**Building bridges to improve
Brain Injury Treatment and Research**
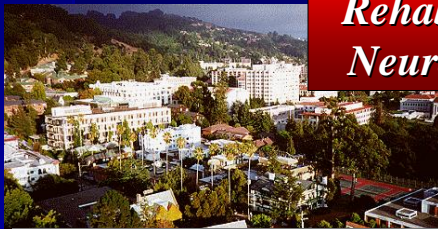
**VA Medical Centers in
Martinez and San Francisco**

**California Pacific
Regional Rehabilitation
Center**

*Program in
Rehabilitation
Neuroscience*

**Neuroscience Institute, University
of California, Berkeley**

**UCSF Neuro-Rehab &
Neuroscience Imaging Center**

# Rehabilitation of Frontal Systems Functioning

## *Finding the right path after TBI*

**Anthony J-W Chen MD**
Program in Rehabilitation Neuroscience
VA Medical Centers, SF and Martinez
University of California, Berkeley and UCSF

# In the moment of an instant...

- A *blast* went off next to our vehicle
- We plowed into a ditch– My head struck the side of the vehicle.

I must have blacked out for a minute...

and I can't remember much of what happened in the next half hour...

# ...to the aftermath

- I vaguely remember getting out of the vehicle and shooting.
- After the mission, I felt dazed (but we always felt dazed and confused in the field.)
- I tried to 'shake it off.' I think I did my job pretty well on '*autopilot*.'
- I really had problems *after I got home*...
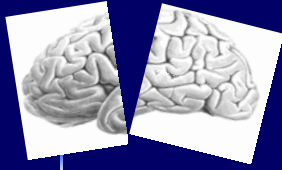
## …to the aftermath…

- **Difficulty concentrating, easily distracted**
- **Sensitive to non-relevant noise (environmental or otherwise)**
- **Easily overwhelmed, especially by multiple tasks**
- **Poor organization, difficulty prioritizing, planning and solving problems**
- **Can't get things done…**

- **Symptoms** **'executive** **dysfunction**
- **Often 'invis** **extremely**
- **Most appar** **complex,** **unstructure** **environme** **we're** *not* **to do**

Provided by Tatjana Novakovic-Agopian

## 'Executive Control Dysfunction???'

Establishing attentional set

Self-Awareness

Adjustments of behavior

Error monitoring

Selection of information based on goal-relevance

Maintenance of information

Discrepancy detection

'Automatic' attention and orienting

'Executive' manipulation of information

Prospective memory

Motivation

Episodic memory

Energization

Emotional self-regulation

Schematization

Prioritization & Sequencing

Reward-based feedback learning

Strategic retrieval

Goal-sub-goal management

Multi-tasking

Planning

## … to Treatment Targets??

---

## Who cares about cognitive dysfunction? (Why should we focus on this?)

- Who solves this person's problems?
  - The brain as its own teacher–allows the person to adapt and learn.
  - E.g. When a limb is injured…adaptation
  - E.g When motor cortex of the brain is injured…rehabilitation
  - E.g. When cognitive functioning is injured… ???
- Where is this person going?
  - Re-integration into the home, work, community
  - What happens if he/she can't take care of herself?

# Treatment Development: From Theory to Intervention, Measurement and Testing



**THEORY of Function (and Dysfunction)**

**Treatment theory**

**Measurement(s)**

**Intervention**

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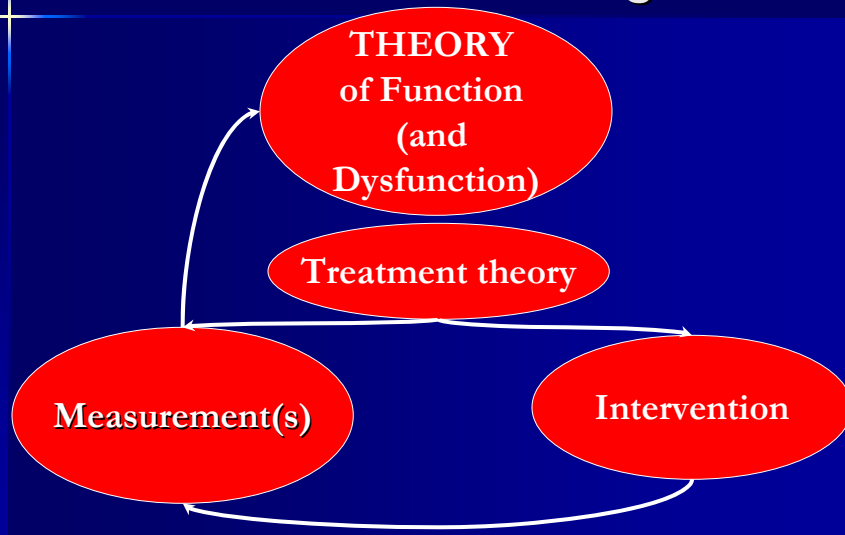
# What are 'Executive control functions'?



- Aspects of the direction of neural-behavioral processes to achieve goals

  •Depend on *frontal systems* Basic mechanisms for top-down control
    1. Selection
    2. Maintenance and manipulation

  ▪Disrupted by not only frontal injuries, but also disconnection of *networks*
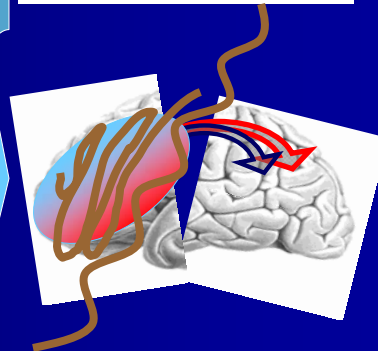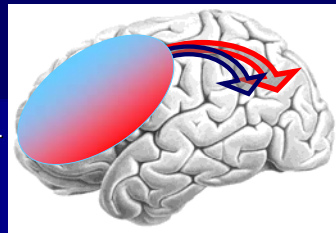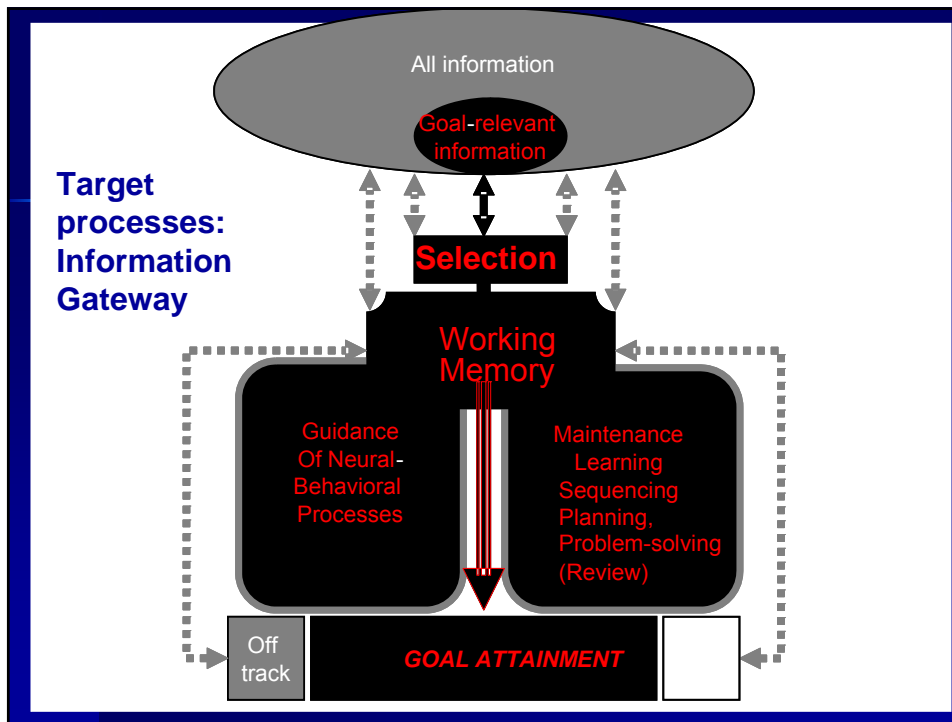
# Focus on Gateways as Treatment Targets

ATTENTION

WORKING MEMORY
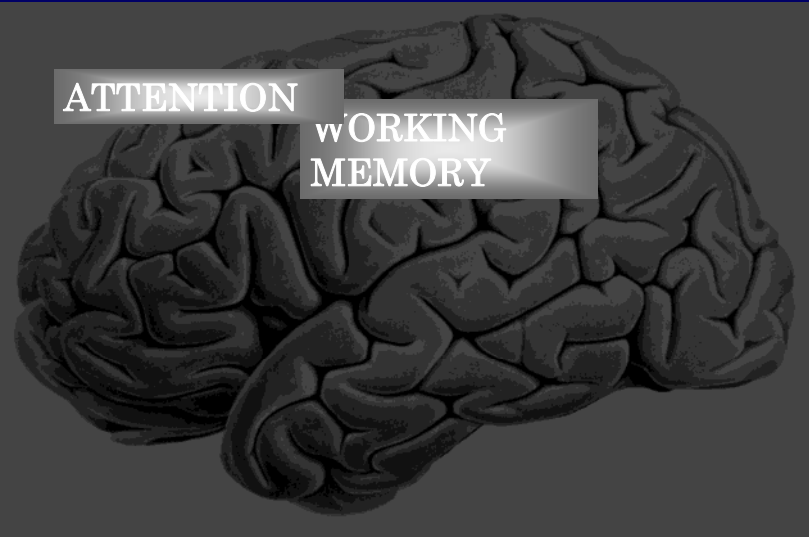
# Pathway from information to action and goal attainment: Gateway to Executive Control

n of inform

All information

Goal-relevant information

**Target processes: Information Gateway**

**Selection**

Working Memory

Guidance Of Neural-Behavioral Processes

Maintenance Learning Sequencing Planning, Problem-solving (Review)

Off track

*GOAL ATTAINMENT*

---

## Targeting the Information GATEWAY to Executive Control-

*A pilot integrated rehabilitation neuroscience study*

- I. Targets: Selective information processing for goal attainment
- II. Intervention: Goal-directed attentional self-regulation
  - "Goal-based self-management" (GBSM)
- III. Measurements:
  - Neuro-cognitive test performance– selective information processing
  - Biomarkers: Goal-direction of information processing in the brain (fMRI)
  - Functional Outcomes in the 'real world'

# INTERVENTION
# Training of goal-directed attention regulation

'Goal-based Self-Management'
training protocol

Novakovic-Agopian, Chen, Rome, 2006

# Intervention synopsis

- Intro of the importance of goal-directed selection
  - Stop-Relax-Refocus
  - Practice holding goal-relevant information in mind, while 'letting go' of distractors (non-relevant)
- Application and progressive applied practice
  - Apply to progressively more challenging situations in training sessions and daily life

## Training intervention, cont.

- Application to higher level goals:
  - Identify feasible functional goals of personal interest
  - Apply to 1) a group goal / project
  - 2) an individual goal / project
- Execution and completion of projects
- Training time:
  - 10 sessions (two hours each) of group training,
  - 3 hours of individual training
  - ~20 hours of homework over 5 weeks.

## Pilot intervention study objectives

- **1: Is the training protocol feasible in a clinical research setting? Are measurement protocols feasible and informative?**
- **2: Does participants' performance improve in neuro-cognitive domains targeted by training (i.e. complex attention and executive control)?**
- **3: Does the intervention sharpen the neural processes of goal-directed control of information processing?**
- **4: Are participants able to apply the skills learned to their own real-life situations? (Is there *generalization…*?)**
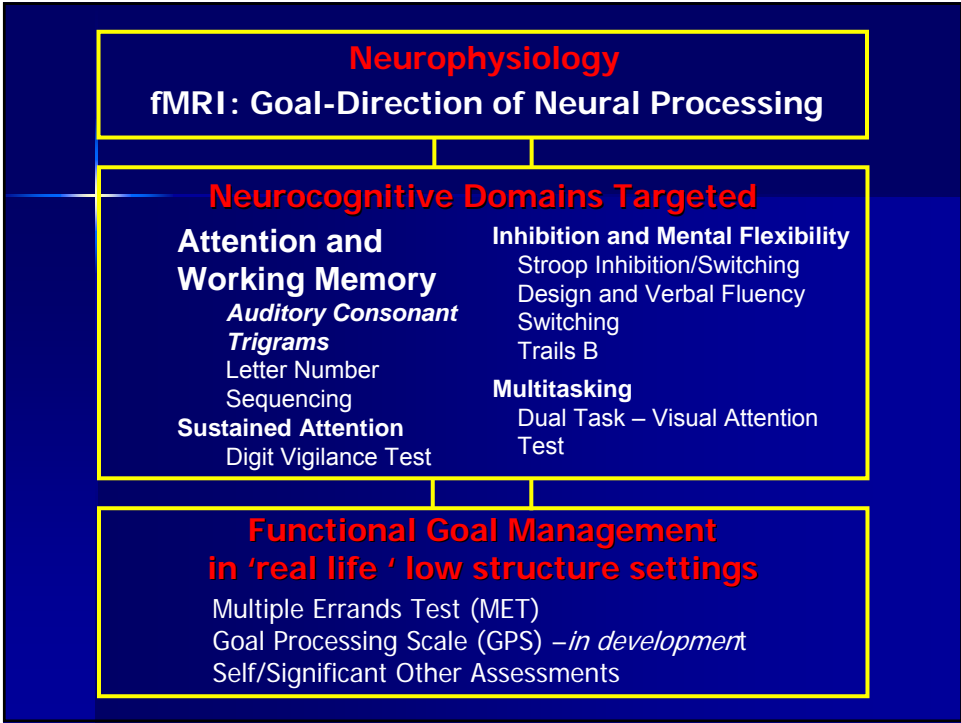
## Study Design

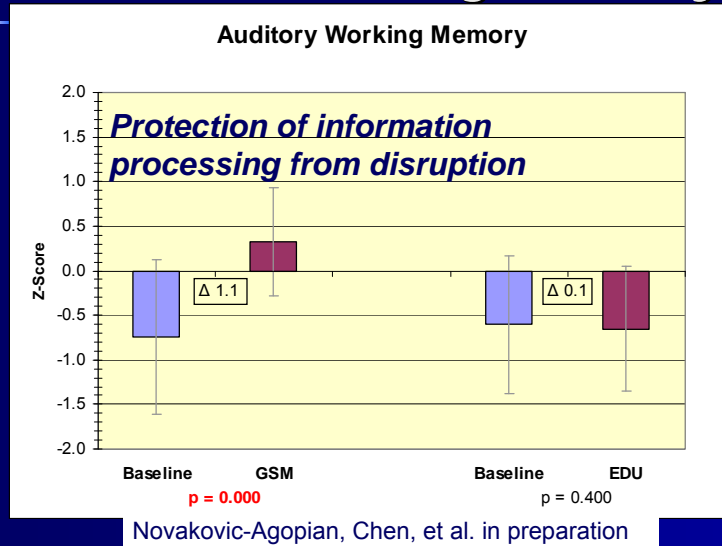| Baseline | Weeks 1 - 5 | | Weeks 6 - 10 | |
|---|---|---|---|---|
| **Group 1** | **GBSM** 5 week Training | **Assessment 2** | One 2 hour **EDU** session | **Assessment 3** |
| **Group 2** | One 2 hour **EDU** session | | **GBSM** 5 week Training | |

*(Assessment 1 column between Baseline and Weeks 1–5)*

Participants:
- To date, 13 patients with chronic executive dysfunction from trauma and other acquired brain injuries
- 7 participants started with the GBSM, followed by EDU
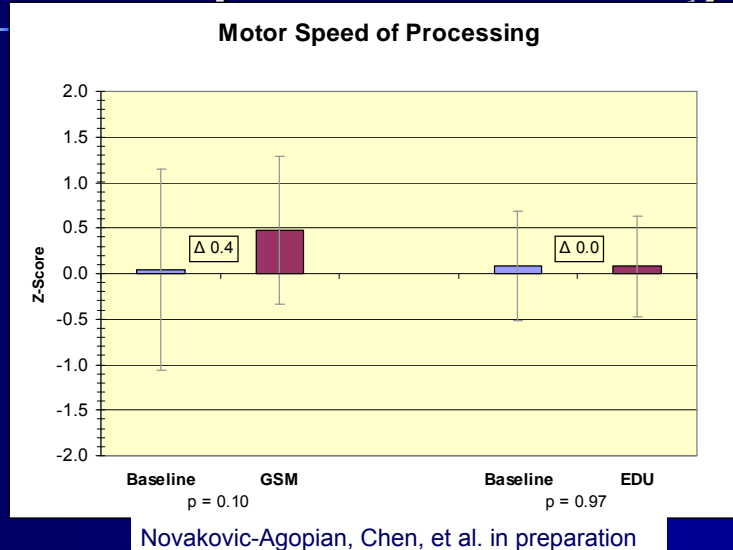- 6 started in the reverse order.

# Measurements: Mechanisms and Outcomes

## Neurophysiology
### fMRI: Goal-Direction of Neural Processing

## Neurocognitive Domains Targeted

**Attention and Working Memory**
- *Auditory Consonant Trigrams*
- Letter Number Sequencing

**Sustained Attention**
- Digit Vigilance Test

**Inhibition and Mental Flexibility**
- Stroop Inhibition/Switching
- Design and Verbal Fluency Switching
- Trails B

**Multitasking**
- Dual Task – Visual Attention Test

## Functional Goal Management in 'real life ' low structure settings

- Multiple Errands Test (MET)
- Goal Processing Scale (GPS) –*in development*
- Self/Significant Other Assessments

---

# Preliminary Results: Neuro-cognitive performance

# Effect of Training on Selective Working Memory

**Auditory Working Memory**

*Protection of information processing from disruption*

Δ 1.1

Δ 0.1

| Baseline | GSM | Baseline | EDU |

p = 0.000

p = 0.400

Y-axis: Z-Score (2.0, 1.5, 1.0, 0.5, 0.0, -0.5, -1.0, -1.5, -2.0)

Novakovic-Agopian, Chen, et al. in preparation

# No Effects of Training on Motor Speed of Processing

**Motor Speed of Processing**

Δ 0.4

Δ 0.0

| Baseline | GSM | Baseline | EDU |

p = 0.10

p = 0.97

Y-axis: Z-Score (2.0, 1.5, 1.0, 0.5, 0.0, -0.5, -1.0, -1.5, -2.0)

Novakovic-Agopian, Chen, et al. in preparation

# Does the intervention change functioning in 'real life?'

# Multiple Errands Test

**Multiple-Errands Test**

Number of Task Failures

| | |
|---|---|
| Baseline | GSM |
| **p = 0.039** | |
| Baseline | EDU |
| p = 0.206 | |
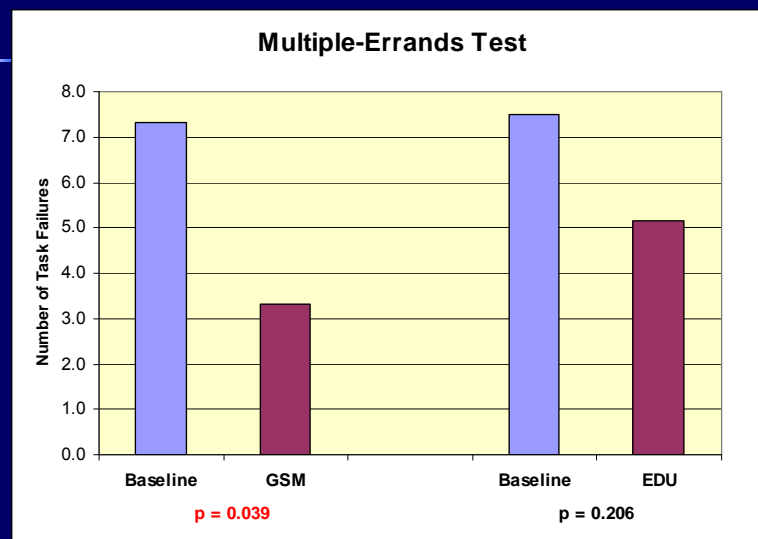
Assessed using Wilcoxon's Matched Pairs Test

13

## Participants Self Rating Relative to Baseline
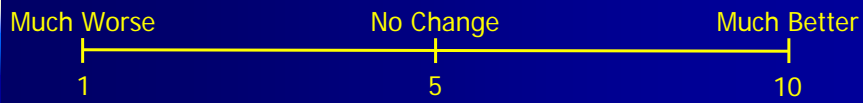
| Much Worse | No Change | Much Better |
|---|---|---|
| 1 | 5 | 10 |

| | |
|---|---|
| Ability to **stop and relax** during stressful times | 7.8 |
| Ability to **stop and refocus** on the current goal. | 7.7 |
| Ability to divide a complex task into more manageable tasks. | 7.5 |
| Ability to **hold and maintain important information in mind.** | 7.4 |
| Ability to **finish** something that was started. | 7.0 |

## Sharpening of distributed neural representations by Goal-direction

Translation from concept to measurement

# Neural Biomarkers: Measuring the gateway

- How do we index this 'gateway' process of the goal-direction of information processing?

**Goalrelevant information**

**???**
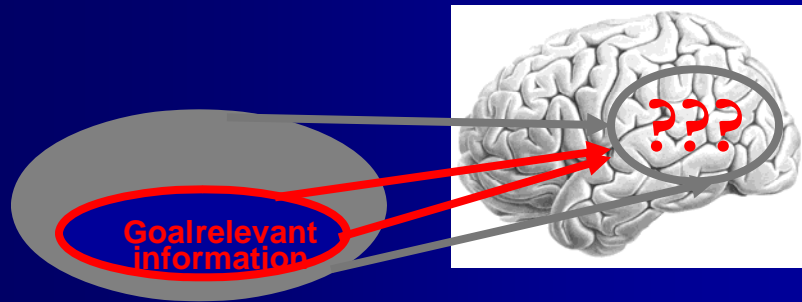
# View these images…

**Dynamic sharpening of the distinctiveness of neural representations by goal-direction**
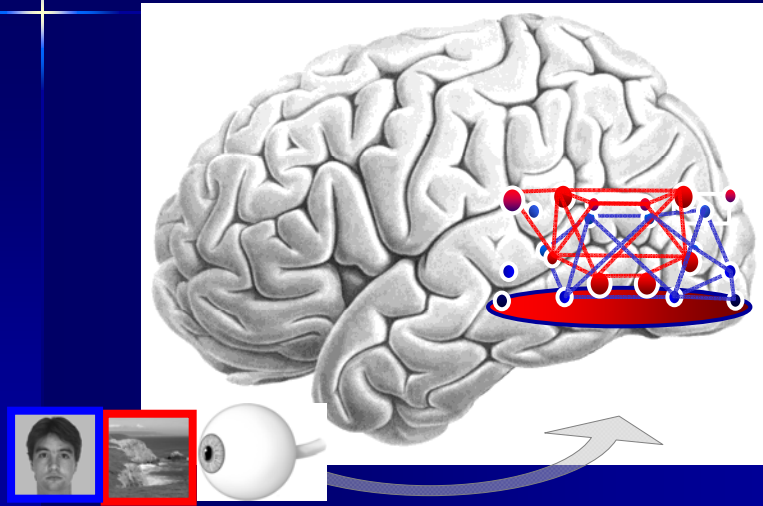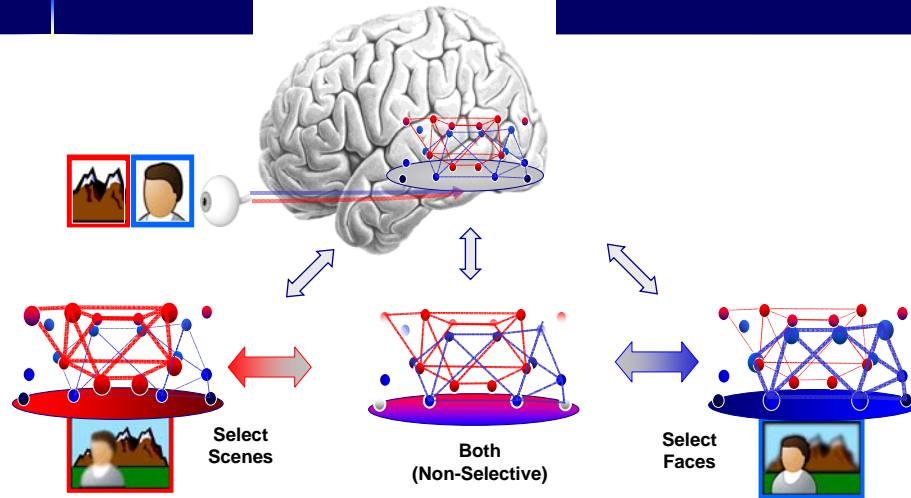


**Select and hold in mind…SCENES (Ignore Faces)**

**Dynamic sharpening of the distinctiveness of neural representations by goal-direction**
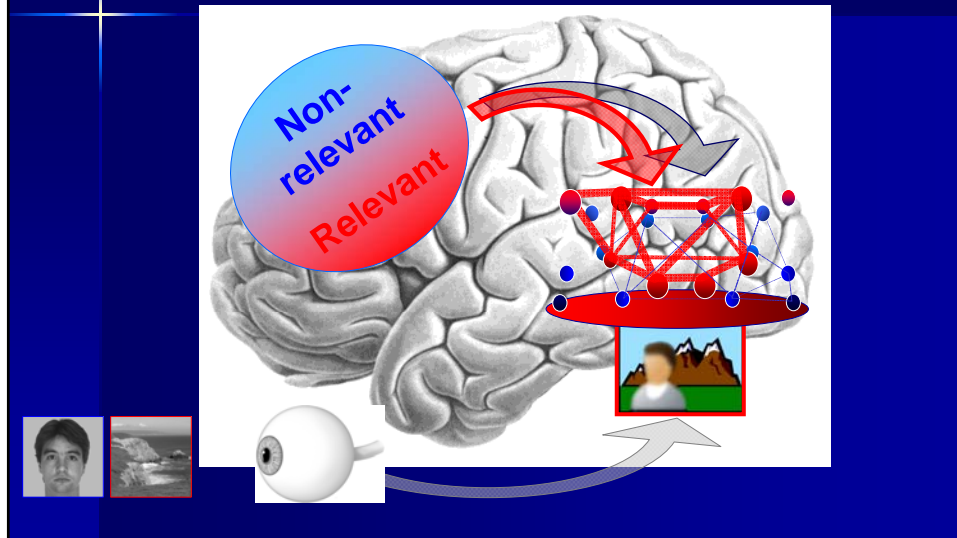


**Dynamic sharpening of the clarity of neural representations by goal-direction**
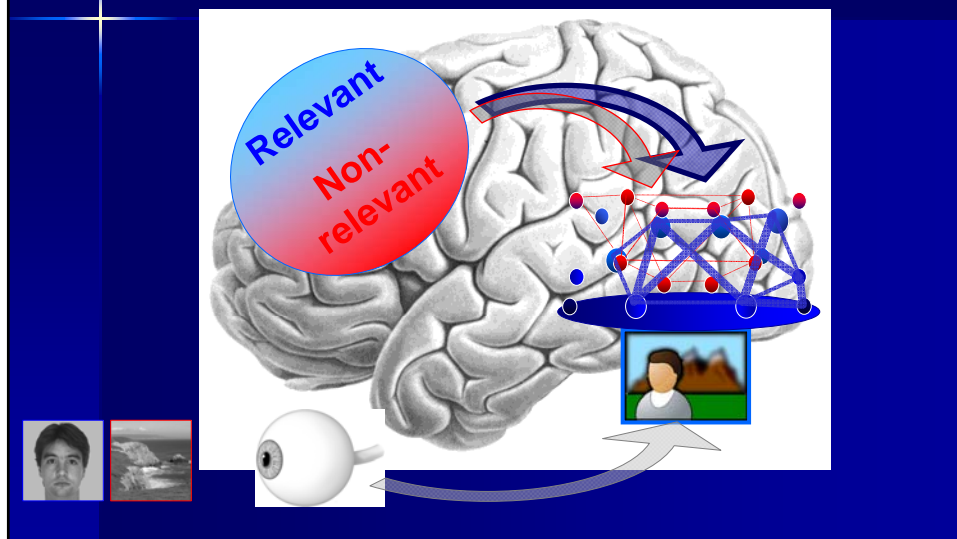
## Conceptual Model: Attentional Selection of Neural Information Representations



**Select Scenes**

**Both (Non-Selective)**

**Select Faces**

---

## Measuring the *clarity* of distributed neural patterns

### Machine as Brain

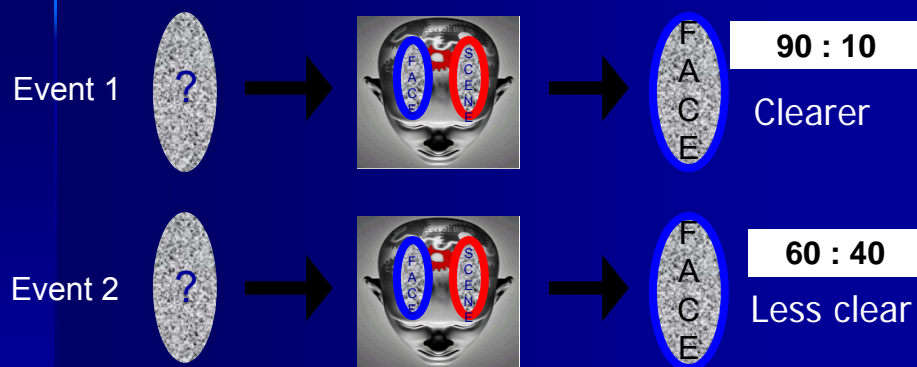From fMRI Patterns to Reading the Neural code
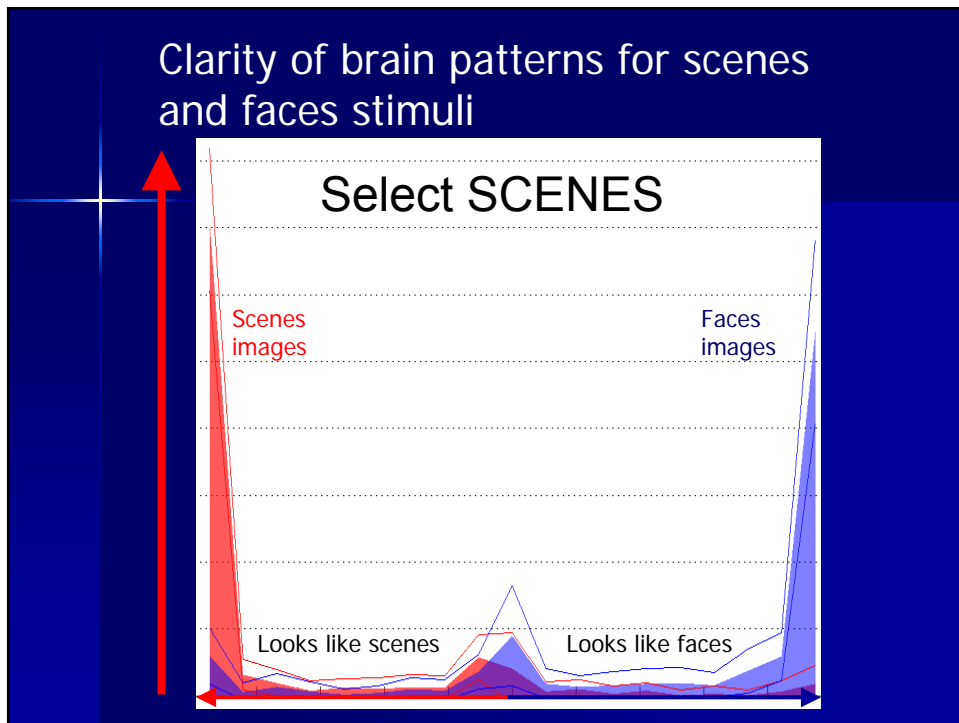
Using a neural network pattern classifier
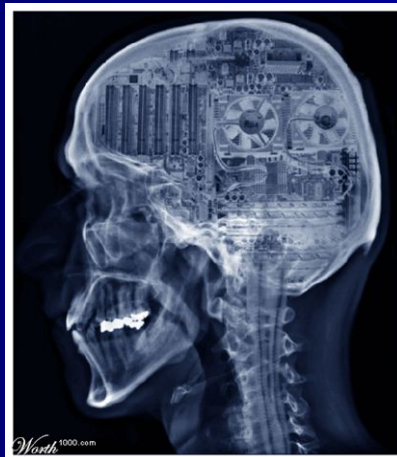


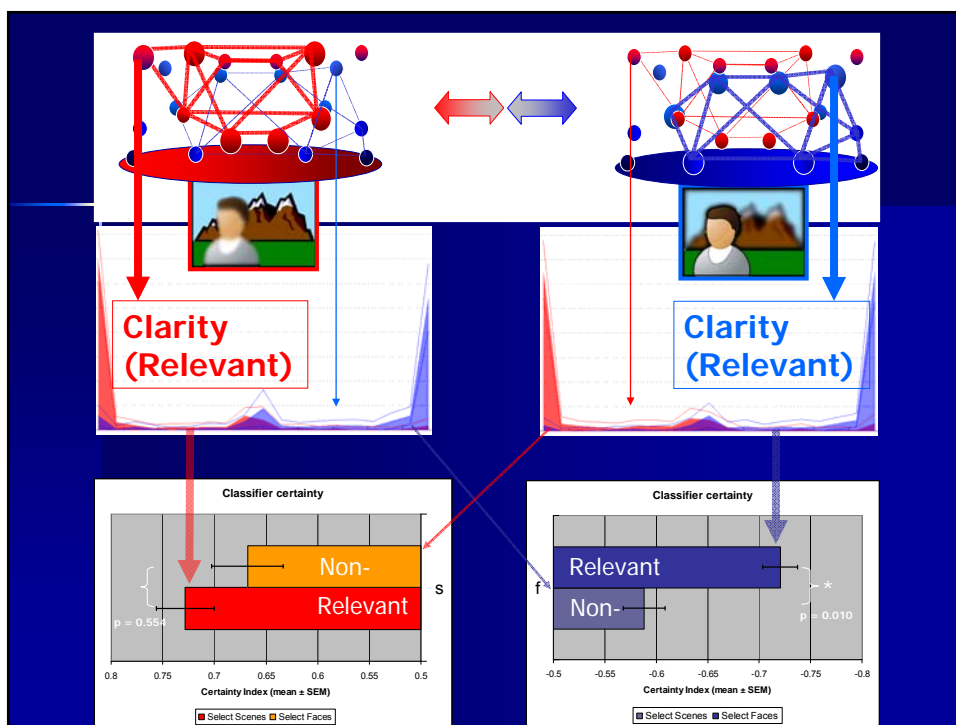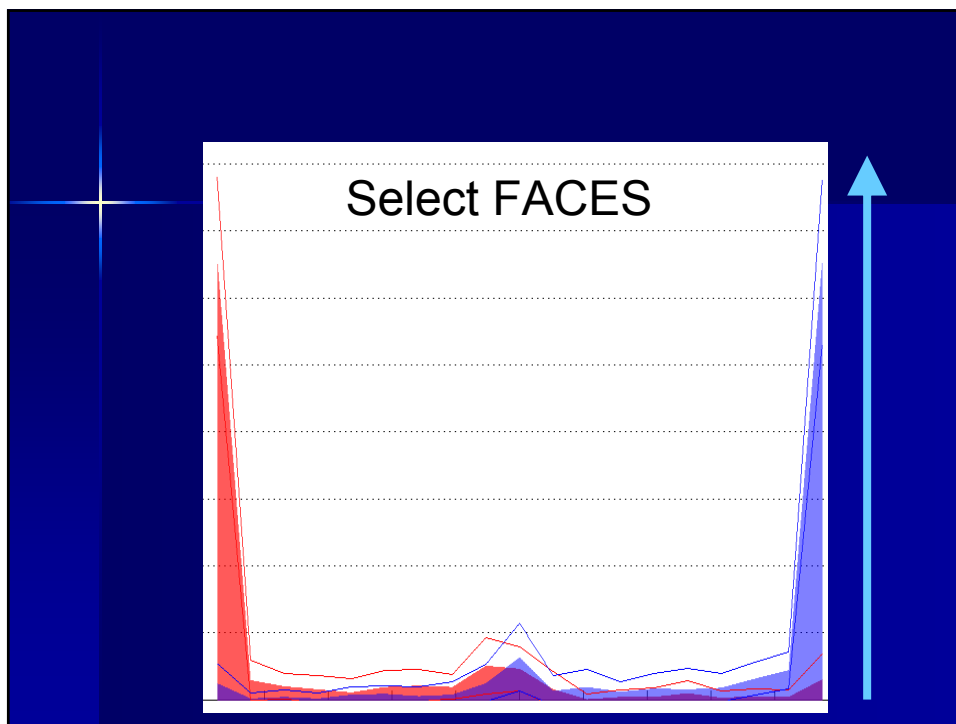http://www.wachadoo.com/forum/files/brain_as_computer_252.jpg

Multi-Voxel Pattern Analysis: Training of Classifier
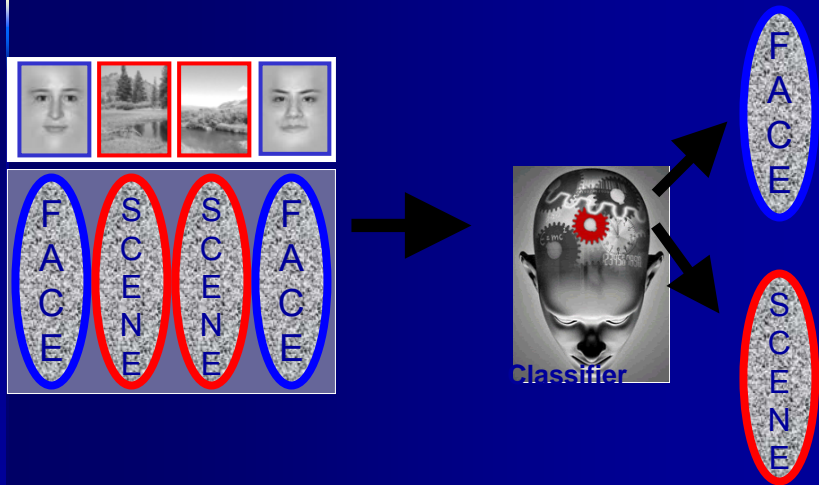


"Certainty" of classification as a measure of the clarity of the information representation

Event 1 — FACE — 90 : 10 — Clearer

Event 2 — FACE — 60 : 40 — Less clear

Clarity of brain patterns for scenes and faces stimuli

Select FACES



Clarity (Relevant)

Clarity (Relevant)

Classifier certainty

Non-
Relevant

s

p = 0.554

0.8  0.75  0.7  0.65  0.6  0.55  0.5
Certainty Index (mean ± SEM)

Select Scenes  Select Faces

Classifier certainty

Relevant

Non-

f

*
p = 0.010

-0.5  -0.55  -0.6  -0.65  -0.7  -0.75  -0.8
Certainty Index (mean ± SEM)

Select Scenes  Select Faces

21

Does training in attention regulation **enhance the goal-directed selection effect (sharpen the goal-relevant neural representations)?**

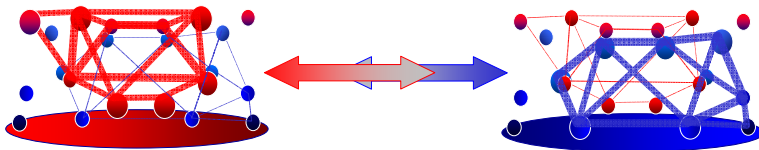# Brain Injury Patients Pre- and Post-Training(n=8)
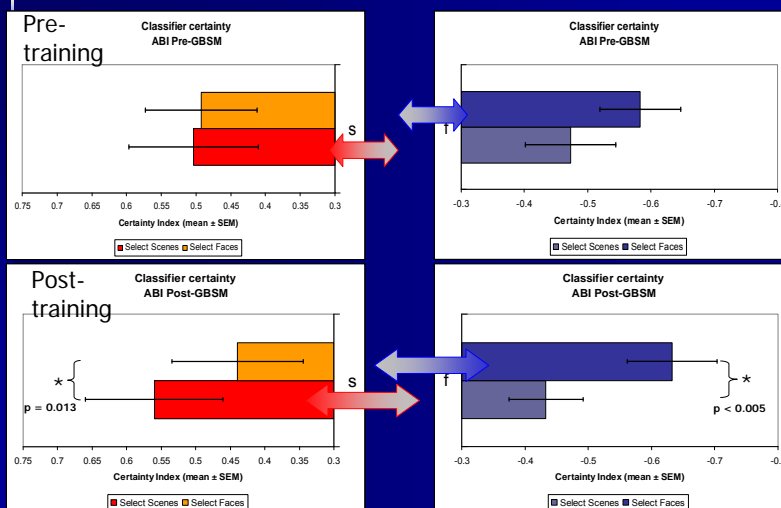
## Training increases goal-directed selection of information processing
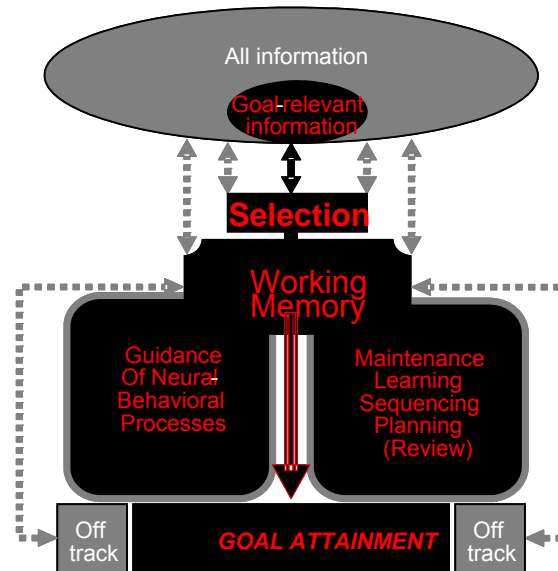


*Pre-training*
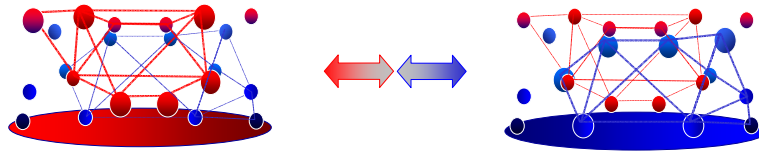
*Post-training*

## Preliminary conclusions: Proof of principle

- Intervention designed based on theory
- Practically applicable in research setting, engaging
- Preliminary results support effects on the targeted neuro-cognitive processes, with *generalization to real-world functioning.*

**Testing of Gateway Theory**

**Neural biomarkers:** Rationally constructed indices of the target processes showing increases in the goal-direction of information processing

All information

Goal-relevant information

Selection

Working Memory

Guidance Of Neural Behavioral Processes

Maintenance Learning Sequencing Planning (Review)

Off track

GOAL ATTAINMENT

Off track

# Current VA study

- Current study: Veteran's with TBI and mild cognitive dysfunction
- Goal-based self-management intervention
- Randomized cross-over study with active comparison intervention matched for time and attention
- Assessments: Neuro-cognitive, Brain structure and function, Functional outcomes

## Ongoing challenges: sharpen intervention tools

- **Increase targeted training: Computer-assisted training therapies**
- Specifically target different component processes of executive control
- Process targeted, but embedded in the complex scenarios that demand executive functioning
    - (Training specific muscles, but in a functional setting)
- Scenarios to intensively practice the application of trained skills and strategies
- Progressive, adaptable and individualized 'dials' for each patient
- Web-deployed, allows home practice with data tracking

## Ongoing challenges: sharpen measurement tools

- Development and validation of measurements of real-world functioning
- Combined /concurrent application of complementary measures to test different levels
    - Relationships of neural to behavioral and functional measurements
    - Value of biomarkers in understanding sources of variability in treatment responses?

## Breaking the barriers of biology

- **What can be done to improve the benefits of rehabilitation interventions?**
- **What are the neural bases of improvement in a process of interest (when they do occur?)**
- *These become possible new targets for enhancing learning and recovery*

---

## THANKS!

**Tatjana Novakovic-Agopian, PhD**

**Co-director Program in Rehabilitation Neuroscience**

**Supervisor, Neurobehavioral Assessments and Interventions**

**Scott Rome, MD**
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California Pacific
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**Gary Abrams, MD**
Chief Neurological
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**Mark D'Esposito, MD**
Director, Brain Imaging
Center, UC Berkeley
Neurobehavioral
Neurology, VA NCHCS,
Martinez

# THANKS!

- *Participating patients*  CLINICAL TEAMS



# Support

- VA Rehab R and D
- California Pacific Medical Center Foundation
- Brain Imaging Center (BIC), UC Berkeley
- Neuroscience Imaging Center (NIC), UCSF
- DOD/Congressionally-directed Medical Research Program

# Neural Processes and Biomarkers: 'Top-down' goal-direction of information processing
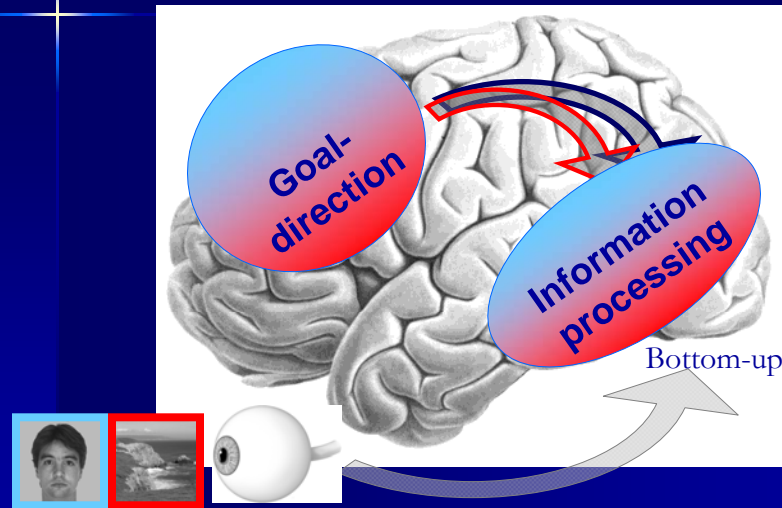


# Effect of intervention on goal-directed enhancement of the clarity of representations



Goal-directed change in classifier certainty Pre- and Post-GBSM training
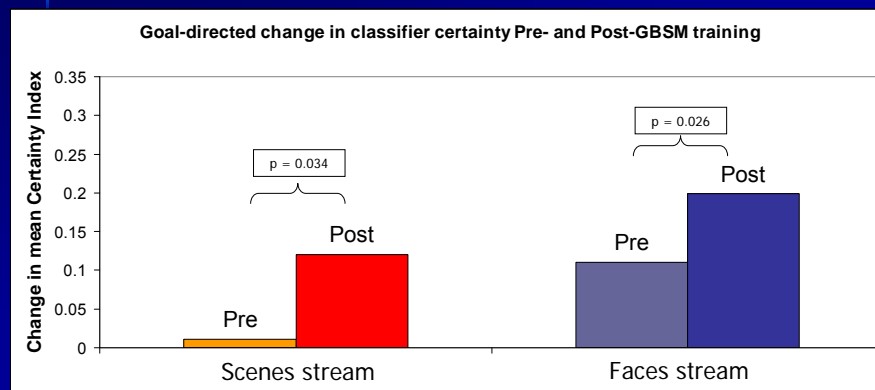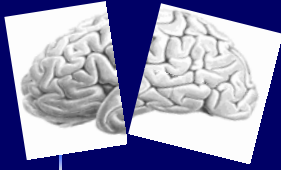
## ...to the aftermath...

- **Trauma to the brain can change the core of a person's being– their thinking, memory, personality and behavior.**
- **Even 'mild' trauma can result in brain injury.**
- ***Most* individuals get better, but deficits in cognitive processes are some of the most persistent and disabling consequences of brain injury.**