Sharpening cognition after brain injuries

Investigating changes in neural processing using pattern classification of brain activity measured with fMRI

Anthony J-W Chen MD
Assistant Prof of Neurology
Director, Program in Rehabilitation Neuroscience

VA Medical Centers, SF and Martinez
University of California, Berkeley and San Francisco
In the moment of an instant...

- A blast went off next to our vehicle
- We plowed into a ditch—

I must have blacked out ...
I can’t remember much of what happened after that...
TBI: 1 year later...

- Difficulty concentrating, easily distracted. I feel like I’m in a fog all the time.
- I can’t hold anything in mind.
- Easily overwhelmed, especially by new, multiple or complex tasks
- I’m told I’m disorganized, easily thrown off track... At the end of each day, I seem to not have gotten anything done...
- I feel like I have lost control of my life.
Diagnosis?  ‘Executive Control Dysfunction’

Challenges

Rx? What do we treat? How?

How do we measure the effects?

What are the neural mechanisms that support improved attentional control? (When they do occur?)
Intermediate step: How would we improve attentional control?

Target process and intervention
Executive control

[simplified]

neurologic functions important for the direction of neural-behavioral processes based on goals
Simple goal? *(Real life)*

Indiana Jones getting the morning paper
A few distractions

Diversions
Subgoals
Problem-solving
Stay on goal!
Goal attainment
Disruptions: distractions, intervening actions, non-relevant paths, unwanted memories, anxieties, habits...
Training of Goal-oriented Attentional Self-Regulation (GOALS)

Disruptions

Sources of information

Maintain goal-direction: Protect from disruptions

Working Memory → Learning/Decisions → Action → Goal Outcome

Train full connections from attention to working memory to goal management

Robertson, Levine, Manly, Goal Management Training (2005)
Intervention study: Clinical-behavioral effects of Goals training?

Tatjana Novakovic-Agopian, Anthony J-W Chen, Scott Rome, Holli Castelli, Annemarie Rossi, Ryan McKim, Gary Abrams, Nancy Hills, Mark D’Esposito
The participants

- 16 patients with **chronic** (6+ months) acquired brain injury.
- 11 of the participants had a history of TBI, 3 had a history of CVA, 1 had brain tumor, and 1 leukoencephalopathy.
- **chronic mild to moderate difficulties on daily tasks involving distractibility, poor organization, problem solving, multitasking.**
## Study Design

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Study period 1: Weeks 1 - 5</th>
<th>Study period 2 Weeks 6 - 10</th>
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<td>Assessment 1</td>
<td></td>
<td>Assessment 2</td>
</tr>
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**Goals training:**
- 20 hours in small groups and individual sessions
- 20 hours homework – integrated into daily life activities

**Education:** brief session discussing brain injury, resources
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(b) Group 1- maintenance of *goals training* into period 2;
(c) Group 2- cross-over to *goals training* after *edu*
GOALS training effects summary

- Feasible as *standardized* experimental training protocol
- Did patients notice changes with training?
- Does ‘functional’ training improve the theoretically targeted cognitive domains?
  - Performance on neurocognitive testing improved in domains of attention and executive functioning
- Does functional performance in *real world settings* improve with training?
  - Multiple Errands Test- improved task completion
  - Goal Processing Scale- improved overall performance and in specific domains of executive control
What’s going on inside...? What neural changes support sharpened goal-directed cognition?

Ideal features of fMRI methods for rehabilitation neuroscience studies

You, the clinician...
An *ideal* biomarker for brain injury rehab studies?

- The results would directly index the target process of interest (a biomarker)
  - Intervention target: goal-directed control of neural processing
- How would we quantify changes in this target process?
fMRI measurements that index the process of interest while being robust to patho-anatomical differences.

Differing pathology

All have executive dysfunction
Meaningful results for a small # of participants?
  - E.g. Rehab studies often include N= few or even 1

Rehabilitation is longitudinal: Assessments of *change within subject* across time or intervention (not cross-sectional)
Key principle of neural information processing: Functional integration

- Meaning and mechanisms *emerge* from the interactions between units/regions

Local and inter-regional networks

→ Multi-variate methods that take into account the functional integration of neural processing given the distributed nature of encoding in the brain...
‘Dis-integration’ of brain networks

• How would we measure how clearly information is represented brain networks?
Measurements robust to inter-individual differences in localization of ‘activations’

- Each pattern may be meaningful for that individual

Person 1
Person 2
Person 3…
Basic perception: View these images... What are they?

Thanks to Jeff Cooney, Josh Hoffman, Adam Gazzaley for stimuli
Representation of perceptual information in distributed neural codes
Information representation in (overlapping) brain network codes
Maintain goal-direction: Protect from disruptions

Sharpening of neural representations for goal-relevant information

Selective attention conditions

External (Perception)

Working Memory

Select Scenes

Selective n-back task

Jittered, event-related design
Information Selection

Select Faces
fMRI Measurements: How *sharp* are the neural representations encoded in brain activity patterns?

How *clearly* does this code represent X or Y?

Successfully decoded → sharper representations
Training of Pattern Classifier

- Back-propagation feed-forward neural network pattern classifier (Multi-layer perceptron with 1 hidden layer, 10 hidden nodes)
- Validation by Leave-One-Out method: Train on 4 runs then test on 5th

- Matlab (Netlab Neural Network Toolkit) (Chris Bishop) and Multivoxel Pattern Analysis Toolbox (Ken Norman et al., Princeton)
Determining the clarity of neural representations: *Select Scenes*

**Inputs**: View a scene

**Hidden layer**: Scene representation

**Output nodes**: Face representation

**Output**: Recognition sub-scores

- Scene: 90
- Face: 10

\[ \text{Difference} = \text{certainty of classification} \]

\[ \rightarrow \text{Index of Clarity of representation} \]
Degraded representations of 'non-relevant' scenes: Select Faces

(viewing a scene)

Difference = certainty of classification

→ Index of Clarity of representation
Data samples: Visual association cortex

- Parahippocampal, Fusiform, Lingual gyri
- Distributed codes representing information regarding object category (e.g. Haxby 2001, O’Toole 2005, Hanson 2005)
- Modulated by attention demands (e.g. O’Craven 1999, Gazzaley 2005)
Does selective attention sharpen goal-relevant vs. non-relevant representations in visual cortex?

N=16 healthy participants  * p< .001

A J W Chen, T Nycum, G Turner, S Song, E Jacobs, M D’Esposito
Representation codes in a source of attentional control– lateral prefrontal cortex

Goal-directed modulation of information processing

- Middle Frontal Gyrus
Does selective attention alter the balance of representation of relevant vs. nonrelevant information in PFC?

- Select Faces
- Select Scenes

*Correlation with selectivity of subsequent memory R2 = .52, p < .001

A J W Chen, T Nycum, G Turner, S Song, E Jacobs, M D’Esposito
Index of attentional control

Select Scenes

Select Faces

Output: Recognition sub-scores

certainty of classification for Relevant stream

relevant - Non-relevant Differential Certainty

certainty of classification for Non-relevant stream

related - Non-related Differential Certainty
Does training augment the goal-directed sharpening of neural representations by attention?

fMRI study Subset of patients N=12
Visual cortex

Predictions?
Visual association cortex

- Pre vs. Post
- Goals vs. Training
- Pre vs. Post Edu

Differential (Relevant - Non-relevant)

Certainty

Edu p < .05

* Individual subject vs. Mean
Improved attention regulation—what are the changes in lateral prefrontal cortex codes?

Goal-directed modulation of information processing

Middle Frontal Gyrus
Dorsolateral Prefrontal Cortex:

Changes depend on baseline state

\[ R = -0.9, \ p < .001 \]
Mechanism of improved attentional self-\textit{regulation}:

Shifting the \textit{balance} of neural representations for each individual?
Summary for GOALS intervention study

- For patients with chronic cognitive dysfunction from brain injury...
- Training improves theoretically targeted cognitive domains and generalizes to real-world functioning.
- Increases goal-directed control over neural processing in visual cortex.
- Changes in PFC functioning depended on baseline functioning
  - Hypothesis: Re-balancing of prefrontal control mechanisms.
Measurement challenges for rehabilitation neuroscience

- **Biomarkers** that index mechanisms of control over neural processing
- Functional MRI measurements that index the processes of interest **on individual basis**, allowing for **varied pathology**
- **Repeated measures across time**
- Methods that allow decoding of information **acknowledging the importance of functional integration across brain networks**, resulting in meaningful patterns of activity
Ongoing measurement challenges for rehabilitation neuroscience: Limitations

- Hypothesis-driven: Must have strong a prior conceptual model and hypotheses - less useful for explorations
- Limited testing of anatomy-based hypotheses
Methods questions to consider in application

- What pattern classifier approach?
  - Linear, non-linear, etc.
- What input features to enter to classifier?
- How to handle nuisance variables or other ‘covariates’?
- Brain-behavioral relationship analyses are simplified—only at the level of final variables
  - Take into account behavioral variables during brain multi-variate analyses
Methods branches: New information?

- Kinetics of *information* coded in brain regions (vs. hemodynamic time courses)
- Different simultaneous information representations within the same brain regions
- *Stability vs. variability* in neural representations of information
- *Functional connectivity* based on information codes in different regions of the brain
**Frontier:** Enhancing *core mechanisms* for learning and rehabilitation

**Cognitive control (LEARNING Goals)**

Translation to learning, adaptation and improved functioning in other domains
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

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THANKS!

Participating patients

Tatjana Novakovic-Agopian, PhD
Program Co-director
Supervisor, Neurobehavioral
Assessments and Interventions

Mark D’Esposito, MD
Director, Brain Imaging Center, UC Berkeley
Neurobehavioral Neurology, VA NCHCS, Martinez

Scott Rome, MD
Medical Director California Pacific Regional Rehabilitation Center

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