THE BENEFIT OF ENRICHED ENVIRONMENT AFTER ACQUIRED BRAIN INJURY

RESULTS FROM PRECLINICAL STUDIES

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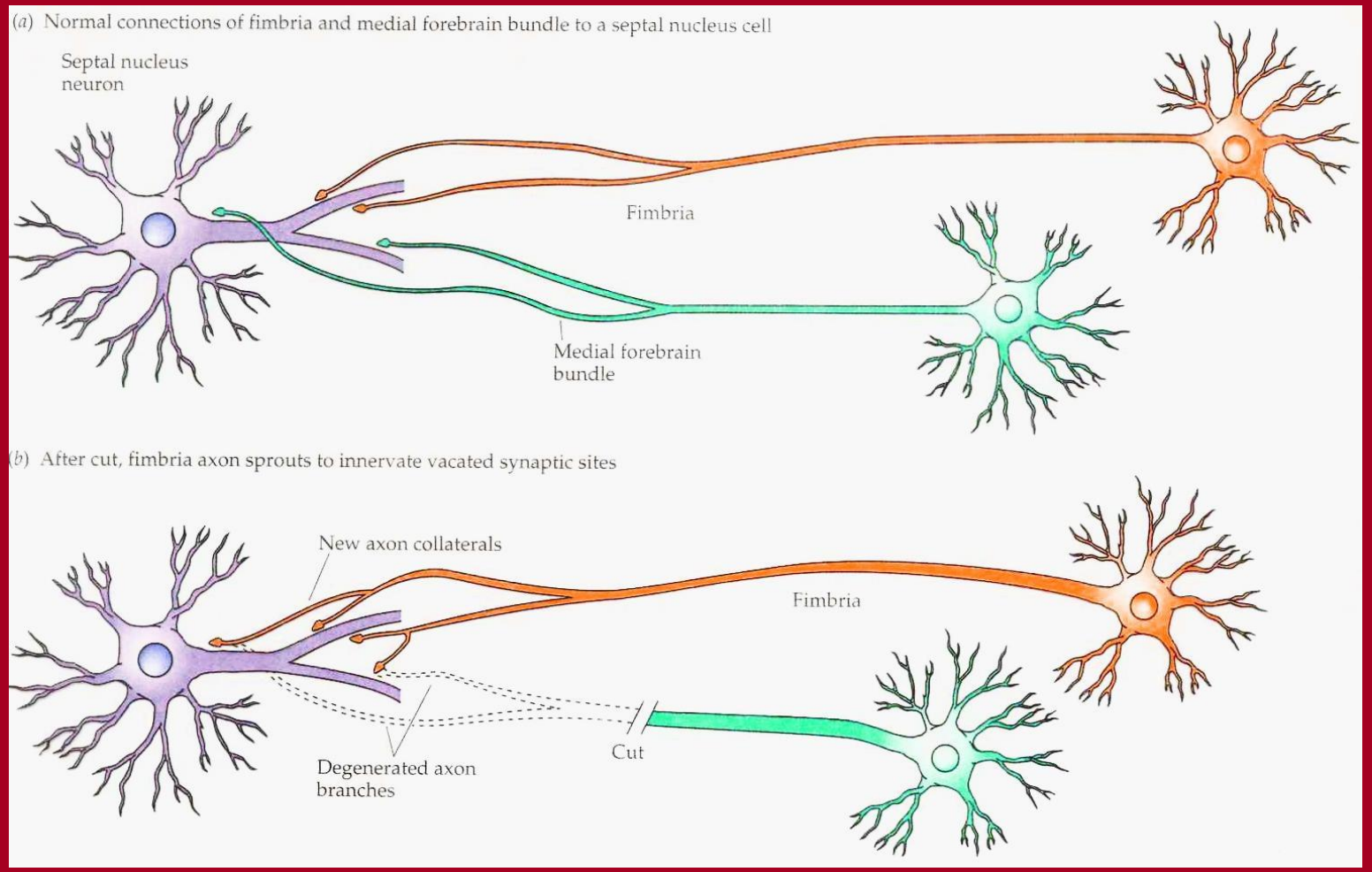
RECOVERY OF FUNCTION AFTER STROKE
=> YOU HAVE TO EXPERIENCE IT
AND DO THE HARD WORK YOURSELF

Benefits of EE after ABI-preclinical studies by Hana Mala Rytter

NEURAL PLASTICITY
RAPID REORGANISATION OF SYNAPTIC COMMUNICATION PATTERNS ...



PLASTICITY AND NEUROREHABILITATION – "THE DARK SIDE"

ABI-induced plasticity takes places regardless whether we ask for it or not

- Neurogenesis is linked to epilepsy after ABI
- Learned non-use
- Formation of bad habits
- Compensatory behaviours
- Tinitus

It is not a reason-controlled process

PLASTICITY POINTS AT WHY REHABILITATIVE TRAINING AFTER ABI IS A MUST – NOT AN OPTION

IF NEUROREHABILITATION IS TO BE EFFICIENT, IT NEED TO HARNESS BRAIN PLASTICITY TOWARDS ADAPTIVE REORGANISATION

WHAT IS THE OPTIMAL THERAPEUTIC SETTING FOR THAT?

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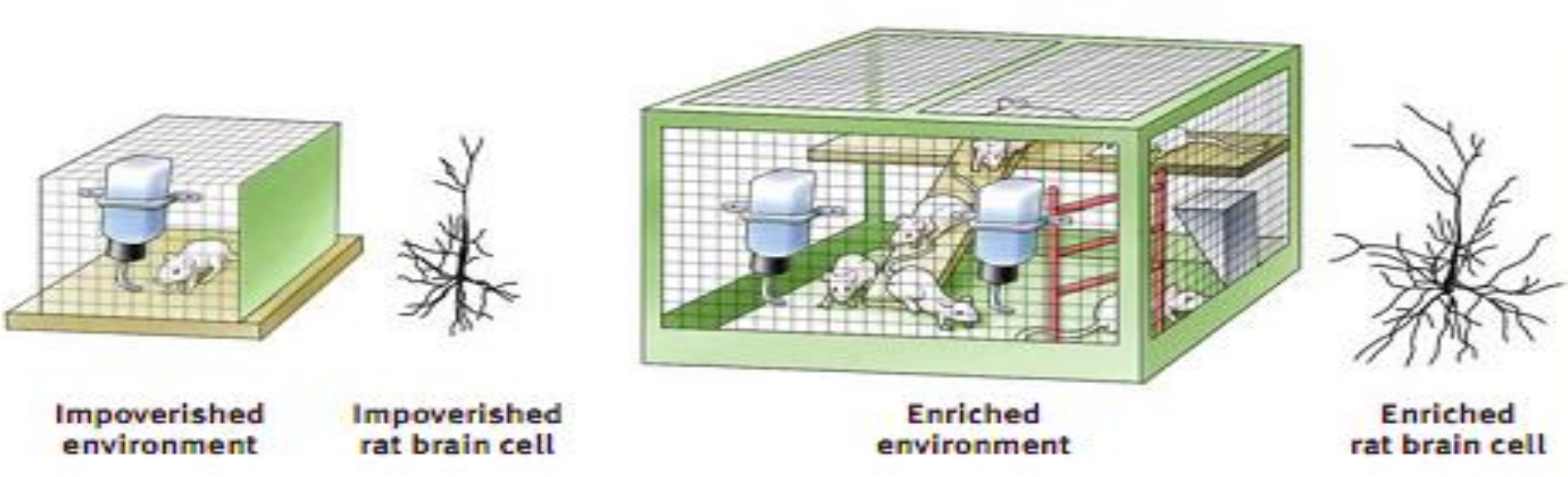
ENRICHED ENVIRONMENTS



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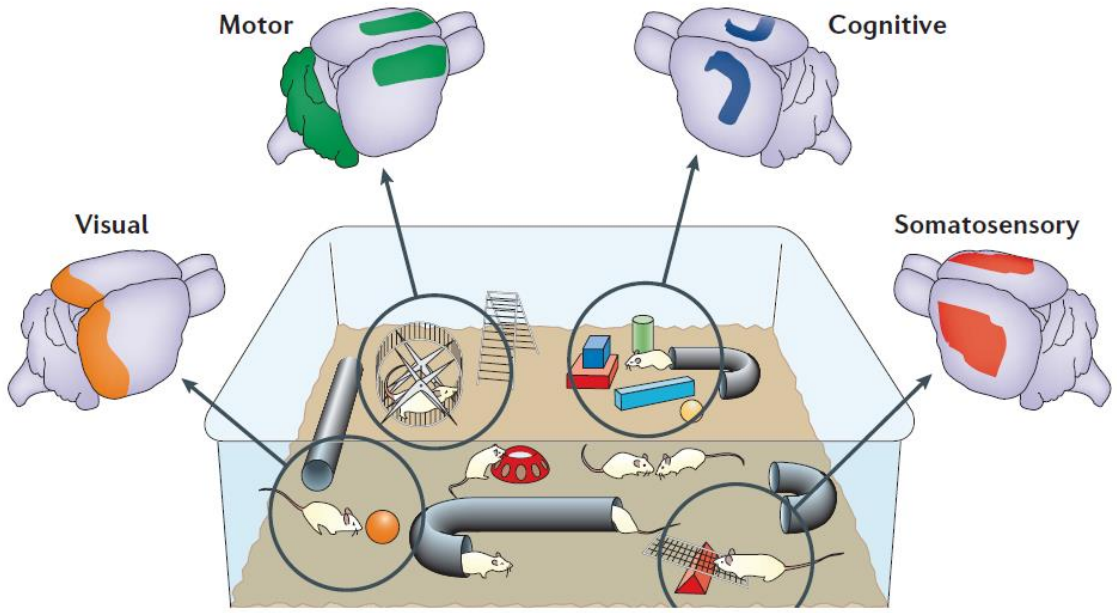
EE IN NEUROLOGIC DISEASE

Stroke, TBI, PD, HD, AD, Epilepsy, chronic hypoxic injury, Fragile X Syndrome, Down Syndrome

Effects on neurophysiological and functional outcomes



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E.G. EE EFFECTS IN STROKE

MOLECULAR

- Increased expression of neurotrophic factors (BDNF, NGF-A, NGF-B)
- Rescued deficit in glucocorticoid receptor II expression
- Rescued deficit in mineralocorticoid receptor expression

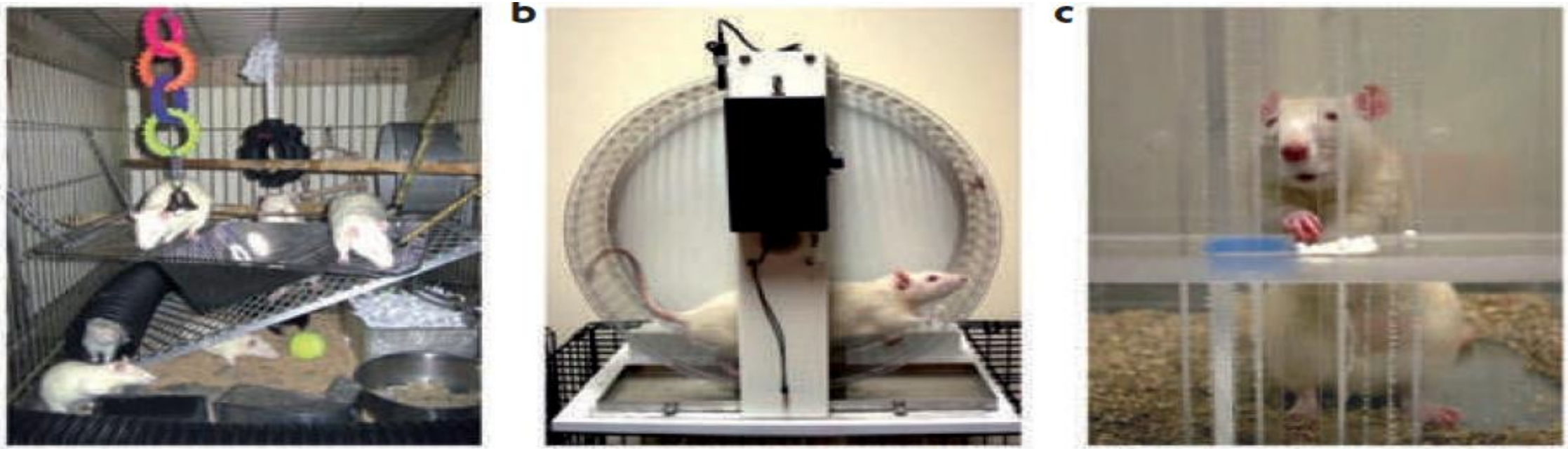
CELLULAR

- Decreased infarct volume
- Increased spine density
- Increased number of neural stem cells
- Increased number of astrocyte and oligodendrocyte progenitors
- Normalized astrocyte-to-neuron ratios

BEHAVIOURAL

- Improved motor recovery
- Improved cognitive recovery

TYPES OF EE



TYPICAL EE:

1. **INCREASED EXPLORATION AND PHYSICAL ACTIVITY;**
2. **INCREASED SENSORY STIMULATION;**
3. **INCREASED LEVEL OF SOCIAL STIMULATION**

ATYPICAL EE: PURELY SOCIAL STIMULATION

ENRICHED REHABILITATION: EE +TASK-SPECIFIK TRAINING

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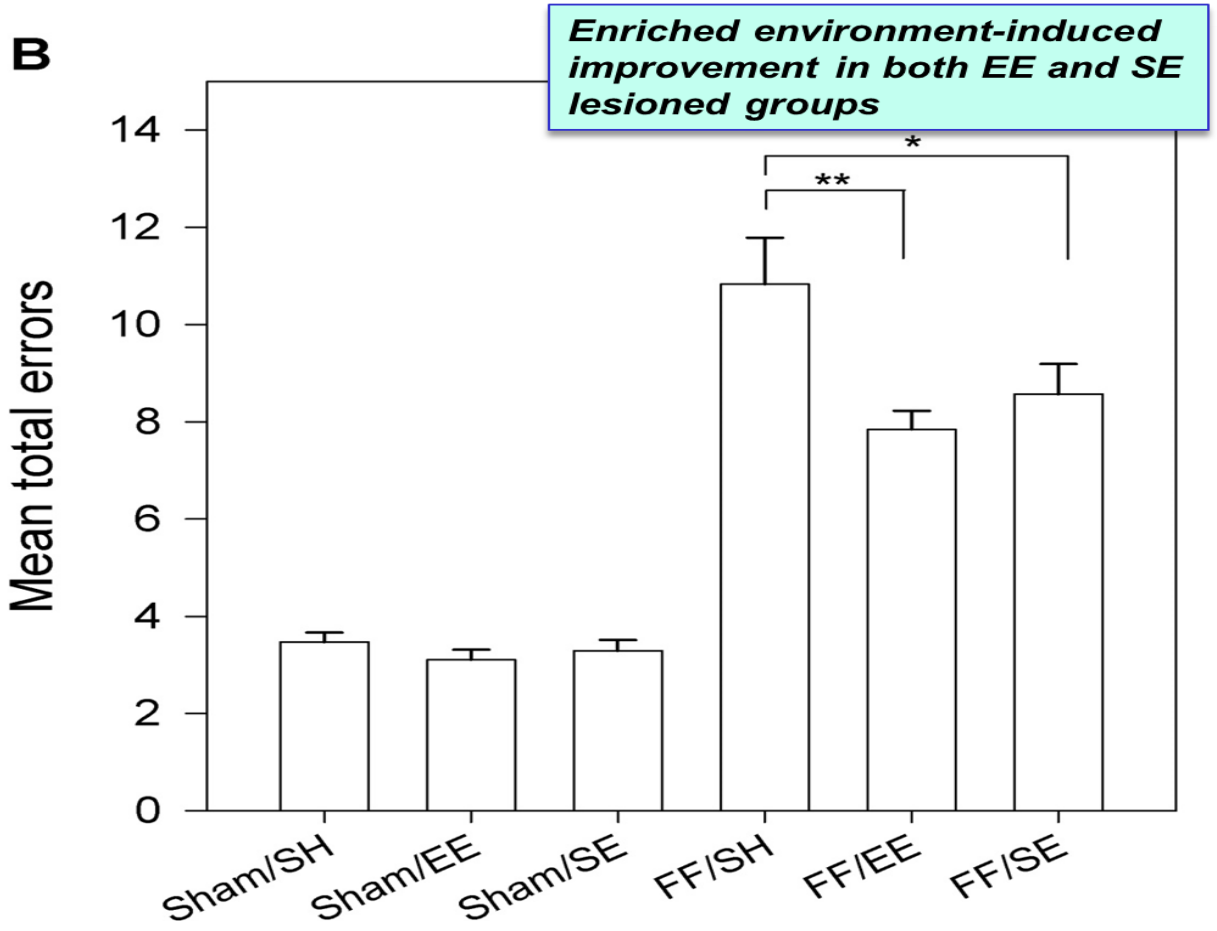
EFFECTS OF TYPICAL (EE) AND PURELY SOCIAL (SE) ENRICHMENT ON COGNITIVE TASK



- Both typical and purely social EE improved post-lesion cognitive performance (WM task)
- Different neural substrates – SE less dependent on DA signalling compared to typical EE

Gram, Gade, … Malá 2015

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IS THERE A COMBINED EFFECT BETWEEN EE AND OTHER THERAPIES?

Restorative Neurology and Neuroscience 35 (2017) 25–64
DOI 10.3233/RNN-160682
IOS Press

The effect of combined therapies on recovery after acquired brain injury: Systematic review of preclinical studies combining enriched environment, exercise, or task-specific training with other therapies

Hana Malá* and Camilla Pihl Rasmussen
The Unit for Cognitive Neuroscience, Department of Psychology, University of Copenhagen, Copenhagen, Denmark

OTHER THERAPIES: another behavioral activation paradigm, pharmacological intervention, stem cells, neural graft, or growth factor?

RESULTS

Combination	Motor effects	Cognitive/ emotional effects	Cerebral changes
EX + CIMT + reach training	-	×	-
ETT + Atipamezole	1	×	-
EX + Quercetin	2	×	10
EE + reach training	-	×	11
Exercise enriched TT + CIMT	3	×	-
Reach training + NEP 1-40	3	×	×
EX + d-amphetamine	×	×	-
EX + Citicoline	×	-	-
ER + EPO/EGF	-	×	-
EE + Buspirone	-	-	-
EE + 8-OH-DPAT	-	-	12
EE + 8-OH-DPAT	-	-	-
TT including botulinum toxin-induced constraint + Minocycline	-	-	-
EE + MEOS	/	×	×
TT + Fasidul	4	×	/
EE + MEOS	/	×	/
EE + MEOS	/	/	/
EX + Bryostatin-1	5	×	13
EE + Progesterone	-	9	-
EE + TT + d-amphetamine	1	×	14
EE + Selegiline	×	-	-
EEE + Atipamezole	×	-	×
ETT + d-amphetamine	6	×	14
Rotarod + S-nitrosoglutathione	-	×	-
EE + Resveratrol	-	×	15
Rotarod + Progesterone	7	×	-
EE + NGF	-	×	-
EE + Piracetam	×	×	-
EE + Inosine	8	×	-

No. in red: improvement
- : no effect
X: did not measure
/: only monotherapy

CONCLUSIONS

- 29 studies out of 2.168 unique studies
- Mostly focus on cerebral and motor outcomes, lack of focus on cognitive outcomes !
- Very few studies found combined effects of either EE/exercise + drug or growth factor treatment
- The EE-induced improvements were rarely potentiated by drug treatment
- However, EE may be a necessary prerequisite for a successful transplantation of stems cells/grafts.

WHAT TO TAKE FROM THIS

- **EE : appears an attractive option – preferably combined with exercise and task specific training**
- **EE has gainfull effects from molecules to behaviour regardless of neurological etiology**
- **EE seems to prime neuroplasticity and makes to brain more receptible to other treatments**
- **No adverse effects are reported**

- **EE is meaningful candidate for translation to bedside – especially given the low activity levels in post-ABI patients** (e.g. Åstrand et al. 2016, Rosbergen et al. 2017, Hokstad et al. 2015, Prakash et al. 2016)**.**

- **Can this be done?**

KEY CHARACTERISTICS OF ENRICHED ENVIRONMENTS

EE starts early post-injury

EE is based on patient-driven activity and individual engagement

EE fosters joy

EE provides multimodal stimulation

EE focus on change, novelty and challenges

EE underscores social interaction

EE stimulates to physical exercise

EE provides general stimulation as well as task specific training

EE provides a context – more than sum of the individual parts

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INTERDISCIPLINARY REHAB-ENVIRONMENTS - = ENRICHED ENVIRONMENT ???

HOUSING IN EE

PRECLINICAL EE	CLINICAL EE
Housing can be standardized	Differs from hospital to hospital
Easily changed	Difficult to change
All animals have access	Access varies (ABI severity, other precautions)
ABI severity uniformed across animals	Varied ABI severity
Only ABI animals present	Patients, staff, visitors
Standard length of stay – based on biology of recovery	Varied length of stay – based on funding, pragmatism, etc.

After McDonald et al. 2018

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INTERDISCIPLINARY REHAB-ENVIRONMENTS - = ENRICHED ENVIRONMENT ???

PATIENTS, CARE, TREATMENT

PRECLINICAL EE	CLINICAL EE
Young male rodents	Older, mixed sex patients
Activities spontaneous, initiated by the animal	Activities induced by therapist
Access only to the cage	Access to environments beyond the ward
Activity engagement possible right away, at any desired level of intensity	Engagement in and intensity of activity affected by available resources (e.g. therapists to assist), physical setting, hospital procedures
Stable daily routines	Daily routines frequently interrupted
No involvement of others	Staff that facilities engagement in EE is crucial
Stable activity level pre-ABI, typically, no previous experience with EE, animals comes from standard housing with limited stimulation,	Great variability in pre-ABI activity level, some patients come from “EE” pre-stroke already, others have much lower starting point

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WHAT IS NEEDED IN ORDER TO SUCCEED ?...

Physical surroundings

Effort of the treating personnel

Relevant neuro-knowledge across the groups of the interdisciplinary team

Devoted ledership

Training and therapeutical knowledge

Communication towards patients, relatives and others

Motivation

Technology ?

QUESTIONS AND COMMENTS

THANK YOU !

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