COMBINING AEROBIC EXERCISE With COGNITIVE TRAINING To RESTORE FLUID INTELLIGENCE In CHRONIC STROKE

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Recovery & Performance LABORATORY

MEMORIAL UNIVERSITY

Potential Conflicts of Interest

- I received support from the following private companies to provide lectures: Novartis

- I receive or have received funding from the following public and not-for profit agencies to support my research:

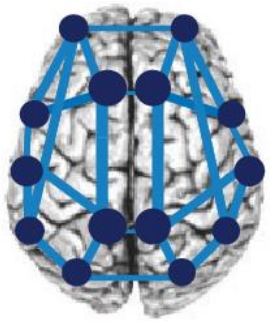
Canada Research Chairs Program, Canadian Institutes for Health Research, Canada Foundation for Innovation, MS Society of Canada, Heart and Stroke Foundation Canadian Partnership for Stroke Recovery, Physiotherapy Foundation of Canada, NL Centre for Applied Health Research, Government of NL

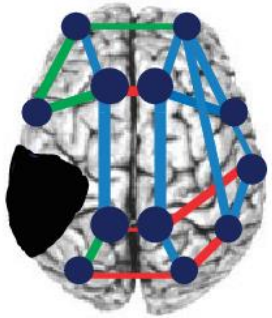
- I have not received funding from private entities to support my research

Learning Objectives

- Describe post-stroke cognitive impairment and how it interferes with rehabilitation and community integration.
- Discuss the concept of ‘priming’ and how aerobic exercise could ‘prime’ the brain to foster recovery from stroke.
- Describe the results of a randomized controlled trial to test whether aerobic exercise could enhance cognitive functioning in chronic stroke.

A Model of Stroke Recovery





<u>THREE MAJOR ELEMENTS</u>

<u>A. Spontaneous (biological) recovery</u>

Resolution of swelling
Change in diaschisis
Neuroplasticity

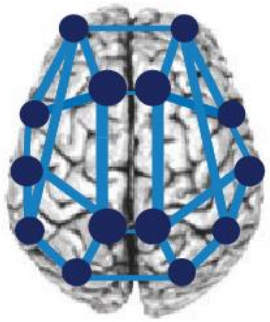
<u>B. Intrinsic learning/adaptation</u>

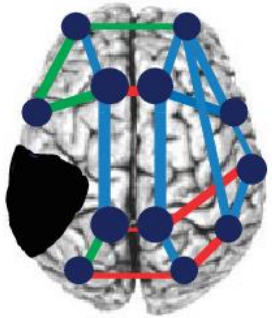
Compensation
(using different strategies)
Neuroplasticity (Learning)

<u>C. Extrinsic (re) learning</u>

Rehabilitation

A Model of Stroke Recovery





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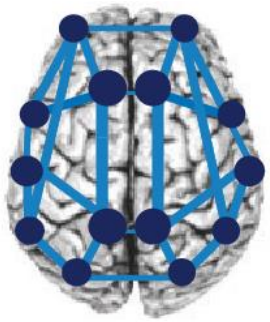
MAJOR INFLUENCING FACTORS

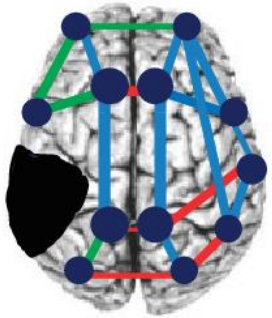
A. BRAIN ENVIRONMENT
Extent of Damage
Co-morbidities

B. CAPACITY WITHIN EXISTING NETWORKS
Age
Genetics

C. COGNITIVE CAPACITY
Attention
Mood
Intellectual capacity
Language

A Model of Stroke Recovery





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Cognitive Impairment is common after stroke and impacts the ability of stroke patients to fully participate in rehabilitation

Cognitive impairment measured using sensitive assessments has been reported to be as high as **83%** in acute stroke units and **71%** at 3 month follow-up*

The fact that cognition and motor recovery are linked is typically disregarded in rehabilitation

**Jokinen et al. Post-stroke cognitive impairment is common even after successful clinical recovery. Eur J Neurol 2015*

Predicting Length of Stay, Functional Outcome, and Aftercare in the Rehabilitation of Stroke Patients

The Dominant Role of Higher-Order Cognition

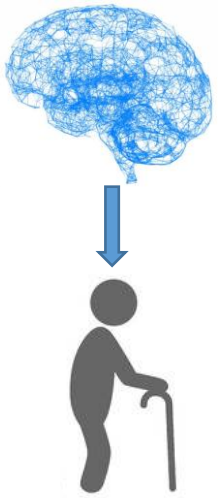
Thomas Galski, PhD; Richard L. Bruno, PhD; Richard Zorowitz, MD; John Walker, ACSW

(*Stroke*. 1993;24:1794-1800.)

Reviewed 86 medical charts
N=36 **Stroke**
N=50 Orthopedic injury

Presence of deficits abstract thinking, judgement, verbal memory, comprehension

Predicted lower functional status and longer length of stay (even when accounting for stroke severity)



"Good Outcome" Isn't Good Enough

Cognitive Impairment, Depressive Symptoms, and Social Restrictions in Physically Recovered Stroke Patients

Arunima Kapoor, MSc; Krista L. Lanctôt, PhD; Mark Bayley, MD; Alex Kiss, PhD; Nathan Herrmann, MD; Brian J. Murray, MD; Richard H. Swartz, MD, PhD

(*Stroke*. 2017;48:1688-1690.

Telephone interviews and chart audits of 142 discharged patients

Of the 96 with good functional outcome,

Over half were cognitively impaired and had participation restrictions

Two potentially potent interventions

Aerobic Exercise

Increases levels of neurotrophins like BDNF and IGF-1 that improve brain health.
(Ploughman and Kelly 2016)

Stimulates neuronal networks and enhances subsequent learning.
(Roig 2012, Quaney 2009)

Cognitive Rehabilitation

Emerging field but the evidence is weak or nonexistent
(Chung Cochrane Review 2013, das Nair Cochrane Review 2016)

Recent studies suggest computerized or virtual reality cognitive training is showing positive benefits.
(Faria 2016, Bogdanova 2016)

A Single Bout of Exercise Improves Motor Memory

Marc Roig[1,2]*, Kasper Skriver[1,2], Jesper Lundbye-Jensen[1,2], Bente Kiens[2], Jens Bo Nielsen[1,2]

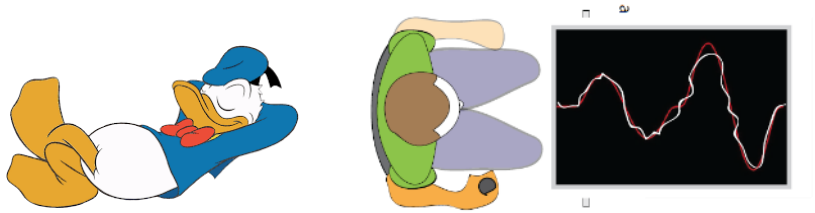
1 Department of Neuroscience and Pharmacology, University of Copenhagen, Copenhagen, Copenhagen, Denmark, 2 Department of Exercise and Sport Sciences, University of Copenhagen, Copenhagen, Denmark

PLOS ONE | September 2012 | Volume 7 | Issue 9 | e44594

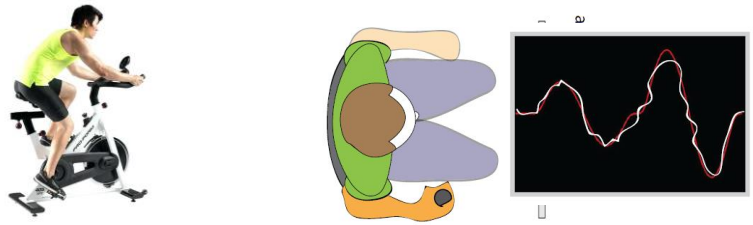
48 young male subjects

Three Groups

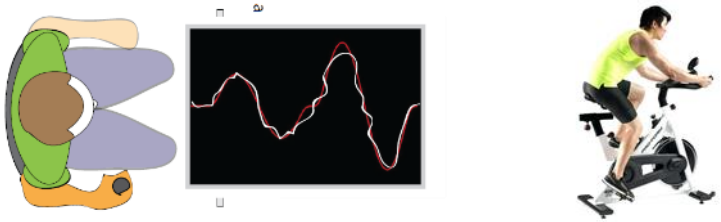
1
REST

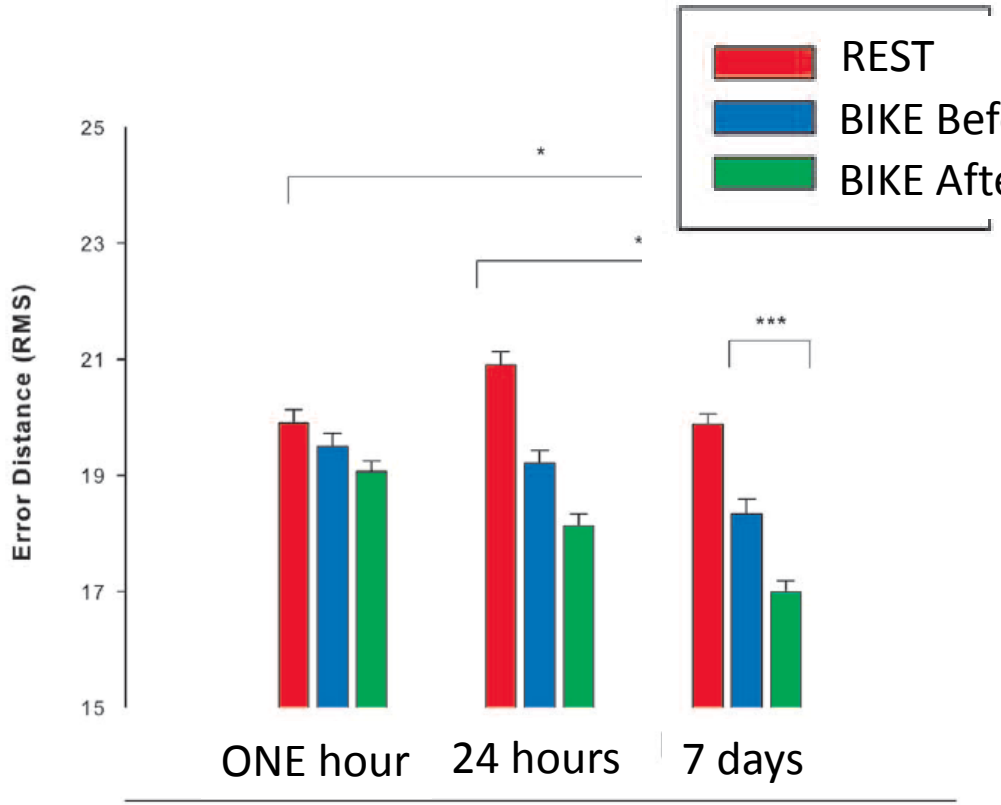


2
BIKE
BEFORE



3
BIKE
AFTERWARDS





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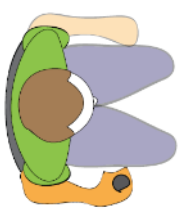
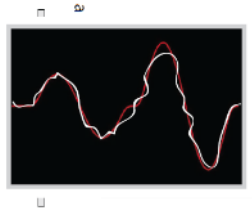
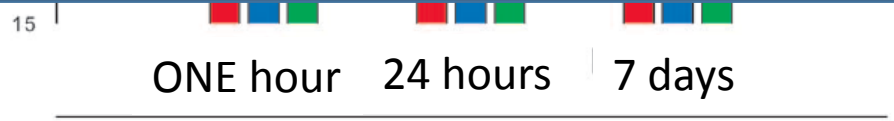
AFTERWARDS







Even one bout of exercise can enhance motor memory.

The benefit persisted for 7 days.

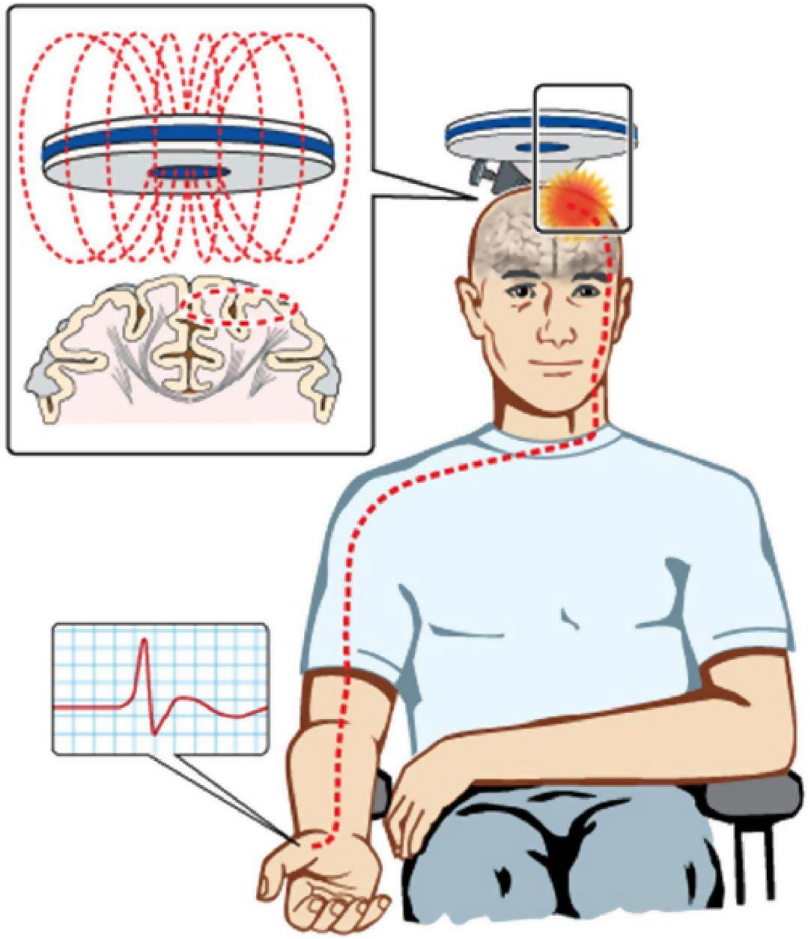
Could aerobic exercise have a similar benefit in people with stroke?

frontiers in Physiology

A Bout of High Intensity Interval Training Lengthened Nerve Conduction Latency to the Non-exercised Affected Limb in Chronic Stroke

ORIGINAL RESEARCH
published: 02 July 2018
doi: 10.3389/fphys.2018.00827

*Beraki Abraha†, Arthur R. Chaves†, Liam P. Kelly, Elizabeth M. Wallack, Katie P. Wadden, Jason McCarthy and Michelle Ploughman**



A coil is placed over the motor cortex.

Under the coil, an electrical pulse stimulates neurons on the surface of the brain.

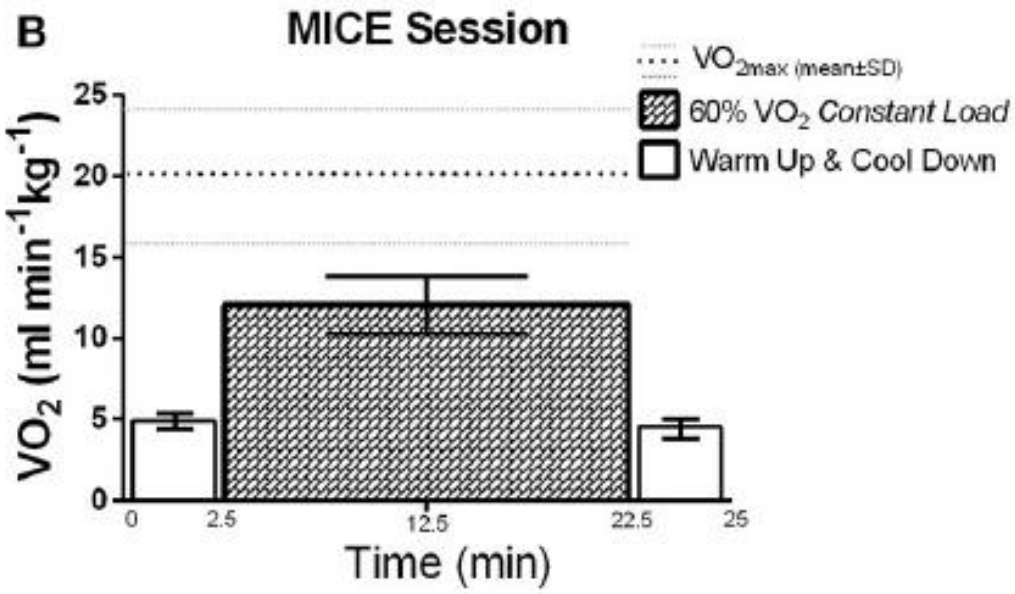
Using single or paired pulses we can examine the integrity of brain motor circuitry

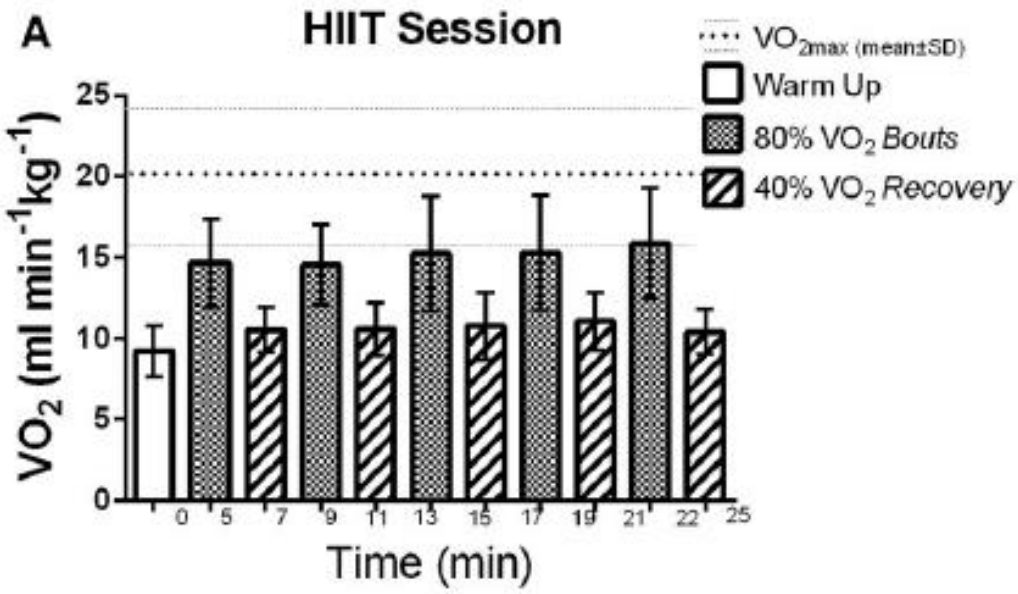
Participants: **Twelve stroke survivors**
> 6 months post-stroke

Cross-over trial

Exercise on a recumbent stepper

- Moderate Continuous Exercise (**MICE**)
- High Intensity Interval Training (**HIIT**)





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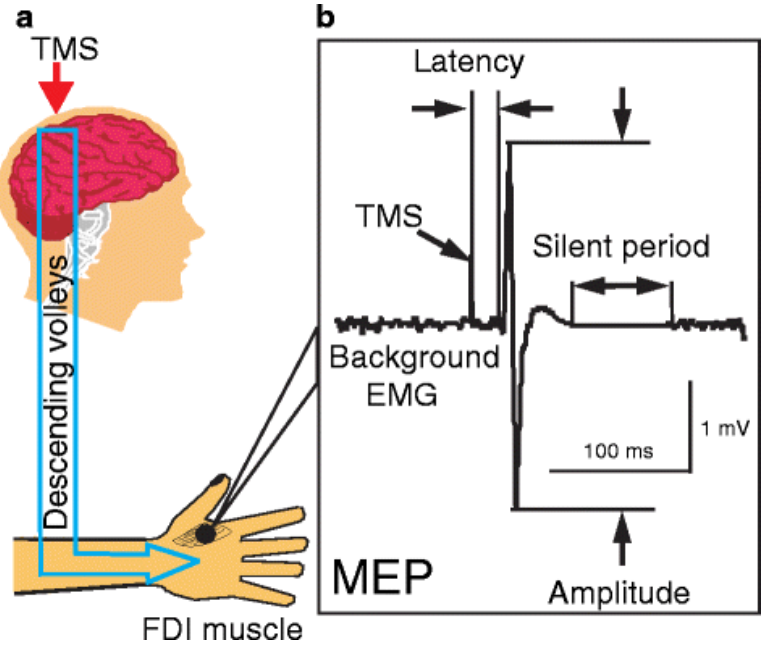

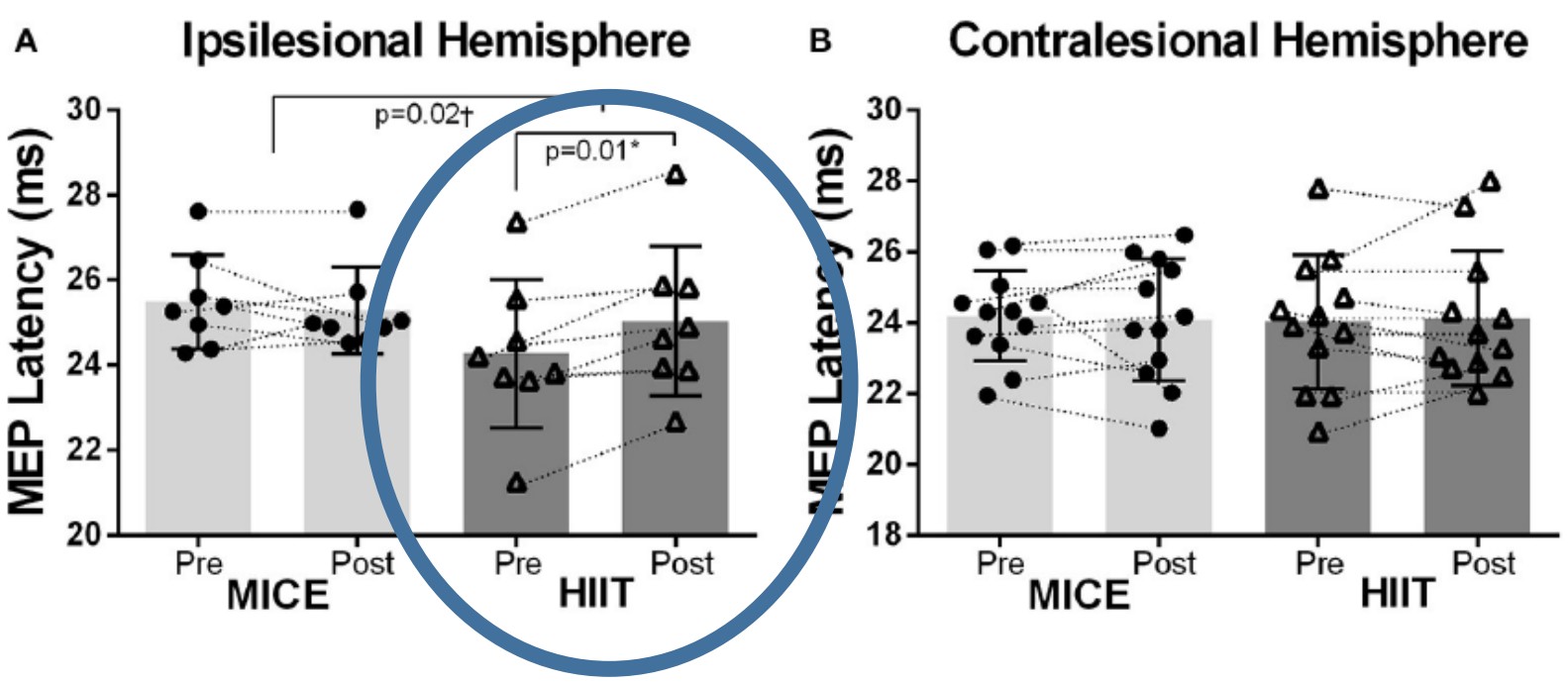

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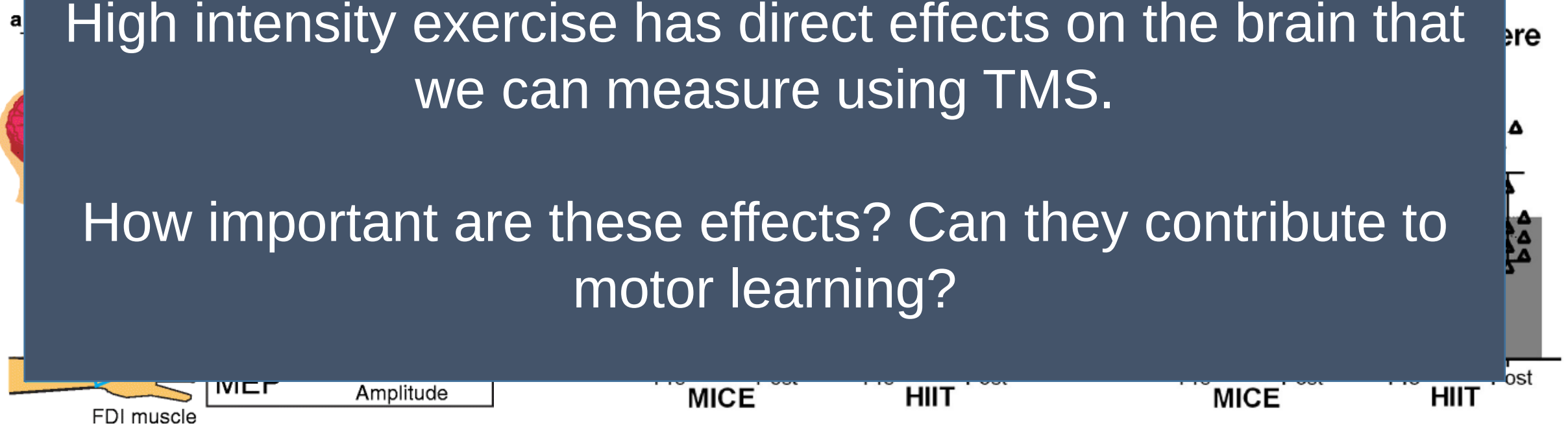
High intensity exercise has direct effects on the brain that we can measure using TMS.

How important are these effects? Can they contribute to motor learning?



Research Articles

Neurorehabilitation and
Neural Repair
Volume 23 Number 9
November/December 2009 879-885

10.1177/1545968309338193
http://nnr.sagepub.com

Aerobic Exercise Improves Cognition and Motor Function Poststroke

Barbara M. Quaney, PT, PhD, Lara A. Boyd, PT, PhD, Joan M. McDowd, PhD, Laura H. Zahner, PT, Jianghua He, PhD, Matthew S. Mayo, PhD, and Richard F. Macko, MD

Question:

Will aerobic exercise produce changes in:

1. cognitive function and,

2. motor learning of the LESS-AFFECTED upper extremity in people with chronic stroke?

Participants: 38 stroke survivors > 6 months post-stroke

Randomized controlled trial

Group A: EXERCISE

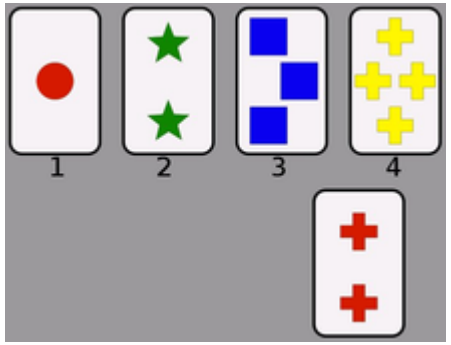
- **Moderate to vigourous progressively challenging continuous exercise (MICE) on a stationary bicycle 3 times per week for 8 weeks (70% of max HR: target HR was based on Karvonen's formula)**

Group B: STRETCHING at home

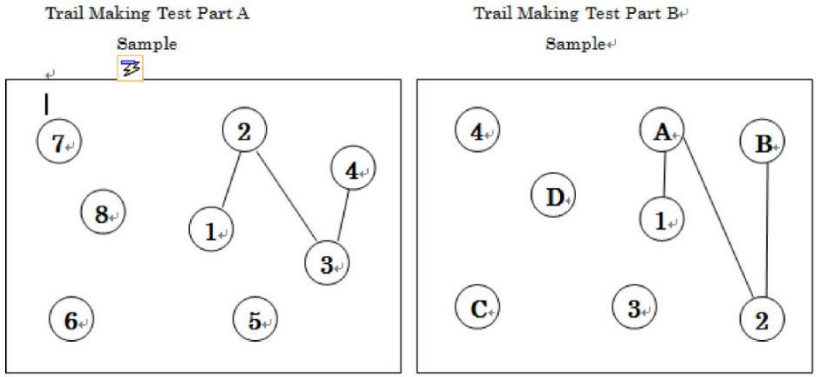
- **Upper and lower extremity exercise 3 times per week for 8 weeks. Therapist contacted patients each week by phone.**

COGNITIVE

Wisconsin Card Sorting Task
Learning and remembering sorting rules

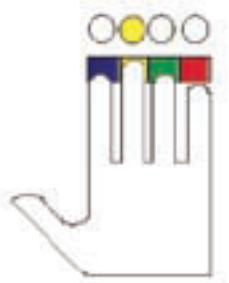


Trail Making Task A and B
Visual search and working memory

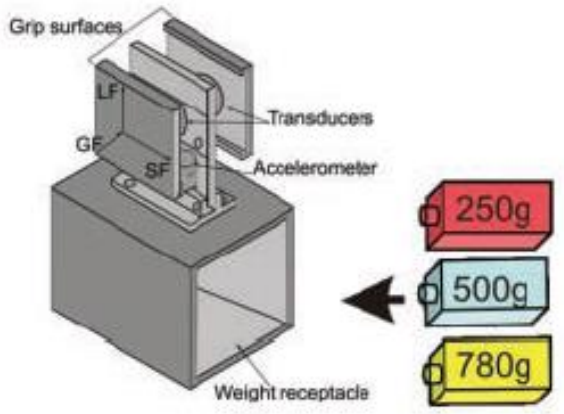


MOTOR LEARNING

Serial Reaction Timed Task
Implicit learning with LESS-affected hand



Predictive Grip Force Modulation
Conditional learning by matching grip force to colour of the weight with LESS affected hand

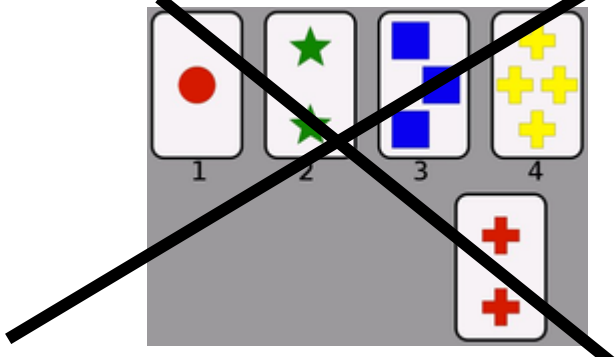


RESULTS

COGNITIVE

No Benefit

Wisconsin Card Sorting Task
Learning and remembering sorting rules



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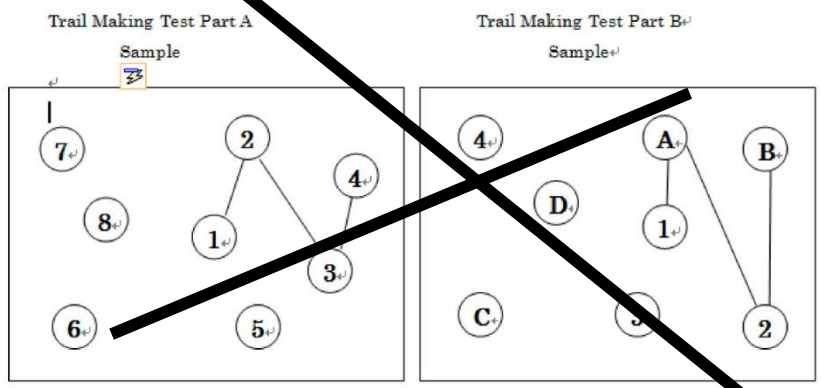
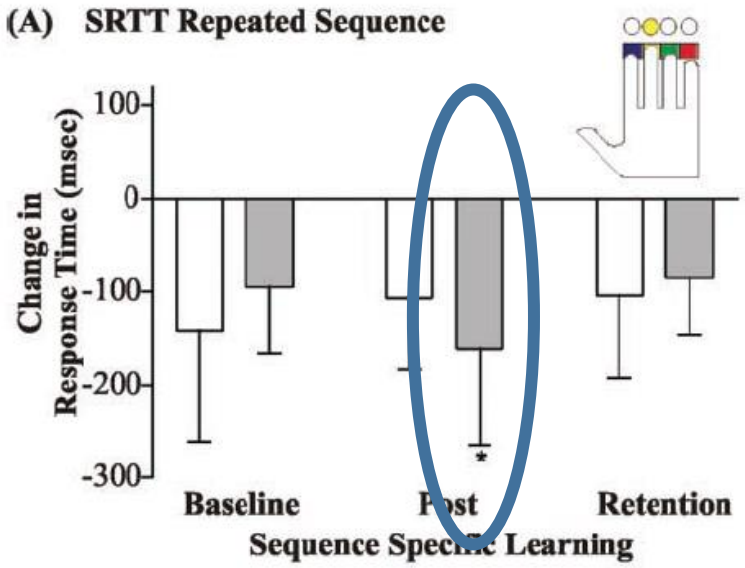


MOTOR LEARNING

Short-term benefit

SE (Control)
AEX (Intervention)

Serial Reaction Timed Task



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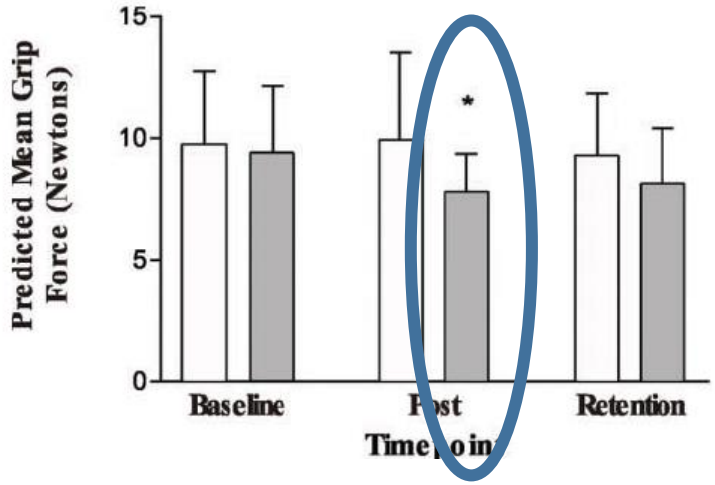


RESULTS

COGNITIVE

Wisconsin Card Sorting Task
Learning and remembering sorting rules

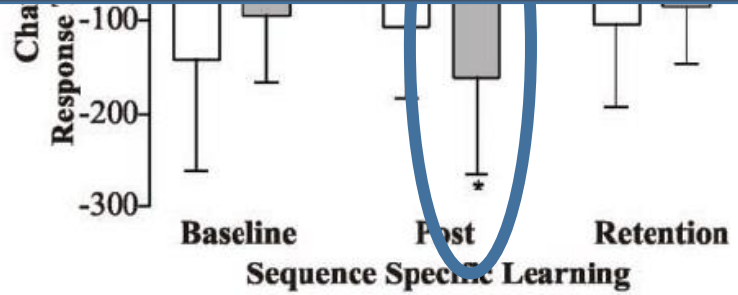
Trail Making Task A and B
Visual search and working memory

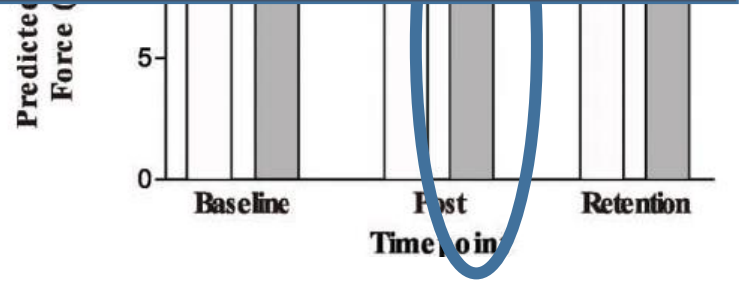
Aerobic exercise provided short-term improvements in motor learning but there was no cognitive benefit.

Could pairing aerobic exercise together with cognitive training 'prime' the brain and achieve greater benefit?

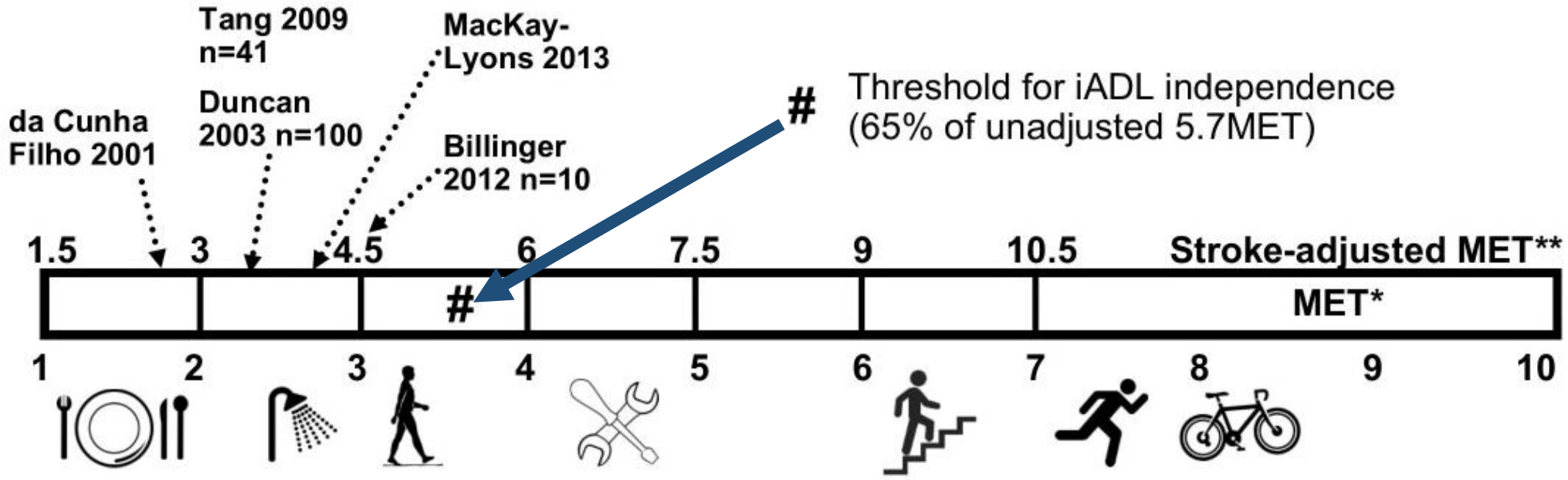
Short-term benefit

SE (Control)
AEX (Intervention)





Stroke patients have extremely low activity tolerance



Such low fitness levels create a 'ceiling to neuromotor recovery'; limiting both the number of repetitions that can be completed within a session and the total intensity at which they can be sustained.

For example, routine rehabilitation reaches about 4.5 METS, levels not achievable by most stroke patients. *Ploughman & Kelly Current Opinion in Neurology 2016

TOPICS IN STROKE REHABILITATION, 2018
https://doi.org/10.1080/10749357.2018.1458461

Taylor & Francis
Taylor & Francis Group

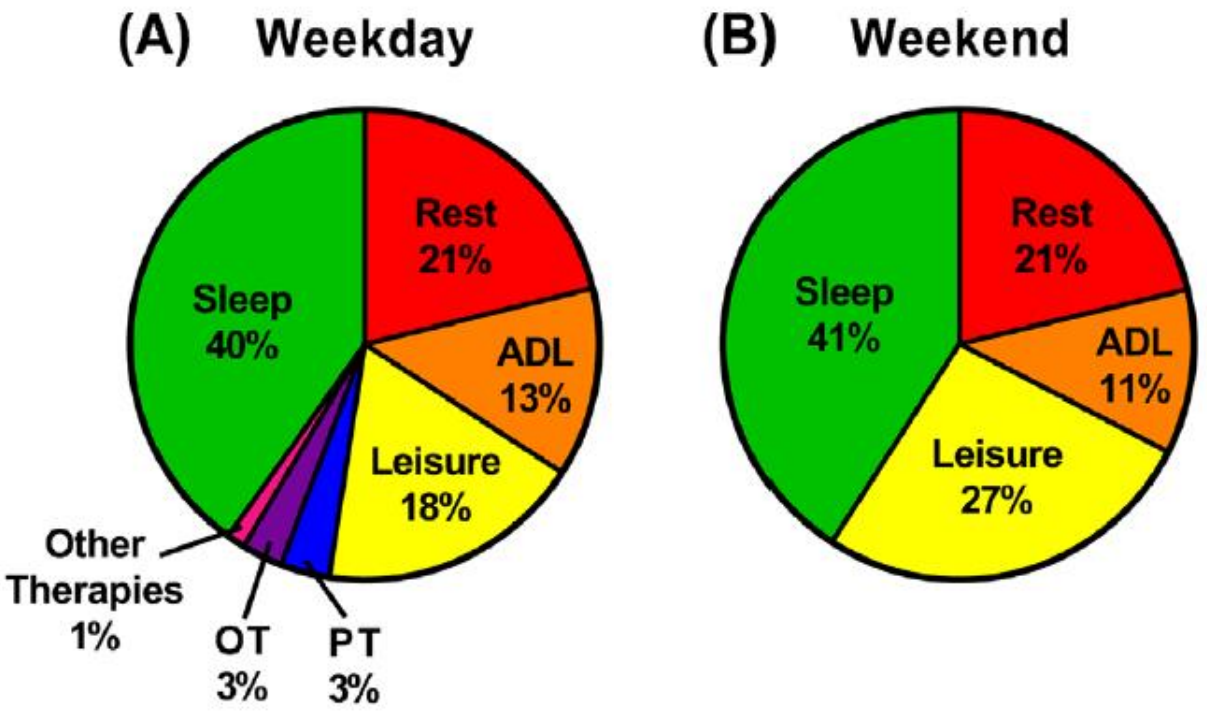
ORIGINAL ARTICLE

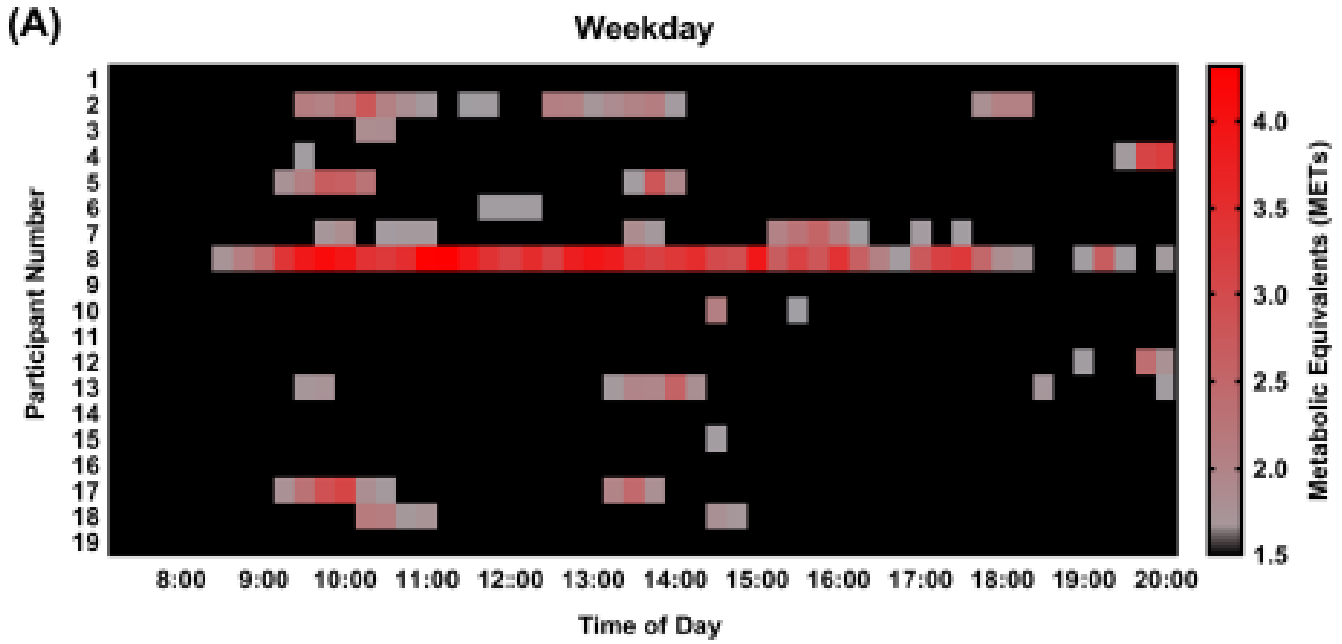
Excessive sedentary time during in-patient stroke rehabilitation

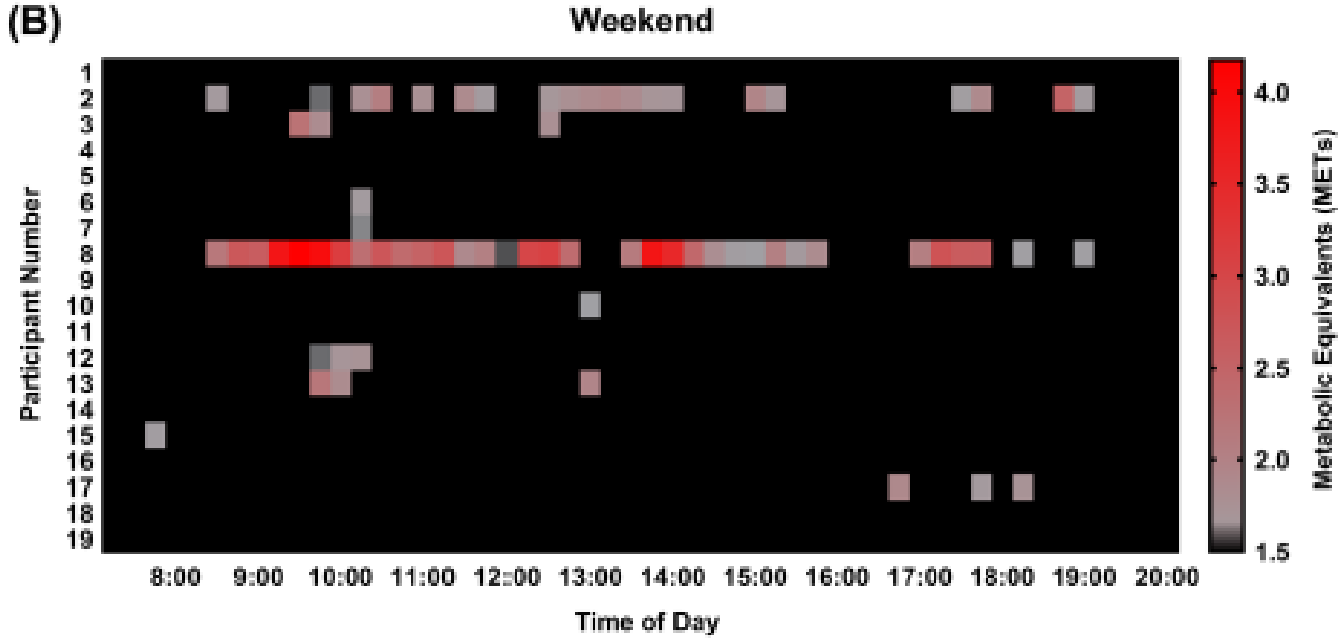
Matthew Barrett[a], John Charles Snow[a], Megan C. Kirkland[a], Liam P. Kelly[a], Maria Gehue[a], Matthew B. Downer[a], Jason McCarthy[a,b] and Michelle Ploughman[a]

[a]Recovery & Performance Laboratory, Faculty of Medicine, Memorial University of Newfoundland, St. John's, Canada; [b]Rehabilitation and Continuing Care Program, Eastern Health Authority, St. John's, Canada

One lead ECG and accelerometer for one week in 19 consecutive patients admitted to the stroke unit







SEDENTARY

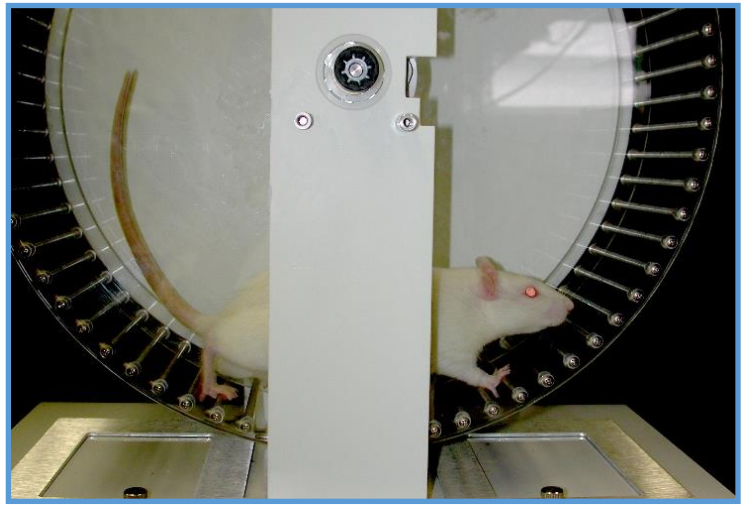
ACTIVE

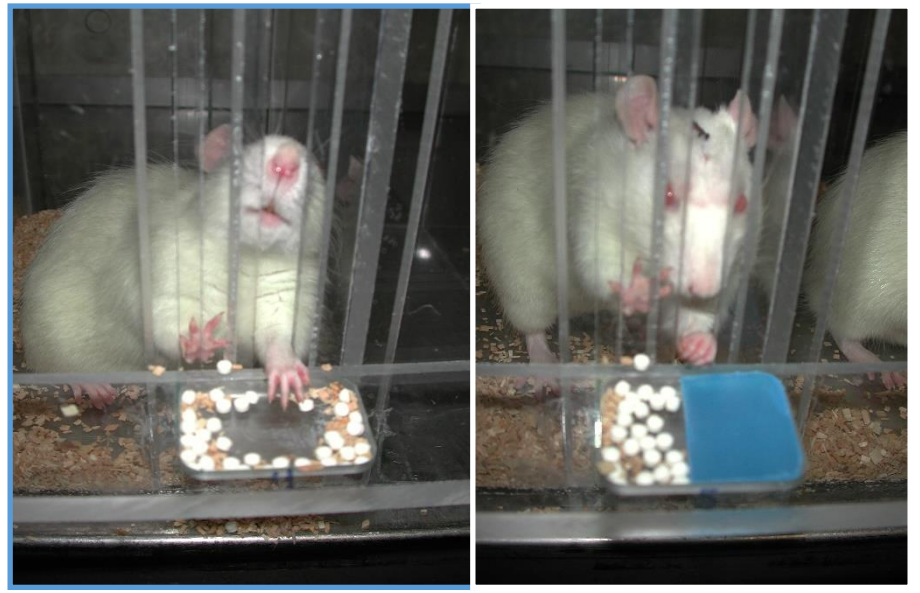
87% of waking hours were sedentary

62% of time spent in PT was sedentary

77% of time spent in OT was sedentary

Can we ‘prime’ the brain with aerobic exercise to improve learning of subsequent tasks? If so, how does it work/ What are the mechanisms?



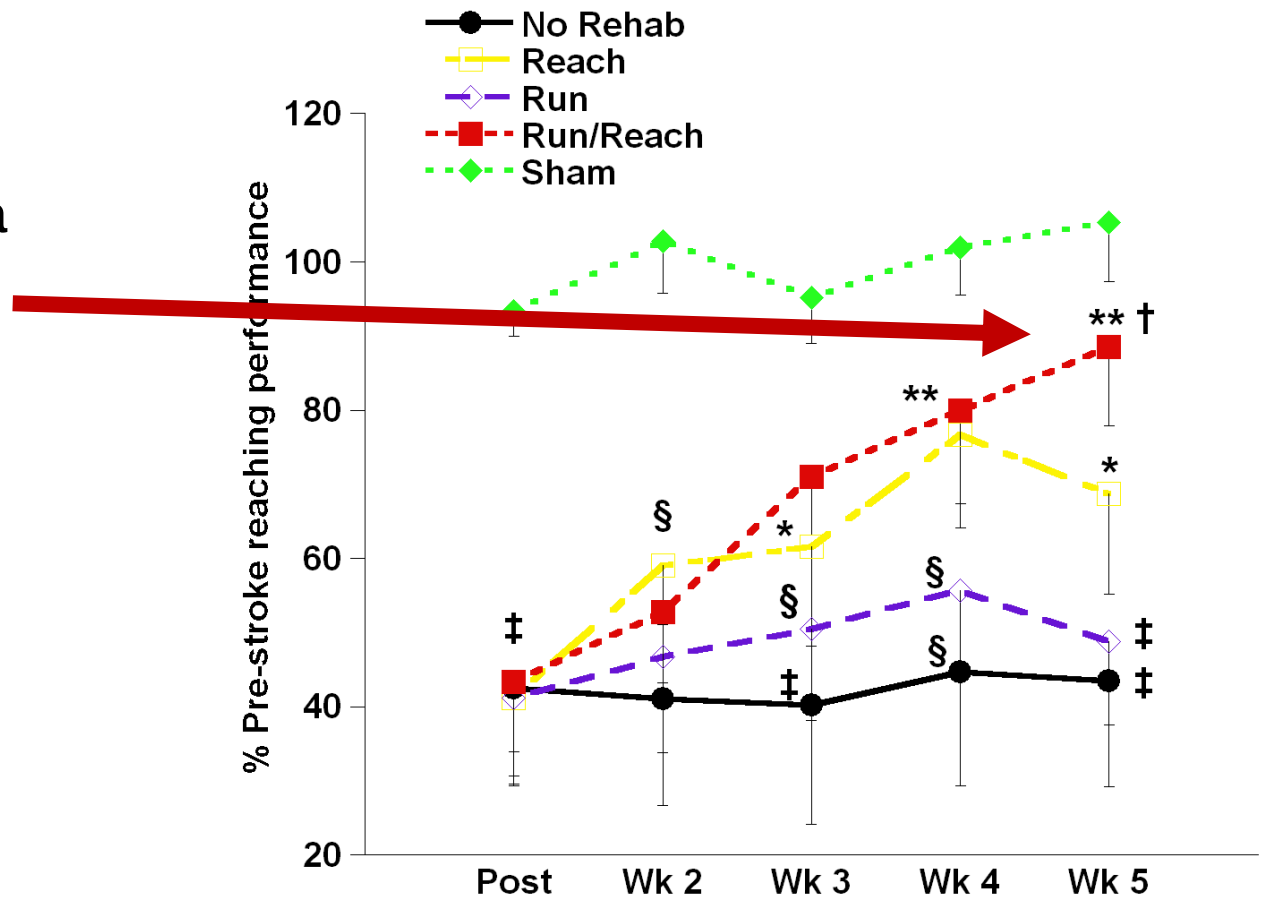


European Journal of Neuroscience, Vol. 25, pp. 3453–3460, 2007 doi:10.1111/j.1460-9568.2007.05591.x

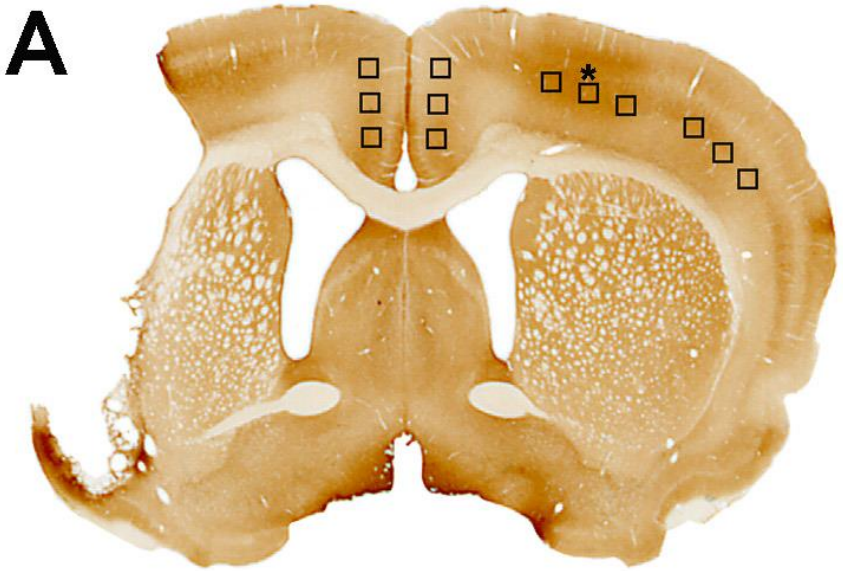
Endurance exercise facilitates relearning of forelimb motor skill after focal ischemia

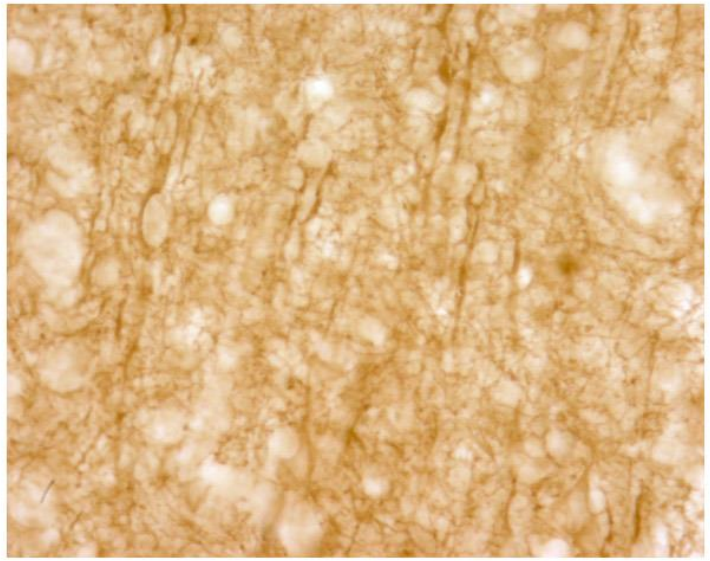
Michelle Ploughman, Zachary Attwood, Nicole White, Jules J. E. Doré and Dale Corbett
Basic Medical Sciences, Faculty of Medicine, Memorial University, St. John's, NL, Canada A1B 3V6

In an animal model of stroke, adding <u>aerobic exercise</u> before a reaching task improved learning of the task over 5 weeks



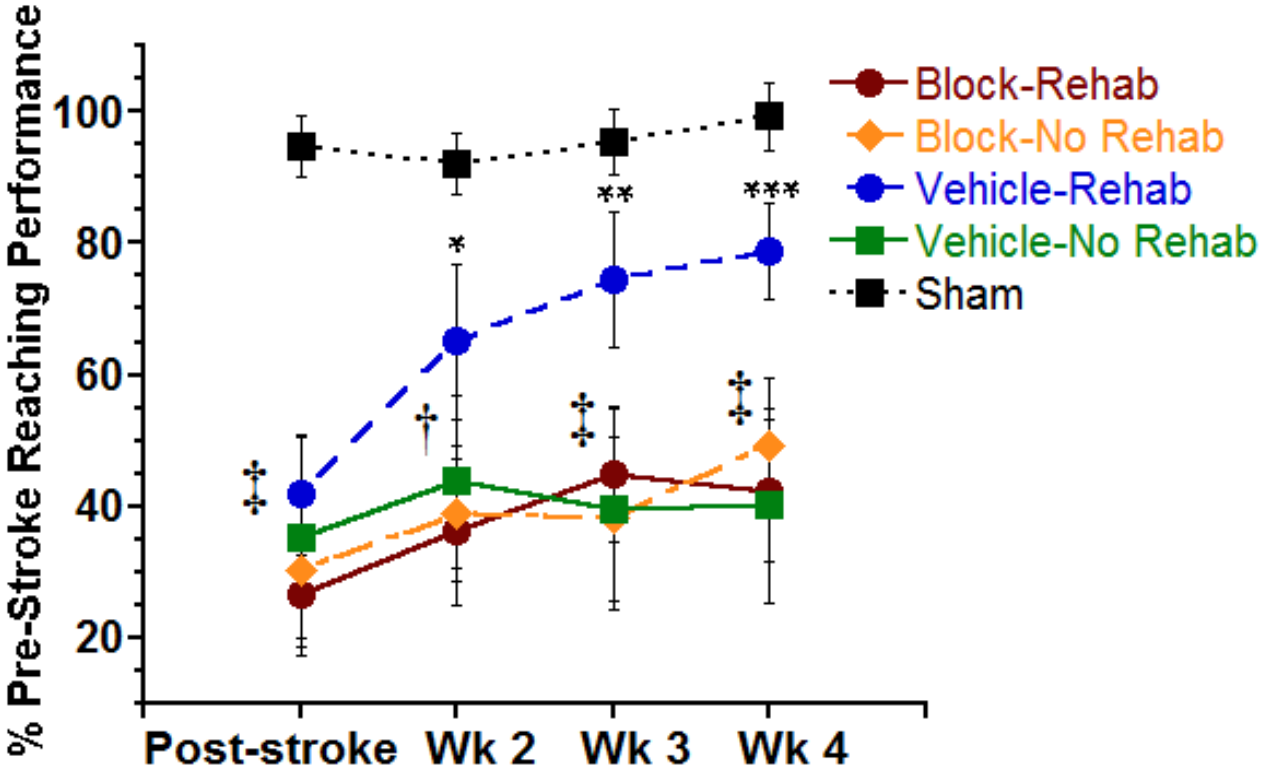
Functional improvement was paralleled by enhanced dendritic branching within the motor cortex





(Ploughman et al 2007 European Journal of Neuroscience)

In an animal model of stroke, the benefits of the combined <u>aerobic exercise + reaching</u> were lost when you blocked the neurotrophin BDNF



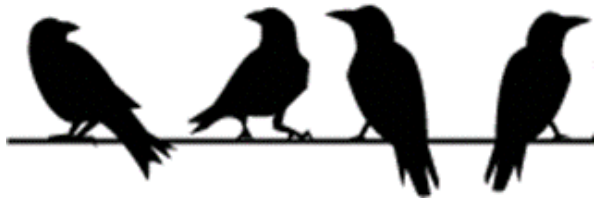
Brain-Derived Neurotrophic Factor Contributes to Recovery of Skilled Reaching After Focal Ischemia in Rats

Michelle Ploughman, PhD; Victoria Windle, PhD; Crystal L. MacLellan, PhD; Nicole White, BSc; Jules J. Doré, PhD; Dale Corbett, PhD

(*Stroke*. 2009;40:1490-1495.)

How do you prescribe aerobic exercise that will concurrently promote brain repair, enhance plasticity, improve fitness and metabolic health?

Is it possible to target four birds with one stone?



Finding the ‘right’ dosage of aerobic exercise Using F.I.T.T.I. principles

FREQUENCY

INTENSITY

TIME

TYPE

INTIATION POST-STROKE

Four birds with one stone? Reparative, neuroplastic, cardiorespiratory, and metabolic benefits of aerobic exercise poststroke

Michelle Ploughman and Liam P. Kelly

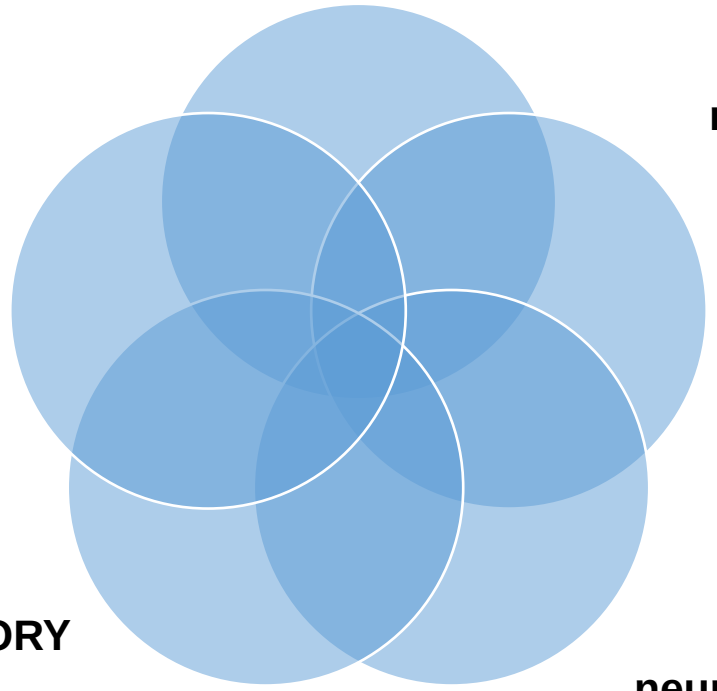
BRAIN REPAIR

Lesion size, cell death, inflammation

NEUROLOGICAL OUTCOMES

Relearning of skilled movements, executive function

METABOLIC HEALTH



CARDIORESPIRATORY FITNESS

PLASTICITY
Neurotrophins, neuroplasticity markers, fMRI, TMS

Aerobic exercise effects on brain repair, neuroplasticity and neurological recovery

Neuroscience Research 87 (2014) 8–15

Contents lists available at ScienceDirect

Neuroscience Research

journal homepage: www.elsevier.com/locate/neures

Review article

Aerobic exercise effects on neuroprotection and brain repair following stroke: A systematic review and perspective

Mark W. Austin[a], Michelle Ploughman[a,*], Lindsay Glynn[b], Dale Corbett[c]

Transl. Stroke Res.
DOI 10.1007/s12975-014-0357-7

REVIEW ARTICLE

The Effects of Poststroke Aerobic Exercise on Neuroplasticity: A Systematic Review of Animal and Clinical Studies

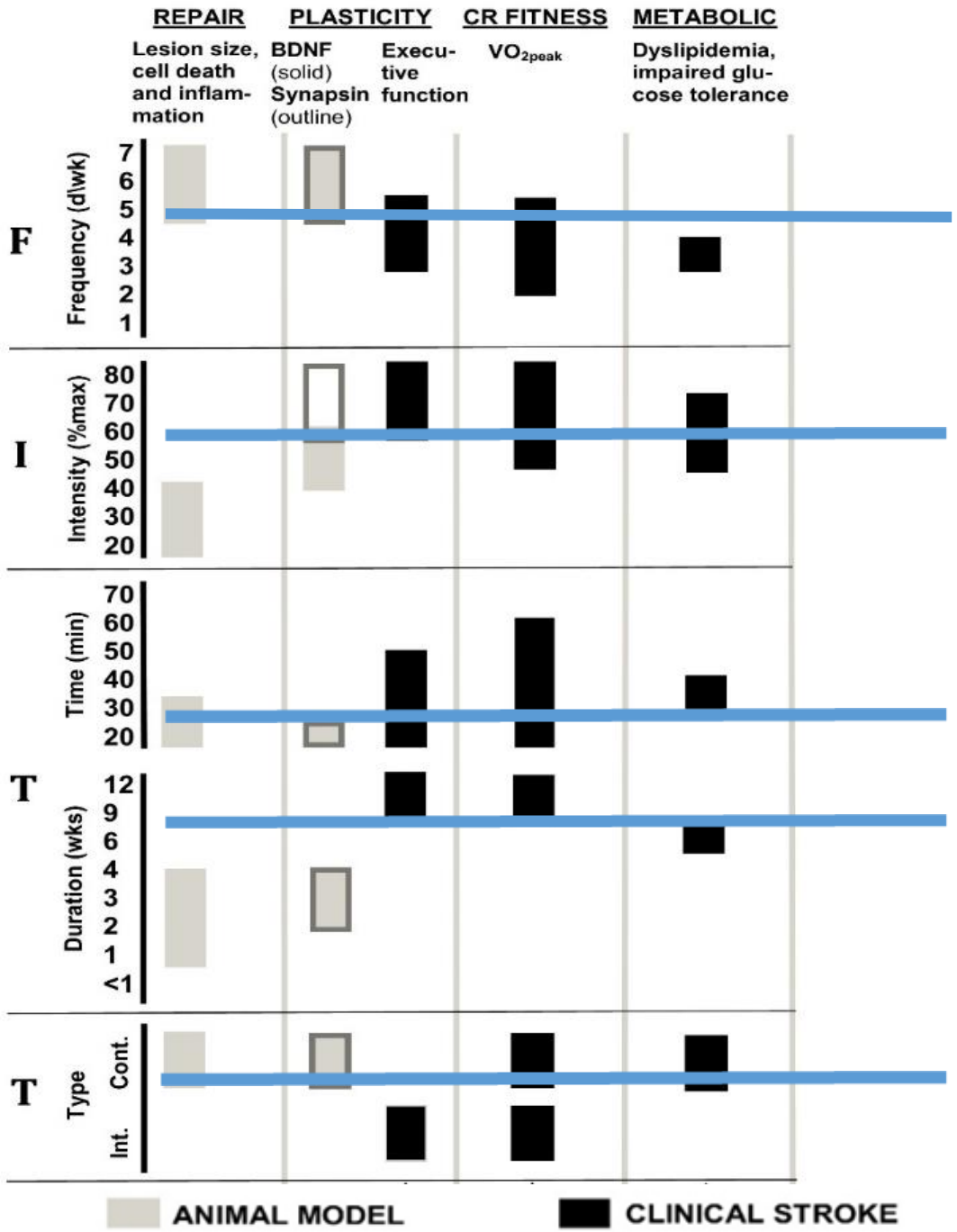
Michelle Ploughman · Mark W. Austin · Lindsay Glynn · Dale Corbett

Hindawi Publishing Corporation
Neural Plasticity
Volume 2016, Article ID 2961573, 12 pages
http://dx.doi.org/10.1155/2016/2961573

Review Article

Defining Optimal Aerobic Exercise Parameters to Affect Complex Motor and Cognitive Outcomes after Stroke: A Systematic Review and Synthesis

S. M. Mahmudul Hasan, Samantha N. Rancourt, Mark W. Austin, and Michelle Ploughman



Optimal training parameters to cut across all domains

Frequency 3-5 X week

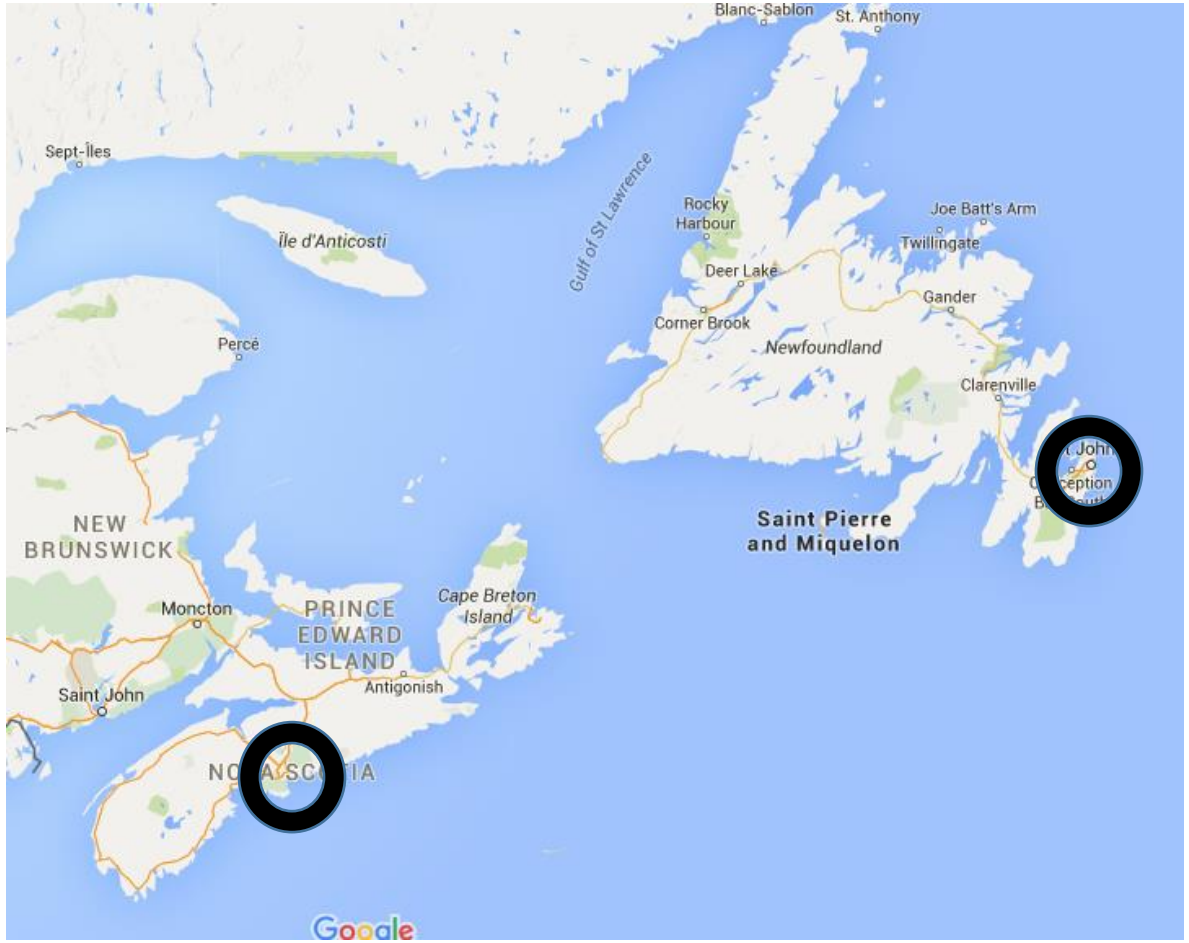
Intensity >60% maximum (Vigorous)

30 min

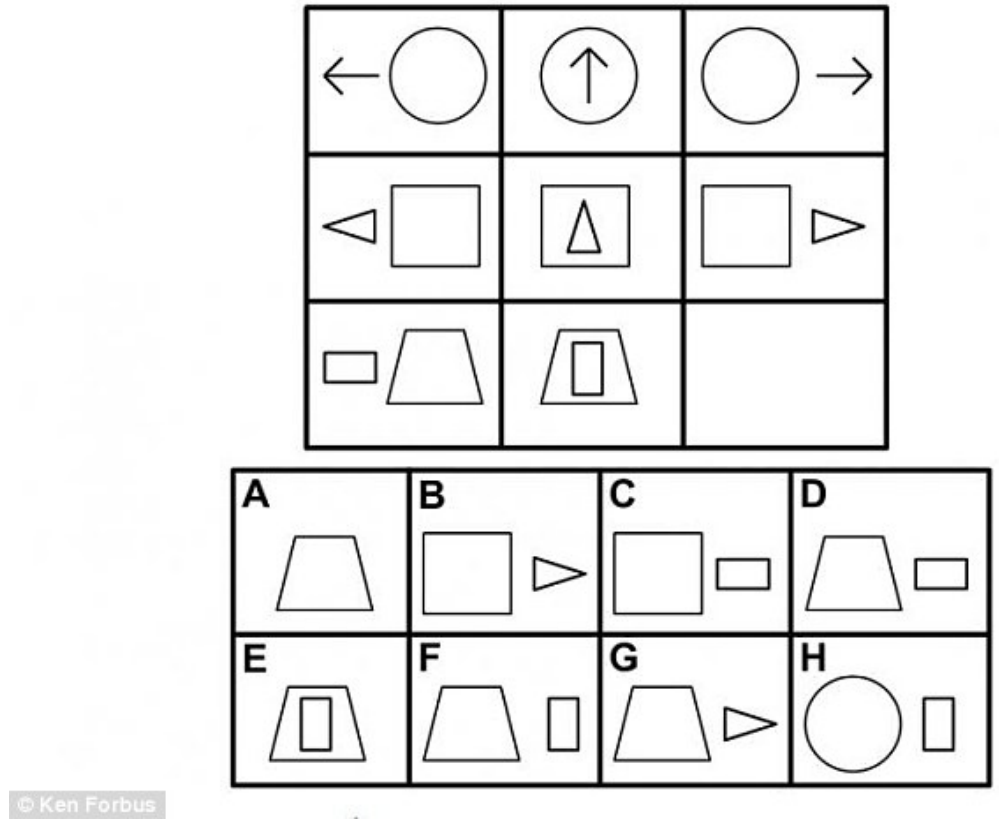
>8 weeks

Continuous (emerging evidence for HIIT)

Two-site RCT



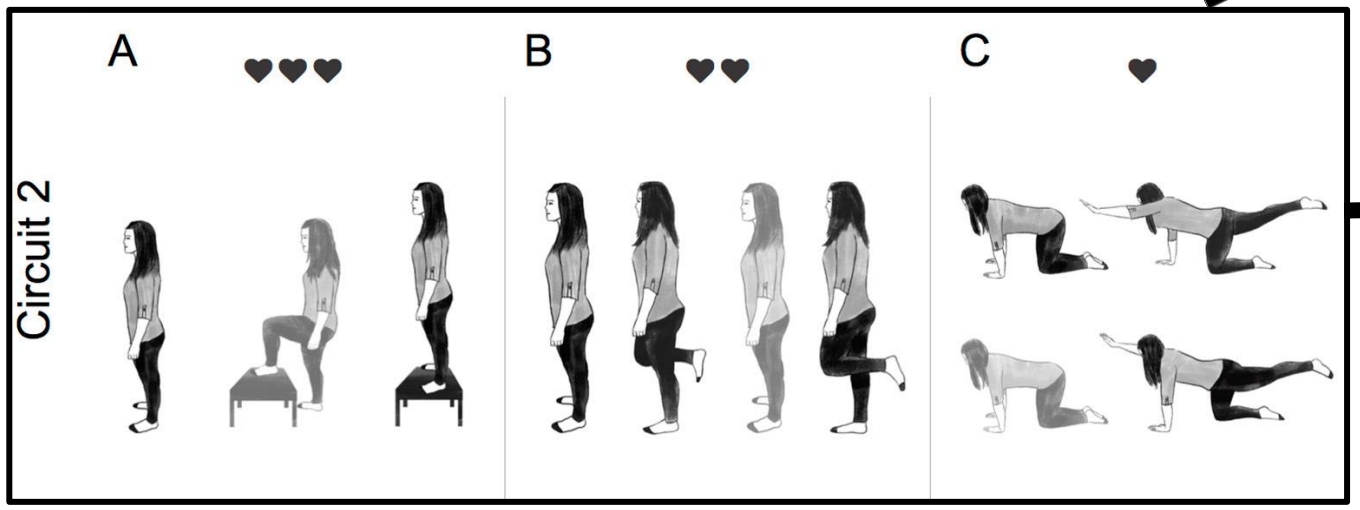
Primary Outcome
Raven's Progressive Matrices Test



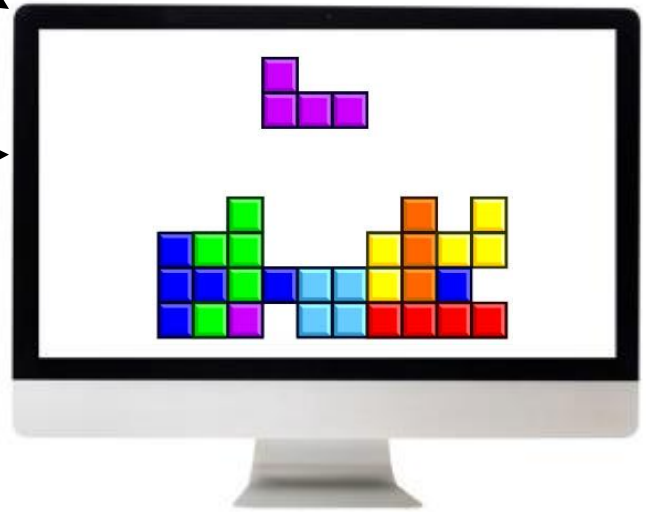
AEROBIC

DUAL-n-BACK (COG)

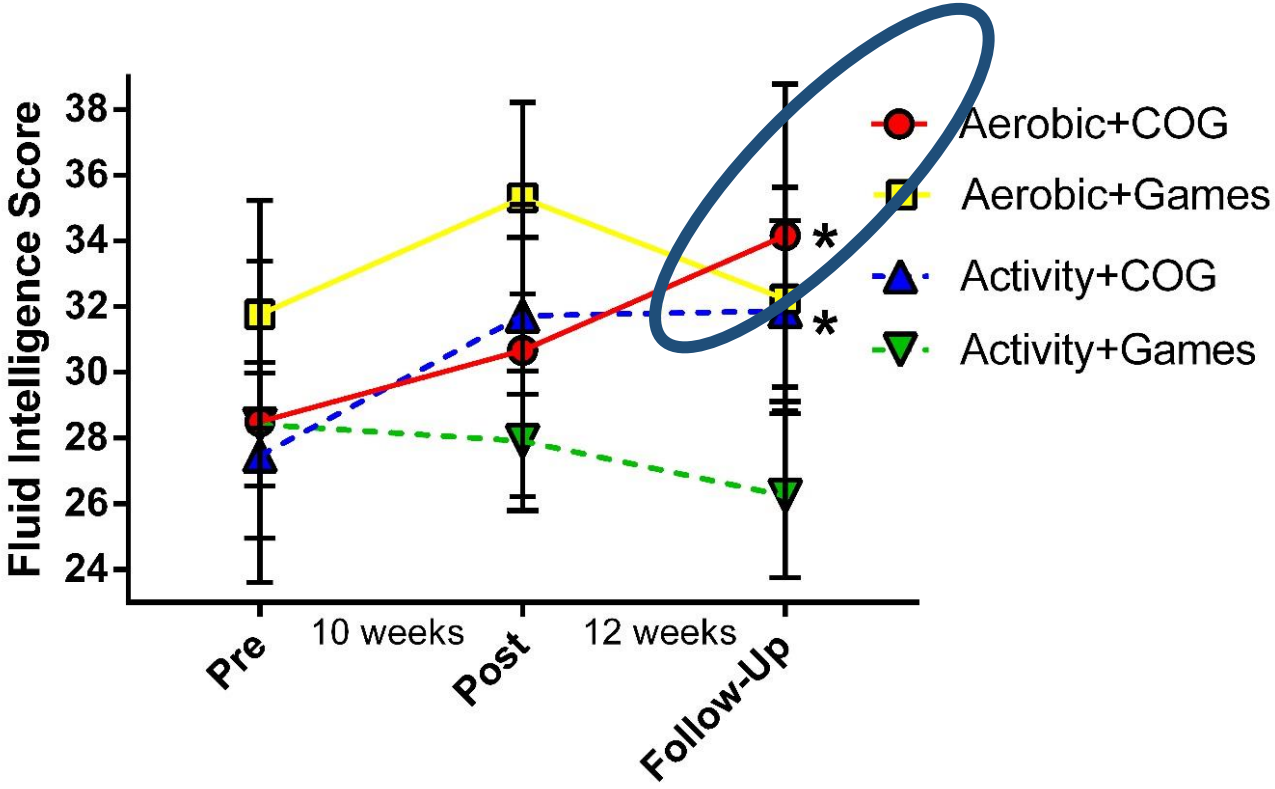
ACTIVITY

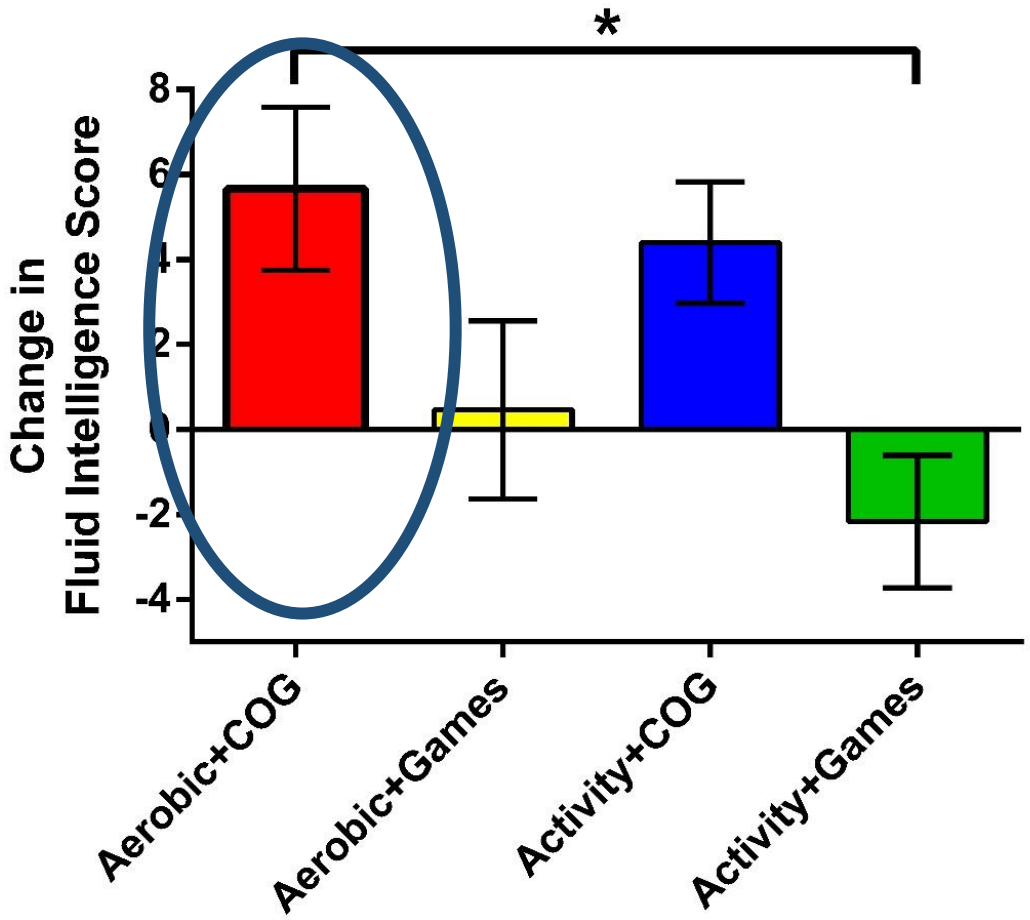


GAMES

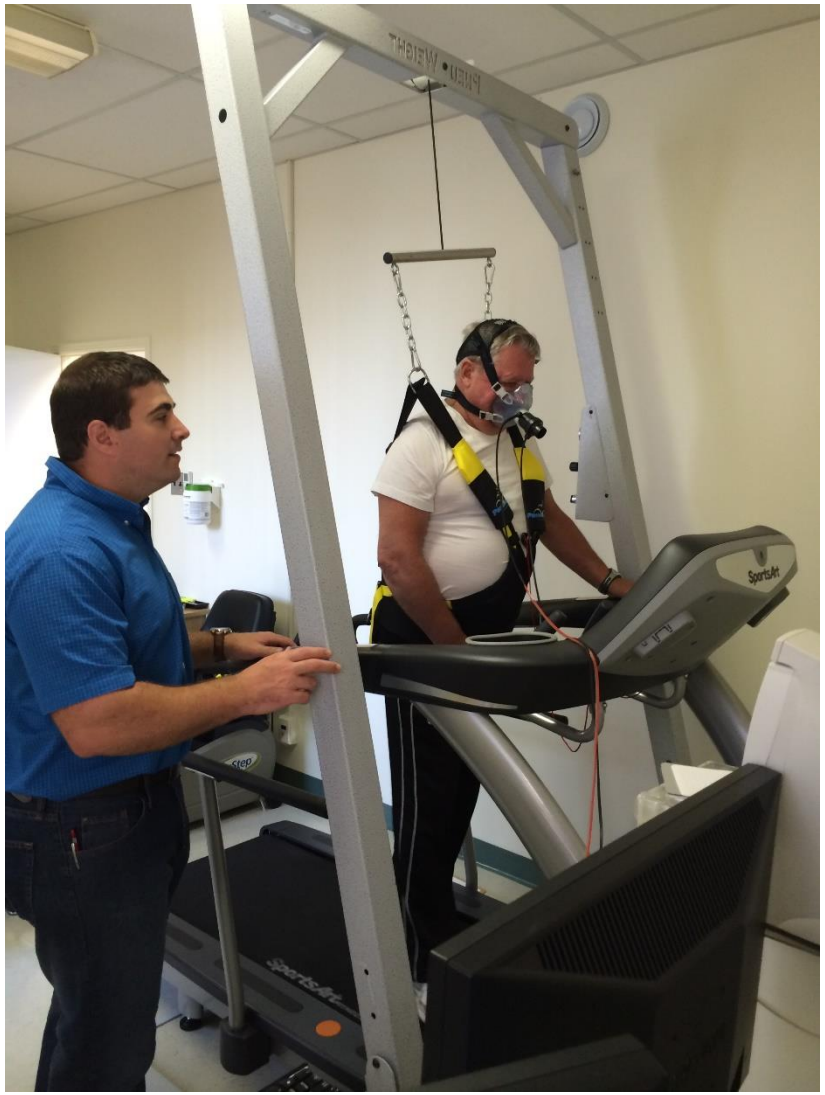


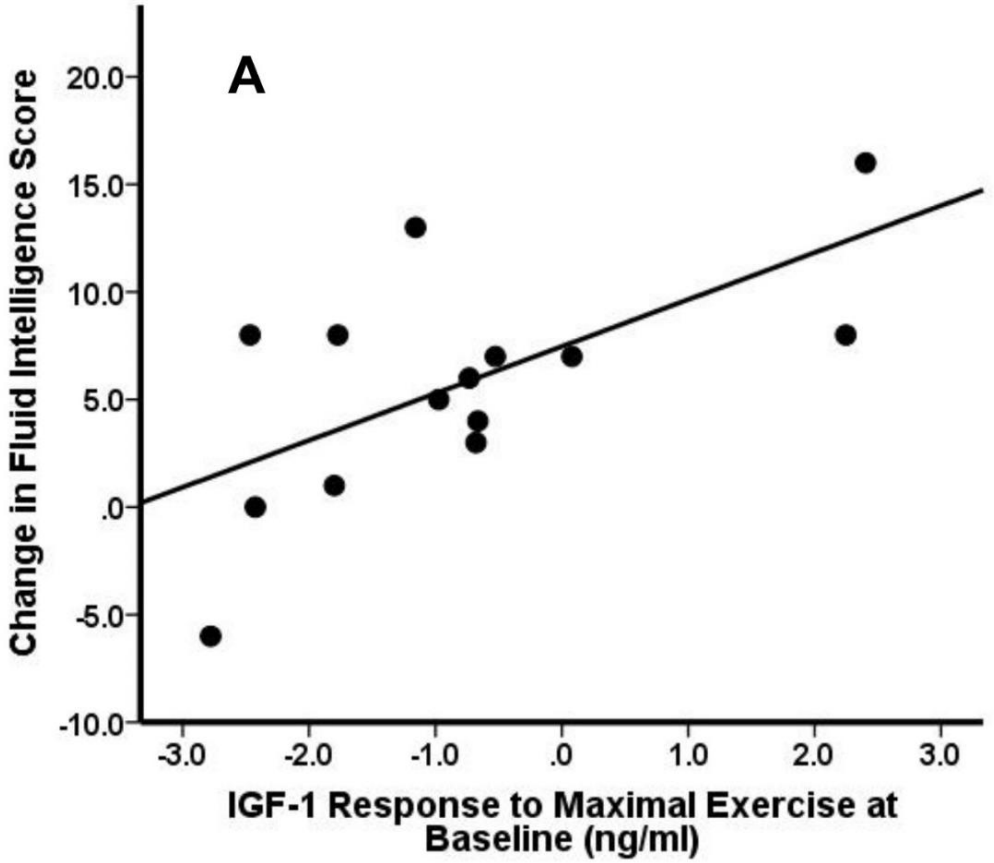
Aerobic exercise + Cognitive training
Improved fluid intelligence nearly 50% at follow-up





Responsiveness of IGF-1 at baseline predicted 40% variability in cognitive outcome



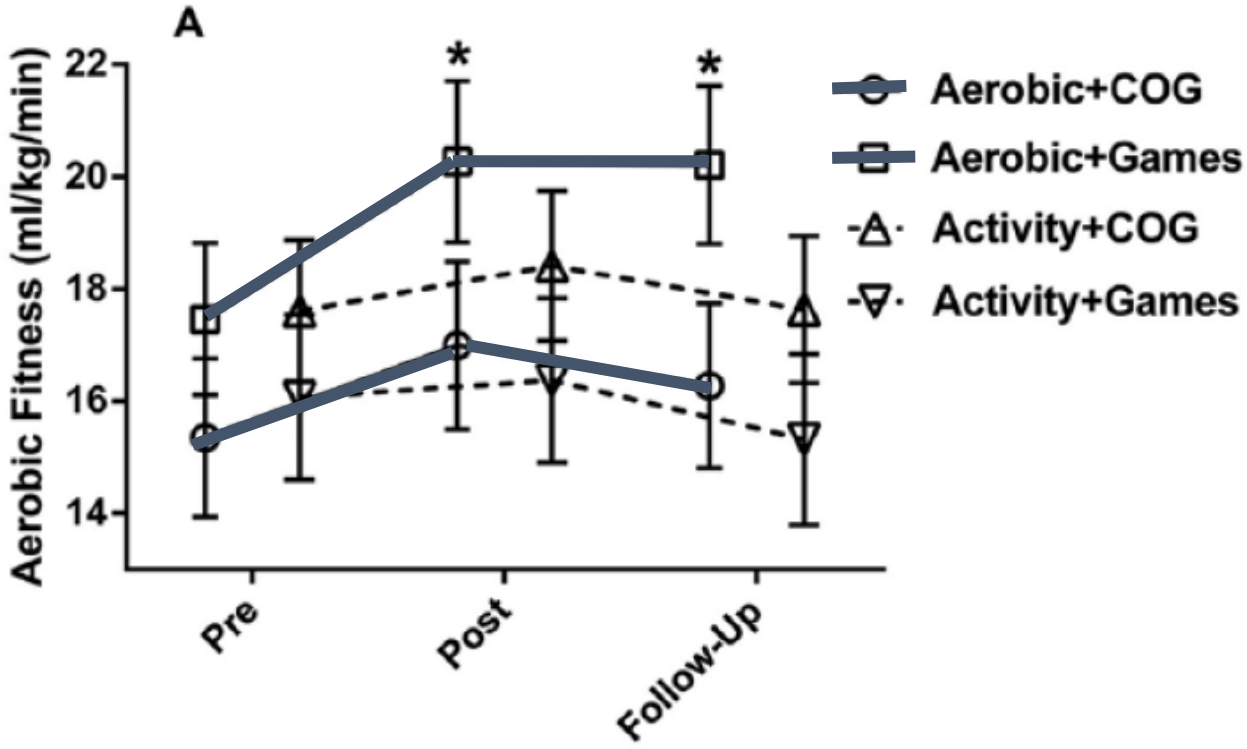


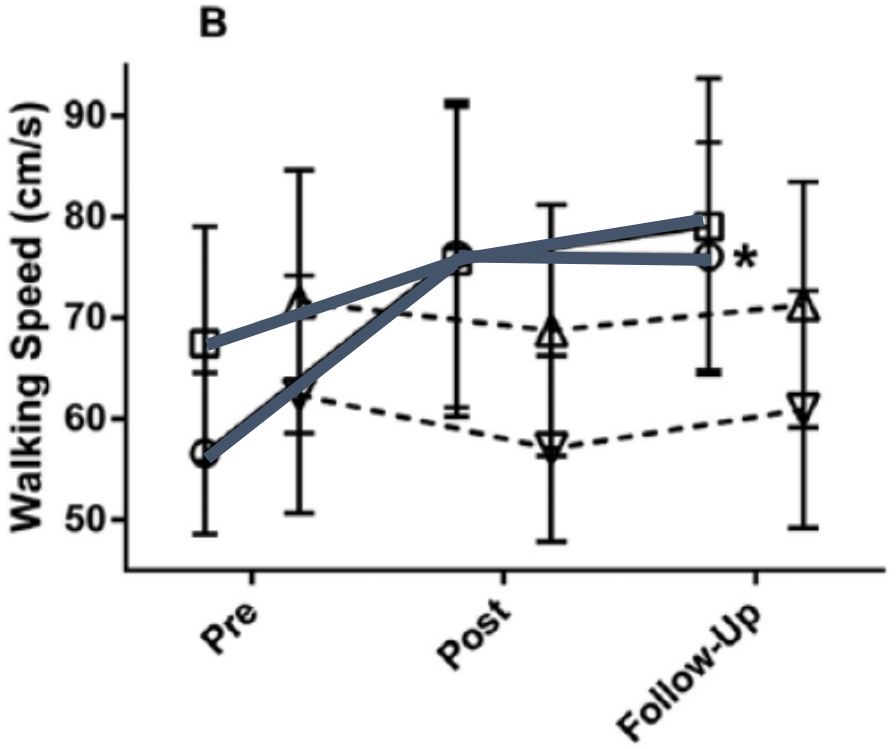
FITNESS

WALKING

Aerobic training groups made significant and sustained improvements in Fitness

Aerobic training groups made significant and sustained improvements in Walking





FITNESS

Aerobic training groups made significant and sustained improvements in Fitness

WALKING

Aerobic training groups made significant and sustained improvements in Walking

Combining aerobic and cognitive training together 3X week for 10 weeks improves three aspects of recovery simultaneously: 1. cognition, 2. fitness and 3. walking

How can we practically incorporate aerobic exercise into rehabilitation?

frontiers in Physiology

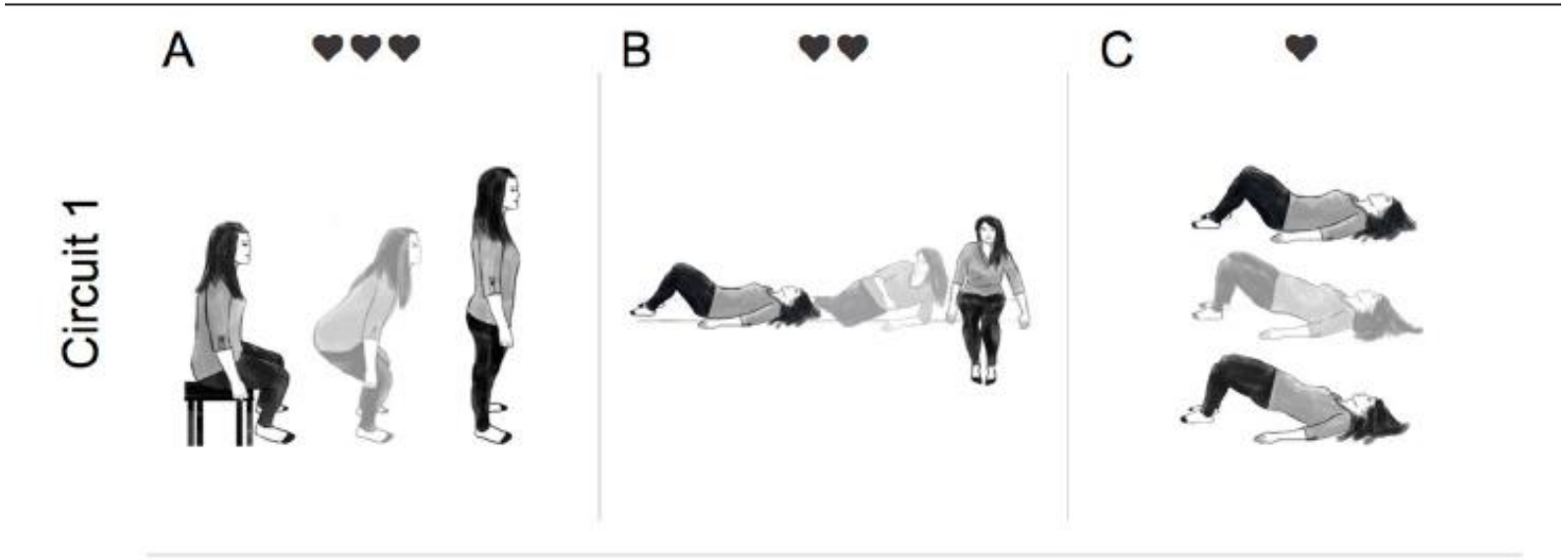
ORIGINAL RESEARCH
published: 26 October 2017
doi: 10.3389/fphys.2017.00809

Intensifying Functional Task Practice to Meet Aerobic Training Guidelines in Stroke Survivors

Liam P. Kelly[1], Augustine J. Devasahayam[1], Arthur R. Chaves[1], Elizabeth M. Wallack[1], Jason McCarthy[1], Fabien A. Basset[2] and Michelle Ploughman[1]*

Can everyday tasks be practiced in such a way to provide aerobic challenge?

YES!



10 people with chronic stroke

One session of functional tasks while wearing portable mask

TABLE 1 | Participant characteristics.

Sub.	Age (years)	Sex (M,F)	Weight (kg)	BMI (kg/m^2)	Stroke type	Months since stroke	NIHSS (/42)	Combined Chedoke (/14)	Hypertension	Diabetes	Dyslipidemia
01	61	M	119	35.9	Ischemic	24	1	13	✓	✓	✓
02	43	M	64	20.4	Ischemic	27	7	4	✓	✗	✓
03	62	M	82	26.2	Ischemic	33	4	7	✗	✗	✗
04	69	M	85	27.2	Ischemic	26	1	13	✗	✓	✗
05	49	F	85	30.5	Hemorrhagic	12	5	9	✓	✗	✗
06	79	F	61	28.0	Ischemic	24	0	12	✗	✗	✗
07	76	M	79	25.1	Ischemic	131	3	11	✗	✓	✗
08	67	M	90	29.8	Ischemic	32	3	12	✗	✓	✓
09	59	F	65	23.0	Hemorrhagic	40	2	9	✓	✗	✗
10	81	M	82	27.4	Hemorrhagic	31	3	12	✓	✗	✓

10 people with chronic stroke

One session of functional tasks while wearing portable mask

TABLE 1 | Participant characteristics.

Sub.	Age	Sex	Weight	BMI	Stroke type	Months	NIHSS	Combined	Hypertension	Diabetes	Dyslipidemia
01									✓	✓	✓
02									✓	✗	✓
03									✗	✗	✗
04									✗	✓	✗
05									✓	✗	✗
06									✗	✗	✗
07									✗	✓	✗
08									✗	✓	✓
09									✓	✗	✗
10									✓	✗	✓

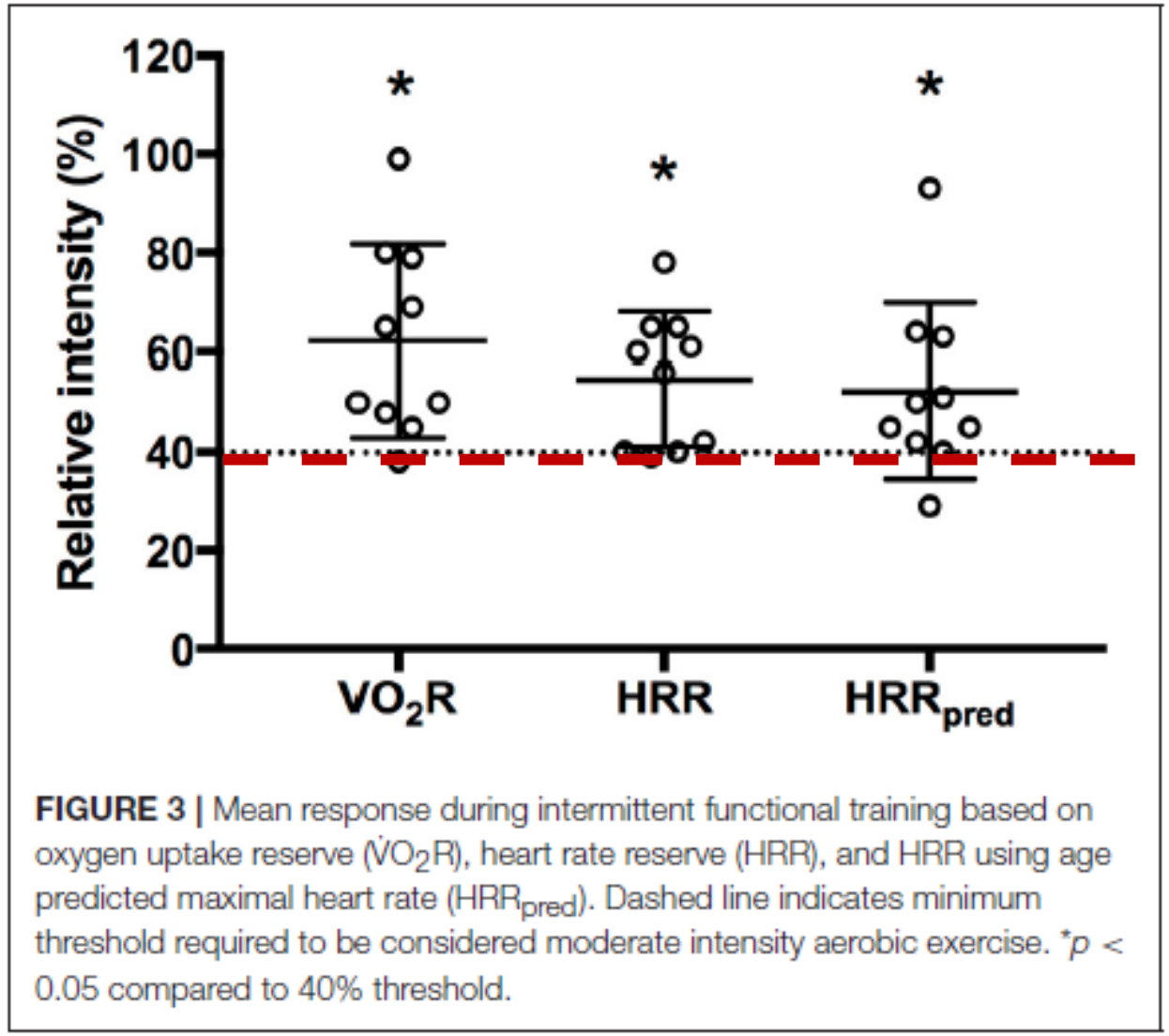


FIGURE 3 | Mean response during intermittent functional training based on oxygen uptake reserve ($\dot{V}O_2R$), heart rate reserve (HRR), and HRR using age predicted maximal heart rate (HRR_{pred}). Dashed line indicates minimum threshold required to be considered moderate intensity aerobic exercise. *$p <$ 0.05 compared to 40% threshold.

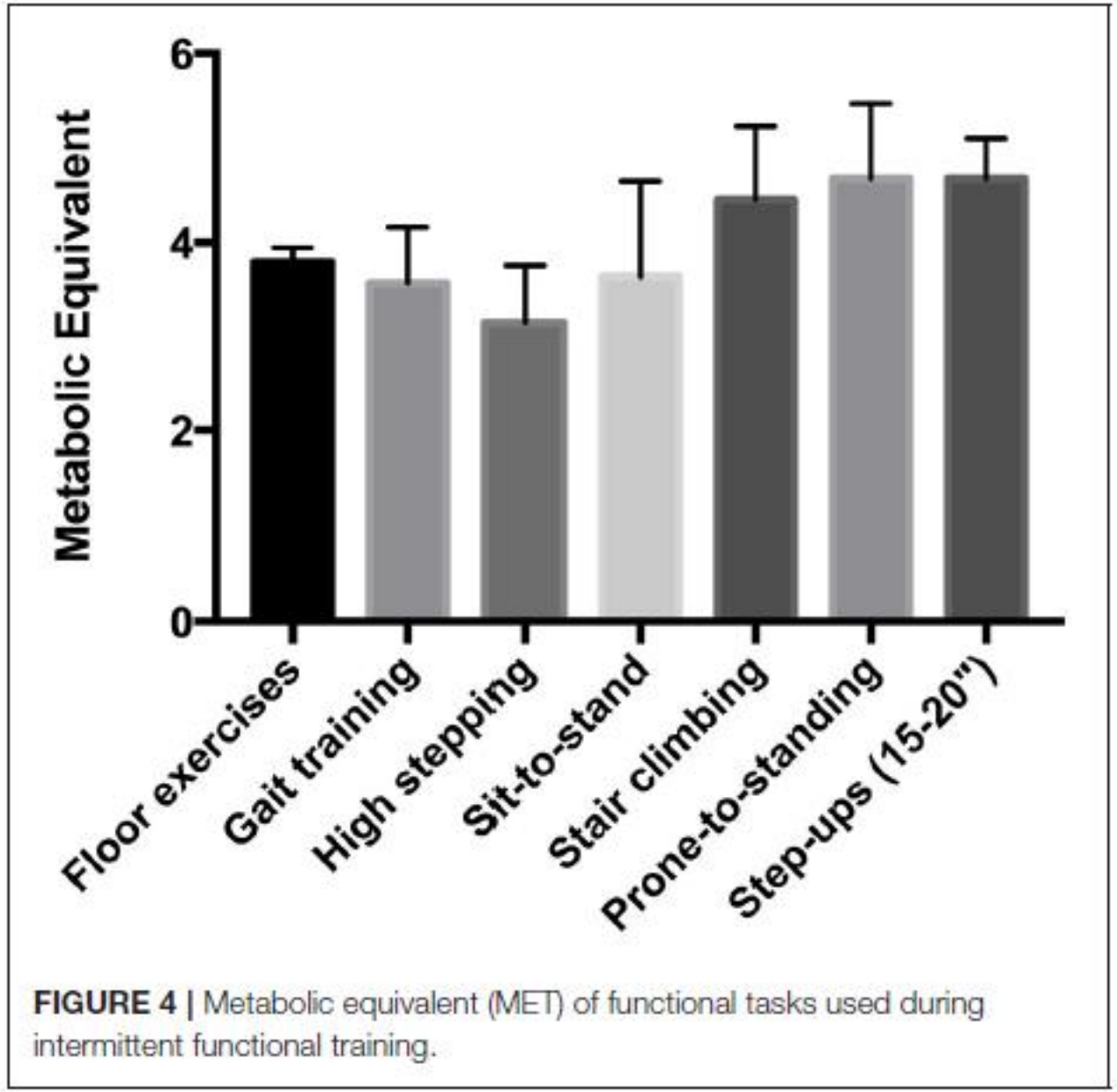


FIGURE 4 | Metabolic equivalent (MET) of functional tasks used during intermittent functional training.

Learning Objectives

- Describe post-stroke cognitive impairment and how it interferes with rehabilitation and community integration.
- Discuss the concept of ‘priming’ and how aerobic exercise could ‘prime’ the brain to foster recovery from stroke.
- Describe the results of a randomized controlled trial to test whether aerobic exercise could enhance cognitive functioning in chronic stroke.

Recovery & Performance LABORATORY

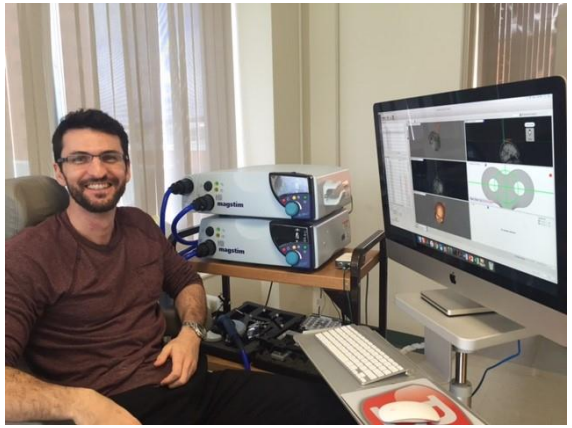
MEMORIAL UNIVERSITY

Liz Wallack

Marie Curtis

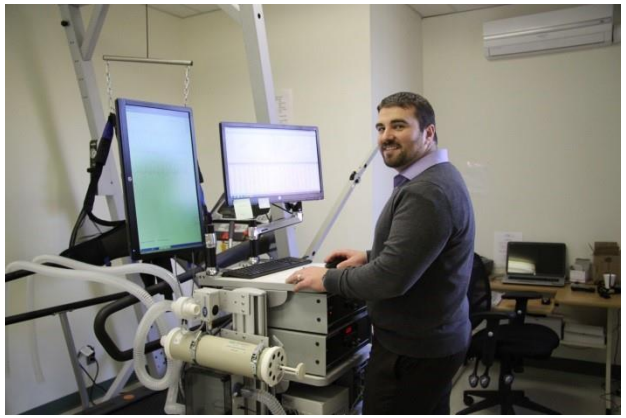
Megan Kirkland
MD-PhD student

Arthur Chaves PhD student



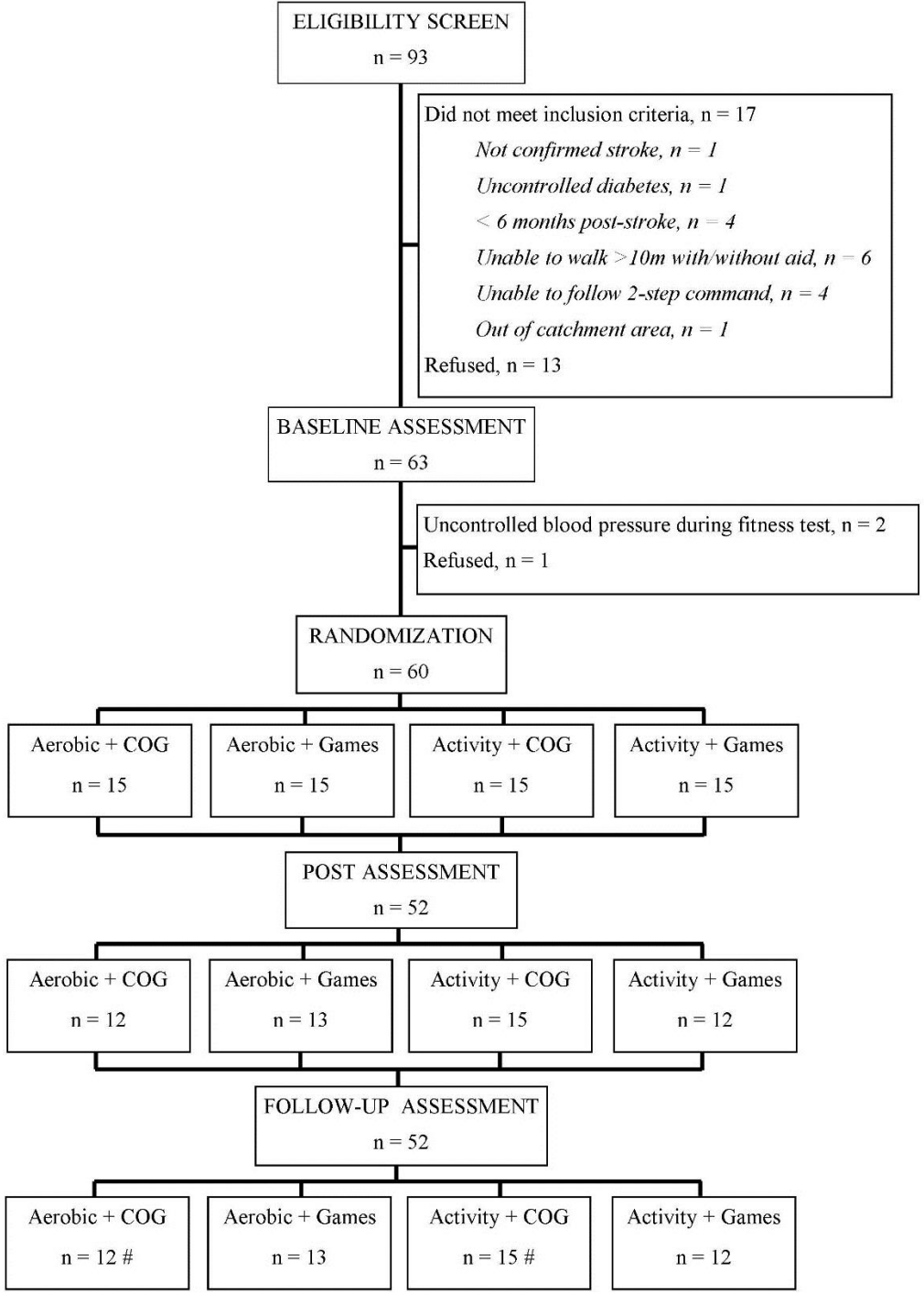
Dr. Katie Wadden post-doc

Augustine Devasahayam PhD student



Liam Kelly PhD student

This project was supported by grants from the Heart and Stroke Foundation Canadian Partnership for Stroke Recovery (MP, JM), the Canada Research Chairs program (MP), the Canada Foundation for Innovation (MP), The Newfoundland & Labrador Research and Development Corporation (MP), the Nova Scotia Health Research Foundation (MML), Capital Health Research Foundation, Halifax Nova Scotia (MML) and the Dalhousie University Faculty of Health Professions Innovation Fund (MML).


ELIGIBILITY SCREEN
n = 93
Did not meet inclusion criteria, n = 17
Not confirmed stroke, n = 1
Uncontrolled diabetes, n = 1
< 6 months post-stroke, n = 4
Unable to walk >10m with/without aid, n = 6
Unable to follow 2-step command, n = 4
Out of catchment area, n = 1
Refused, n = 13
BASELINE ASSESSMENT
n = 63
Uncontrolled blood pressure during fitness test, n = 2
Refused, n = 1
RANDOMIZATION
n = 60
Aerobic + COG
n = 15
Aerobic + Games
n = 15
Activity + COG
n = 15
Activity + Games
n = 15
POST ASSESSMENT
n = 52
Aerobic + COG
n = 12
Aerobic + Games
n = 13
Activity + COG
n = 15
Activity + Games
n = 12
FOLLOW-UP ASSESSMENT
n = 52
Aerobic + COG
n = 12 #
Aerobic + Games
n = 13
Activity + COG
n = 15 #
Activity + Games
n = 12