The Therapeutic Efficacy of Environmental Enrichment and Methylphenidate Alone and in Combination after Controlled Cortical Impact Injury

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Abstract

Environmental enrichment (EE) and methylphenidate (MPH) independently confer significant benefit to behavioral recovery after controlled cortical impact (CCI) injury. Given that combinational therapies may be more clinically translatable than monotherapies, the aim of the current study was to test the hypothesis that a combined treatment regimen of EE and MPH would provide greater therapeutic efficacy than either one alone. Anesthetized adult male rats received either a CCI of moderate severity or sham injury and were then randomly assigned to EE or standard (STD) housing where they received either intraperitoneal (ip) MPH (5 mg/kg) or vehicle (VEH; 1.0 mL/kg; ip) beginning 24 h after injury and once daily for 19 days. Motor and cognitive assessments were conducted on post-injury days 1–5 and 14–19, respectively. No differences were observed in sham controls regardless of treatments, and thus their data were pooled. The traumatic brain injury (TBI)+EE+VEH and TBI+EE+MPH groups exhibited enhanced beam balance and beam walk performance relative to the TBI+STD+VEH group ($p < 0.05$), but did not differ from one another ($p > 0.05$). No effect of MPH treatment alone was observed in either motor task. In contrast, MPH improved spatial learning and memory when presented alone and also when combined with EE relative to VEH-treated STD controls ($p < 0.05$). In addition, both EE groups performed significantly better than the TBI+STD+MPH group ($p < 0.05$), but did not differ from one another ($p > 0.05$). These data replicate previous findings that both EE and MPH confer cognitive benefits after TBI and extend the findings by revealing that combining EE and MPH does not produce effects greater than either treatment alone, which does not support the hypothesis. The lack of an additive effect may be because of the robustness of the EE.

Keywords: behavioral outcome; controlled cortical impact; dopamine agonist; environmental enrichment; functional recovery; learning and memory; Morris water maze; traumatic brain injury

Introduction

THE ANNUAL INCIDENCE of traumatic brain injury (TBI) in the United States amounts to more than 2 million cases when accounting for emergency and outpatient departments, as well as office-based physician visits combined.^{1,2} Of these, more than 120,000 persons have marked chronic functional impairments,³ which frequently manifest as cognitive and motor dysfunction, particularly in those with moderate or severe TBI.^{4–6} When also taking into account the estimated \$76.5 billion annual economic burden of TBI incurred via medical and rehabilitative services as well as lost productivity,^{2,7,8} it is apparent that therapeutic strategies are needed to address the persistent disability faced by many TBI survivors.

Although a variety of pre-clinical treatments have shown promise for enhancing the recovery of cognitive and behavioral

function after TBI,^{9–18} few of these therapeutic strategies have successfully translated to clinical practice.^{19,20} This lack of translational realization may be related to the heterogeneity of human injury characteristics, but also to the majority of basic science TBI studies attempting treatment using a monotherapeutic approach.

Margulies and colleagues²¹ proposed that combined pharmacological interventions targeting numerous and/or complementary systems affected by TBI are needed to evaluate the potential for additive or synergistic efficacy, beyond that of a single treatment. This recommendation provides a reasonable starting point, but in the subacute phase after TBI, patients frequently receive rehabilitation in concert with pharmacological agents. Thus, experimental models that combine noninvasive rehabilitative paradigms with pharmacological interventions may be important to maximize post-injury recovery.

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The aim of the present study was to evaluate a combined regimen of two treatment strategies that have been shown to individually benefit post-injury motor and cognitive recovery after a controlled cortical impact (CCI) injury. The first treatment paradigm, environmental enrichment (EE), is a model of pre-clinical neurorehabilitation consisting of an enlarged living space, increased socialization, and novel stimuli with which animals frequently interact. EE has consistently been shown to promote neurogenesis, attenuate histopathology, and enhance cognitive and behavioral recovery after experimental TBI in both CCI and fluid percussion injury models.^{22–32}

The second strategy, daily methylphenidate (MPH) administration, which is a dopamine (DA) reuptake inhibitor acting on the DA transporter and a D₂ receptor agonist,³³ has also been shown to confer benefits to cognitive recovery after experimental TBI.^{14,35,36} MPH has been associated with improvements in motor speed, attention, memory, processing speed, and mental fatigue in clinical patients with TBI.^{37–42} In addition, MPH is currently regarded as the first-line treatment for attention and processing speed deficits in patients with TBI.⁴³ The hypothesis to be tested was that combining MPH and EE after CCI injury would produce greater benefits on behavioral recovery than either treatment individually.

Methods

Subjects

Forty-eight adult male Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing 300–325 g on the day of surgery were housed in standard steel-wire mesh cages and maintained in a temperature (21 ± 1°C) and light (on 7:00 a.m. to 7:00 p.m.) controlled environment with food and water available *ad libitum*. After 1 week of acclimatization, all rats underwent a single day of beam walk training, which consisted of 3–5 trials to traverse the beam. On the day of surgery, the rats were pre-assessed on the beam balance and beam walk tasks to determine baseline performance. Following training the rats were randomly assigned to one of the following group conditions: TBI+standard [STD]+vehicle [VEH] (1.0 mL/kg; *n* = 8), TBI+STD+MPH (5 mg/kg; *n* = 8), TBI+EE+VEH (*n* = 8), TBI+EE+MPH (*n* = 8), Sham+STD+VEH (*n* = 4), Sham+STD+MPH (*n* = 4), Sham+EE+VEH (*n* = 4), or Sham+EE+MPH (*n* = 4).

All experimental procedures were approved by the Institutional Animal Care and Use Committee at the University of Pittsburgh. Every attempt was made to limit the number of rats used and to minimize suffering.

Surgery

A CCI injury was produced as described previously.^{28–32,34,44} Briefly, surgical anesthesia was induced and maintained with inspired concentrations of 4% and 2% isoflurane, respectively, in 2:1 N₂O:O₂. After endotracheal intubation, the rats were secured in a stereotaxic frame, ventilated mechanically, and core temperature was maintained at 37 ± 0.5°C with a heating blanket. Using aseptic procedures, a midline scalp incision was made, the skin and fascia were reflected to expose the skull, and a craniectomy (6-mm in diameter) was made in the right hemisphere (encompassing bregma and lambda and between the sagittal suture and the coronal ridge) with a hand-held trephine. The bone flap was removed and the craniectomy was enlarged further with cranial rongeurs.

Subsequently, the impacting rod was extended and the impact tip (6 mm, flat) was centered and lowered through the craniectomy until it touched the dura mater; then the rod was retracted and the impact tip was advanced 2.8 mm farther to produce a brain injury of moderate severity (2.8 mm tissue deformation at 4 m/sec). Im-

mediately after the CCI, anesthesia was discontinued, and the incision was promptly sutured. The rats were subsequently extubated and assessed for acute neurological outcome. Sham rats underwent similar surgical procedures but were not subjected to the impact.

Acute neurological evaluation

Hindlimb reflexive ability was assessed immediately after the cessation of anesthesia by gently squeezing the rat's paw every 5 sec and recording the time to elicit a withdrawal response. Return of the righting reflex was determined by the time needed to turn from the supine to the prone position.

Housing conditions: Environmental manipulation

After surgery and after the effects of anesthesia abated (as evidenced by spontaneous movement in the holding cage), the rats were returned to the colony where those designated for enrichment were immediately placed in specifically designed steel-wire cages (91 × 76 × 50 cm). The EE cages consisted of three levels with ladders to ambulate from one level to another and contained various toys (e.g., balls, blocks, and tubes), nesting materials (e.g., paper towels), and *ad libitum* food and water.^{22,23} To maintain novelty, the objects were rearranged every day and changed each time the cage was cleaned, which was twice per week. Ten to 12 rats, which included VEH and MPH-treated TBI and sham controls, were housed together. Rats in the STD conditions were placed in standard steel-wire mesh cages (two rats per cage) with only food and water.

Drug administration

MPH was purchased from Sigma (Sigma-Aldrich, Inc., St. Louis, MO) and was prepared daily by dissolving in sterile saline, which also served as the VEH. MPH (5 mg/kg) or a comparable volume of VEH (1.0 mL/kg) was administered intraperitoneally beginning 24 h after CCI or sham injury and once daily (15 min before daily behavioral testing) thereafter for a total of 19 days. The dose of MPH was selected based on a previous study from our laboratory showing cognitive efficacy after a CCI injury of similar severity.³⁴

Motor tasks: Beam balance and beam walk

Motor function was assessed using well-established beam balance and beam walk tasks.^{28–32} Assessment of the beam balance entails that each rat be placed onto an elevated narrow wooden beam (90 cm above floor level and 1.5 cm wide) and the time spent maintaining its balance is recorded for a maximum of 60 sec per trial. Three trials are conducted during assessment of pre-injury baseline and subsequent test days 1–5. Testing on the beam walk consists of recording the elapsed time to traverse an elevated narrow wooden beam (90 cm above floor level, 2.5 cm wide, and 100 cm in length). A maximum of 60 sec was allotted to traverse the beam, with an intertrial interval of 30 sec. Three trials are conducted during assessment of pre-injury baseline and subsequent test days 1–5. The average daily scores for each rat in each task were used in the statistical analyses.

Cognitive performance: Spatial learning

Spatial learning was assessed using a Morris water maze (MWM) task⁴⁵ that is sensitive to TBI-induced deficits and subsequent recovery.^{28–32} Briefly, the maze consisted of a plastic pool (180 cm diameter; 60 cm high) filled with tap water (26 ± 1°C) to a depth of 28 cm and was situated in a room with salient extra-maze cues. The platform was a clear Plexiglas stand (10 cm diameter, 26 cm high) that was positioned 26 cm from the maze wall in the southwest quadrant and held constant for each rat.

Acquisition of spatial learning began on post-operative day 14 and consisted of providing a block of four daily trials for 5

consecutive days (14–18) to locate the platform when it was submerged 2 cm below the water surface (i.e., invisible to the rat). On day 19, the platform was raised 2 cm above the water surface (i.e., visible to the rat) as a control procedure to determine the contributions of nonspatial factors (e.g., sensory-motor function, motivation, and visual acuity) on cognitive performance.

For each daily block of trials, the rats were placed in the pool facing the wall at each of the four possible start locations (north, east, south, and west) in a quasi-randomized manner. Each trial lasted until the rat climbed onto the platform or until 120 sec had elapsed, whichever occurred first. The rats that failed to locate the escape platform within the allotted time were manually guided to it. All rats remained on the platform for 30 sec before being placed in a heated incubator between trials (4-min intertrial interval). The times of the four daily trials for each rat were averaged and used in the statistical analyses.

Cognitive performance: Memory retention

One day after the final acquisition training session (day 19), all rats were given a probe trial to measure retention. Briefly, the platform was removed from the pool, and the rats were placed in the MWM from the location point most distal to the quadrant where the platform was previously situated (i.e., “target quadrant”) and allowed to freely explore the pool for 30 sec. Typically, rats that have learned the location of the escape platform exhibit a spatial bias and spend significantly more time in the target quadrant searching for the absent platform. The data were obtained using a spontaneous motor activity recording and tracking (SMART) system (San Diego Instruments, San Diego, CA).

Statistical analyses

Analyses were performed using Statview 5.0.1 software (Abacus Concepts, Inc., Berkeley, CA) on data collected by experimenters blinded to the pharmacological treatments. The motor and cognitive analyses were conducted using repeated-measures analysis of variance (ANOVA). The acute neurological data (i.e., hindlimb withdrawal reflex and righting reflex) as well as the data for the visible platform, probe trial, and swim speed were analyzed using one-factor ANOVAs. When the overall ANOVA revealed significant effects, the Newman-Keuls *post hoc* test was used to determine specific group differences. The results are expressed as the mean $\pm$ standard error of the mean (SEM) and were considered significant when $p \leq 0.05$.

Results

No significant differences in any of the end-point measures were revealed between the sham controls regardless of treatment (i.e., housing or drug), and thus their data were pooled into one group designated as SHAM.

Acute neurological function

No differences were observed among the TBI groups in hindlimb withdrawal reflex after a brief paw pinch (left range = 180.9 ± 5.6 sec to 192.3 ± 4.3 sec, $p > 0.05$; right range = 174.7 ± 4.8 sec to 183.3 ± 4.2 sec, $p > 0.05$) or for righting reflex (range 412.4 ± 10.7 sec to 423.0 ± 6.2 sec, $p > 0.05$) after the termination of anesthesia. The lack of significant differences with these acute neurological indices suggests that all groups experienced an equivalent level of injury and anesthesia.

Motor function: Beam balance

No pre-surgical differences were observed among groups because all rats were capable of balancing on the beam for the allotted

60 sec during the baseline assessments (Fig. 1). The repeated measures ANOVA revealed significant Group ($F_{4,43} = 7.250$, $p = 0.0001$) and Day ($F_{5,215} = 33.938$, $p < 0.0001$) differences, as well as a significant Group $\times$ Day interaction ($F_{20,215} = 4.013$, $p < 0.0001$). After the cortical impact, all groups were impaired relative to the SHAM controls ($p < 0.01$).

While beam balance performance improved in all TBI groups over the 5 days of testing, the *post hoc* analysis revealed that the TBI+EE+VEH and TBI+EE+MPH groups recovered significantly faster than the TBI+STD+VEH group (p 's < 0.05). No differences were observed between the two EE groups, regardless of whether receiving VEH or MPH ($p > 0.05$). Moreover, MPH on its own did not provide a benefit as revealed by the lack of significance when compared with the VEH alone group ($p > 0.05$). No other comparisons were statistically different (Fig. 1).

Motor function: Beam walk (time to traverse)

No pre-surgical differences in time to traverse the beam were noted among groups because all rats were proficient and reached the goal box in under 5 sec during the baseline assessments (Fig. 2). The repeated measures ANOVA revealed significant Group ($F_{4,43} = 26.277$, $p < 0.0001$) and Day ($F_{5,215} = 156.192$, $p < 0.0001$) differences, as well as a significant Group $\times$ Day interaction ($F_{20,215} = 16.283$, $p < 0.0001$). *Post hoc* analyses revealed that all TBI groups differed from the SHAM controls ($p < 0.0001$), and that the TBI+EE+VEH and TBI+EE+MPH groups recovered faster than the TBI+STD+VEH group (p 's < 0.05). No differences were observed between the TBI+EE+VEH and TBI+EE+MPH groups ($p > 0.05$). Similar to the beam balance findings, the TBI+STD+MPH group did not differ from the TBI+STD+VEH group ($p > 0.05$). No other comparisons were statistically different (Fig. 2).

FIG. 1. Mean ($\pm$ standard error of the mean) time (sec) balancing on an elevated narrow beam before and after traumatic brain injury (TBI) or sham injury. * $p < 0.05$ vs. TBI+STD+VEH. ** $p < 0.05$ vs. all TBI groups. No other comparisons were statistically significant. STD, standard; VEH, vehicle; MPH, methylphenidate; EE, environmental enrichment.

FIG. 2. Mean ($\pm$ standard error of the mean) time (sec) to traverse an elevated narrow beam before and after traumatic brain injury (TBI) or sham injury. * $p < 0.05$ vs. TBI+STD+VEH. ** $p < 0.05$ vs. all TBI groups. No other comparisons were statistically significant. STD, standard; VEH, vehicle; MPH, methylphenidate; EE, environmental enrichment.

Cognitive function: Acquisition of spatial learning

The repeated measures ANOVA on the water maze data revealed significant Group ($F_{4,43} = 29.012$, $p < 0.0001$) and Day ($F_{4,172} = 43.05$, $p < 0.0001$) differences in locating the hidden platform. The *post hoc* test indicated that the SHAM group was significantly better than all TBI groups ($p < 0.05$), except the TBI+EE+VEH [$p > 0.05$]. The TBI+STD+MPH, TBI+EE+VEH, and TBI+EE+MPH groups located the position of the escape platform significantly sooner than the TBI+STD+VEH group (p 's < 0.05). Moreover, both EE groups performed better than the STD-housed MPH group ($p < 0.05$).

No significant difference was revealed between the TBI+EE+VEH and TBI+EE+MPH groups ($p > 0.05$). Swim speed did not differ among the groups (range = 29.9 ± 1.2 cm/sec to 33.2 ± 1.6 cm/sec; $p > 0.05$). Last, the ANOVA did not reveal a difference in the time to find the visible platform [$F_{4,43} = 2.248$, $p = 0.08$]. The latter two findings suggest that neither motor impairments nor visual disparities influenced the acquisition of spatial learning (Fig. 3).

Cognitive function: Probe trial

Analysis of the probe data revealed a difference among the groups ($F_{4,43} = 5.731$, $p = 0.0009$). The *post hoc* analysis specified that significant memory retention, as evidenced by a greater percentage of the 30 sec allotted time spent in the target quadrant, was observed in all but the TBI+STD+VEH group. Specifically, the TBI+STD+MPH (34.7 ± 2.7 %), TBI+EE+VEH (39.0 ± 2.3 %), TBI+EE+MPH (36.6 ± 2.4 %), and SHAM (42.1 ± 2.3 %) groups were significantly better versus the TBI+STD+VEH group (26.1 ± 2.5 %) (p 's < 0.05). The SHAM group was also better than the TBI+STD+MPH group ($p < 0.05$). No other comparisons were significant (Fig. 4).

FIG. 3. Mean ($\pm$ standard error of the mean) time (sec) to locate a hidden (submerged) or visible platform in a water maze. * $p < 0.05$ vs. TBI+STD+VEH. ^ $p < 0.05$ vs. TBI+EE+VEH and TBI+EE+MPH. ** $p < 0.05$ vs. all traumatic brain injury (TBI) groups, except the TBI+EE+VEH. No other comparisons in seeking the hidden platform were statistically significant. Moreover, there was no significant difference among the groups to locate the visible platform. STD, standard; VEH, vehicle; MPH, methylphenidate; EE, environmental enrichment.

Discussion

When provided individually as therapeutic approaches in pre-clinical models of TBI, EE and MPH have been shown to facilitate neurobehavioral recovery.^{14,22–32,35} Concurrently, many other therapeutic interventions have also been reported to enhance

FIG. 4. Mean ($\pm$ standard error of the mean) percentage of time spent in the target quadrant (i.e., where platform was previously located) after a single probe trial 19 days after cortical impact or sham injury. * $p < 0.05$ vs. TBI+STD+VEH. ** $p < 0.05$ vs. TBI+STD+VEH and TBI+STD+MPH. No other comparisons were statistically significant. The dotted line represents performance at the chance level (25%). TBI, traumatic brain injury; STD, standard; VEH, vehicle; MPH, methylphenidate; EE, environmental enrichment.

behavioral outcome after TBI using various pre-clinical models;^{9–18} however, most of these strategies have not successfully translated from the bench to the bedside.^{19,20}

While numerous factors may account for the lack of translation, one salient reason may be the use of single therapies for a disease that exhibits multiple pathophysiological events. Acknowledging this limitation, a TBI and combination therapy workshop was initiated several years ago to discuss the potential efficacy of combining therapies.²¹ The National Institutes of Health request for applications (RFA) that emerged from the combination therapy workshop provided a resurgence in such research. Unfortunately, a recent published review of the funded projects found that only one of the studies showed an increased advantage with two therapies.⁴⁶ Although the authors discussed numerous relevant limitations for the lack of efficacy, a salient plausible explanation for the lack of added or synergistic effects may be that in all of the studies involved with the RFA, the potential benefit of rehabilitation itself was omitted.⁴⁶

Hence, the present behavioral study was designed to investigate whether the combined therapeutic potential of EE, a pre-clinical model of neurorehabilitation,^{18,47–49} and chronic administration of MPH would be greater than that of either treatment alone on recovery of motor and cognitive function. The beam balance and beam walk data revealed that both the MPH and VEH groups assigned to EE displayed improved performance relative to the STD-housed groups regardless of whether receiving MPH or VEH. Also, MPH alone after TBI did not result in motor benefits, which replicates both an earlier study from our laboratory,¹⁴ as well as a more recent study in which intraperitoneal MPH (3 mg/kg) did not affect motor activity in pre-adolescent male rats pre-natally exposed to alcohol.⁵⁰

In contrast, MPH was effective in facilitating spatial learning and memory retention in the MWM compared with the VEH control. This effect has also recently been reported in non-TBI studies; Carmack and colleagues⁵¹ (2014) demonstrated that MPH enhanced spatial learning acquisition and memory retention in mice, and that the effects persisted when animals were tested off drug. Further, our study shows that the concurrent MPH and EE administration paradigm produced benefits in both spatial learning and memory that were above those observed with MPH alone.

On face value, this finding suggests that the combination treatment provided an additive benefit on cognition. The caveat, however, is that the combination group did not differ from the EE group receiving only VEH. Hence, these data do not support the hypothesis that combining MPH and EE after CCI injury would produce greater benefits on behavioral recovery than either treatment individually because the combined treatment paradigm of MPH plus EE did not yield benefits above that of the single treatments.

A possible interpretation regarding the lack of additive effects with MPH + EE may be that EE confers more robust effects than MPH, at least at the current dose evaluated in this study. The lack of additional behavioral benefits, however, when EE is presented concomitantly with other pharmacological agents, that on their own have been shown to produce benefits, is not new. Previous studies conducted in our laboratory evaluating continuous EE exposure together with chronic administration of the 5-HT_{1A} receptor agonists 8-OH-DPAT and buspirone also did not reveal greater effects of combinational therapies on neurobehavioral and cognitive endpoints.^{11,28,29}

Moreover, Perry and coworkers⁵² also reported a similar ceiling effect after enrichment exposure that precluded a synergistic effect in combination with MPH. Specifically, rats reared in an enriched housing condition showed higher mean adjusted delay scores (i.e., reduced impulsive choice) in a delay dis-

counting task compared with rats reared in an isolated condition. MPH treatment decreased impulsive choice in isolated rats, but did not further alter impulsive choice in enriched rats, alluding to a maximal effect conferred by EE alone.

Both treatment strategies used in this study have been shown to reduce the reuptake of DA in the synaptic cleft by inhibiting DA transporter function,^{53–56} thus prolonging the action of DA on post-synaptic neurons, which likely contributes to cognitive recovery in the spatial learning task. Dosing of MPH, however, can greatly affect neurobehavioral outcome. Considering that MPH, like other methamphetamine-like compounds can also inhibit, albeit to a lesser extent, norepinephrine transporter function, chronic administration of higher doses (10 or 20 mg/kg/day) has significantly increased anxiety and depressive-like behaviors while suppressing cognitive function.⁵⁷

While we only administered a 5 mg/kg daily dose of MPH, it is not unreasonable to consider that in combination with EE, it may have reduced DA transporter activity to suboptimal levels, such that an overabundance of DA failed to provide additional spatial learning benefits on MWM performance in the TBI+EE+MPH group. While MPH induces therapeutic benefit by primarily targeting DA neurotransmission, EE supports post-injury recovery through multiple pathways or mechanisms including DA system regulation,⁵⁵ reductions in pro-inflammatory cytokines,²⁷ increased neurogenesis, nerve growth factor, and dendritic arborization,^{58–61} or attenuation of medial septal cholinergic cell loss.²⁸

A recent study demonstrated that rats raised in EE exhibit decreased maximal transport velocity (V_{max}) for [³H]DA uptake in medial prefrontal cortex, but increased V_{max} for [³H]DA uptake in the orbitofrontal cortex, thus suggesting that EE produces region-dependent long-lasting alterations in DA transporter function via a trafficking-independent mechanism,⁶² which may influence the overall effectiveness of MPH treatment when provided concurrently. By supporting recovery through multiple avenues, EE emerges as a more well-rounded approach to functional recovery after experimental TBI.

Conclusion

Although no additive or synergistic effects were observed when combining EE and MPH in this study, the findings support the need for continued exploration of combination therapies in experimental TBI that incorporate EE to maximize recovery. Providing dual EE and MPH was effective as a therapeutic strategy in that these treatments did not antagonize one another, which is in contrast to other combination therapies that negated the benefits provided by individual strategies.^{63–66} Indeed, the recent review from the RFA described earlier reported that one study demonstrated worse results with the combination therapy relative to the monotherapy.⁴⁶

In addition, EE alone rendered substantial therapeutic benefit to functional outcomes, suggesting that identification of specific complementary pharmacotherapies, or quantification of more appropriate dosages, may help to maximize the therapeutic effect of this paradigm. For example, the real-world applicability of the continuous EE paradigm (i.e., 24 h per day) is limited, because even inpatients do not receive around-the-clock rehabilitation services.^{67–69}

We have shown previously that an abbreviated EE exposure (6 h per day) confers therapeutic benefit similar to continuous EE;³⁰ thus, future studies combining MPH with this temporally realistic intervention may increase the potential for a synergistic action between EE and MPH on cognitive recovery and help create a

pre-clinical combination therapy paradigm that more accurately mimics the clinical setting and ultimately facilitates translation into the rehabilitation setting.

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Author Disclosure Statement

No competing financial interests exist.

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