Neurotechnology and Clinical Innovation in Rehabilitation Post-Severe Brain Injury

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Learning Objectives

1. Investigate diffuse axonal injury and paroxysmal autonomic instability following traumatic brain injury in case study format
Learning Objectives

2. Consider prognostic indicators in the acute neurologic setting: and how these factors may contribute towards selection of patient’s who may benefit most from clinical innovation strategies.
Learning Objectives

3. Identify areas for future growth and development utilizing neuro-technology to improve clinical outcomes in more severe cases
Learning Objectives

4. Identify future needs for clinical research given a biochemical model of the brain based upon motivation and increased intensity.
"Youthfulness is not a time of life, but a state of mind, a temper of the will, a quality of the imagination, a predominance of courage over timidity, of the appetite for adventure over the love of ease. It does not accept the failures of today as a reason for the cruelties of tomorrow. It believes that one can make a difference and people of good will, working together, can grasp the future and mold it to our will".

Robert F. Kennedy
What is knowledge translation?

- Bridging a gap between biomedical research and clinical practice
- At the center of knowledge translation is the individual patient and family
- Many other stakeholders are involved: in an ideal world, there would be some degree of communication between all

Damiano & Leonard, 2014
What is knowledge translation?

- When gaps exist between evidence and practice: **the patient does not benefit from advances in health care**
- This results in a poorer quality of life, and a loss of personal and societal productivity

Damiano & Leonard, 2014
With this introduction and basis in mind: let us consider how knowledge translation may be applied to acute brain injury rehabilitation
Factors influencing acute brain injury rehabilitation

• “Unfortunately, there are many biases and variables that affect outcome...”

• “If the treating team has a negative view of potential recovery, there may be fewer options considered for the patient. If there is a more positive perspective of what is possible, patients may be offered more opportunities to achieve goals” (Zasler, Katz, Zafonte, 2013)

• And ultimately, their ability to return to society
Importance of acute rehabilitation

- Patients post-traumatic brain injury receiving rehabilitation late (post-35 days in one study) required twice as much therapy as those receiving intensive rehabilitation within the first 35 days of injury (Ashley & Persel, 1999)
- “The more quickly severe brain injured persons can be moved into intensive rehabilitation, the less expensive rehabilitation efforts will be” (Ashley & Persel, 1999)
“Based on growing evidence for behaviorally driven neural plasticity after brain injury and the increasing number of scientists and clinicians who are now designing therapeutic approaches grounded in neuroplasticity principles, some have suggested that we are fast approaching an impending paradigm shift in neurorehabilitation therapy” (Zasler, Katz, Zafonte, 2013)
Paradigm shift

• “In the coming years, advances in behavioral principles, robotics, pharmacotherapeutics, brain imaging, genetics, genomics, nanoelectronics, and neural prosthetics are likely to change the landscape of functional restoration after brain injury” (Zasler, Katz, Zafonte, 2013)
Knowledge translation

• As a rehabilitation field we must be able to keep pace with these scientific advances, and allow patient’s to benefit from this rapid knowledge expansion

• Application of newer research and technologies may be a great asset to facilitate that positive perspective towards **what is possible**: both now and into the future
Knowledge translation focus: Diffuse axonal injury

- The most significant contribution to disablement and morbidity post traumatic brain injury (TBI)
- Involves shearing and twisting of the axon as a result of trauma

http://www.tbibraininjurysurvivor.com/
Knowledge translation focus: Diffuse axonal injury

- This shearing injury is most frequently associated with acceleration/deceleration, or rotational injuries such as in high speed motor vehicle accidents and rollover accidents.
- Up to $\frac{1}{2}$ of TBI presentations may involve DAI.

http://emedicine.medscape.com/article/339912-overview
Knowledge translation focus:
Diffuse axonal injury

- Typically loss of consciousness occurs in addition to contributing towards prolonged vegetative states
- There is a secondary neuro-degenerative process: so often clinical presentations are disproportionate to initial brain imaging
Diffuse axonal injury: Pathobiology

- Within 24-48 hours of injury: cytoskeletal structure of the axon is altered
- Axonal flow continues in the neuron up to the point of damage
- This creates an axonal bulb

http://www.nature.com/nrneurol/journal/v10/n3/full/nrneurol.2014.15.html
Diffuse axonal injury: Pathobiology

- This blockage of neuronal transport products results in a termination of the axon from its distal components within 24-72 hours.

http://www.nature.com/nrneurol/journal/v10/n3/full/nrneurol.2014.15.html
Diffuse axonal injury: Pathobiology

- In conjunction with shearing and compression forces are creation of multiple vascular micro-hemorrhages
- This injury affects primarily white matter areas of the brain: such as within the brainstem, internal capsule, corpus callosum, basal ganglia, thalamus, and cerebral hemispheres

http://www.nature.com/nrneurol/journal/v10/n3/full/nrneurol.2014.15.html
Diffuse axonal injury: Pathobiology

- Ultimate result: disconnection and disruption of white matter tracks and circuitry
- This model suggests diffuse axonal injury as a secondary brain injury which occurs after the initial trauma, and may be an ongoing process in initial acute care

http://www.nature.com/nrneurol/journal/v10/n3/full/nrneurol.2014.15.html
Diffuse axonal injury: Severity grades

• Grade 1: scattered lesions on cerebral cortex
• Grade 2: involves the cortex, and also lesions on the corpus callosum
• Grade 3: worst severity involving the cortex, corpus callosum and now brainstem level involvement (Park et al, 2009)
Diffuse axonal injury:
Mean number of days required to regain consciousness

- Grade 1: 3.7
- Grade 2: 12.5
- Grade 3: 59.5 (Park et al, 2009)
- So with grade 3 level involvement, the mean number of days remaining in a vegetative state is approximately 2 months
Diffuse axonal injury: Recovery mechanisms

- Neuroplasticity of intact or spared networks induced by goal directed activity
- Over time this may further unmask dormant circuits and produce new synaptic connections allowing for a restoration or modification of neural networks
- Affected or non-spared neurons also do hold some capacity to reorganize and repair
Diffuse axonal injury: Recovery mechanisms

• Such collective neuroplasticity may be **adaptive** for increased functionality of the person, or maladaptive for decreased or pathological functionality
How does this knowledge translate to mobility?

- The role of rehabilitation is to guide the nervous system towards adaptive neuroplasticity through appropriate grading and sequencing of sensory-motor experience.
How does this knowledge translate to mobility?

- Innovative new approaches to physical and cognitive rehabilitation based upon a dynamic model of brain response following traumatic injury may be considered.
Each person will be unique: their therapeutic needs and what they respond best to will also be unique.

This requires a blend of scientific knowledge application and creativity in thinking.
Knowledge translation focus:
Paroxysmal Autonomic Instability with Dystonia

- Frequently associated with DAI
- “Brain storming”: observed mostly in severe TBI in intensive care settings
- However this may persist into inpatient settings: in some cases it may increase as the person progresses through the initial stages of neurological recovery being ongoing for weeks or months (Zasler, Katz, Zafonte, 2013)
Knowledg translation focus:
Paroxysmal Autonomic Instability with Dystonia

• Presents with motor posturing of the trunk and extremities and with significant hypertension, tachycardia, and diaphoresis

• Many acute rehabilitation centers will not accept these patients secondary to medical complexity (Zasler, Katz, Zafonte, 2013)
Paroxysmal Autonomic Instability with Dystonia: (PAID)

Pathophysiology

- Dysfunction of autonomic centers in the thalamus or hypothalamus and their connections to both cortical and subcortical/brainstem regulation centers
- All white matter pathways that are subject to injury with grade 3 DAI
- Results in early loss of blood pressure and heart rate regulation
Paroxysmal Autonomic Instability with Dystonia: Pathophysiology

- Extension posturing is resultant of lesions to the midbrain
- Inhibitory signals to pontine and vestibular nuclei are blocked: leading to tonic activity
- Misinformation is then relayed via these nuclei to the cortico-spinal tracts to trunk and limb musculature (Blackman et al, 2004)
Beat to beat heart rate changes
“Triggering” associated with voices of friends in room; or during therapy session Zasler, Katz, Zafonte, 2013
Paroxysmal Autonomic Instability with Dystonia:

- How does this knowledge change the context of your therapeutic intervention?
- There will be varying degrees of severity
- But even in mild degrees: simple things such as the tone of your voice (low versus high), clinician calmness versus anxiety: can influence heart rate over-responsiveness of the patient
- Initially even a single transfer may substantially increase both the heart rate and blood pressure
Paroxysmal Autonomic Instability with Dystonia: Clinical approach

- Your initial goals are truly those of constant vital monitoring and of building of graded activity tolerance.
- Applying situational de-escalation with both your demeanor and approach will be valuable.
- Identification of “triggers” with close communication with medical management: beta-blockers reducing severity of paroxysms (Zasler, Katz, Zafonte, 2013).
Paroxysmal Autonomic Instability with Dystonia: Recovery mechanisms

- Sensory experience drives a motor (or autonomic) response
- These brainstem pathways are very plastic as in DAI recovery
- Graded physical and cognitive experiences in conjunction with medical management are critical for functional recovery!
- Let us next consider neuroplasticity in greater depth prior to the case study
Science to Clinical Application: 

Brain Derived Neurotrophic Factor (BDNF)

- The essential chemical substrate that underlies the synaptic plasticity process at a biochemical level following neurological injury
- May reverse the neurodegenerative process of DAI (Yu et al, 2011)

How does BDNF apply to clinical science?

- Recent biochemical models of the brain: which link graded intensity of aerobic activity to the up-regulation of BDNF, and neurogenesis within the hippocampus (Swain et al, 2012)
- This biochemical activity model will also directly influence memory, and cognition and learning: in addition to the motor or physical recovery of function
Bench to bedside:

• A recent study looking at exercise response in the brains of rats following a structured rigorous exercise regimen found that:
  • Protein levels of BDNF as well as the molecular and genetic expression of BDNF remained elevated for several weeks post cessation of a daily exercise program (Swain et al, 2012)
Bench to bedside:

- These authors concluded that over time, maintenance of a consistent exercise program could result in profound structural and neurophysiological changes in the brain (Swain et al, 2012)
Bench to bedside:

• Another animal study compared the effects of pharmacological administration of BDNF directly into the hippocampus versus exercise induced BDNF response.

• Pharmacological measures were not effective as exercise induced BDNF response in increasing cognitive measures post-TBI (Griesbach et al, 2009).
Bench to bedside:

• The basis of this study was that exercise parameters are a non-invasive means taking advantage of the brains own intrinsic pharmacologic system (Griesbach et al, 2009)
• Therefore, exercise may indeed be medicine
Bench to bedside: Human Studies
Neuroplasticity and exercise?

• A 2015 study investigated two groups of people watching a movie: both groups wore an eye patch on one eye
• One group watched the movie while exercising on a stationary bike with moderate levels of perceived exertion, the other group was sedentary (Lunghi & Sale, 2015)
Prior research has demonstrated that when a person wears an eye patch: the cortical representation of the covered eye within the visual cortex becomes much more sensitive to compensate for this new lack of visual information (Lunghi et al, 2011)
Bench to bedside: Human Studies
Neuroplasticity

- Your visual cortex becomes biased towards the eye not receiving information!
- This is termed monocular deprivation: and is an area of current research in the treatment of certain eye disorders: amblyopia or “lazy eye”
Bench to bedside: Human Studies
Neuroplasticity

• The exercise group in this study demonstrated a substantially greater response in cortical activity with “monocular deprivation”
• This finding has driven new research efforts combining visual rehabilitation in combination with moderate physical exertion to improve clinical outcomes and neuroplasticity
• A secondary finding of this study: is that exercise further decreases the concentration of the neurotransmitter GABA: which inhibits neuronal activity
• “It’s as if physical activity removed the brakes, to trigger plasticity”
• So in addition to increasing BDNF, exercise primes the brain for plasticity (Lunghi & Sale, 2015)
“Our results are more surprising because it indicates that
**moderate levels of physical exercise can promote plasticity in the visual cortex**, a structure that is thought to be lacking plasticity in adulthood. For this reason the fact that a non-invasive manipulation such as physical activity can boost plasticity in the visual cortex is particularly surprising and important. It indicates that **the effect of physical activity on brain plasticity is pervasive and very strong.**”

Neuroplasticity

- All models of motor learning considered: if we do not achieve enough cardiovascular intensity to facilitate this type of response in the brain: we are missing a major window to neuroplasticity
• Exercise alone will not result in neuroplasticity
• However: exercise in combination with a task specific activity: will allow for a much more malleable brain, and optimal biochemical environment of the nervous system to adapt
• Versus simply the task specific activity alone
Case study: Background information

- 24 year old female who sustained a severe TBI following a rollover motor vehicle accident
- Bilateral subdural hemorrhage, subarachnoid hemorrhage, and intraperitoneal hemorrhage
- Diffuse axonal injury grade 3: greatest severity with brain stem level involvement
- Described as a Rancho Los Amigos (RLA) level 2-3 indicating an emerging level of consciousness
Case study:
Negative prognostic information

• Both subdural and subarachnoid hemorrhage present as individual negative prognostic indicators
• DAI grade 3: negative prognostic indicator, with recent literature indicating a mean number of 2 months prior to return of consciousness (patient admitted 1 month post-injury) (Park et al, 2009)
Case study: Positive prognostic information

- Age (24)
- Education: patient was a full time graduate student pursuing a masters degree in education
Case study:
Positive prognostic information: Education

• Educational attainment is a “robust” independent prognostic indicator of disability free recovery from moderate to severe TBI
Case study:
Positive prognostic information: Education

• Person’s holding a college degree demonstrate up to a 7-fold greater likelihood of being considered disability free than those not having completed a high school equivalent degree one year post-injury (Schneider et al, 2014)
Case study:
Positive prognostic information: Education

• Neurobiological explanation unknown
• Theorized that establishment of greater cognitive reserve may assist in either development or unmasking of new neural pathways (Schneider et al, 2014)
Initial delay of consciousness followed by PAID:

- Upon initial presentation: the patient began to follow simple one step commands with inconsistent visual tracking
- Initial activity tolerance demonstrated heart rate response of up to 150 beats per minute with a total assistance low pivot transfer
- Serial casting was required for tone inhibition and to allow lower extremity weight acceptance
Initial delay of consciousness followed by

PAID:

- Standing frame trials began in the long term acute care hospital, and progressed to inpatient rehabilitation
- Initially limited to 2-3 minutes with constant blood pressure and heart rate assessment
Initial delay of consciousness followed by PAID:

- Strategies for reticular activating system were incorporated such as the Snoezelen Room
- Allowing a variety of sensory stimulation and command following activities: such as pressing a button to change the color of the bubble tube in seated balance
Initial delay of consciousness followed by PAID:

- Following the initial delay of consciousness, the individual’s RLA score quickly progressed to a 3-4 (confused and agitated) within three weeks of admission
- Progression to static standing frame trials of 15-17 minutes with stable vitals as measured by pre and post blood pressure and heart rate assessment
Initial delay of consciousness followed by PAID:

- Consistent with RLA 4: there was an increase in motor restlessness requiring maximum assistance of consistently three to four persons for trunk and head control, upper limb control, and bilateral lower limb approximation in the standing frame
- Motor agitation with kicking/elbowing
- Approximately two month’s post-admission: progression to greater than 30 minutes activity tolerance with standing frame
Resolution of PAID and initiation of aggressive mobilization strategies:

• At three month’s post-admission, the individual had progressed to an RLA 4-5 (confused and inappropriate)
• Consistent 30 minutes upright activity tolerance for at least 3 consecutive sessions with stable vitals and physiological response was the protocol for initiation of neuro-technology usage
• Progressed to a motorized elliptical device: the SportsArt ICARE providing body weight support for upright trunk and postural control
Resolution of PAID and initiation of aggressive mobilization strategies:

- Ramp/wheelchair access
- Swivel seat allowing low pivot transfers
- Body weight assistance/suspension system
- Motor assistance elliptical meaning device can provide up to 100% guidance force for initiation of reciprocal stepping even in the absence of volitional motor control
Resolution of PAID and initiation of aggressive mobilization strategies:

• Upon initial trial, the individual required approximately 100% body weight assistance secondary to a crouched stance position and the inability to actively achieve an upright vertical stance
• This was progressed to 50-70% body weight assistance
• The individual was first able to tolerate bouts of seven minutes and ten minutes showing a stable blood pressure and heart rate response
Resolution of PAID and initiation of aggressive mobilization strategies:

- She required a three person assistance for trunk/hip stability, and bilateral lower limb approximation with facilitation of quadriceps during stance phase transitions in the elliptical device to greater simulate gait mechanics.
- Four trials of motorized body weight assisted elliptical training were performed, progressing to single bouts of up to 25 minutes.
Resolution of PAID and initiation of aggressive mobilization strategies:

- As tolerated with physiological activity tolerance parameters, motorized elliptical training was transitioned to robotic assistive gait training using the Hokoma Lokomat© device to allow for greater kinematic control of the trunk and lower extremities with gait simulation.
Lokomat parameter progression:

Hip gait kinematics

Range of motion
Adjustment increases both flexion and extension motion: therefore adjusting stride length

Offset
Brings the hip into either more flexion or extension in relation to trunk: influences initial contact gait

http://knowledge.hocoma.com/training-material/lokomat/pre-training.html
Lokomat parameter progression:

Knee gait kinematics

Range of motion
Only allows increase in flexion: utilized to improve foot clearance during swing

Offset
Can only be offset towards flexion: however very useful to correct knee hyper-extension

http://knowledge.hocoma.com/training-material/lokomat/pre-training.html
Lokomat parameter progression:  
Speed: Neuroplasticity principles

• 0.5-3.2 km/hour
• Lower speeds: initially, lower speeds will also provide more time for training conscious control over gait kinematics.
• Higher speeds: will allow greater repetition and intensity: and also retrain the automatic/subconscious control over gait kinematics which is of greater context in this case.
• Initial speed of 1.0-1.5 km/hour with incremental increases in gait speed with each session.
Lokomat parameter progression: Guidance force

• The percentage in which the limb movements are guided by the robotic orthosis 100% would be passive motion, less than 100% is active assistive
• Providing only as much as needed

http://knowledge.hocoma.com/training-material/lokomat/pre-training.html
Lokomat parameter progression:
Guidance force

• Motor learning environment: if patient excessively deviates their gait pattern from that established once they become “stronger” than the Lokomat (i.e. with lower guidance percentages) the machine shuts down automatically
• Therefore feedback is provided for the success of their gait pattern, allowing the safe opportunity to make errors, and learn from errors with the objective of not shutting down the motor

*External feedback versus internal*
**Lokomat parameter progression:**

**Body weight assistance**

- Consistent with established research: the ultimate goal is to progress body weight assistance from an initial higher range (40-50% maximum) to subsequently lesser assistance with each progressive session.

http://knowledge.hocoma.com/training-material/lokomat/pre-training.html
Lokomat parameter progression: Mode

• A dynamic body weight assistance mode is available on the Lokomat which accommodates for vertical displacement during gait
• Meaning the body weight assistance amount in kg will be adapted according to the vertical movement of the patient while walking
• Interestingly: there are pathways from the vestibular system to the central pattern generators in the spinal cord which theoretically are intact given a traumatic brain injury
• Can we tap into this neural plasticity with automatic gait?

http://knowledge.hocoma.com/training-material/lokomat/pre-training.html
Lokomat parameter progression:

• A total of 19 robotic assistive gait training sessions were performed.
• Body weight assistance progressed to less than 30%, lower extremity guidance force progressed to 50%, and total duration sessions 40-45 minutes ambulating upwards of 1 mile distances in a single session.
Initial challenge with extensor posturing:
• Cues (verbal, visual, tactile) for cervical flexion
• With lower extremity extension tone: as safety function of Lokomat, resistance of the orthosis will shut the motor down and stop the device
• Worked closely with physical medicine rehabilitation physician: gabapentin was introduced to medical regimen to allow progression of training parameters as migraine was determined to be a trigger of the extension posturing
• Utilizing robotic assistive gait training and the Karvonen formula, the patient was able to achieve up to 70% maximum heart rate training zone
• An advantage of this strategy, is that you have very high specificity in adjusting gait kinematics (so it is highly task specific); and addition, it allows for activity progression up to 45 minutes therefore allowing the cardiovascular training response to be attained
• In contrast: this type of manual facilitation would be infeasible or exhausting to a therapist to maintain for that same duration of time.

• These approaches are not in competition with each other: research and systematic reviews have supported that the combination of both approaches (technology and manual facilitation) together, are superior to either on their own.

• Tapping into neuroplasticity
Overground applications:

Neurofacilitation
Overground applications:
Body weight assisted gait progression

• Robotic assistive gait training will be an initial training tool: with the ultimate goal to advance towards overground gait training
• A overhead suspension system harness was utilized allowing open environment error learning
## Overground applications: Body weight assisted gait progression

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Overground applications:

Body weight assisted gait progression
Overground applications:

Body weight assisted gait progression
Final outcome:
Discharge day

Final outcome: Functional outcome

• At home and community discharge the individual was able to ambulate household distances with 2 family members and no assistive device
• Outdoor gait training across sidewalks, ramps, and dirt terrain allowed for a community outing with physical and occupational therapy during the final weeks of inpatient stay.
Final outcome:
Functional outcome

- Achievement of greater societal independence than initially anticipated given early functional prognostic indicators
- Arguably, if sufficient time and intensity had not been provided, such as in a skilled nursing setting, these gains may have not been achieved, contributing to a much greater long term burden/cost of care and likely a decreased life expectancy with increased physical disability.
Closing remarks:

“No longer can we falsely assume that brain injury survivors can recover only for a certain period or that they are destined to regain only a limited number of skills. The potential for improvement is far greater than previously believed possible. With the right interventions, TBI survivors can continue to make progress repairing their brain’s health and their lives for many years. That knowledge should significantly change the way we think about—and address—this enormous public health challenge.”

Reference and questions:

http://www.tandfonline.com/eprint/KrzCwHF3jmbvVs6lhTxX/full

2016 publication: Robotic gait assistive technology as means to aggressive mobilization strategy in acute rehabilitation following severe diffuse axonal injury: a case study

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References:


23. Picture references on individual slides