Building bridges to improve Brain Injury Treatment and Research

Program in Rehabilitation Neuroscience

Rehabilitation of Frontal Systems Functioning

Finding the right path after TBI

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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 of ‘executive control dysfunction’

- Often ‘invisible’ yet extremely disabling
- Most apparent in complex, unstructured environments; when we’re not told what to do

Provided by Tatjana Novakovic-Agopian
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?
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

Pathway from information to action and goal attainment: Gateway to Executive Control
Guidance Of Neural-Behavioral Processes
Maintenance Learning
Sequencing
Planning
Review

All information
Goal-relevant information

Selection
Working Memory

Target processes: Information Gateway

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

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Baseline</th>
<th>Weeks 1 - 5</th>
<th>Weeks 6 - 10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assessment 1</td>
<td>GBSM 5 week Training</td>
<td>One 2 hour EDU session</td>
</tr>
<tr>
<td>Group 2</td>
<td>One 2 hour EDU session</td>
<td>GBSM 5 week Training</td>
<td></td>
</tr>
</tbody>
</table>

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](fMRI.png)

## Neurocognitive Domains Targeted

<table>
<thead>
<tr>
<th>Attention and Working Memory</th>
<th>Inhibition and Mental Flexibility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Auditory Consonant Trigrams</strong></td>
<td>Stroop Inhibition/Switching</td>
</tr>
<tr>
<td>Letter Number</td>
<td>Design and Verbal Fluency</td>
</tr>
<tr>
<td>Sequencing</td>
<td>Switching</td>
</tr>
<tr>
<td>Sustained Attention</td>
<td>Trails B</td>
</tr>
<tr>
<td>Digit Vigilance Test</td>
<td>Multitasking</td>
</tr>
<tr>
<td></td>
<td>Dual Task – Visual Attention Test</td>
</tr>
</tbody>
</table>

## 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

Motor Speed of Processing

Novakovic-Agopian, Chen, et al. in preparation
Does the intervention change functioning in ‘real life?’

Multiple Errands Test

Assessed using Wilcoxon's Matched Pairs Test
### Participants Self Rating Relative to Baseline

<table>
<thead>
<tr>
<th>Ability</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to <strong>stop and relax</strong> during stressful times</td>
<td>7.8</td>
</tr>
<tr>
<td>Ability to <strong>stop and refocus</strong> on the current goal.</td>
<td>7.7</td>
</tr>
<tr>
<td>Ability to divide a complex task into more manageable tasks.</td>
<td>7.5</td>
</tr>
<tr>
<td>Ability to <strong>hold and maintain important information in mind.</strong></td>
<td>7.4</td>
</tr>
<tr>
<td>Ability to <strong>finish</strong> something that was started.</td>
<td>7.0</td>
</tr>
</tbody>
</table>

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**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?

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

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.wachadpo.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

Event 2
Clarity of brain patterns for scenes and faces stimuli

Select SCENES

<table>
<thead>
<tr>
<th>Scenes images</th>
<th>Faces images</th>
</tr>
</thead>
</table>

Looks like scenes  Looks like faces
Select FACES

Classifier certainty

0.50
0.55
0.60
0.65
0.70
0.75
0.8

Certainty Index (mean ± SEM)

Select Scenes

Select Faces

* p = 0.554 p = 0.010

Clarity (Relevant)

Clarity (Relevant)

Classifier certainty

Relevant
Non-

p = 0.010

Relevant
Non-

p = 0.010

Clarity (Relevant)
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)

Pre-training

Post-training
Training increases goal-directed selection of information processing

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.

GOAL ATTAINMENT

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!

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- Participating patients

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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

- Pre: Scenes stream (p = 0.034)
- Post: Faces stream (p = 0.026)

Change in mean Certainty Index
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.