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Professor Dale Corbett

Brain and Mind Research Institute – University of Ottawa

Titre: ***Rethinking Approaches to Stroke Recovery***

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BIOGRAPHICAL SKETCH

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NAME: Dale Corbett

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POSITION TITLE: Professor, Scientific Director, Heart & Stroke Canadian Partnership for Stroke, Cellular & Molecular Medicine, University of Ottawa, ON, Canada

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Dalhousie University, Halifax, NS, Canada	BA	1971	Psychology
Memorial University, St. John's, NL, Canada	MSc	1975	Behavioural Neuroscience
Concordia University, Montreal, QC, Canada	PhD	1978	Behavioural Neuroscience
McGill University, Montreal, QC, Canada	PDF	1978-80	Behavioural Neuroscience

A. Personal Statement

I am Professor of Neurosciences in the Department of Cellular and Molecular Medicine at the University of Ottawa and Scientific Director of the Heart and Stroke Canadian Partnership for Stroke Recovery. Prior to my relocation to the University of Ottawa, I held a Tier I Canada Research Chair in Stroke and Neuroplasticity at Memorial University in St. John's Newfoundland. I obtained my PhD from Concordia University followed by post-doctoral studies at McGill University. Subsequently, I was a faculty member at Harvard University and also an Alfred P. Sloan Research Fellow. My laboratory is known for pioneering research on the protective effects of prolonged, mild hypothermia that led to the use of "therapeutic hypothermia " in the treatment of cardiac arrest and perinatal asphyxia. My current research concerns promoting recovery of motor and cognitive function following stroke using novel forms of rehabilitation, exercise, and stem cells. My lab is particularly interested in the potential of biomarkers for prescribing effective doses of rehabilitation to enhance recovery in moderate and severe stroke. Related work focuses on the metabolic, vascular and cognitive consequences of obesity and a sedentary lifestyle.

B. Positions and Honors

Academic Positions:

Assistant/Associate Professor of Psychobiology (1980-85)	Harvard University
Associate Professor Neurosciences (1985-93)	Memorial University
Professor of Neurosciences (1993-2011)	Memorial University
Professor of Neurosciences (2010-)	University of Ottawa
Scientific Director, Heart & Stroke (2010-) Canadian Partnership for Stroke Recovery	"

Awards and Honors:

1976-78, Quebec Doctoral Scholarship, Concordia University
1978-80, NSERC Post-Doctoral Fellowship, McGill University
1982-84 Alfred P. Sloan Research Fellow, Harvard University
2003-2010 Tier I Canada Research Chair in Stroke and Neuroplasticity ($1,400,000.)
2005- Paul Morley Mentorship Award, Canadian Stroke Network
2010-2017 Tier I Canada Research Chair in Stroke and Neuroplasticity ($1,400,000.)- **declined**
2011 Fellow Canadian Academy of Health Sciences

C. Contributions to Science

Throughout my career I have been dedicated to translational research. My work with prolonged hypothermia culminated in the worldwide use of "therapeutic hypothermia" in the treatment of cardiac arrest and perinatal hypoxia-ischemia. To date this represents one of the most successful translations of preclinical stroke research to the clinic.

Subsequently, I switched focus to stroke recovery because it offers the most hope for the greatest number of people. Here my laboratory made several important findings regarding the optimal timing and intensity of post-stroke rehabilitation. Specifically, we identified a "critical period" when the brain is most receptive to rehabilitation (Biernaskie et al., J Neuroscience 2001, 2004). This work has attracted considerable clinical interest and provided evidence for earlier stroke rehabilitation. These are very highly cited papers (**1221 citations**), as is a review paper dealing with plasticity and stroke recovery (Murphy & Corbett, Nat Rev Neurosci, 2009; **1013 citations**). We also determined that a "threshold" amount of reaching repetition during rehabilitation must be attained to achieve recovery of forelimb function and to increase levels of Brain Derived Neurotrophic Factor (BDNF) (MacLellan et al, Neurorehab Neural Repair, 2011). In contrast, patients receive ~ 32 repetitions during therapy sessions which is well below the optimal levels identified in our preclinical work. These data provide compelling evidence for employing earlier and more intensive rehabilitation for patients. More recently, we have been attempting to identify biomarkers that would be predictive of stroke recovery (Jeffers et al, Neurorehab Neural Repair, 2018 a,b). This work has led us to develop an algorithm for prescribing individualized doses of rehabilitation to achieve significant gains in motor recovery even in animals with moderate to severe stroke injury. Similar individualized approaches to stroke rehabilitation in humans may be possible based on our model.

D. Additional Information: Research Support and/or Scholastic Performance

1. Heart & Stroke Canada: 2016-2019 Removing the brakes on post-stroke recovery (Dale Corbett PI, Numa Dancause – Univ of Montréal, co-investigator)

2. CIHR Canadian Consortium in Neurodegeneration and Aging: 2014-2019 Preclinical Development of a Novel, Multi-Target Intervention to Treat Vascular Cognitive Impairment (D. Corbett, B. Stefanovic (Sunnybrook) and J. McLaurin (Sunnybrook, PIs)

3. Canadian Partnership for Stroke Recovery: 2016-2018 Engaging skeletal muscle and vascular plasticity to promote hindlimb functional recovery in a rat model of ischemic stroke Dale Corbett (PI), Baptiste Lacoste, co-PI).

4. Canadian Partnership for Stroke Recovery: 2017- 2019: Using focused ultrasound to promote functional recovery by reopening the post-stroke window of neuroplasticity (Dale Corbett PI, Kullervo Hynynen, co-PI, Sunnybrook Research Institute, Isabelle Aubert, co-investigator, Sunnybrook Research Institute.

Pending applications:

1. Networks of Centres of Excellence: 2019-2023 – D. Corbett, PI

2. Canadian Consortium of Neurodegeneration and Aging – Remote Ischemic Conditioning and Vascular Cognitive Impairment: 2018-2020 – D. Corbett & B. Stefanovic, Co-PIs

Recently completed projects:

1. CIHR: 2013-2018 - Promoting cognitive recovery using endogenous neural stem cell activation and rehabilitation following stroke (C. Morshead, PI Univ of Toronto; M. Shoichet, Univ of Toronto, co-investigator and D. Corbett, co-investigator).

E. Peer Reviewed Publications 2015-2018 (career: 147 total, 4 submitted, h-index=54, citations=11894)

1. McDonald MW, Hayward KS, Rosbergen ICM, Matthew S Jeffers MS, Corbett D Is environmental enrichment ready for clinical application in human post-stroke rehabilitation? Frontiers in Behav Neurosci, 2018, Jul 11;12:135. doi: 10.3389/fnbeh.2018.00135. eCollection.

2. Ould-Brahim F, Nath Sarma S, Syal C, Jiaqi Lu K, Seegorbin M, Carter A, Jeffers MS, Dore C, Stanford W, Corbett D, Wang J Metformin Preconditioning of Human iPSC-derived Neural Stem Cells Promotes Their Engraftment and Improves Post-Stroke Regeneration and Recovery, Stem Cells & Development, 2018, Jul 18. doi: 10.1089/scd.2018.0055. [Epub ahead of print].

3. Mallet KH, Shamloul RM, Pugliese M, Power E, Corbett D, Hatcher S, Shamy M, Stotts G, Zakutney L, Dukelow S, Dowlatshahi Dar, RecoverNow: A patient perspective on the delivery of mobile tablet-based stroke rehabilitation in the acute care setting, Int J Stroke, 2018, in press.

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5. Jeffers MS, Corbett D Synergistic effects of enriched environment and task-specific reach training on post-stroke recovery of motor function, Stroke, 2018**,** doi: 10.1161/STROKEAHA.118.020814. [Epub ahead of print]PMID:29752347.

6. Nusrat KL, Livingston-Thomas J, Vaakiny Raguthevan J, Adams K, Vonderwalde I, Corbett D Morshead CM Cyclosporin A-mediated activation of endogenous neural precursor cells promotes cognitive recovery in a mouse model of stroke, Frontiers in Aging Neurosci, 2018, doi: 10.3389/fnagi.2018.00093. eCollection 2018.PMID:29740308.

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8. Jeffers MS, Karthikeyan S, Corbett D Does stroke rehabilitation Matter? Part A: Proportional stroke recovery in the rat, Neurorehab Neural Repair, 2018a, 32, 3-6.

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Original Contribution

Synergistic Effects of Enriched Environment and Task-Specific Reach Training on Poststroke Recovery of Motor Function

Matthew Strider Jeffers, MSc; Dale Corbett, PhD

Background and Purpose—Reach training in concert with environmental enrichment provides functional benefits after experimental stroke in rats. The present study extended these findings by assessing whether intensive task-specific reach training or enrichment initiated alone would provide similar functional benefit. Additionally, we investigated whether the 70% recovery rule, or a combined model of initial poststroke impairment, cortical infarct volume, and rehabilitation intensity, could predict recovery in the single-pellet task, as previously found for the Montoya staircase.

Methods—Rats were trained on single-pellet reaching before middle cerebral artery occlusion via intracerebral injection of ET-1 (endothelin-1). There were 4 experimental groups: stroke+enrichment, stroke+reaching, stroke+enrichment+reaching, and sham+enrichment+reaching. Reaching rehabilitation utilized a modified Whishaw box that encouraged impaired forelimb reaching for 6 hours per day, 5 days per week, for 4 weeks. All treatment paradigms began 7 days after ischemia with weekly assessment on the single-pellet task during rehabilitation and again 4 weeks after rehabilitation concluded.

Results—Rats exposed to the combination of enrichment and reaching showed the greatest improvement in pellet retrieval and comparable performance to shams after 3 weeks of treatment, whereas those groups that received a monotherapy remained significantly impaired at all time points. Initial impairment alone did not significantly predict recovery in single-pellet as the 70% rule would suggest; however, a combined model of cortical infarct volume and rehabilitation intensity predicted change in pellet retrieval on the single-pellet task with the same accuracy as previously shown with the staircase, demonstrating the generalizability of this model across reaching tasks.

Conclusions—Task-specific reach training and environmental enrichment have synergistic effects in rats that persist long after rehabilitation ends, and this recovery is predicted by infarct volume and rehabilitation intensity.

Visual Overview—An online visual overview is available for this article. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.118.020814.)**

Key Words: animals ■ forelimb ■ ischemia ■ rats ■ stroke rehabilitation

The burden of stroke is increasing because demographic changes, earlier average stroke onset, and improved patient survival lead to an increased need for stroke rehabilitation.[1,2] Many patients with severe stroke are left with long-term residual impairments even after the conclusion of rehabilitation.[3] Previous rodent focal ischemia experiments indicate that environmental enrichment in combination with intensive task-specific rehabilitation (ie, reach training) promotes recovery of both task-specific (ie, staircase/single pellet) and generalized motor functions (ie, beam walking/cylinder).[4–6] Surprisingly, despite the efficacy of this rehabilitation strategy, the respective contribution of each of these components to functional recovery has not been directly compared.

Enriched housing is multifaceted, comprised of many elements, such as social interaction, exercise, and nonspecific sensory, motor, and cognitive stimulation, that make it difficult to determine which factors are the most important for promoting recovery.[7] Nonetheless, interaction of these elements facilitates changes in the brain that are thought to be beneficial in the poststroke milieu, including changes in neuronal activity,[8] dendritic morphology,[9] resting-state functional connectivity,[10] and suppression of plasticity-inhibiting factors.[11] In humans, task-specific physical therapies are thought to capitalize on the reorganizational capacity of the injured brain by using regular and repeated activation of stroke-impaired limbs to induce cortical reorganization.[12,13] In animals, this reorganization is characterized by recruitment of nonaffected regions of the nervous system in both training-induced[10,14] and spontaneous recovery.[15] Critically, plasticity in a variety of structures has been shown to contribute to poststroke recovery depending on the specific size and location of injury within an individual experiment. Preclinical studies have demonstrated

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frontiers in Behavioral Neuroscience

REVIEW
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Is Environmental Enrichment Ready for Clinical Application in Human Post-stroke Rehabilitation?

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Environmental enrichment (EE) has been widely used as a means to enhance brain plasticity mechanisms (e.g., increased dendritic branching, synaptogenesis, etc.) and improve behavioral function in both normal and brain-damaged animals. In spite of the demonstrated efficacy of EE for enhancing brain plasticity, it has largely remained a laboratory phenomenon with little translation to the clinical setting. Impediments to the implementation of enrichment as an intervention for human stroke rehabilitation and a lack of clinical translation can be attributed to a number of factors not limited to: (i) concerns that EE is actually the "normal state" for animals, whereas standard housing is a form of impoverishment; (ii) difficulty in standardizing EE conditions across clinical sites; (iii) the exact mechanisms underlying the beneficial actions of enrichment are largely correlative in nature; (iv) a lack of knowledge concerning what aspects of enrichment (e.g., exercise, socialization, cognitive stimulation) represent the critical or active ingredients for enhancing brain plasticity; and (v) the required "dose" of enrichment is unknown, since most laboratory studies employ continuous periods of enrichment, a condition that most clinicians view as impractical. In this review article, we summarize preclinical stroke recovery studies that have successfully utilized EE to promote functional recovery and highlight the potential underlying mechanisms. Subsequently, we discuss how EE is being applied in a clinical setting and address differences in preclinical and clinical EE work to date. It is argued that the best way forward is through the careful alignment of preclinical and clinical rehabilitation research. A combination of both approaches will allow research to fully address gaps in knowledge and facilitate the implementation of EE to the clinical setting.

Keywords: environmental enrichment, stroke, rehabilitation, neuroplasticity, recovery, clinical translation

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EARLY BEGINNINGS

History of Environmental Enrichment

Environmental enrichment (EE) was first studied by Canadian scientist Donald Hebb, who raised rats in his home and later showed they were superior to laboratory raised animals in tests of problem solving ability (Hebb, 1947). His influential book, the Organization of Behavior: A Neuropsychological Theory (Hebb, 1949), emphasized the importance of experience in shaping behavior and provided the stimulus for research examining how EE changes the brain and subsequently behavior. Much of the work in the 1960's focused on the effects of EE on the undamaged brain. Seminal studies by Rozenzweig and others showed that brain plasticity (e.g., dendritic branching) was dramatically altered by varying experience (Rosenzweig et al., 1962; Bennett et al., 1964; Diamond et al., 1964; Greenough et al., 1973). These use-dependent neuroplastic changes can be induced across the life span and are associated with improved performance on various learning and memory tasks. Later efforts investigated how EE affected the damaged brain (Will et al., 2004). For example, studies showed that EE attenuated the effects of frontal cortex injury (Kolb and Gibb, 1991), as well as both global (Farrell et al., 2001) and focal ischemia (Ohlsson and Johansson, 1995; Johansson, 1996; Puurunen et al., 2001; Risedal et al., 2002).

Based on relatively little preclinical evidence many "so-called" neuroprotective drugs were advanced into clinical stroke trials where they met universal failure (O'Collins et al., 2006). In contrast, an overwhelming amount of preclinical evidence, accumulated over several decades, shows that EE enhances learning and memory, promotes various forms of neuroplasticity and consistently improves recovery from brain injury, including stroke. In spite of this evidence there has been limited translation of this promising intervention into the clinical setting (Livingston-Thomas et al., 2016). The purpose of this review article, is to summarize the widespread preclinical evidence for utilizing EE as a therapeutic intervention for stroke recovery and examine why EE has largely remained a laboratory phenomenon. Additionally, how preclinical and clinical investigators can facilitate the transition of EE into the clinical setting is discussed.

Defining Environmental Enrichment

A major impediment to clinical translation has been inconsistency in how EE is defined experimentally. This has created confusion in the clinical community because it's unclear which EE paradigm or what critical elements of EE should be adapted for patients. As originally conceived, EE was designed to provide a more enriching, stimulating environment for animals to more closely mimic conditions encountered in the wild. There is no standardized form of EE; for some, enrichment means little more than housing several animals together in a standard sized cage containing a tube and a running wheel. Other configurations are much more elaborate and engaging, consisting of a very large, multi-level cage, that includes toys, ramps, ladders and ropes, which are replaced or moved at intervals (e.g., daily, or weekly) throughout an experiment. The elements of the enrichment cage (**Figure 1**) provide opportunities for social interaction, to stimulate exploration (e.g., multi-level floors connected by tubes) and engage in activities (e.g., nesting, crossing beams and hanging platforms) that tax balance, strength and provide somatosensory stimulation. The replacement of objects and changing their location within the cage provides

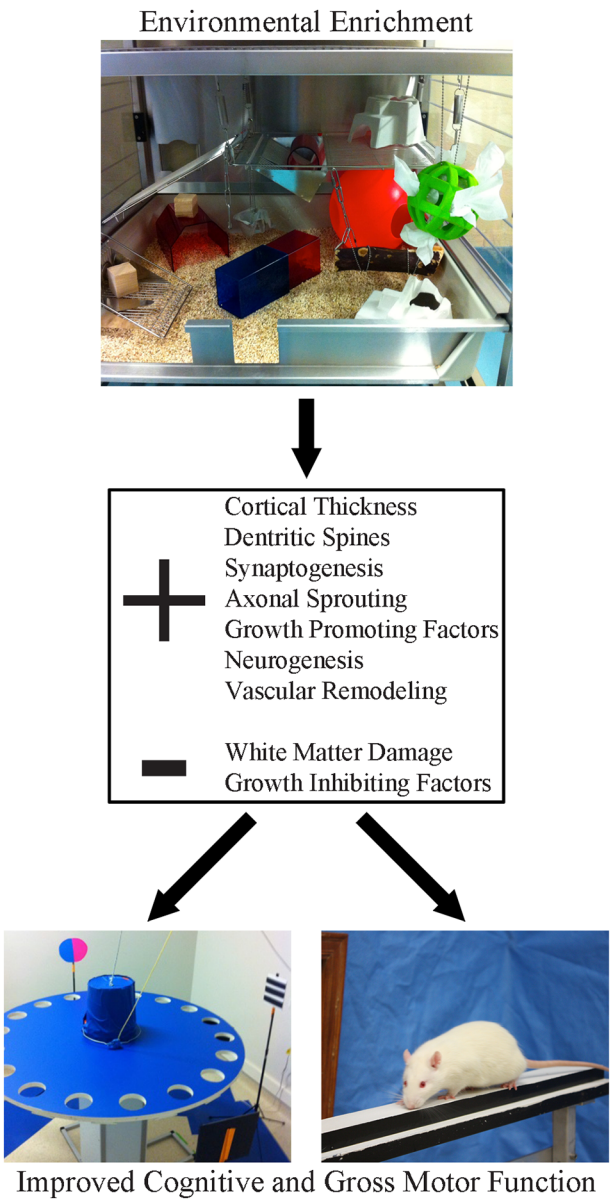

FIGURE 1 | Environmental enrichment (EE) is a multi-faceted form of housing that provides enhanced motor, cognitive, sensory and social stimulation, relative to the standard conditions of rodent housing. This form of housing has been shown to create widespread changes in the neuroplastic milieu of the brain. Following stroke, these beneficial changes create a neural environment that is permissive to recovery, resulting in robust improvements in both cognitive and gross motor function.

cognitive stimulation, additional olfactory and visual stimulation and further encourages exploration and physical activity. Introduction of new materials into the cage can be used to provide added sensory stimulation (Zubedat et al., 2015). In the context of stroke recovery, it is important to recognize that EE needs to include a task specific component that targets the animals' primary deficits. For example, upper limb impairment is very common clinically (Duncan et al., 1992; Kwakkel et al., 2003) and consequently, most preclinical investigators target the forelimb motor cortex in their stroke studies (Murphy and Corbett, 2009; Corbett et al., 2017). EE alone is not effective in promoting recovery of skilled forelimb movements (e.g., reaching; Grabowski et al., 1993), since there is no opportunity to engage in this activity in standard EE configurations. As such, to fill this void our group adds a daily reaching task component to EE which dramatically improves the level of recovery provided by EE (Biernaskie and Corbett, 2001; Biernaskie et al., 2004; Jeffers and Corbett, 2018). Thus, the ideal definition of EE, unlike typical stroke rehabilitation in the clinic, encompasses a changing environment that encourages socialization, exercise, sensory and cognitive stimulation, and task-specific therapy targeting the primary impairment.

Most animal studies provide unlimited access to enrichment 24 h a day, 7 days a week with relatively few studies using shorter enrichment exposures (Leger et al., 2015). This feature of EE raises immediate concerns with clinicians when attempting to extrapolate results from animal studies where not only the configuration of EE, but also practical concerns, limit the duration or amount of therapy time that can be allocated to EE vs. other forms of patient care. Another important consideration related to the duration of EE is that most of the demonstrated benefits in fostering stroke recovery, and the postulated mechanisms underlying these benefits, may not hold if shorter durations of EE are employed. This is an important consideration in view of translational limitations inherent in most preclinical exercise studies. For example, running wheel exercise has long been known to enhance neurogenesis (van Praag et al., 2000; Voss et al., 2013) which in turn is suggested to contribute to improvements in learning, memory, and recovery from brain injury, including stroke (Voss et al., 2013). However, access to this form of exercise, like EE, is typically provided to rodents 24 h per day. It is unclear how such prolonged exercise regimens could be possible for stroke patients who typically are older, experience fatigue, have sensorimotor impairments and are much more sedentary than age-matched controls (Bernhardt et al., 2004; Duncan et al., 2012). In animal studies, the effects on neurogenesis are much more modest when running wheel access has been limited to several hours per day on alternate days (Nguemeni et al., 2018).

A concern with the implementation of EE in the clinic is that rodents experience a relatively impoverished environment in standard animal facilities, and EE may simply normalize typical living conditions (Würbel, 2001). If this is indeed the case, then EE may not be effective in humans who are viewed as already living in an enriched, stimulating environment. However, Bernhardt et al. (2004) have shown that after stroke patients spend a large proportion of time in isolation and physically inactive (Fini et al., 2017). Further, patients frequently report the rehabilitation setting as being unstimulating and boring (Kenah et al., 2017). Thus, the early post-stroke environment for humans and impoverished animals may actually be relatively similar.

Environmental Enrichment as a Combination Therapy

A question, often encountered when discussing the beneficial effects and potential mechanisms underlying the neuroplasticity enhancing actions of EE, is what element of the EE is most important? Is it socialization, exercise, sensorimotor activation or cognitive stimulation? There have been a number of attempts to dissect EE into the relative importance of its individual components. Prior to bilateral cortical injury, rats given 2 h per day of EE for 25 days performed better on a motor task than those given the same amount of running wheel exercise (Gentile et al., 1987). Similarly, improved motor outcomes of EE compared to running wheel exercise-alone have also been observed after middle cerebral artery occlusion (MCAo) in rats, indicating the important influence of socialization on recovery (Johansson and Ohlsson, 1996; Risedal et al., 2002). Using a modified EE paradigm in which EE was combined with daily reach training (i.e., enriched rehabilitation, ER), it was found that EE, running exercise and reach training all produce a uniform pattern of activation throughout all layers of the sensorimotor cortex after stroke, however ER causes a more specific pattern of activation, targeting layer II and layer III motor neurons (Clarke et al., 2014). Recently, we showed that ER is more effective than either EE alone or reach training alone at restoring skilled forelimb function after stroke (Jeffers and Corbett, 2018). Similarly, others have shown a synergistic benefit when EE is paired with either resistance exercise or increased social interaction (Brenes et al., 2016; Prado Lima et al., 2018).

The pattern emerging from studies using EE to promote post-stroke recovery is that the whole is greater than the sum of the parts (Jeffers and Corbett, 2018). In this regard, EE shares similarity with other pleiotropic treatments such as exercise, hypothermia and ischemic tolerance, that have proven to be effective in reducing ischemic damage to the brain (Iadecola and Anrather, 2011). Cell death, like stroke recovery, is not dependent on a single mechanism. Indeed, attempts to rescue cells from ischemic injury or restore lost function after stroke with single target interventions have been met with little success (Murphy and Corbett, 2009; Iadecola and Anrather, 2011; Corbett et al., 2014; Hayward et al., 2014; Carmichael, 2016). The advantage of using EE or ER is that these synergistic approaches engage multiple, potentially beneficial mechanisms (described below and listed in **Table 1**) whereas the single target approach has failed completely in stroke neuroprotection and other conditions, including Alzheimer's disease (Iadecola and Anrather, 2011; Corbett et al., 2014). As such, EE and ER should be viewed as combination therapies that create a permissive, regenerative state in the brain that is receptive to use-dependent, task-specific forms of rehabilitation and other recovery promoting treatments.

TABLE 1 | Potential underlying mechanisms of environmental enrichment (EE) beneficial for promoting stroke recovery.

EE-induced plasticity	References
↓ Lesion volume	Buchhold et al. (2007) and Zhang et al. (2017)
↑ Dendritic remodeling	Biernaskie and Corbett (2001) and Johansson and Belichenko (2002)
↑ Synaptogenesis	Jones et al. (1999), Xu et al. (2009) and Hirata et al. (2011)
↑ Axonal remodeling	Papadopoulos et al. (2009) and Li et al. (2015)
↓ White matter damage	Hase et al. (2017, 2018)
↑ Antioxidant activity	Cechetti et al. (2012)
↑ Angiogenesis	Hu et al. (2010), Matsuda et al. (2011), Zheng et al. (2011), Yang et al. (2012), Ma et al. (2013), Seo et al. (2013) and Zhang et al. (2017)
↓ BBB leakage	Hase et al. (2017) and Zhang et al. (2017)
↑ Neurogenesis	Komitova et al. (2005a,b, 2006); Buchhold et al. (2007), Wurm et al. (2007) and Venna et al. (2014)
↑ Growth-promoting factors (BDNF, Gap43, FGF-2)	Gobbo and O'Mara (2004), Ploughman et al. (2007), Mizutani et al. (2011), Seo et al. (2013) and Venna et al. (2014)
↓ Growth-inhibiting factors (aggrecan-containing perineuronal nets, NOGO-A)	Madinier et al. (2014) and Li et al. (2015)

Up and down arrows indicate an increase or decrease in the corresponding factor in response to EE, respectively.

HOW DOES ENRICHMENT ENHANCE PLASTICITY AND RECOVERY FROM STROKE?

Underlying Mechanisms

Until the work of Mark Rosenzweig and Marian Diamond in the 1960s it was generally thought that the adult brain was fixed and unable to undergo any degree of neuroplasticity. Their work was the first to show that the brains of rats that lived in an EE weighed more, had increased cortical thickness, and demonstrated increased cortical acetylcholinesterase activity compared to their restricted littermates (Rosenzweig et al., 1962; Bennett et al., 1964; Diamond et al., 1964). In response to stroke, synaptogenesis, axonal sprouting, gliogenesis and neurogenesis are significantly upregulated, creating an environment that is highly permissive to behavior-driven plasticity (Murphy and Corbett, 2009; Zeiler and Krakauer, 2013; Carmichael, 2016). It is now recognized that an EE stimulates a number of neuroplastic processes, such as structural changes (dendritic arborization, synaptogenesis, and axonal sprouting), enhanced brain activity, angiogenesis, neurogenesis, and the release of growth factors (brain-derived neurotrophic factor (BDNF), growth-associated protein 43 (GAP43)). Importantly, the upregulation of the aforementioned processes and growth factors play a significant role in facilitating motor and cognitive recovery following ischemic stroke. As discussed above, EE is multi-faceted, incorporating a number of behavioral experiences. The mechanisms upregulated in response to EE alone, or in combination with other components of ER paradigm (exercise, task-specific training), are discussed in relation to their role in promoting recovery following stroke (**Table 1**).

Structural Changes (Dendritic Arborization, Synaptogenesis, Axonal Sprouting, White Matter, Lesion Volume)

While some have demonstrated reduced lesion volume following EE (Buchhold et al., 2007; Zhang et al., 2017), the vast majority of studies do not show a difference in the size of the infarct in standard housed animals compared to EE (Johansson and Ohlsson, 1996; Biernaskie and Corbett, 2001; Risedal et al., 2002; Hirata et al., 2011; Clarke et al., 2014; Madinier et al., 2014). In fact, if EE is introduced within the first few days after stroke it can increase infarct volume and cell loss (Risedal et al., 1999; Farrell et al., 2001). These findings indicate that the beneficial effects of EE for stroke recovery go beyond simple neuroprotection.

A prevailing view of how stroke rehabilitation reduces neurological impairments is by enhancing use-dependent activation of intact tissue adjacent to the infarct and contralesional cortical regions, thereby shaping neural reorganization (Nudo et al., 1996a,b; Dijkhuizen et al., 2001; Binkofski and Seitz, 2004). Experience-induced plasticity following stroke results in remodeling of dendrites in perilesional tissue, and possibly protects vulnerable neurons from further damage (Johansson and Belichenko, 2002; Brown et al., 2008). In healthy rats, EE alone also increases dendritic spines in all cortical layers (Johansson and Belichenko, 2002), while social isolation has been reported to have the opposite effect (Bryan and Riesen, 1989). In hypertensive rats, EE following MCAo increases dendritic spines in pyramidal neurons in layers II/III compared to standard housing conditions (Johansson and Belichenko, 2002). Further, pairing a task-specific reaching paradigm with EE 15 days after MCAo results in increased basilar dendritic growth in layer V pyramidal neurons within the uninjured motor cortex, and corresponding improved functional recovery (Biernaskie and Corbett, 2001). Similarly, EE promotes synaptogenesis in perilesional and contralesional cortex and enhances use-dependent activity in perilesional cortex compared to standard housing (Jones et al., 1999; Hirata et al., 2011; Clarke et al., 2014). Following MCAo the change in synaptic density and structure following 2 weeks of EE has also been associated with improved functional recovery on a spatial memory task (Xu et al., 2009). Further, both exercise and EE enhance axonal sprouting and reduce white matter damage (Papadopoulos et al., 2009; Li et al., 2015; Hase et al., 2017, 2018). Running wheel exercise, often included in EE paradigms and associated with improved functional recovery, enhances axonal remodeling following focal cortical stroke (Li et al., 2015). In models of chronic hypoperfusion, glial

damage in white matter, and neuroinflammation, is also attenuated in mice exposed to EE (Hase et al., 2017, 2018). Similarly, chronic cerebral hypoperfusion and oxidative stress in the hippocampus are prevented following 12 weeks of EE in rats, likely due to heightened antioxidant enzyme activity (Cechetti et al., 2012).

Vasculature

The cerebrovasculature plays a potentially important role in promoting post-stroke recovery (Ergul et al., 2012). Following stroke, angiogenesis is upregulated in order to increase blood flow to damaged tissue and thereby engage endogenous recovery mechanisms such as synaptogenesis, synaptic plasticity and neurogenesis. Similar to the proangiogenic effects of exercise alone (Hu et al., 2010; Matsuda et al., 2011; Zheng et al., 2011; Yang et al., 2012; Ma et al., 2013), EE delivered in the recovery period following ischemic stroke can stimulate angiogenesis throughout the brain and perilesional tissue through vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), and astrocytic high-mobility group box-1/interleukin-6 (HMGB1/IL-6) signaling (Seo et al., 2013; Yu et al., 2014; Chen et al., 2017; Zhang et al., 2017). Importantly, these changes in the cerebrovasculature occur in parallel with varying degrees of functional recovery post-stroke such as grip strength, motor coordination and function (Seo et al., 2013; Yu et al., 2014), decreased depression and anxiety (Chen et al., 2017), and enhanced learning and memory (Yu et al., 2014). Additionally, EE also attenuates blood brain barrier leakage following focal cerebral ischemia and in models of vascular cognitive impairment (Hase et al., 2017; Zhang et al., 2017).

Neurogenesis

Migration of new immature neurons to the site of stroke damage has been shown to occur following ischemic cell death, and in close association with newly formed vasculature (Ohab et al., 2006). Significant literature has demonstrated the benefit of EE on neurogenesis concurrent with enhanced spatial learning and memory (van Praag et al., 2000; Simpson and Kelly, 2011; Leger et al., 2015). Likewise, enhanced neurogenesis is recognized to be upregulated following EE in different models of stroke (Komitova et al., 2005b, 2006; Buchhold et al., 2007; Wurm et al., 2007; Venna et al., 2014). For example, after MCAo in rats, both early (24 h post-stroke) and late (7 days post-stroke) administration of EE for 5 weeks results in significantly more newly born cells in both ipsi- and contra-lateral cortical regions than standard housing (Komitova et al., 2006). This increase in neurogenesis is often accompanied by improved cognitive and sensorimotor function (Komitova et al., 2005a; Wurm et al., 2007). Furthermore, the exercise component of EE may be largely responsible for these neurogenic effects (Grégoire et al., 2014), which is confounded by findings that exercise also results in upregulation of many neuroplasticity-promoting factors such as BDNF (Bechara and Kelly, 2013). This suggests that although neurogenesis and post-stroke recovery may occur in tandem, this may be coincidental, with recovery being more directly related to the upregulation of a variety of growth-promoting factors such as BDNF and GAP43 (Rossi et al., 2006; Ploughman et al., 2009; Clarkson et al., 2011; Mizutani et al., 2011; Cook et al., 2017).

Growth Promoting and Inhibitory Factors

Both the early phase following stroke and initiation of EE are associated with an increase in growth promoting factors (glial-derived synaptogenic thrombospondin 1 and 2, GAP43, MARKS, CAP23, BDNF, etc.) that have varying effects on the aforementioned changes in neuronal structure (Murphy and Corbett, 2009). Thus, the timing of when rehabilitation is delivered is important, with the goal to actively engage in this early time period post-stroke (Corbett et al., 2015). BDNF has a major role in spontaneous and rehabilitation-induced recovery following stroke (Ploughman et al., 2009; Clarkson et al., 2011; Cook et al., 2017). For example, administration of BDNF intravenously or via a hydrogel significantly improves tissue repair and motor recovery in two different rodent models of stroke (Schäbitz et al., 2004; Cook et al., 2017). While EE increases BDNF in some studies of ischemic brain injury (Gobbo and O'Mara, 2004; Venna et al., 2014), others have reported negative findings (Risedal et al., 2002; Hirata et al., 2011). However, it is important to note that rehabilitation and exercise intensity are significant determinants as to whether rehabilitation is accompanied by increases in BDNF and whether significant functional recovery occurs (Ploughman et al., 2007; MacLellan et al., 2011a). Likewise, in the perilesional cortex of rats with cortical injury, running wheel exercise has been associated with increased GAP43, as well as its phosphorylated form (pSer41-GAP43), a key protein involved in neuronal plasticity (Mizutani et al., 2011). Other neurotrophic factors such as insulin-like growth factor-1 (IGF-1), FGF-2, nerve growth factor (NGF) and neurotrophin-3 (NT-3) are also increased by varying amounts of EE (Hu et al., 2013; Seo et al., 2013; Yu et al., 2016).

A critical window for stroke recovery has been linked to post-stroke upregulation of growth promoting factors (described above), with closing of this window related to the upregulation of growth inhibiting genes, such as NOGO and chondroitin sulfate proteoglycans (CSPGs; Murphy and Corbett, 2009). In order for recovery to occur beyond this finite period, interventions should attempt to promote a more permissive environment for neuroplasticity and recovery. For example, administering chondroitinase ABC, which degrades inhibitory CSPGs in the extracellular matrix, or blocking neurite inhibitory protein Nogo-A, enhances sensorimotor recovery following focal stroke due to new axonal connections and increased dendritic arborization in contralesional cortex (Papadopoulos et al., 2002, 2006; Soleman et al., 2012). Similarly, providing EE for 9 weeks after photothrombotic stroke results in a reduction of aggrecan-containing perineuronal nets surrounding parvalbumin containing GABAergic neurons in the peri-infarct area (Madinier et al., 2014). Additionally exercise results in a downregulation of Nogo-A signaling in perilesional tissue, promoting axonal remodeling (Li et al., 2015).

Establishing which EE-induced mechanisms are critical for stroke recovery is difficult to investigate experimentally, with the vast majority of studies being correlative in nature.

A substantial body of preclinical work has focused on the potential role of neurogenesis, yet the precise role of neurogenesis or the degree to which it occurs in adult humans has recently been questioned (Sorrells et al., 2018). Nonetheless, the aforementioned mechanisms and processes discussed above likely have a collective role in promoting recovery following stroke rather than any single one. Indeed, the post-stroke time course of these neuroplasticity processes strongly relate to the functional recovery observed across different domains (cognitive, sensorimotor, etc.).

BENEFITS OF ENVIRONMENTAL ENRICHMENT ON FUNCTIONAL RECOVERY IN ANIMALS

Sensitive Periods Following Stroke: The Importance of Maximizing Therapy Dose in the Early Post-stroke Phase

Corresponding with the aforementioned changes in growth factors, recovery of post-stroke motor impairment is thought to plateau within the first 4–5 weeks in rodents (Biernaskie et al., 2004; Murphy and Corbett, 2009) and the first 3–4 months in humans (Jørgensen et al., 1995; Kwakkel et al., 2006; Langhorne et al., 2011), with a large degree of improvement during this time being attributable to spontaneous recovery in both species (Prabhakaran et al., 2008; Krakauer et al., 2012; Winters et al., 2015; Jeffers et al., 2018a,b). Although recovery can still occur outside of this period, these changes may be mediated by compensatory strategies, rather than restitution of neurological impairments (Zeiler and Krakauer, 2013). This highlights the need for preclinical work to consider more sensitive measures of sensorimotor recovery, such as kinematics (Corbett et al., 2017). Furthermore, although some degree of recovery may occur at any time following stroke, the rate of change becomes more limited as time post-stroke increases (Lohse et al., 2016). Evidence from both preclinical and clinical studies suggest that rehabilitation therapies should be maximized in the early weeks and months following stroke, with caution being taken to not intervene too early (i.e., <3 days), when intensive therapy may have contradictory, or even detrimental effects (Humm et al., 1998; Risedal et al., 1999; Farrell et al., 2001; Dromerick et al., 2009; Lang et al., 2015; Langhorne et al., 2017).

Despite some experiments not finding a relationship between therapy dose and recovery (Winstein et al., 2016), overall meta-analysis across clinical trials have indicated that increased therapy dose augments recovery across a range of post-stroke impairments, using a variety of intervention strategies and outcome measures (Lohse et al., 2014; Schneider et al., 2016). Additionally, the benefits of post-stroke task-specific training have been shown to be transferrable to non-trained tasks (Schaefer et al., 2013). As rehabilitation resources are often limited, alternative methods for increasing therapy dose are highly desirable. EE may provide one such adjunctive intervention for increasing non-specific therapy dose, as this treatment paradigm provides a stimulating environment that enhances stroke recovery in rodents across a variety of impairment domains without requiring provision of specific training (Ohlsson and Johansson, 1995; Risedal et al., 2002; Livingston-Thomas et al., 2016). Furthermore, this stimulating environment has a potentiating effect on task-specific therapy, resulting in recovery beyond what would have occurred with either EE, or task-specific therapy alone (Jeffers and Corbett, 2018).

Efficacy of Environmental Enrichment in Non-motor and Motor Recovery Domains

As previously mentioned, early work with EE focused on how stimulating early life experience promotes enhanced cognitive development (Hebb, 1947). Later, cortical injury models in rodents were used to probe the various functions and network connectivity of the brain, while investigating how early-life EE could ameliorate impairments in learning and memory associated with these injuries (Kolb and Elliott, 1987; Kolb and Gibb, 1991). EE's efficacy in improving cognitive function in these studies led to utilization of this treatment for adult focal ischemia in rodents, with a continued focus on cognitive performance. Following stroke, EE has been shown to significantly enhance spatial learning of the Morris Water Maze (Risedal et al., 1999; Dahlqvist et al., 2004; Rönnbäck et al., 2005; Sonninen et al., 2006) and spatial memory in Radial Arm Maze tasks (Buchhold et al., 2007). These benefits appear to be robust across injury types, as similar benefits of EE have been observed in Morris Water Maze acquisition (Puurunen et al., 1997) and switching between relevant reward-cues in the Win/Shift-Win/Stay version of the T-maze task (Farrell et al., 2001) in models of global ischemia. EE also alleviates depression-like behaviors in mice (Jha et al., 2011), which is an important consideration, as depression in humans after stroke is common (Arwert et al., 2018). Overall, these studies (see **Table 2**) demonstrate the robust cognitive benefits of EE, and the potential for this treatment to be applied to other domains of impairment in preclinical models of stroke.

The preclinical stroke field has primarily used EE to promote motor recovery and study its underlying neuroplastic mechanisms. Many studies have demonstrated benefits of EE on post-stroke recovery of a variety of sensorimotor tasks (see **Table 2**), including: rotarod (Ohlsson and Johansson, 1995; Johansson and Ohlsson, 1996; Johansson, 1996; Nygren and Wieloch, 2005; Nygren et al., 2006; Buchhold et al., 2007), ladder crossing (Biernaskie et al., 2004; Windle et al., 2007; Wurm et al., 2007), limb placement (Puurunen et al., 2001), and adhesive strip removal (Kuptsova et al., 2015). While some studies have shown neutral, or slightly negative effects of EE on similar sensorimotor tasks (Hicks et al., 2008), meta-analysis of these results indicates that EE has a significant benefit on general sensorimotor function (Janssen et al., 2010). Furthermore, these benefits also extend to models of intracerebral hemorrhage (Auriat and Colbourne, 2008), which receives relatively little attention compared to focal ischemia in the preclinical literature.

TABLE 2 | Benefits of EE on functional recovery in animals following stroke.

Benefits	Task	References
↑ Spatial learning	Morris Water Maze	Puurunen et al. (1997), Risedal et al. (1999), Dahlqvist et al. (2004), Rönnbäck et al. (2005) and Sonninen et al. (2006)
↑ Spatial memory	Radial Arm Maze	Buchhold et al. (2007)
↑ Working memory	T-maze	Farrell et al. (2001)
↓ Depression-like behaviors	Tail suspension test, open-field and sucrose preference test	Jha et al. (2011)
↑ Motor recovery	Rotarod	Ohlsson and Johansson (1995), Johansson (1996), Johansson and Ohlsson (1996), Nygren and Wieloch (2005), Nygren et al. (2006) and Buchhold et al. (2007)
	Ladder crossing	Biernaskie et al. (2004), Windle et al. (2007) and Wurm et al. (2007)
	Limb placement	Puurunen et al. (2001)
	Adhesive strip removal	Kuptsova et al. (2015)
	Montoya staircase	Biernaskie and Corbett (2001) and Jeffers et al. (2014)
	Single pellet reaching	Jeffers and Corbett (2018)

Up and down arrows indicate an increase or decrease in the corresponding factor in response to EE, respectively.

One caveat to this positive outlook on EE for enhancing motor recovery is that tasks of fine motor dexterity, such as pellet retrieval, do not demonstrate the same benefits as less-skilled motor outcomes (Grabowski et al., 1993; Ohlsson and Johansson, 1995; Auriat and Colbourne, 2008; Kuptsova et al., 2015). As such, EE may not substitute for task-specific (e.g., upper limb) therapy; however, it could potentially serve as an adjunct to conventional care that would enable greater recovery than possible with task-specific training alone (Livingston-Thomas et al., 2016). This adjunctive approach to EE and task-specific training is supported by evidence that such combination therapies augment recovery of fine-motor skills that normally do not benefit from EE alone, in both models of focal ischemia (Biernaskie and Corbett, 2001) and intracerebral hemorrhage (MacLellan et al., 2011b; Caliaperumal and Colbourne, 2014). Additional combinations of EE with various pharmacological agents has also yielded promising synergistic results; however, this work is still in its infancy (Corbett et al., 2014; Mering and Jolkkonen, 2015; Malá and Rasmussen, 2017). Our previous work has demonstrated that the combination of EE, task-specific reaching and growth factor administration accelerates the rate of recovery of fine motor dexterity (Jeffers et al., 2014). Studies such as these further emphasize that the naturalistic behaviors and heightened activity encouraged by EE has the potential to produce a powerful synergistic interaction to promote recovery of even very specific skilled functions post-stroke (Zeiler and Krakauer, 2013; Corbett et al., 2015).

Generalization of the Benefits of Environmental Enrichment

An important consideration in attempting to translate a potential preclinical stroke treatment, such as EE, to human clinical practice is the robustness of the benefits observed in the preclinical environment. Stroke is a heterogeneous disorder, affecting both sexes at all points throughout the lifespan, causing damage in diverse brain regions and an array of functional impairments (Ramsey et al., 2017). In contrast, preclinical rodent studies of stroke typically utilize young adult, male rats, with cortical lesions that do not represent those most commonly observed in clinical studies (Edwardson et al., 2017). These factors hamper the translation of preclinical stroke treatments to clinical practice, and have led to concerted international efforts to better align preclinical and clinical experimental methodologies in stroke (Bernhardt et al., 2017a; Corbett et al., 2017). As a general principle, before considering translation to the clinic, a potential preclinical therapy should demonstrate robust benefits across a range of experimental conditions.

Undoubtedly EE has been studied under an array of conditions and preclinical demographics (Simpson and Kelly, 2011). In addition to the diverse benefits outlined above, EE has also been shown to exhibit significant effects throughout the lifespan, from neonatal (Kolb and Gibb, 1991; Rojas et al., 2013) to aged animals (Buchhold et al., 2007). However, with aging, animals may need to be subjected to more intense stimulation than younger animals in order to obtain the same benefits of EE (Bennett et al., 2006). The literature regarding sex-differences in the efficacy of EE is much less clear. Studies have shown greater benefits of EE for females (Pereira et al., 2008), males (Langdon et al., 2014), or similar effects between sexes (Frick et al., 2003; Saucier et al., 2010; Schuch et al., 2016). As only ∼17% of EE studies have included both male and female animals, and of this subset only a minority of studies has been concerned with the effects of stroke, or stroke recovery, it is unlikely that enough data currently exists in the literature to definitively answer the conditions under which sex-specific effects of EE may occur (Simpson and Kelly, 2011). As previously outlined, EE has shown beneficial effects for both cognitive and motor recovery using a variety of models of neurological damage including: global ischemia (Farrell et al., 2001), neonatal hypoxia-ischemia (Pereira et al., 2007; Rojas et al., 2013), intracerebral hemorrhage (Auriat and Colbourne, 2008), and cortical injury in a variety of regions using different lesion induction methods (Kolb and Gibb, 1991; Johansson, 2004; Buchhold et al., 2007; Windle et al., 2007; Jeffers et al., 2014; Kuptsova et al., 2015). Another important consideration is whether the beneficial effects of EE are lasting, since the vast majority of preclinical EE studies maintain enrichment until the time of sacrifice. One study provided ER for 9 weeks, at which time animals post-stroke recovery had plateaued. Thereafter, animals were given two cycles ("tune-ups") of 5 weeks of no treatment followed by 2 weeks of additional ER. However, these

tune-ups provided no additional benefits to recovery. Re-testing throughout this period revealed that the initial functional gains from the first 9-week exposure to ER were maintained, suggesting the benefits of ER are long lasting (Clarke et al., 2009). The demonstrated efficacy of EE across a wide variety of stroke models and conditions, together with the overall positive effects on stroke recovery in meta-analysis, suggests that EE may be an ideal intervention for clinical trial assessment (Janssen et al., 2010).

ENVIRONMENTAL ENRICHMENT AS AN ADJUNCTIVE THERAPEUTIC IN HUMANS

Current State of Post-stroke Activity Levels

Despite the above-mentioned literature highlighting the importance of experience to shape behavior and recovery, people with stroke who are inpatients in hospital have limited exposure to a range of experiences, activities and therapy opportunities. A large body of evidence has demonstrated that stroke patients in hospital (up to 3 months post-stroke) consistently exhibit an activity profile of "inactive and alone". In 2004, Bernhardt et al. reported that stroke patients spend 50% of their time resting in bed, 88.5% in their bedroom and 60% of time alone (Bernhardt et al., 2004) and little has changed in the ensuing years. Patients remain inactive, alone and in their bed/bedroom for large proportions of the day (**Table 3**, Fini et al., 2017). While evidence is limited, it also appears that stroke patients demonstrate low levels of social and cognitive activity: in acute care, social activity represented ∼29.3% of time observed, while cognitive activity represented ∼44.7% of time (Rosbergen et al., 2016) and in subacute rehabilitation, social activity occurred in 32% of observations and cognitive activity in only 4% of observations (Janssen et al., 2014).

These low activity levels of stroke patients raise concerns regarding the rehabilitation environment and demonstrates that little patient-initiated therapeutic activity (i.e., without a therapist) occurs during acute and subacute stroke rehabilitation. Synthesizing perspectives and preferences of stroke patients in acute and subacute inpatient rehabilitation shows that patients highly value physical activity and believe that physical activity levels are highly related to enhanced recovery (Luker et al., 2017). Stroke survivors indicate that they want to practice meaningful activities and have more opportunities to engage in recreational activities (Luker et al., 2017). Indeed, a recent review showed that boredom was a very common experience during inpatient rehabilitation for patients with acquired brain injuries (Kenah et al., 2017). Patients highlight that communal areas and outdoor spaces, which provide opportunities for engagement in activities, reduce boredom (Kenah et al., 2017). Importantly, patients recognize that current inpatient rehabilitation is not meeting their activity needs and remain insufficiently engaging.

Animal studies of ER have provided opportunities for very intensive therapy, whereas human stroke patients are typically limited in this regard. From observational studies, direct therapist time focused on active upper limb therapy has been found to be <5 min per day in the acute setting and <17 min per day in the subacute setting (Hayward and Brauer, 2015), and consistent with ∼32 repetitions (Lang et al., 2009). With regards to lower limb activities, Fini et al. (2017) reported across acute and subacute settings, 9.2% of therapy time was directed to standing and walking. Mean time spent walking was 31 min per day in subacute rehabilitation, with likely even less time spent on walking in acute stroke units as patients are more dependent early after stroke.

As outlined above, the present clinical setting contrasts dramatically with preclinical EE and ER where animals are exposed to a high level of social interaction, cognitive stimulation, opportunities for physical activity and intensive rehabilitation to achieve sensorimotor stimulation (Biernaskie et al., 2004). Therefore, optimization of how stroke patients spend their day in acute or subacute inpatient rehabilitation after stroke may be an avenue for improving stroke outcome by emulating preclinical EE in patient care.

Optimizing the Post-stroke Environment

It is essential to explore alternative opportunities to promote greater social, cognitive, and physical activity post-stroke. EE and ER may be a critical aspect that has been long overlooked in rehabilitation units. Similar to animal models, a

TABLE 3 | % of observed time in bed, in bedroom and alone.

Study	Location	% Observations in bed	% Observations in bedroom	% Observations alone
Bernhardt et al. (2004)	Acute	50	88.5	60
Askim et al. (2012)	Acute and subacute	30.3	–	–
Åstrand et al. (2016)	Acute group	33	82	54
	Subacute group	21	53	52
English et al. (2014)	Subacute	0	55	47
Hokstad et al. (2015)	Acute and subacute	44	74	56
Janssen et al. (2014)	Acute and subacute		Inactive and alone 40	
King et al. (2011)	Subacute	52	76	47
Prakash et al. (2016)	Acute and subacute	52	15	78
Rosbergen et al. (2017)	Acute	68	94.5	58.9
Skarin et al. (2013)	Subacute	38	–	52
van de Port et al. (2012)	Acute and subacute	62	87	61
West and Bernhardt (2013)	Acute and subacute	60	76.1	51.9

natural environment for a human is quite enriched; however, hospital environments have been generally considered to be impoverished. An EE is a non-direct therapy approach that can help to equip stroke survivors with the skills to drive their own activity levels and recovery (Barker and Brauer, 2005). Creating an EE that stimulates activity beyond direct therapy time is an important line to explore in the clinical setting and could address the needs of therapists and stroke survivors. While translation is in its infancy, there are global efforts to learn from animal models of enrichment and translate the EE and ER approach to human stroke rehabilitation settings. This line of research will be discussed in order of stroke progression (i.e., acute to subacute), but will not include enrichment strategies that target a specific activity domain alone such as physical activity through group therapy (English et al., 2015), personalized out of therapy protocols (Harris et al., 2009); or social activity using groups (Higgins et al., 2005).

Translation to Acute Stroke Unit

The acute stroke unit is a unique rehabilitation environment, as the majority of stroke patients are more dependent and require frequent assistance from staff to undertake activities. The EE adaptation tested by Rosbergen et al. (2017) in the acute stroke unit included access to communal areas with a variety of equipment to enhance activities away from the bedside including iPads, books, puzzles, newspapers, games, music and magazines available 24 h a day. Daily group sessions (1-h duration) were provided with a focus on different aspects of stroke recovery such as stroke education, emotional support, communication and upper limb, balance, mobilization activities. An opportunity for communal breakfast and lunch was included to stimulate frequency of mobilization and social interaction, as well as encourage sitting upright for mealtimes (Rosbergen et al., 2016). In addition to environmental changes, stroke patients and families received information that explained the importance of activity after stroke, outlined organizational structure of the unit and how stroke patients and families could contribute to encourage activity out of therapy hours (Rosbergen et al., 2016). Under this protocol, the EE group (n = 30) spent a significantly higher proportion of their day engaged in "any" activity (71% vs. 58%) compared to the usual care group (n = 30) and were significantly more active in physical (33% vs. 22%), social (40% vs. 29%) and cognitive domains (59% vs. 45%). Furthermore, the enriched group experienced significantly fewer adverse events (e.g., falls), with no differences found in serious adverse events (e.g., death). The increased activity levels remained evident in the acute stroke unit environment 6-months post-implementation of the EE paradigm.

Translation to Inpatient Rehabilitation

Janssen et al. (2014) focused on access to communal and personal enrichment spaces with the view to increase activity that was driven by the environment. Patients were recruited during the first 4 weeks post-stroke and communal enrichment strategies included computers with internet connection, reading material, jigsaw puzzles, board games and tablets. Strategies targeting personal enrichment were also used and included access to music, audio books, books, puzzles and board games; family members were encouraged to bring in hobbies and activities that patients enjoyed pre-stroke; staff were advised to encourage stroke patients to access communal areas or use personal enrichment resources when patients were observed inactive. Per this 2-week protocol, Janssen et al. (2014) demonstrated that stroke survivors engaged in an EE were: (a) 1.2 times more likely to do "any activity" compared to individuals with stroke in the control group with no EE (activity change from timepoint 1 to timepoint 2 (ΔT1-T2): 13% EE vs. 2% control observations); (b) 1.1 times more physical (ΔT1-T2: 8% EE vs. 5% control); (c) 1.2 times more social (ΔT1-T2: 3% EE vs. −5% control); and (d) 1.7 times more cognitively active (ΔT1-T2: 7% EE vs. 1% control). This pilot study was small (n = 15 intervention group) but was a critical piece of translation work showing how the field is beginning to approach the post-stroke environment.

An alternative approach to enrichment was explored by Khan et al. (2016) in a larger sample using a randomized controlled trial (n = 103, 51% stroke survivors). Individual and communal EE was offered, including an activity stimulating area, the "activity arcade." In contrast to Janssen, where access to activities was available throughout the entire day, in Khan et al. (2016), access to the activity arcade was for 2-h per day only. Activities provided in the arcade were consistent with Janssen et al. (2014) including computers with internet access; workstations with gaming technology; books; music; life-size mirrors for visuo-perceptual deficits; as well as novel training tasks including simulated shopping corner with groceries, electronic payment machines, and bank teller machines; wood workshop, and other activities. This multifaceted approach is more comparable to preclinical EE, where rodents are exposed to a variety of activities in enrichment chambers (Hannan, 2014). Findings (for stroke patients only) demonstrated significant improvements in depression (Depression Anxiety Stress Scale, DASS mean difference from baseline −24.1 (95%CI −40.1, −7.2) and general function (Functional Independence Measure motor, FIM-motor mean difference from baseline 6.7 (95%CI 0.2, 13.1) at discharge compared to the control group, who received standard therapy on the ward at the same time as enrichment patients. However, no differences in Cognition (Montreal Cognitive Assessment and FIM-cognition) and overall health (EQ-5D) were found between groups and improvements were not maintained within patients at 3-months follow-up. As observation of activity levels was not an outcome measure, the impact of enrichment on activity levels remains unknown.

Collectively the studies completed to date demonstrate important outcomes in activity and function, as well as the ability to embed adjunctive indirect therapy through enrichment of the environment within acute and subacute rehabilitation settings.

Contrasts Between Preclinical and Clinical Enriched Environments

To date, it is clear that the approaches used in preclinical and clinical stroke rehabilitation settings have differed.

TABLE 4 | Differences between preclinical and clinical housing conditions, delivered care and therapy routines.

Housing conditions	
Preclinical EE	**Clinical EE**
Animal cages can be built to have standardized physical environments	Stroke and rehabilitation units physical build varies widely from hospital to hospital
Easy to change housing environment	Difficult to change housing environment (e.g., built floor plan, walls and communal space locations)
Animals unlimited access to all areas	Patient with contact precautions and higher stroke severity (e.g., unable to mobilize independently) have limited access
Controlled number of animals with uniform stroke severity in the environment	Controlled number of patients, but large number of staff, visitors, and non-stroke patients also interacting in environment
Length of stay is based on biology of recovery	Length of stay is pragmatic and limited by funding
Species, care and therapy	
Predominantly young, male rodents	Stroke patients are largely older, mixed sex populations
Controlled daily routine	Daily routine frequently interrupted (e.g., medical investigations, visitors, medical emergencies on acute ward)
Rodents activities are spontaneous, rather than directed by a therapist	Humans activities based on learned behaviors and influenced by therapists, carers and other medical staff
Rodents can engage in any activities as soon as they desire, at any level of intensity (not restricted by investigator)	Human activities may be restricted by care givers (e.g., number of people to assist to mobilize) and/or hospital procedures (e.g., safety measures to prevent falls)
Rodents access only the cage	Humans have access to areas beyond the unit e.g., therapy spaces, outdoor areas, hospital grounds and beyond
Rodent EE encourages more physical, social, and cognitive activity and often contains a variety of self-initiated opportunities for exercise, and in ER, includes intensive reaching practice	Human EE also encourages more physical, social, and cognitive activity, but has fewer opportunities for strenuous exercise or task-specific reaching practice

Key distinctions between animal and human stroke studies are presented in **Table 4**. A significant barrier to clinical implementation is configuration of the EE environment. In animal studies cages are not difficult to standardize, it is easy to increase the novelty of objects and tasks while allowing unlimited access to all areas of the cage. In human stroke rehabilitation it is much more difficult to standardize EE conditions across sites, since stroke rehabilitation units vary, some patients have limited access due to impairment levels, length of stay can vary, and due to cost restrictions, the EE cannot be physically rearranged very easily. Although no sex-specific differences in EE have been identified with regards to stroke rehabilitation, a limitation in preclinical work to date is that most studies have utilized young male rodents. While clinical EE has attempted to mirror the physical, social and cognitive focus of preclinical EE, the opportunity for more strenuous exercise, similar to rodent running wheels, is lacking. Further, few clinical studies to date have attempted to include more task-specific rehabilitation into their EE paradigm similar to ER, which preclinical work has shown to be even more advantageous than EE alone (Jeffers and Corbett, 2018). Nonetheless, taking these differences into account, there are considerable research opportunities to better align preclinical and clinical EE and ER research.

Implementation of EE in Clinical Practice: Are We Ready?

Before wide-spread implementation of EE in a clinical setting, stronger evidence for its benefits in post-stroke patients is required. So far, no large scale clinical trials of effectiveness and cost efficacy have been undertaken (e.g., Phase III). To date, the few small to medium sized studies (n = 14 to n = 52 stroke patients) have demonstrated that activity levels can be increased (Janssen et al., 2014) and appear to remain sustained over time within units (Rosbergen et al., 2017), but not within individuals (Khan et al., 2016). However, we have limited evidence of improved stroke recovery in terms of disability (e.g., modified Rankin Scale), function (e.g., Fugl Meyer Assessment, Action Research Arm Test, walking ability) or participation (e.g., return to meaningful activities); nor evidence of biological changes (e.g., altered functional connectivity, growth factors, etc.) like that found in animal models. It is likely that enrichment is one piece of a complex rehabilitation intervention and thus, trial design is challenging.

There is considerable cause for optimism that EE can increase stroke patient activity indirectly, but potential translational roadblocks need to be addressed prior to wide-spread implementation of EE in a clinical setting. There is a need to consider how we best design an effectiveness trial (e.g., cluster trial), but to progress translation of EE to the clinical setting we need early phased studies as well. Such studies need to focus on building an understanding of how EE works, focusing on the neurobiology and individual differences. While human research cannot always probe the same biological mechanisms available to preclinical research, human studies can use data collected preclinically to guide key biomarkers of interest for the clinic (Boyd et al., 2017). This includes using functional imaging such as resting and functional MRI, EEG and MEG to understand the influence of EE on cortical and subcortical networks, as well as TMS to investigate cortical excitability and inhibitory patterns. Further, structural changes at the macrolevel can be probed, for example using diffusion weighted imaging to explore whole brain white matter fiber integrity, as well as various MRI scans to model microlesion load. Inclusion of blood (to model potential growth-promoting and inflammatory biomarkers) and genetic (to explore BDNF polymorphisms) assays could also

be included to help understand who might benefit most from EE. Exploring biomarker candidates that have been identified in parallel preclinical research may also inform stratification of patients in future trials (Jeffers et al., 2018b).

A better understanding of the optimal dose of EE is required. Trials that attempt to understand the dose characteristics of EE could use novel 3 + 3 designs that progressively increase exposure across physical, social, and cognitive activities that may shape behavior. This can allow sophisticated and detailed analysis of the effect of EE on activity levels, well-being, functional outcomes and fatigue levels. As well, any models of EE must consider the impact of ER evidence in animals. We cannot assume that EE alone will be the recovery breakthrough without considering the need to substantially increase the dose of complex and challenging therapy opportunities. While human studies use behavioral mapping to profile individual patient activities, technological advancements have also enabled rodent tracking on the individual level, using methods such as video shape recognition, or RFID tagging. This alignment of preclinical and clinical research methodologies will enable parallel, and complementary, research to be conducted across species in order to determine the optimal EE environment for promoting neuroplasticity and stroke recovery.

Finally, EE requires the environment to be novel and complex. At present there are limited opportunities for stroke patients to engage in physical, social and cognitive activities within the inpatient rehabilitation environments. To enable access to meaningful activity for stroke patients there is a need to create activities that are accessible outside of therapy. Self-directed upper limb and mobility activities, including smart use of technology such as gaming, robotics and virtual reality may contribute to enhance EE translation.

FUTURE DIRECTIONS

As discussed by the international Stroke Recovery Roundtable group, for stroke recovery research to progress forward there is a need for closer alignment of preclinical and clinical research (Bernhardt et al., 2017a,b; Boyd et al., 2017; Corbett et al., 2017). Despite a significant amount of preclinical research being conducted on the ability of EE and ER to enhance stroke recovery, questions still remain to translate this adjunctive model of therapy to the clinic. For example, while rehabilitation strategies that promote neuroplasticity are important for functional recovery following stroke it is also recognized some forms of neuroplasticity may actually be maladaptive (Jones, 2017). Training the unaffected limb on a reaching task following focal stroke actually worsens behavioral recovery in the affected limb (Allred and Jones, 2008). This maladaptive plasticity is mediated by transcallosal projections (Allred et al., 2010), and has also been linked to abnormal synaptogenesis and decreased neural activation of perilesional cortex (Allred and Jones, 2008; Kim et al., 2015). To lessen the potential for aberrant neuroplasticity when engaging in rehabilitation, such as EE, it is important to try and limit compensatory strategies using the unaffected limb. However, the way in which EE may promote or negate compensatory strategies and learned-nonuse of the stroke-affected limb has not been widely studied in preclinical and clinical studies.

To date, studies that have investigated different EE paradigms in the clinical setting have incorporated a number of cognitive and social components that have been shown to promote greater activity. While increasing any aspect of physical, cognitive, or social activity is important, preclinical EE also has motor components that provide the ability to engage in intense physical activity, more akin to exercise (running wheel, climbing, beam walking, etc.). Since preclinical work has shown that the effects of EE are multi-factorial in nature, to demonstrate clinical efficacy future clinical translation should attempt to better mirror animal EE environments. Integrating more opportunities for patient-initiated goal directed exercise into clinical EE would likely be quite valuable, tapping into both cognitive and motor domains. Indeed, evidence from animal work demonstrates that exercise and cognitively stimulating environments alone do not provide the same magnitude of benefits as when they are provided together (Langdon and Corbett, 2012).

On the other hand, preclinical experiments should attempt to mirror the clinical setting more closely. As previously mentioned, the majority of animal studies have used young male adult rodents (Simpson and Kelly, 2011) while within the clinical setting stroke patients' characteristics vary widely in age, stroke features, comorbidities, and prior living situations. Further, most preclinical EE studies have also administered EE 24 h a day, something that is not achievable in the clinical setting. Experiments that mimic variables encountered in the human stroke population can further contribute to the translation of EE.

Lastly, future design of acute stroke and inpatient rehabilitation units should facilitate early rehabilitation and indirect therapeutic activity. Hospitals are currently moving away from co-location of multiple patients in a bedroom to single patient bedrooms to minimize risk of infection, which results in reduced social stimulation (Anåker et al., 2017). However, to facilitate brain repair and recovery processes after stroke the architectural layout needs to promote early rehabilitation and safe indirect therapeutic activity. In this modern era for clinical practice, there is a need to break down the barriers between the disciplines that can support optimal translation and work collaboratively across the translation pipeline (Bernhardt et al., 2017a,b). This means increasing communication between preclinical and clinical researchers, as well as architecture and technology experts, and health care consumers (i.e., patients and caregivers) to create optimal health environments for stroke survivors that promote activity and recovery. Co-design is a novel methodology that could be integral to unravelling the translational hurdles of EE.

Decades of preclinical research have established that EE is a robust intervention for fostering brain plasticity and recovery from various types of brain injury, including stroke. A number of important questions remain regarding the optimal delivery of EE for promoting recovery from stroke. However, aligning the preclinical and clinical approaches to these questions may greatly accelerate our ability to undertake these challenges, and to work towards implementation of EE into the clinical domain on a large scale.

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MM, KH, IR, MJ and DC contributed to the conception, literature search, drafting and revising of the manuscript. Furthermore, all authors approve the publication of this content and agree to be accountable for all aspects of the work.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

significant functional recovery based on neuroplastic changes within both perilesional[5,14] and contralesional cortex,[16] spinal cord,[17,18] and rubrospinal tracts.[19,20] This has led to the view that by utilizing task-specificity principles and focusing treatment on surviving networks and their connections, it will be possible to tailor rehabilitative strategies to maximize poststroke recovery.[21–23]

Previous investigations have demonstrated the efficacy of combining of environmental enrichment and task-specific reach training to promote poststroke recovery.[5,24] These studies utilize the premise that enrichment creates a neuroplastic milieu that is permissive for recovery after a stroke.[25,26] Task-specific training may then be used to capitalize on this permissive environment to induce neuroplastic change with maximal efficiency.[16,27] A similar concept has been successfully applied in previous studies by combining rehabilitation therapy with administration of various plasticity-promoting factors.[6,16,18,25,28–30] The primary objective of the study sought to assess the efficacy of this adjunctive treatment strategy by using environmental enrichment and task-specific reach training both independently and in combination. We hypothesized that coadministration of these therapies would have a synergistic effect on motor recovery resulting in superior performance than either element alone.

The secondary objective of the study was to determine whether recovery could be predicted on an individual animal basis using the variables of initial poststroke impairment, cortical infarct volume, and rehabilitation intensity. Human studies of functional recovery from stroke have identified these factors as important predictors of change in task performance.[31–34] In a previous study, we showed that these factors could be combined to successfully predict improvement of individual animals in staircase pellet retrieval (PR).[35] Based on the congruency of these findings with the human literature, it is plausible that common biological stroke recovery processes that are engaged by these variables might exist across mammalian species.[36] In humans, it has been demonstrated that this proportional recovery rule can be used to predict recovery of impairments within a variety of functional domains, including both upper[32,33,37] and lower limbs,[38] aphasia,[39] and visual neglect.[40] To address this secondary objective, we assessed whether our model of initial poststroke impairment, cortical infarct volume, and rehabilitation intensity[35] could be generalized as predictors of recovery on an additional forelimb motor task (single-pellet reaching).

Materials and Methods

All data and materials that support this study are available from the corresponding author on reasonable request.

Subjects

Fifty-one male Sprague-Dawley (Charles River, Montreal, Canada) rats weighing 300 to 370 g at the time of surgery were handled and housed in pairs on a 12/12-hour reverse day/night cycle with food and water ad libitum. Males were used to replicate the rehabilitation conditions of a previous related experiment.[41] All behavioral training and testing was performed during the dark cycle. Rats (n=7–8 per group after exclusion criteria) were matched according to poststroke deficits in skilled reaching and randomized into 4 groups: sham, stroke+enrichment, stroke+reach training, and stroke+enrichment+reach training. Sample sizes were based on the effect sizes of rehabilitation effects observed in previous studies.[5] All experimental procedures were approved by the Institutional Animal Care Committee of the Memorial University of Newfoundland and comply with guidelines set by the Canadian Council of Animal Care.

Behavioral Training

Before stroke, rats were trained for 10 days (25 trials per day, 5 days per week) on a modified version[24] of the single-pellet reaching test described by Whishaw et al[42] (Figure I in the online-only Data Supplement). Training consisted of daily sessions in which rats learned to reach through a 1.1-cm-wide vertical slot to obtain 45-mg food pellets (5TUL; TestDiet) that were placed in a small well on a Plexiglas shelf located 2.0 cm from the front wall of the Plexiglas test box. The height of the shelf was adjustable, but for training and testing was located 3.5 cm above the floor of the test chamber. To minimize poststroke learning effects, the number of successful PRs was scored, and animals that were unable to retrieve at least 50% of pellets before stroke were excluded from the study (n=18). Subsequent testing was performed at poststroke weeks 1, 2, 3, 4, 5, and 9 (Figure 1A). At all training and testing time points, rats were restricted to 14 g of food the day before testing to increase motivation to engage in the task. Rats were not food restricted during rehabilitation procedures.

Surgical Procedures

Focal ischemia was induced by intracerebral injection of ET-1 (endothelin-1; ab120471; Abcam) as described previously.[5] Briefly, animals were anesthetized with 2% halothane in a gas mixture containing 30% oxygen and 70% nitrous oxide. Middle cerebral artery occlusion was produced by stereotaxic injections of 3.0-µL ET-1 (60 pmol/µL) dissolved in sterile saline into the region of the middle cerebral artery. The following stereotaxic coordinates (relative to bregma) were used for injections: +0.9-mm anterior, −5.2-mm lateral, and −8.2-mm ventral (from skull surface). Injections were performed for 3 minutes, with the injection needle left in place for a further 5 minutes to minimize backflow before withdrawal. Subsequently, the wound was sutured, anesthesia discontinued, and the animal placed in a cage on a warming blanket for several hours. Rectal temperature was maintained at ≈37.0°C during surgery by a feedback-regulated blanket system. Sham surgery consisted of all steps except for skull drilling and ET-1 delivery. Three animals died during surgery, leaving N=30 in the final data set.

Poststroke Testing

One week poststroke, rats were retested on the single-pellet reaching task to assess the level of stroke-induced impairment before rehabilitation. Testing on poststroke weeks 2, 3, 4, and 5 was performed to assess recovery of function with rehabilitation, and a final test point at poststroke week 9 was used to assess retention of rehabilitation-induced benefits. At each poststroke test point, 25 trials of single-pellet reaching were performed, with the number of successful PRs used as the outcome measure.

Rehabilitation Paradigms

After behavioral assessment at 1 week poststroke, 3 rehabilitation paradigms (4-week duration) were initiated to promote poststroke recovery. This delayed poststroke time point (1 week) was chosen as both environmental enrichment[43] and reaching rehabilitation[4,44] have been shown to exacerbate neuronal injury if initiated within the first few days after stroke. Human trials have also demonstrated worsened outcomes if rehabilitation is initiated early after stroke.[45] One intervention consisted of housing in environmental enrichment cages in groups of 5 to 6 rats per cage for 24 hours per day. These large, wire mesh cages (length, 105 cm; width, 67 cm; height, 75 cm) included a variety of novel elements for the rats, such as toys, round and rectangular beams for balance practice, grid/mesh devices for climbing, and multiple levels to induce exploration and encourage physical activity (Figure 1B). Seven animals received enrichment as the sole method of rehabilitation.

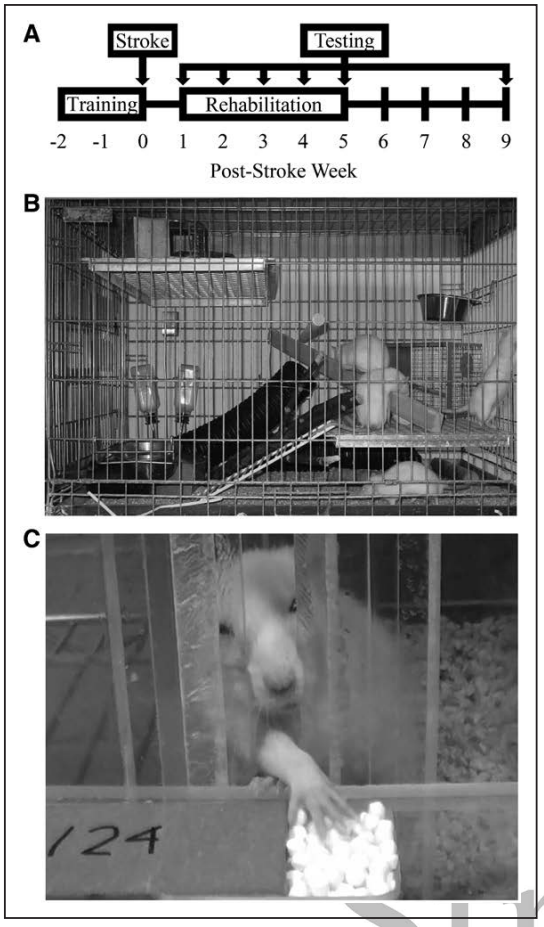

Figure 1. Experiment summary and examples of rehabilitation apparatus. **A**, Timeline of experimental procedures. **B**, Example of environmental enrichment cage used for enrichment and enrichment+reaching conditions. **C**, Example of rat reaching for pellets during reaching or enrichment+reaching conditions. An interior wall in the reaching chamber restricted rats positioning their body so that only their impaired limb could be used to retrieve pellets during rehabilitation.

A second group of animals (n=7) was housed under standard conditions (2 rats per cage) but received access to task-specific reaching rehabilitation for 6 hours per day, 5 days per week. This reaching rehabilitation consisted of access to the same reaching box used for the single-pellet reaching task. However, instead of reaching only 1 pellet, rats had access to a trough of pellets that they could retrieve ad libitum (Figure 1C). The trough height was adjusted throughout the rehabilitation period to encourage recovery of limb function using a variety of postures (Table 1). The third rehabilitation group (n=8) and the sham surgery group (n=8) received the combination of both the housing in the environmental enrichment cages (18 hours per day during week, 24 hours on weekend) and the task-specific reaching therapy paradigms (6 hours per day). Rehabilitation continued for 4 weeks, with periodic behavioral testing throughout this period.

Histology

After the final behavioral assessment, 9 weeks poststroke, animals were anesthetized with 4% isoflurane in O_2 and transcardially perfused with 0.9% heparinized saline and 4% paraformaldehyde. The infarcted hemisphere was used for cresyl violet staining and assessment of infarct severity. Brains were cryoprotected using a 30% sucrose solution and sectioned at 40 µm using a cryostat at −21°C.

The amount of intact cortical and striatal tissue remaining in the infarcted hemisphere was measured using 14 sections that were evenly distributed throughout the lesioned area. The surface area of intact tissue on each of these sections was measured using ImageJ (National Institutes of Health) and multiplied by the total distance between sections to give an estimated volume of intact tissue remaining in the infarcted hemisphere.

Statistical Analysis

All analyses were performed using IBM SPSS v24, with a significance level set at α=0.05. Repeated measures ANOVA was used as an omnibus test for single-pellet task data, using the Greenhouse-Geisser correction when assumptions of sphericity were violated. The Ryan–Einot–Gabriel–Welsch F post hoc was used for multiple comparisons. Histological data were analyzed using 1-way ANOVA with Ryan–Einot–Gabriel–Welsch F post hoc. Assessment of the predictability of change in PR across time was conducted using linear regression with backward stepwise predictor elimination as described previously.[35] Briefly, change in PR between the initial and terminal poststroke assessments ($\Delta PR_{Observed}=PR_{Terminal}-PR_{Initial}$) was used as the dependent variable for prediction. Volume of surviving cortical, striatal, and corpus callosum tissue, ventricle volume, rehabilitation group, prestroke reaching performance, and poststroke reaching performance were initially entered into the model as possible predictors of recovery. Tabular data of all results can be found in the online-only Data Supplement. An experimenter unrelated to initial data collection and blind to group assignment performed all data analysis.

Results

Synergy of Environmental Enrichment and Reach Training

Repeated measures ANOVA revealed a significant time by group interaction ($F_{[18,156]}=5.721$; $P<0.001$) on the single-pellet reaching task (Figure 2A and 2B). There were significant differences between groups at all time points, except for prestroke ($P<0.001$). Ryan–Einot–Gabriel–Welsch F post hoc analysis revealed that at weeks 1 and 2 poststroke, all stroke groups were significantly impaired relative to sham ($P<0.05$). At week 3 poststroke, all groups were still significantly impaired relative to sham; however, the enrichment+reach training group was performing significantly better than the enrichment-only group ($P<0.05$). At both weeks 4 and 9 poststroke, the enrichment+reach training group was performing significantly better than both of the other treatment groups and was also no longer significantly different than the sham group ($P<0.05$). At week 5, a slight dip in performance on the single-pellet task meant that although the enrichment+reaching group was not significantly impaired relative to sham, they were not performing significantly better than the other 2 treatment groups. At all poststroke time points, the enrichment-only and reach training-only groups were significantly impaired on single-pellet reaching compared with shams ($P<0.05$), whereas those in the enrichment+reaching group appeared to have attained a significant level of recovery after 3 weeks of treatment.

To assess the total amount of recovery that was attained throughout the poststroke period, performance for each animal at week 9 was subtracted from its poststroke test point ($\Delta PR_{Observed}$; Figure 2C). One-way ANOVA indicated that there were significant differences in change in performance between groups ($F_{[3,26]}=3.306$; $P=0.036$). Ryan–Einot–Gabriel–Welsch F post hoc analysis clearly demonstrated that

Table 1. Outline of Reaching Therapy Procedure*

Rehabilitation Day	Trough Fill	Paw Availability	Trough Height, cm	Trough Distance, mm (From Wall)
1–3	Full	Both	4	0
4–5	Full	Both	4	0
6–7	Half	Impaired only	4	0
8–12	Half	Impaired only	13	0
13–16	Half	Impaired only	5	3.2
17–20	Half	Impaired only	5	6.4

*The paw, posture, and range of motion required to successfully retrieve the pellets was varied across time to progressively increase the challenge of the treatment.

the enrichment+reaching group had recovered significantly more than all other groups, even 1 month after the treatment paradigm had been terminated (P<0.05).

Prediction of Change in Performance on Single-Pellet Task

Backward stepwise linear regression was used to investigate the relationship between $\Delta PR_{Observed}$ and the potential predictors of volume of surviving cortical, striatal, and corpus callosum tissue, ventricle size, rehabilitation group, prestroke reaching performance, and poststroke reaching performance. These variables were selected because of previous work indicating that they may be related to poststroke recovery.[35,36] A significant regression equation ($F_{[2,19]}$=8.664; P=0.002; Table 2) with volume of surviving cortical tissue and rehabilitation group was found to predict $\Delta PR_{Observed}$.

Additionally, the proportional recovery rule, which posits that a patient will recover by ≈70% of their maximum possible on a given scale (Change in performance across time=0.7×[maximum performance possible−initial performance poststroke]), was also tested.[32] Maximum performance possible was calculated based on prestroke task performance (individually determined). This method was not able to significantly predict $\Delta PR_{Observed}$ in the single-pellet reaching task at 9 weeks poststroke (P>0.05).

Initial poststroke performance alone was not found to significantly predict $\Delta PR_{Observed}$, as the 70% proportional recovery rule would suggest. Instead, a combination of intact cortical tissue volume and rehabilitation group was found to explain 47.7% of the variance in improvement on the single-pellet task (R=0.691; R^2=0.477; P=0.002; Figure 2D). Interestingly, intact tissue volume of other structures (ie, white matter in corpus callosum) could also be used in concert with rehabilitation

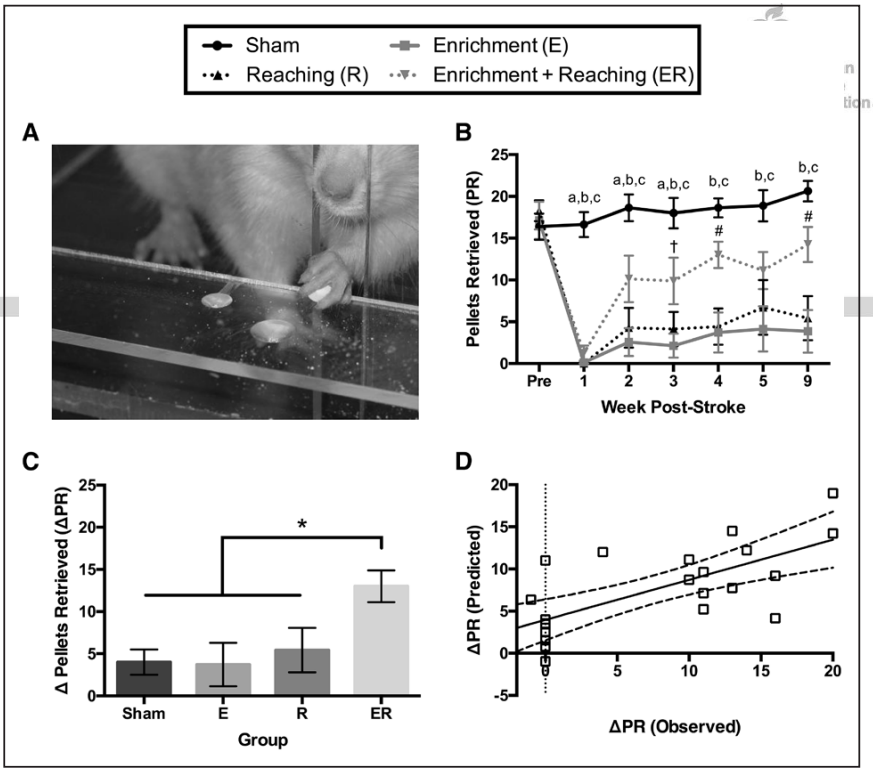

Figure 2. Performance in single-pellet reaching across time (mean±SEM). All significance markings denote P<0.05. **A**, Example of a rat successfully grasping a pellet during single-pellet reaching. **B**, Number of successful pellet retrievals (PRs) at each test point. Sham animals performed significantly better than enrichment+reaching (ER; a) rats until 4 wk poststroke (3 wk of treatment) and better than enrichment only (E; b) and reaching only (R; c) at all poststroke time points. Additionally, the ER group performed significantly better than E only (†) at 3 wk poststroke, and better than both E-only and R-only groups (#) at weeks 4 and 9 poststroke. **C**, Change in PR from weeks 1 to 9 poststroke. The ER group improved significantly more than all other groups (*) and retained this improvement for 1 month after the conclusion of treatment. **D**, The combination of volume of intact cortical tissue and rehabilitation type (Table 2) explained 47.7% of the variance in improvement on the single-pellet task (R=0.691; R^2=0.477; P=0.002).

Table 2. Significant Predicting Characteristics of Change Observed in Single-Pellet Reaching*

Predictor	Unstandardized β	95% Confidence Interval for β		Standardized β	*t* Value	*P* Value
		Lower Bound	Upper Bound			
Intercept	−10.50	−20.55	−0.446		−2.186	0.042
Cortical volume	0.052	0.010	0.094	0.449	2.609	0.017
Rehabilitation group	3.672	0.525	6.819	0.420	2.442	0.025

*Results are for backward stepwise elimination linear regression procedure (entry criterion, $P \leq 0.05$; removal criterion, $P \geq 0.10$).

intensity to produce similar models of recovery (Figure IIA and IIB in the online-only Data Supplement); however, intact cortical tissue volume provided the most highly predictive model based on adjusted R^2. This is likely because of the strong correlation between intact tissue remaining across each measured region (Figure IIC in the online-only Data Supplement; Table II in the online-only Data Supplement). We decided to compare the accuracy of our single-pellet (Table 2; intact cortical tissue and rehabilitation intensity) and staircase (initial poststroke performance, cortical infarct volume, and

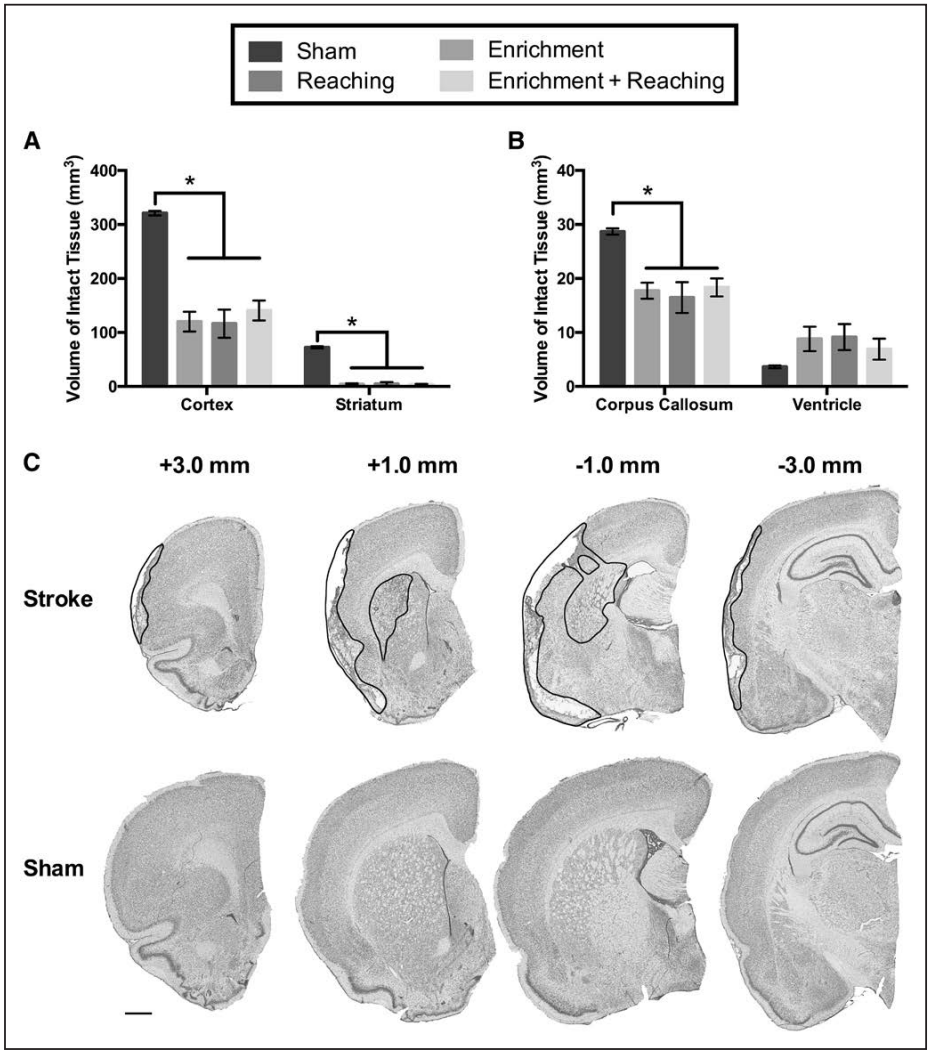

Figure 3. Evaluation of ET-1 (endothelin-1) induced tissue damage (mean±SEM). **A**, Sham surgery rats had significantly more intact tissue in the cortex, striatum, and (**B**) corpus callosum of the ipsilesional hemisphere than any of the other groups (that received ET-1). There were no significant differences in remaining tissue between the enrichment+rehabilitation, enrichment-only, or rehabilitation-only groups. Furthermore, there were no significant differences in ventricle size observed between groups. **C**, Representative images showing the cresyl violet staining and infarcted regions (delineated in black) in the rat with the closest injury to the mean (133.2 mm^3). A series of landmark-matched sham sections is shown below. Note the general atrophy of the stroke hemisphere compared with sham that was observed in all animals. Coordinates of injury, relative to bregma, are shown (scale bar in lower left corner=1 mm). *P<0.05.

rehabilitation intensity; N=123; Methods in the online-only Data Supplement)[35] models for predicting recovery. The reason for this analysis was to see whether the common characteristics of these models (infarct volume and rehabilitation intensity) were of general importance to recovery regardless of the specific task used to measure function. The predicted and observed ΔPR of both datasets were converted to z distributions to allow direct comparison (given that both tasks are measured on different scales). Extra sum-of-squares *F* test indicated that the regression equations of each data set were not significantly different ($F_{[2,141]}$=0.047; *P*=0.954) and that a single equation best described the relationship between predicted and observed PR in both datasets (Figure IID in the online-only Data Supplement).

Histology

Significant between-group differences were observed for the amount of intact tissue remaining in the cortex ($F_{[3,26]}$=60.461; *P*<0.001), striatum ($F_{[3,26]}$=209.552; *P*<0.001), and corpus callosum ($F_{[3,26]}$=10.252; *P*<0.001) using 1-way ANOVA. Post hoc tests indicated that in the cortex, striatum, and corpus callosum, the sham group had significantly more intact tissue than any of the other groups (Figure 3A and 3B; *P*<0.05). There were no significant differences in ventricle size between any group or the amount of intact tissue between the stroke groups that received the varying therapeutic paradigms. The mean area of injury for all stroke groups is shown in Figure 3C.

Discussion

The primary outcome of this study assessed the efficacy of both the individual components and combination of task-specific reach training and environmental enrichment housing to ameliorate poststroke motor impairments. Our goal was to identify potential synergistic interactions of these components of rehabilitation. We demonstrated that the combination of reach training and enrichment resulted in significant improvements in single-pellet reaching at 9 weeks poststroke, whereas animals receiving reaching alone or enrichment alone did not improve their performance relative to shams. Although stroke treatments, such as environmental enrichment alone, have been shown to provide benefits on a wide range of measures of general motor function (such as rotarod and adhesive strip removal),[46,47] these positive effects do not typically extend to skilled reaching tasks, such as the single-pellet task described herein.[48–50] Because all groups in this study had comparable amounts of brain injury, this suggests that the synergy between environmental enrichment and reach training could be explained by a host of factors, including increased neural activity,[8] altered dendritic morphology,[9] resting-state functional connectivity,[10] suppression of plasticity-inhibiting factors,[11] cortical reorganization,[14] and generation of new cell types.[51]

The combined reaching+enrichment rehabilitation paradigm that we used in the present study has been previously shown to induce greater activation of layer II and III neurons in the perilesional cortex than either reaching alone or enrichment alone.[41] However, this previous study did not demonstrate that the increased neural activity induced by this combination therapy translated to improved functional outcomes. The complementary evidence of Clarke et al,[41] and the present study support emerging views that encouraging reorganization of the peri-infarct area[52] and using multifactorial combination therapies[27,30] may be critical for maximizing poststroke recovery of function. This concept is underscored by recent evidence that further combination of reaching+enrichment with application of neuroplasticity-promoting factors accelerates the rate of recovery beyond what is possible with only reaching+enrichment.[6,25,30]

The secondary objective of the study was to assess the generalizability of a recent predictive model of stroke recovery across rodent forelimb grasping tasks. Previously, we demonstrated that rehabilitation intensity, cortical infarct volume, and initial poststroke impairment could be used to predict the final level of forelimb recovery in the Montoya staircase task.[35] The present data validated and extended this finding to the single-pellet reaching task. Indeed, we demonstrated that volume of intact tissue and rehabilitation intensity provided the same level of statistical predictability between experiments and outcome measures. One caveat is that initial level of poststroke impairment was not found to be predictive of change in performance in the single-pellet task, whereas this has previously been shown to be an important factor in prediction of both rodent[36] and human recovery.[32,33] We think that this apparent discrepancy is explained by the nature of the deficits observed in the single-pellet task. After stroke, we observed a floor effect in single-pellet reaching performance, with 86% of rats failing to retrieve any pellets at week 1 poststroke. This creates a problem when attempting to predict change in performance based on this variable because animals with a range of lesion sizes are scored as equally impaired. This highlights the importance of utilizing behavioral measures without a poststroke floor, or ceiling, effect in recovery because these measures may skew predictions of stroke outcome based on initial functional impairment.

Furthermore, the single type of middle cerebral artery occlusion stroke induced in this study may also provide a source of bias to our predictive model. Because this model produces injury that substantially targets the cortex, while also causing less-consistent injuries to the white matter and striatum, this may be an important factor in why cortical infarct volume was the best predictor of recovery in the present study. We expect that other lesion induction models specifically targeting motor-related white matter tracts or other cortical structures would identify these as the best predictors of recovery in future experiments.[34] Indeed, an important message of the present study is that individual lesion location and size can be combined with rehabilitation parameters to predict recovery. By conducting further experiments, and building a database of a variety of lesion and recovery profiles, it may be possible to improve the robustness of recovery prediction. This may be an avenue to move the field toward individualization of rehabilitation prescription based on structural biomarkers of impairment and recovery.[23,35]

Overall, this study provides definitive evidence that the combination of environmental enrichment and task-specific reaching therapy has a synergistic effect that significantly augments

recovery of forelimb motor function poststroke. Although the importance of task specificity in optimizing rehabilitation has been acknowledged for more than a decade,[13,53] general acceptance that environmental enrichment provides robust sensorimotor benefits that may be applicable to clinical rehabilitation has only recently begun to emerge.[25,47] Promising, new clinical studies in stroke rehabilitation are using environmental enrichment principles, resulting in increased patient activity[54] and decreased time spent inactive and alone.[55] Further clinical application of environmental enrichment in conjunction with task-specific training to increase rehabilitation intensity may result in a cost-effective method of improving function and quality of life for stroke survivors.

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Disclosures

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Synergistic Effects of Enriched Environment and Task-Specific Reach Training on Poststroke Recovery of Motor Function

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Supplementary materials for:

Synergistic effects of enriched environment and task-specific reach training on post-stroke recovery of motor function

Matthew Strider Jeffers, MSc,[1] Dale Corbett, PhD,[1,2,*]

Supplementary Methods:

Accuracy of the predictive recovery model wherein animals in the present study received stroke and rehabilitation (N=22) with the single-pellet task as an outcome measure was compared to predictive accuracy of a previously published model of recovery for the staircase task that also used a combined Rehabilitation + Reaching rehabilitation paradigm (N=123).[1] Pellet retrieval on the single-pellet and staircase tasks, cortical infarct volumes, and rehabilitation intensities, were converted to z-scores for both studies to allow direct comparison (to account for different measurement scales on tasks across studies). The regression equations for each model were compared using an Extra sum-of-squares F test to assess if the accuracy of these models differed (Figure II).

Briefly, the Montoya staircase task is a pellet retrieval task in which rats perform reaching, grasping, and pellet retrieval movements that are similar to those in the single-pellet task. In the single-pellet task, rats must position their body and support their weight on their hind limbs while they reach through a narrow slot positioned in front of them to retrieve pellets one at a time. This differs from the staircase, in which rats position their body on a horizontal shelf that supports their weight, and rats must reach ventrally to reach pellets on a descending staircase below themselves, with all possible pellets (21) present from the onset of the task. Each of the 7 steps of the staircase contains 3 pellets, and are sequentially lower than one another, making some pellets more difficult to reach than others, whereas in single-pellet, all pellets are presented in the same position and are equally difficult to retrieve. Finally, in the single-pellet task, rats are only able to make one attempt to reach each of the 25 pellets delivered to them; however, in the staircase rats can make as many attempts as they wish to reach the 21 pellets, with the potential to knock pellets to lower steps and make them harder to retrieve at later attempts. See Supplementary Reference 1 for further details on the relevant animal cohort and staircase procedures.[1]

Supplementary References:

1. Jeffers MS, Karthikeyan S, Gomez-Smith M, Gasinzigwa S, Achenbach J, Feiten A, et al. Does Stroke Rehabilitation Really Matter? Part B: An Algorithm for Prescribing an Effective Intensity of Rehabilitation. *Neurorehabil. Neural Repair*. 2018;32:73–83.

Supplementary Figures/Tables:

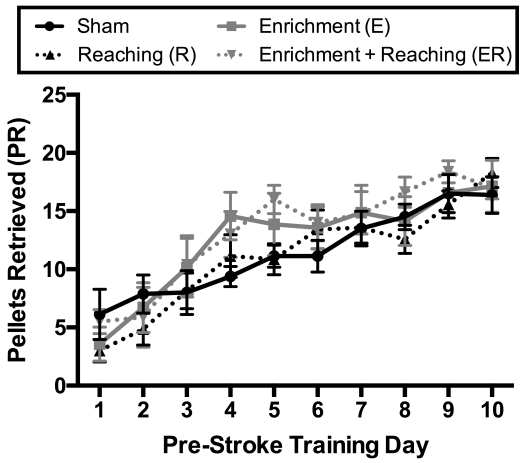

Figure I. Pre-stroke training data for number of pellets retrieved (PR) each day in the single-pellet reaching task for all groups. Pre-stroke training took place over a period of 10 days. There were no significant differences in the training performance of each group. Data are represented as mean ± SEM.

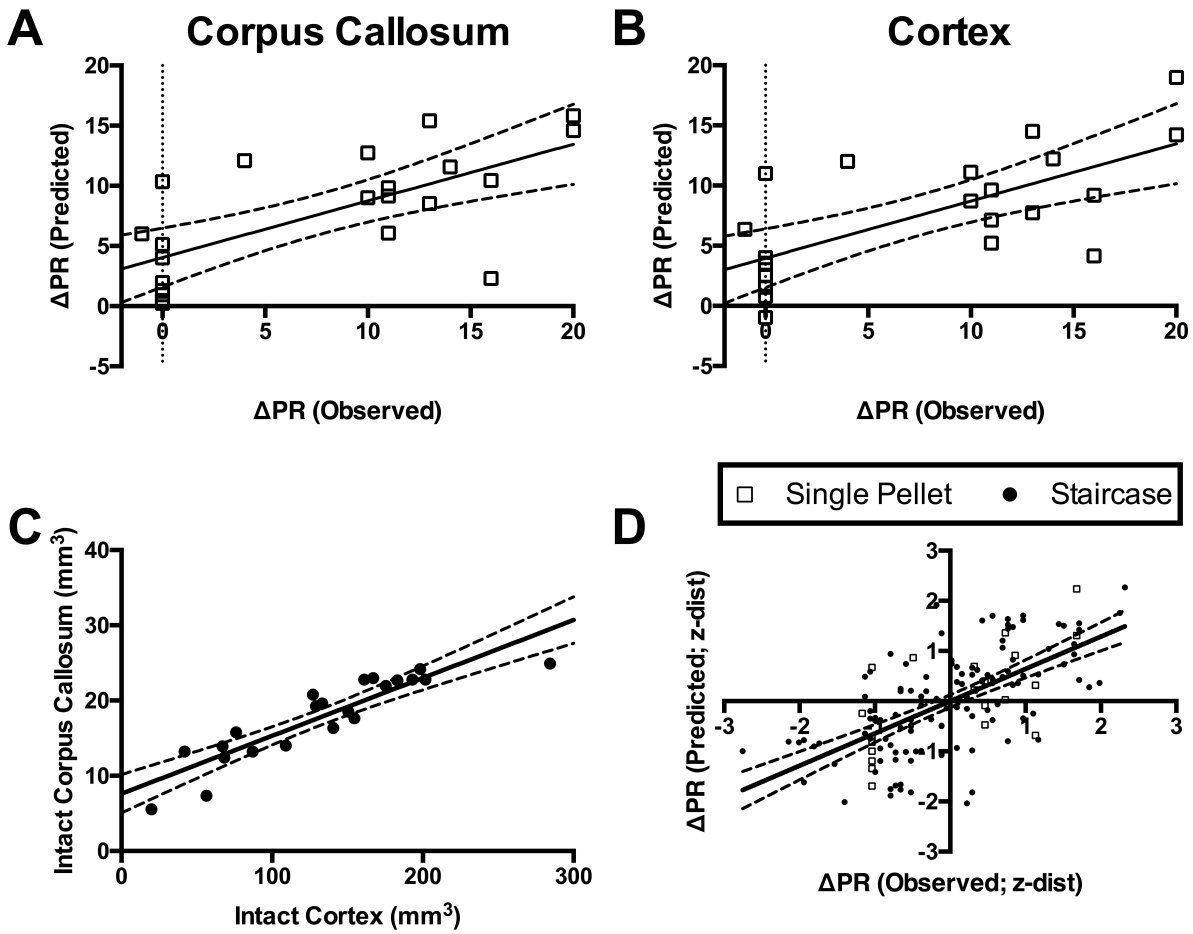

Figure II. (A) A combined model of white matter damage in the corpus callosum, and rehabilitation intensity was also able to predict change in pellet retrieval at 9 weeks post-stroke (R=0.686, R^2=0.471, p=0.002) **(B)** This was a very similar result to that shown in Figure 2D (R=0.691, R^2=0.477, p=0.002) for a combined model of cortical damage and rehabilitation intensity. **(C)** This may be explained due to a strong correlation between cortical and corpus callosum damage in this experiment (Supplementary Table II; R^2=0.810, p<0.001), meaning that either measure could be used as a predictor of recovery. **(D)** The predictive capabilities of the combined model of cortical damage and rehabilitation intensity on the single-pellet task were not statistically different from a similar model for the staircase-reaching task (F=0.047, p=0.954). A single regression equation [y=0.6435X+0.00001987 (R^2=0.414)] was found to best describe both datasets.

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Table I. Checklist of Methodological and Reporting Aspects for Articles Submitted to *Stroke* Involving Preclinical Experimentation

Methodological and Reporting Aspects	Description of Procedures
Experimental groups and study timeline	☑ The experimental group(s) have been clearly defined in the article, including number of animals in each experimental arm of the study. ☑ An account of the control group is provided, and number of animals in the control group has been reported. If no controls were used, the rationale has been stated. ☑ An overall study timeline is provided.
Inclusion and exclusion criteria	☑ A priori inclusion and exclusion criteria for tested animals were defined and have been reported in the article.
Randomization	☑ Animals were randomly assigned to the experimental groups. If the work being submitted does not contain multiple experimental groups, or if random assignment was not used, adequate explanations have been provided. ☑ Type and methods of randomization have been described. ☑ Methods used for allocation concealment have been reported.
Blinding	☑ Blinding procedures have been described with regard to masking of group/treatment assignment from the experimenter. The rationale for nonblinding of the experimenter has been provided, if such was not feasible. ☑ Blinding procedures have been described with regard to masking of group assignment during outcome assessment.
Sample size and power calculations	☑ Formal sample size and power calculations were conducted based on a priori determined outcome(s) and treatment effect, and the data have been reported. A formal size assessment was not conducted and a rationale has been provided.
Data reporting and statistical methods	☑ Number of animals in each group: randomized, tested, lost to follow-up, or died have been reported. If the experimentation involves repeated measurements, the number of animals assessed at each time point is provided, for all experimental groups. ☑ Baseline data on assessed outcome(s) for all experimental groups have been reported. ☑ Details on important adverse events and death of animals during the course of experimentation have been provided, for all experimental arms. ☑ Statistical methods used have been reported. ☑ Numeric data on outcomes have been provided in text, or in a tabular format with the main article or as supplementary tables, in addition to the figures.
Experimental details, ethics, and funding statements	☑ Details on experimentation including stroke model, formulation and dosage of therapeutic agent, site and route of administration, use of anesthesia and analgesia, temperature control during experimentation, and postprocedural monitoring have been described. ☑ Different sex animals have been used. If not, the reason/justification is provided. ☑ Statements on approval by ethics boards and ethical conduct of studies have been provided. ☑ Statements on funding and conflicts of interests have been provided.

Table II. Two-tailed Pearson correlation (R) matrix of intact tissue (mm^3) across regions.

		Total Volume	Cortex	Striatum	Corpus Callosum	Ventricle
Total Volume	R	1	0.997	0.965	0.910	-0.694
	p		<0.001	<0.001	<0.001	<0.001
Cortex	R	0.997	1	0.646	0.900	-0.704
	p	<0.001		0.001	<0.001	<0.001
Striatum	R	0.965	0.646	1	0.562	-0.354
	p	<0.001	0.001		0.007	0.106
Corpus Callosum	R	0.910	0.900	0.562	1	-0.638
	p	<0.001	<0.001	0.007		0.001
Ventricle	R	-0.694	-0.704	-0.354	-0.638	1
	p	<0.001	<0.001	0.106	0.001	

The amount of intact tissue was correlated between most regions. Total, cortical, striatal, or corpus callosum volume could all be used to generate a significant prediction of change in pellet retrieval in single-pellet; however, cortical volume appeared to provide the most robust model, which also generalized to the staircase task.

Table III. Tabular data for Figure 2B.

Group (N=30)	Pre-stroke	Week 1	Week 2	Week 3	Week 4	Week 5	Week 9
Sham (n=8)	16.4 ± 4.5	16.6 ± 4.2	18.6 ± 4.5	18.0 ± 5.2	18.6 ± 3.2	18.9 ± 5.2	20.6 ± 3.4
Enrichment (n=7)	17.1 ± 5.9	0.14 ± 0.4	2.6 ± 4.4	2.1 ± 3.8	3.7 ± 6.3	4.1 ± 7.1	3.9 ± 6.7
Reaching (n=7)	18.3 ± 3.3	0.00 ± 0.0	4.3 ± 6.3	4.1 ± 5.4	4.4 ± 5.7	6.7 ± 8.7	5.4 ± 6.9
Enrichment + Reaching (n=8)	17.0 ± 2.7	1.25 ± 2.5	10.1 ± 7.8	9.9 ± 7.9	13.0 ± 4.5	11.1 ± 6.3	14.3 ± 5.9

Data represents mean pellets retrieved ± standard deviation in the single pellet task at each time point.

Table IV. Tabular data for Figure 2C.

Group (N=30)	ΔPR
Sham (n=8)	4.0 ± 4.2
Enrichment (n=7)	3.7 ± 6.8
Reaching (n=7)	5.4 ± 7.0
Enrichment + Reaching (n=8)	13.0 ± 5.3

Data represents mean change in pellet retrieval (ΔPR) ± standard deviation between weeks 1 and 9 in the single pellet task.

Table V. Tabular data for Figure 3A and B.

Group (N=30)	Cortical Tissue (mm^3)	Striatal Tissue (mm^3)	Corpus Callosum (mm^3)	Ventricle Volume (mm^3)
Sham (n=8)	321.7 ± 11.9	72.5 ± 5.7	28.7 ± 1.6	3.6 ± 0.7
Enrichment (n=7)	120.1 ± 48.9	4.2 ± 4.6	17.7 ± 3.9	8.8 ± 6.0
Reaching (n=7)	116.4 ± 69.3	4.8 ± 8.7	16.5 ± 7.5	9.2 ± 6.3
Enrichment + Reaching (n=8)	140.7 ± 49.2	3.7 ± 3.0	18.3 ± 4.4	6.9 ± 5.1

Data represents mean intact brain tissue remaining ± standard deviation measured using cresyl violet stain after tissue collection.

Awards and Honors:

1976-78, Quebec Doctoral Scholarship, Concordia University
1978-80, NSERC Post-Doctoral Fellowship, McGill University
1982-84 Alfred P. Sloan Research Fellow, Harvard University
2003-2010 Tier I Canada Research Chair in Stroke and Neuroplasticity ($1,400,000.)
2005- Paul Morley Mentorship Award, Canadian Stroke Network
2010-2017 Tier I Canada Research Chair in Stroke and Neuroplasticity ($1,400,000.)- **declined**
2011 Fellow Canadian Academy of Health Sciences

C. Contributions to Science

Throughout my career I have been dedicated to translational research. My work with prolonged hypothermia culminated in the worldwide use of "therapeutic hypothermia" in the treatment of cardiac arrest and perinatal hypoxia-ischemia. To date this represents one of the most successful translations of preclinical stroke research to the clinic.

Subsequently, I switched focus to stroke recovery because it offers the most hope for the greatest number of people. Here my laboratory made several important findings regarding the optimal timing and intensity of post-stroke rehabilitation. Specifically, we identified a "critical period" when the brain is most receptive to rehabilitation (Biernaskie et al., J Neuroscience 2001, 2004). This work has attracted considerable clinical interest and provided evidence for earlier stroke rehabilitation. These are very highly cited papers (**1221 citations**), as is a review paper dealing with plasticity and stroke recovery (Murphy & Corbett, Nat Rev Neurosci, 2009; **1013 citations**). We also determined that a "threshold" amount of reaching repetition during rehabilitation must be attained to achieve recovery of forelimb function and to increase levels of Brain Derived Neurotrophic Factor (BDNF) (MacLellan et al, Neurorehab Neural Repair, 2011). In contrast, patients receive ~ 32 repetitions during therapy sessions which is well below the optimal levels identified in our preclinical work. These data provide compelling evidence for employing earlier and more intensive rehabilitation for patients. More recently, we have been attempting to identify biomarkers that would be predictive of stroke recovery (Jeffers et al, Neurorehab Neural Repair, 2018 a,b). This work has led us to develop an algorithm for prescribing individualized doses of rehabilitation to achieve significant gains in motor recovery even in animals with moderate to severe stroke injury. Similar individualized approaches to stroke rehabilitation in humans may be possible based on our model.

D. Additional Information: Research Support and/or Scholastic Performance

1. Heart & Stroke Canada: 2016-2019 Removing the brakes on post-stroke recovery (Dale Corbett PI, Numa Dancause – Univ of Montréal, co-investigator)

2. CIHR Canadian Consortium in Neurodegeneration and Aging: 2014-2019 Preclinical Development of a Novel, Multi-Target Intervention to Treat Vascular Cognitive Impairment (D. Corbett, B. Stefanovic (Sunnybrook) and J. McLaurin (Sunnybrook, PIs)

3. Canadian Partnership for Stroke Recovery: 2016-2018 Engaging skeletal muscle and vascular plasticity to promote hindlimb functional recovery in a rat model of ischemic stroke Dale Corbett (PI), Baptiste Lacoste, co-PI).

4. Canadian Partnership for Stroke Recovery: 2017- 2019: Using focused ultrasound to promote functional recovery by reopening the post-stroke window of neuroplasticity (Dale Corbett PI, Kullervo Hynynen, co-PI, Sunnybrook Research Institute, Isabelle Aubert, co-investigator, Sunnybrook Research Institute.

Pending applications:

1. Networks of Centres of Excellence: 2019-2023 – D. Corbett, PI

2. Canadian Consortium of Neurodegeneration and Aging – Remote Ischemic Conditioning and Vascular Cognitive Impairment: 2018-2020 – D. Corbett & B. Stefanovic, Co-PIs

Recently completed projects:

1. CIHR: 2013-2018 - Promoting cognitive recovery using endogenous neural stem cell activation and rehabilitation following stroke (C. Morshead, PI Univ of Toronto; M. Shoichet, Univ of Toronto, co-investigator and D. Corbett, co-investigator).

E. Peer Reviewed Publications 2015-2018 (career: 147 total, 4 submitted, h-index=54, citations=11894)

1. McDonald MW, Hayward KS, Rosbergen ICM, Matthew S Jeffers MS, Corbett D Is environmental enrichment ready for clinical application in human post-stroke rehabilitation? Frontiers in Behav Neurosci, 2018, Jul 11;12:135. doi: 10.3389/fnbeh.2018.00135. eCollection.

2. Ould-Brahim F, Nath Sarma S, Syal C, Jiaqi Lu K, Seegorbin M, Carter A, Jeffers MS, Dore C, Stanford W, Corbett D, Wang J Metformin Preconditioning of Human iPSC-derived Neural Stem Cells Promotes Their Engraftment and Improves Post-Stroke Regeneration and Recovery, Stem Cells & Development, 2018, Jul 18. doi: 10.1089/scd.2018.0055. [Epub ahead of print].

3. Mallet KH, Shamloul RM, Pugliese M, Power E, Corbett D, Hatcher S, Shamy M, Stotts G, Zakutney L, Dukelow S, Dowlatshahi Dar, RecoverNow: A patient perspective on the delivery of mobile tablet-based stroke rehabilitation in the acute care setting, Int J Stroke, 2018, in press.

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