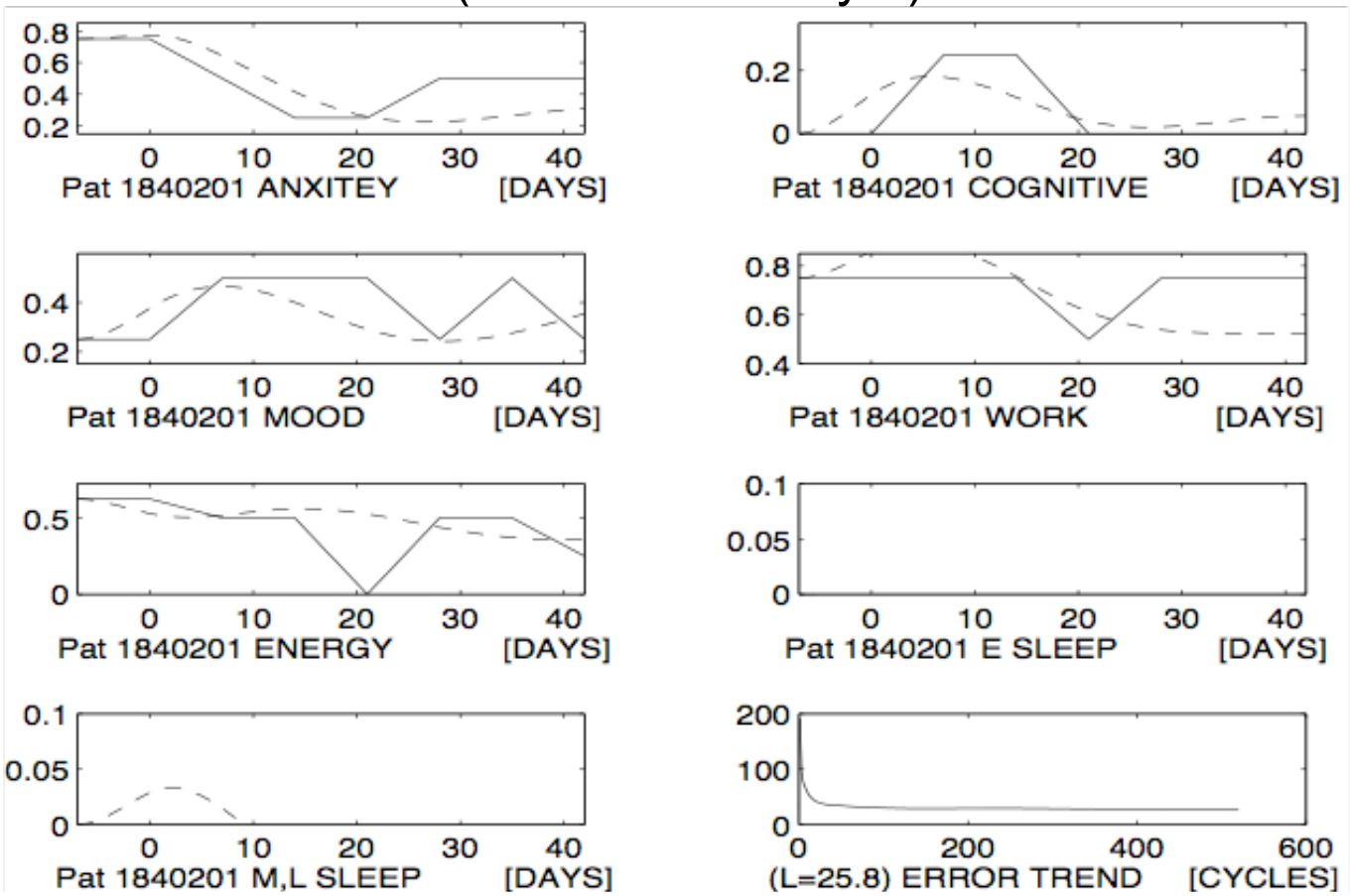
CBT

DMI

Results of Training

(Example CBT Patient)

(we're not there yet)



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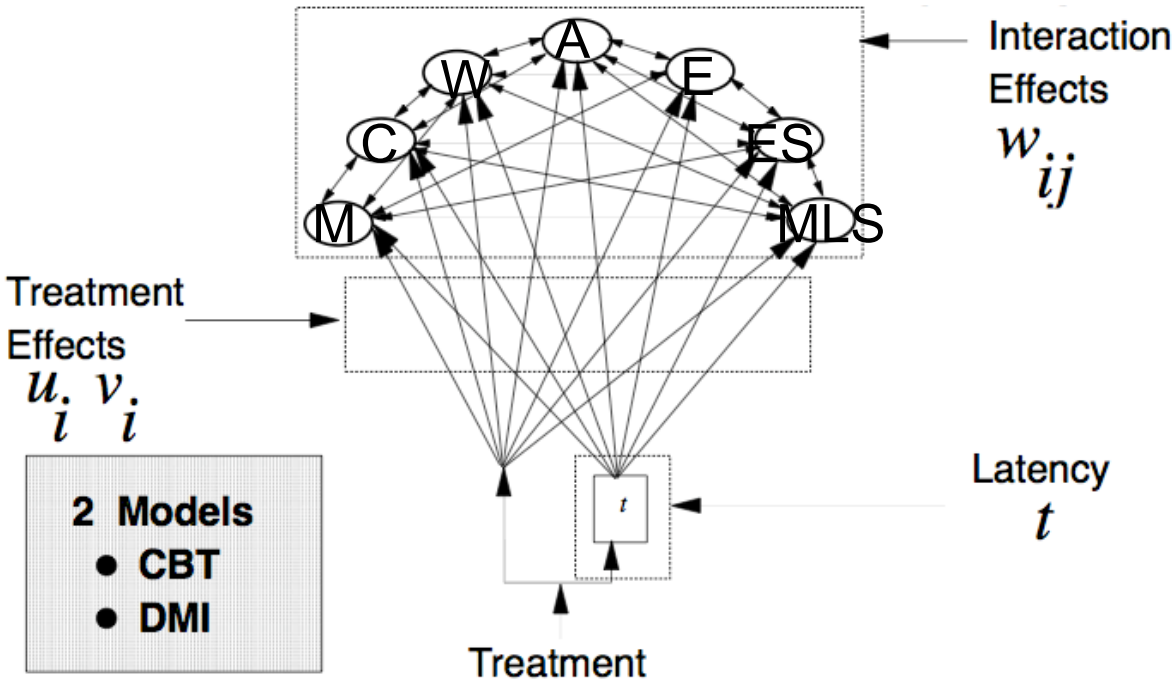
Results

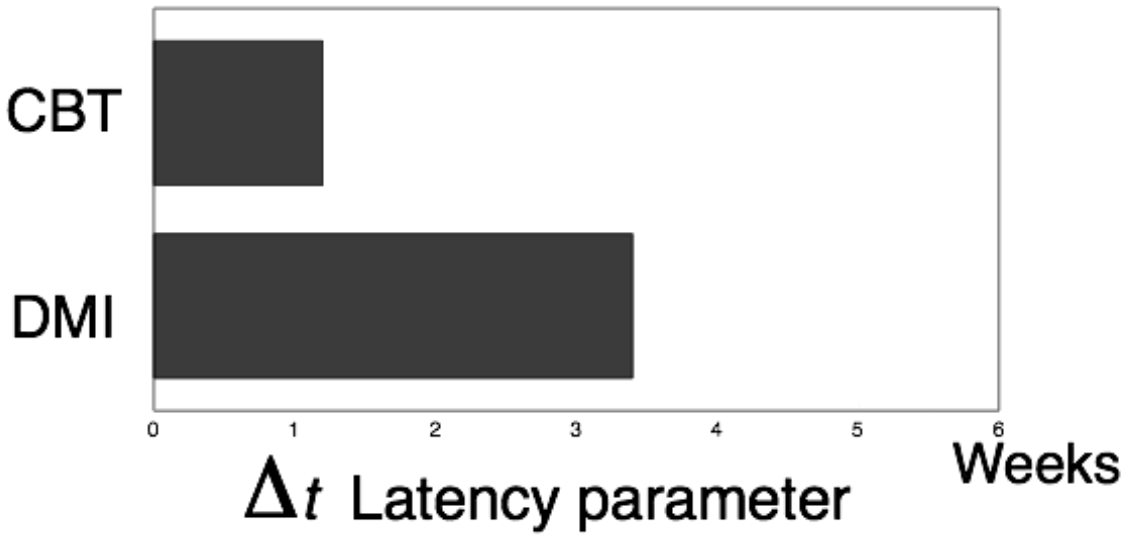
Optimized parameters specify model
Initial conditions predict pattern trajectory



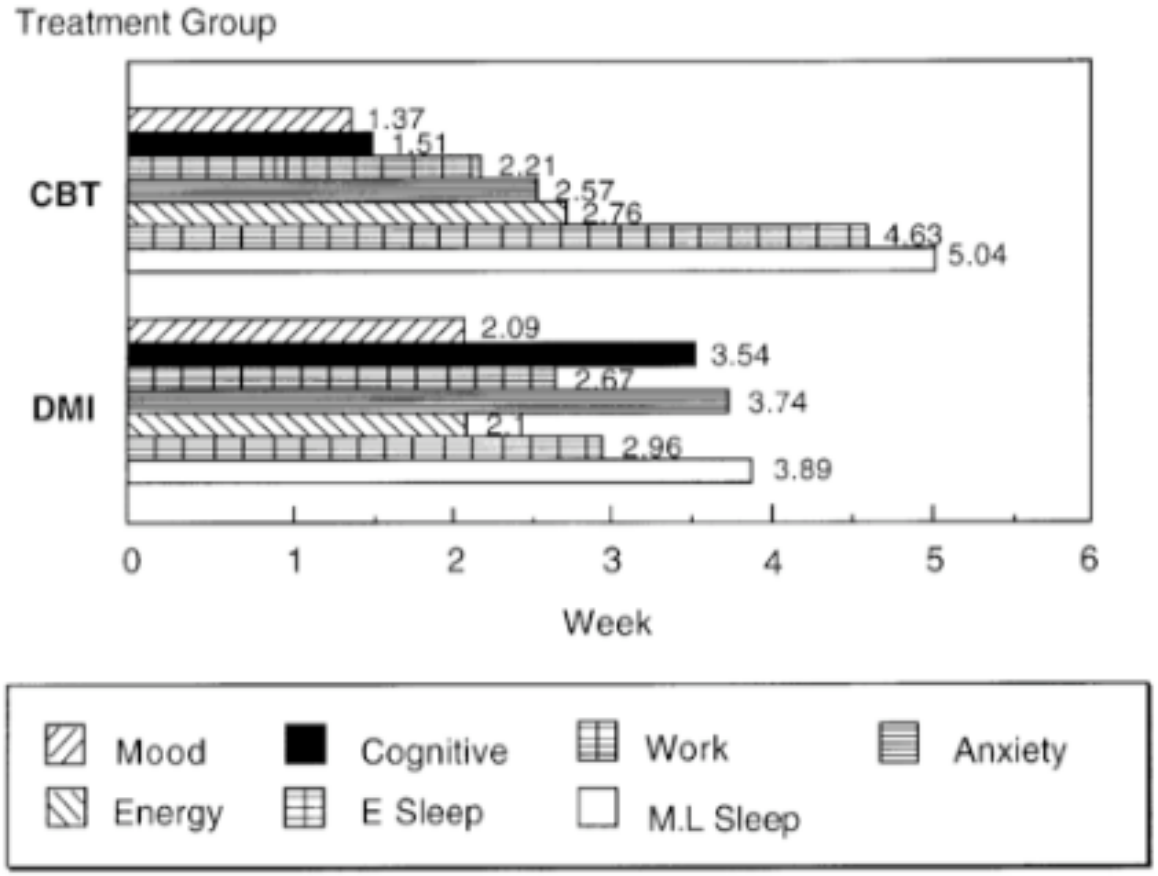
Latency

Δt = response delay

CBT: 1.2 weeks
DMI: 3.4 weeks



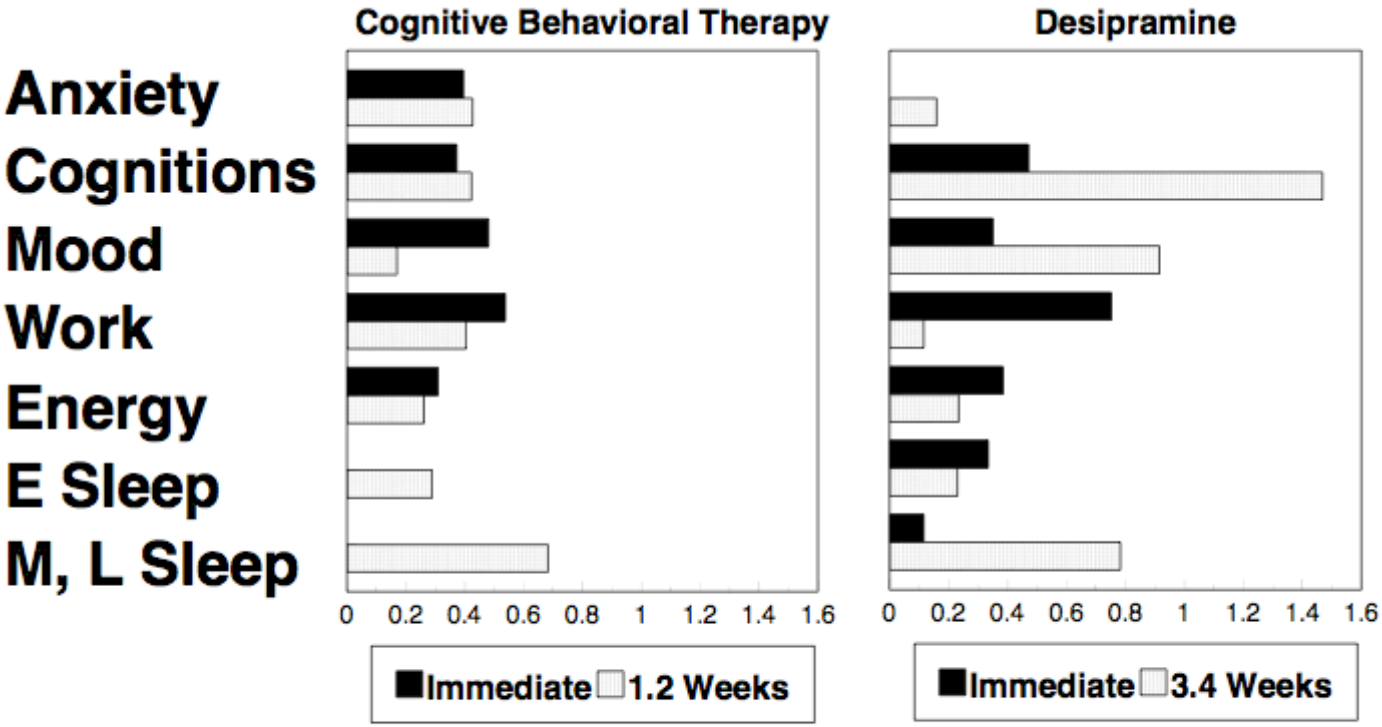
Mean ½ Reduction Time



CBT varies 3.7 wks

DMI varies 1.8 wks

Direct Effect of Treatment

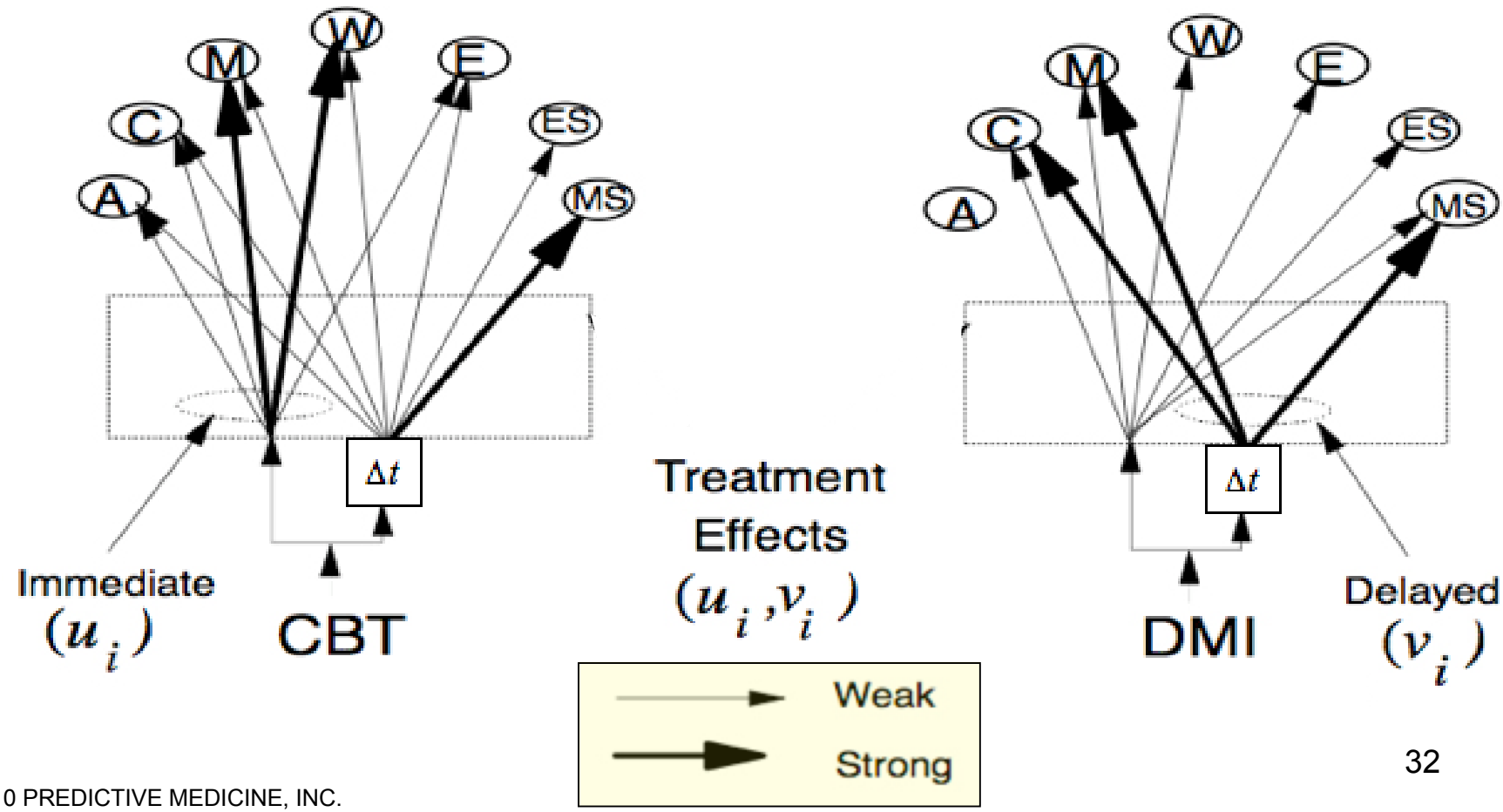


coefficients (strength)

Immediate (u_i) vs. Delayed (v_i)

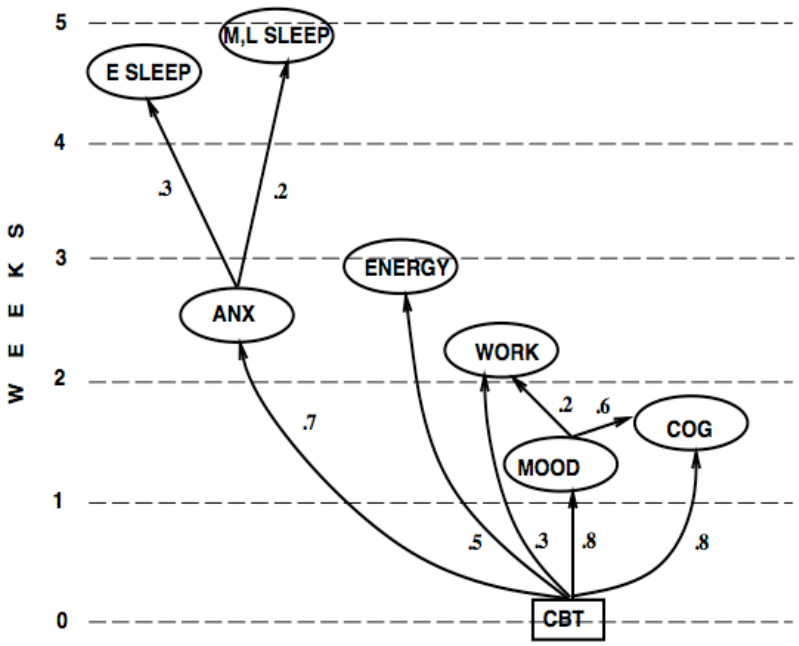
A Anxiety
C Cognitions
M Mood
W Work
E Energy
ES E Sleep
MS M, L Sleep

Treatment Direct Effects Immediate and Delayed

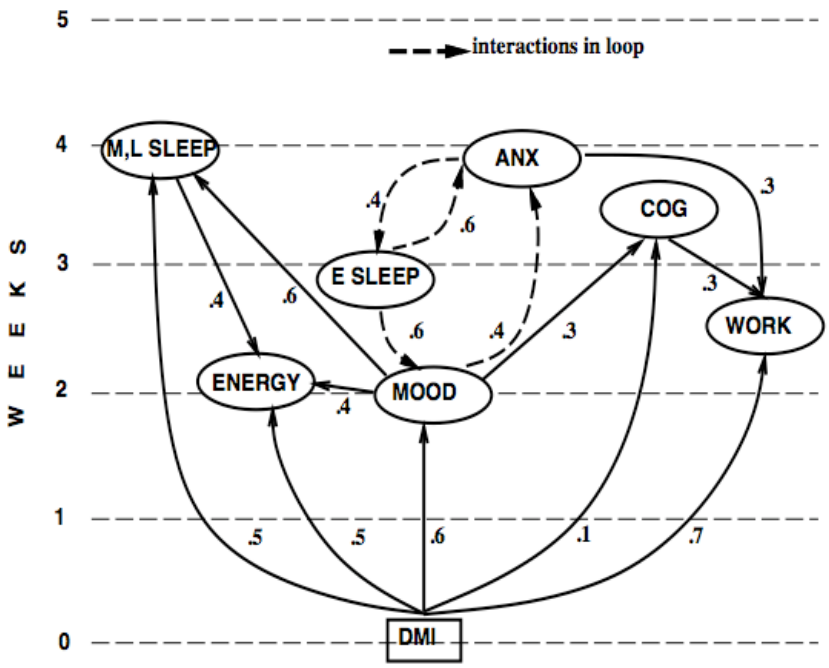


Treatment Effects and Interaction Effects

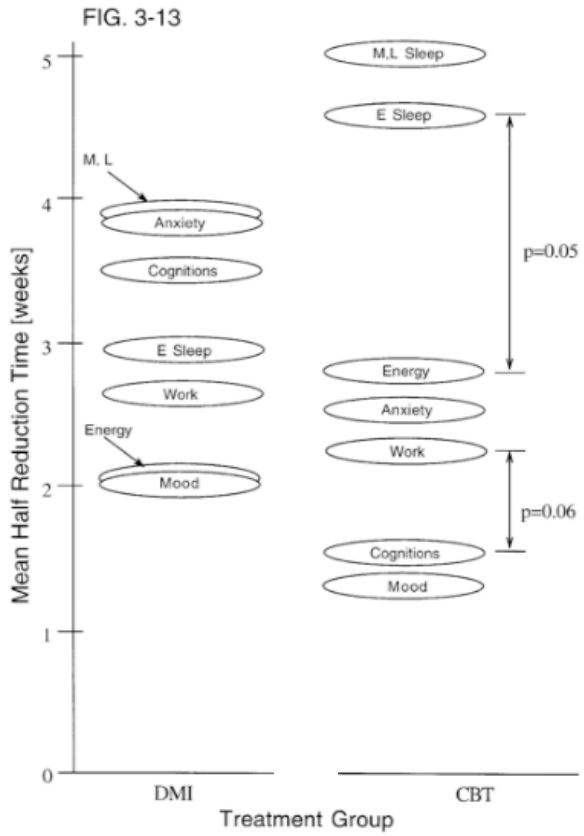
CBT
Sequential



DMI
(delayed)
CONCURRENT



Order and Time of Symptoms Improve is Different for CBT and DMI



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Conclusions

- Recovery patterns differ by treatment
  - Cognitive Behavioural Therapy
    - is **sequential**
  - Desipramine
    - is **concurrent (after delay)**

- Suggests CBT better serves patients with strong cognition and mood symptoms DMI may better serve patients with all the symptoms but are not suicidal

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