Advancing environmental enrichment as a pre-clinical model of neurorehabilitation

Anthony E. Kline, Ph.D.
Professor, Physical Medicine & Rehabilitation, Critical Care Medicine, Psychology, Center for Neuroscience, and Center for the Neural Basis of Cognition

Associate Director, Safar Center for Resuscitation Research
Co-Director, CNUP Summer Undergraduate Research Program
Fellow, International Behavioral Neuroscience Society
President Elect, National Neurotrauma Society

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Traumatic brain injury is a significant health care issue

Affects 1.5 to 2 million in the United States each year

- 300,000 are severe (GCS <8)
- 50,000 die
- 100,000 long-term disabilities
- Estimated cost > $75 billion
- Survivable problem
- Evaluation of potential therapies needed
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Characteristics of environmental enrichment

- 36 x 30 x 20 inches
- Various objects (i.e., toys) for stimulation
- To maintain novelty, the objects are rearranged every day and changed each time the cage is cleaned
- 10-12 rats, which includes a subset of all groups, are housed together
- Non-invasive and reasonable rodent analogue of clinical rehabilitation

- Improves spatial learning after CCI (Kline et al., 2007, 2012; Hoffman et al., 2008; Sozda et al., 2010; Matter et al., 2011; de Witt et al., 2011; Bondi et al., 2014) and FP (Hamm et al., 1996; Hicks et al., 2002; Giza et al., 2005)

- Enhances beam-walking after CCI (Hoffman et al., 2008) or cortical lesions (Held et al., 1985; Gentile et al., 1987; Rose et al., 1987)

- Reduces cortical lesion volume and hippocampal CA$_3$ cell loss after FP (Passineau et al., 2001) and CCI injury (Kline et al., 2007; Hoffman et al., 2008; Monaco et al., 2013; Radabaugh et al., 2016)
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Outline

- Typical EE
- Long-term EE
- Abbreviated EE (early)
- Abbreviated EE (delayed)
- Typical EE + haloperidol
Methods: overview

Well-established model of TBI that mimics many of the characteristics of human brain injury (e.g., contusion, hemorrhage, hematoma, axonal injury, cell loss, alterations in cerebral blood flow, behavioral deficits, etc)
# Environmental enrichment (typical)

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Pre-assessment and surgery</th>
<th>Beam tests</th>
<th>Water maze</th>
<th>Sacrifice</th>
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<tbody>
<tr>
<td>-7</td>
<td>Motor training</td>
<td>Acclimatization</td>
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</table>

**EE (typical)**
- 36” x 30” x 20” cage; sensory stimuli (toys); social housing (10 rats)

**STD (typical)**
- 8” x 9” x 15” cage; no sensory stimuli (no toys); no social housing (2 rats)
Typical EE: beam-walk (males)
Typical EE: water maze (males)
Typical EE: histology (males)

- Normal Appearing CA3 Neurons (% Contralateral Hippocampus)
- TBI+STD
- TBI+EE
- SHAM

Time after injury (3 weeks)
Typical EE: beam-walk (females)
Typical EE: water maze (females)
Typical EE: histology (females)
Summary

- Typical EE improves motor (beam-walking) and cognitive (Morris water maze) performance vs STD in both male and female rats

- Typical EE also protects against hippocampal CA$_3$ cell loss after TBI in both male and female rats
Long-term environmental enrichment
Began with 2X as many EE rats vs STD so that after 3 weeks, ½ would continue in EE for 6 months and the other ½ would be placed in STD housing.

Phase 1: TBI + STD, TBI + EE, Sham STD, Sham EE

Phase 2: TBI + STD, TBI + EE, TBI + EE + STD, Shams
Beam balance: phase 1

![Graph showing time on beam over time after injury for different groups: TBI + STD, TBI + EE *, SHAM **](image-url)
Spatial learning: phase 1

![Graph showing time to platform (sec) against time after injury (days) with different conditions: TBI + STD, TBI + EE *, and SHAM **.](image)
Beam balance: phase 2

Graph showing the time on beam (sec) against time after injury (months) for different groups:
- TBI + STD
- TBI + EE *
- TBI + EE + STD *
- SHAM **
Spatial learning: phase 2

Time after injury (months)

TBI + STD
TBI + EE *
TBI + EE + STD *
SHAM **
**Long term EE (summary)**

- Both motor and cognitive performance was enhanced with the relatively brief EE paradigm, which replicates our previous work.

- All EE groups (even those transferred to STD housing after 3 weeks of enrichment) performed markedly better in the maze during the subsequent six month period vs. STD-housed groups.

- The persistent benefits with this paradigm provide further support for EE as a potential pre-clinical model of rehabilitation.
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Long term EE (summary)

A Relatively Brief Exposure to Environmental Enrichment after Experimental Traumatic Brain Injury Confers Long-Term Cognitive Benefits

Jeffrey P. Cheng,1,2 Kaitlyn E. Shaw,1,2 Christina M. Monaco,1,2 Ann N. Hoffman,1,2,6 Christopher N. Sozda,1,2,7 Adam S. Olsen,1,2,8 and Anthony E. Kline1–5
Abbreviated EE

The typical EE paradigm consists of providing continuous exposure to enrichment after TBI, which is not consistent with clinical rehabilitation.

Thus, the aim of the current study was to determine whether an abbreviated EE strategy (i.e., 2, 4, or 6 hrs per day; REHAB) would confer greater recovery after TBI than STD, and whether the effects would be comparable to typical EE.
**Abbreviated EE**

- **Motor training**
- **Acclimatization**
- **Pre-assessment and surgery**
- **Beam tests**
- **Water maze**
- **Sacrifice**

<table>
<thead>
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<th>Days</th>
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**EE**
- 36x30x20" cage; sensory stimuli (toys); social housing (10 rats)

**STD**
- 8x9x15" cage; no sensory stimuli (no toys); no social housing (2 rats)

**REHAB**
- STD housing + 2, 4, or 6 hours of EE daily
Abbreviated EE: males

Rats were placed in their respective housing conditions (EE and STD) immediately after injury.

<table>
<thead>
<tr>
<th>Groups</th>
<th>TBI</th>
<th>Sham</th>
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</thead>
<tbody>
<tr>
<td>EE</td>
<td>n=10</td>
<td>n=5</td>
</tr>
<tr>
<td>STD</td>
<td>n=10</td>
<td>n=5</td>
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<tr>
<td>REHAB (2, 4, or 6 hrs)</td>
<td>n=30</td>
<td>n=15</td>
</tr>
</tbody>
</table>

N=75
Abbreviated EE: motor

![Graph showing time to traverse beam (sec) over time after injury (days)]
Abbreviated EE: learning

The graph shows the time to platform (seconds) over time after injury (days). The x-axis represents the time after injury (days), while the y-axis represents the time to platform (seconds). Different conditions are indicated by distinct markers and line types:

- **TBI + STD**: Red filled circles
- **TBI + EE**: Orange open triangles
- **TBI + EE (2 hr)**: Yellow filled squares
- **TBI + EE (4 hr)**: Green filled diamonds
- **TBI + EE (6 hr)**: Aqua filled triangles
- **SHAM**: Black filled circles

The graph indicates a trend where the time to platform decreases as the time after injury increases, with some conditions showing a significant improvement over others.
Abbreviated EE: summary

- 6 hr REHAB, but not 2 and 4 hr, comparable to typical EE on beam-walk and water maze, indicating that abbreviated EE is capable of inducing benefit

- Similar findings observed with female rats
Abbreviated EE: summary

- 6 hr REHAB, but not 2 and 4 hr, comparable to typical EE on beam-walk and water maze, indicating that abbreviated EE is capable of inducing benefit

- Similar findings observed with female rats
To create a relevant preclinical model of EE therapy, the goal of the study was to determine whether augmenting the sub-therapeutic doses of EE (2-hr and 4-hr) with the cholinesterase inhibitor galantamine would confer benefits over STD controls. Also, might the benefits be comparable to the continuously enriched rats not receiving GAL.
Limited EE + pharmacotherapy

<table>
<thead>
<tr>
<th>Groups</th>
<th>TBI</th>
<th>Sham</th>
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<tbody>
<tr>
<td>Typical EE + VEH</td>
<td>n=9</td>
<td>n=4</td>
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<tr>
<td>STD + VEH, STD + GAL</td>
<td>n=9, n=9</td>
<td>n=4, n=4</td>
</tr>
<tr>
<td>2-hr and 4-hr EE + GAL</td>
<td>n=9, n=9</td>
<td>n=4</td>
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<tr>
<td>N=61</td>
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</tbody>
</table>
Limited EE + pharmacotherapy

- TBI + STD + vehicle (1 mL/kg)
- TBI + STD + galantamine (2 mg/kg)
- TBI + EE + vehicle (1 mL/kg) *
- TBI + 2-hr EE + galantamine (2 mg/kg)
- TBI + 4-hr EE + galantamine (2 mg/kg)
- SHAM **

**Graph showing time to traverse beam (sec) vs. time after injury (days).**
Limited EE + pharmacotherapy

- TBI + STD + vehicle (1 mL/kg)
- TBI + STD + galantamine (2 mg/kg) *
- TBI + EE + vehicle (1 mL/kg) *
- TBI + 2-hr EE + galantamine (2 mg/kg) * ^
- TBI + 4-hr EE + galantamine (2 mg/kg) * ^
- SHAM

Graph showing the time to platform (sec) over time after injury (days) with different treatment groups.
Rehabilitation-relevant EE  
*(delaying exposure)*

To further optimize a preclinical model of EE therapy, the goal of the study was to determine whether delaying EE exposure by 3 days and abbreviating time spent (in the EE cage) to 6 hours per day would confer the same level of motor and cognitive benefits as rats housed early and continuously (i.e., typical EE).
Rehabilitation-relevant EE

<table>
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<tr>
<td>EE</td>
<td>n=8</td>
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<tr>
<td>STD</td>
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<tr>
<td>REHAB (3 d delay/6 hr day)</td>
<td>n=8</td>
<td>n=4</td>
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N=36
Rehabilitation-relevant EE

Time after injury (days)

Time on beam (sec)

- TBI + STD
- TBI + EE (continuous) *
- TBI + EE (rehabilitation) *
- SHAM **
Rehabilitation-relevant EE

Time after injury (days)

Time to traverse beam (sec)

- TBI + STD
- TBI + EE (continuous) *
- TBI + EE (rehabilitation) *
- SHAM **

Pre 1 2 3 4 5 6 7 8
Rehabilitation-relevant EE

Time after injury (days)

Time to platform (sec)

- TBI + STD
- TBI + EE (continuous) *
- TBI + EE (rehabilitation) *
- SHAM **
Rehabilitation-relevant EE

- Both EE conditions significantly enhanced motor and cognitive performance vs. STD.
- The rehabilitation relevant EE group did not differ from the typical EE group in any task, which suggests that the benefits mediated by EE do not require early and continuous exposure.
Refining EE to advance rehabilitation based research after experimental TBI

Breaking the therapy into two shorter sessions may increase novelty and ultimately enhance recovery.

Hence, the aim of the study was to test the hypothesis that functional and histological outcomes will be significantly improved by daily preclinical neurorehabilitation consisting of two 3-hr periods of EE vs. a single 6-hr session.
Refining EE to advance rehabilitation based research after experimental TBI
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Refining EE to advance rehabilitation based research after experimental TBI
Refining EE to advance rehabilitation based research after experimental TBI

- TBI + STD
- TBI + EE (one 6 hr session) *
- TBI + EE (two 3 hr sessions) *
- SHAM **

Percent time in target quadrant

Time after injury (day 19)
Refining EE to advance rehabilitation based research after experimental TBI
Agitation and aggression after TBI
Agitation and aggression after TBI

- 24% - 96% of patients exhibit agitated behavior
- 11% exhibit aggression
- Agitation and aggression can interfere with assessment, acute treatment, and rehabilitation
- Patient management is imperative
- Pharmacological agents first choice
  - Antipsychotics
Agitation and aggression after TBI

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HAL + environmental enrichment

TBI + STD + VEH (1 mL/kg), TBI + STD + HAL (0.5 mg/kg)

TBI + EE + VEH (1 mL/kg), TBI + EE + HAL (0.5 mg/kg)

Sham STD + VEH and HAL, Sham EE + VEH and HAL
HAL + environmental enrichment

* $p < 0.05$ vs. all TBI groups

** $p < 0.05$ vs. all TBI groups
**HAL + environmental enrichment**

![Graph showing time to traverse beam (sec) vs. time after injury (days)]

- **TBI + STD+ VEH (1.0 mL/kg)**
- **TBI + STD+ HAL (0.5 mg/kg)**
- **TBI + EE + VEH (1.0 mL/kg) * p < 0.05 vs. all TBI groups**
- **TBI + EE + HAL (0.5 mg/kg) ^ p < 0.05 vs. TBI+STD+HAL**
- **SHAM ** p < 0.05 vs. all TBI groups
HAL + environmental enrichment

*p < 0.05 vs. all TBI
^p < 0.05 vs. TBI+STD+HAL and TBI+STD+VEH
**p < 0.05 vs. all TBI groups
The data show that EE can attenuate the negative effects of HAL on cognition, but HAL in turn reduces the efficacy of EE. Clinically, this suggests that if providing HAL chronically while in rehabilitation, the intensity of rehabilitation may need to be increased (to compensate for the reduced efficacy mediated by HAL).
**Take home points**

- Typical EE improves motor / cognitive performance, and hippocampal cell survival vs. STD in males and females
- The benefits of typical EE persist for up to 6 months
- Abbreviated EE confers significant benefits in both sexes
- Sub-therapeutic doses of EE combined with GAL synergize to promote benefits beyond GAL treatment alone
- Delaying / abbreviating EE (3 days / 6 hours per day) is as effective as typical EE in male rats
- No significant differences observed whether EE (i.e., rehab) is provided in 1 longer exposure or 2 shorter sessions (both are equally effective)
- EE can reduce the deleterious effects of HAL, but HAL in turn reduces the benefits of EE
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- EE can reduce the deleterious effects of HAL, but HAL in turn reduces the benefits of EE.
Take home points

- Typical EE improves motor / cognitive performance, and hippocampal cell survival vs. STD in males and females
- The benefits of typical EE persist for up to 6 months
- Abbreviated EE confers significant benefits in both sexes
- Sub-therapeutic doses of EE combined with GAL synergize to promote benefits beyond GAL treatment alone
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Corina Bondi (Phys Med Rehab; Safar Center)
Bob Clark (Critical Care Medicine; Safar Center)
C. Edward Dixon (Neurosurgery; Safar Center)
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