The Effect of Rehabilitation on the Neurobiology of Multiple Sclerosis

Albert Lo MD, PhD
Associate Professor
Neurology and Public Health, Brown University
Providence VA Medical Center
Mandell Multiple Sclerosis Center, Hartford CT
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Learning Objectives

At the conclusion of this activity, the participant will be able to do the following:

1. Describe the history of the exercise controversy in MS
2. Discuss the use of exercise as a disease modifying intervention using examples from animal models
3. Recognize the effect of MS on cognition, neuronal structure, and cellular environment
• Usain Bolt, world’s fastest man. 100 m and 200 m gold medals, 2012 Olympics
• But how would he do on the timed 25 foot walk test?
• 10 foot strides, 27.8 mph
• 0.61 seconds
Nations (London) bidding to host the **Olympics** claim that global sporting events inspire increased physical activity and subsequent **health benefits** in addition to other “legacy” benefits for the host population, justifying expenditures.

Why is physical activity important?

“Low fitness is a **better predictor** of mortality than obesity or hypertension”

Yet we hear about obesity and HTN, but there is very **little attention to fitness and physical activity**

Physical activity correlates with reduction in relative risk for key adverse health outcomes

Figure 2: Associations of moderate-to-vigorous physical activity with key health events, including all-cause mortality
Adapted with permission from Powell and colleagues.¹⁹
State of Affairs for exercise

- AHA/ACSM recommends **30 minutes** of **moderate** exercise **5 times-a-week** (150min), **20 minutes** **vigorous** **3 times-a-week** (60min)

- Recent report suggest that a little as **10%** of US adults participate in moderate amounts of daily physical activity *(Tucker JM, 2011)*

- Persons with MS report **lower** levels of physical activity than general population *(Motl RW, 2005)*

- Physical inactivity is **a major concern** for people with MS *(Motl RW, 2011)*
How does exercise, rehabilitation and physical activity apply to Multiple Sclerosis
Overview

- History of the exercise controversy in MS
- Exercise as disease modifying intervention
  - Lessons from animal models
- Effect on neurological function (cognition)
- Effect on neuronal tissue structure
- Effect on neurotrophic cellular environment
- Conclusions and Recommendations
Rehabilitation, Exercise, Sport

- **Physical Activity**: Any skeletal muscle movement that consumes energy above a basal level.
- **Exercise**: planned performance of repeated movements to improve skill, strengthen or improve performance or physical fitness. Exercises are used during rehabilitation.
- **Sport**: Physical activity or exercises that include rules, objectives, and often times competition. May occur individually or as part of a team.
- **Rehabilitation**: umbrella term, using multiple tools to enhance functional health condition in persons with disorders or diseases.
- Most “rehabilitation” literature covered is Exercise.

(Khan, 2012; CDC, 2011)
Where does Exercise fit in the context of Rehabilitation and other physical activity

Assistive devices...
Compensatory actions...
Symptom management...
Questions about Exercise

- Do you ask your patients about exercise?
- Do you advise them to exercise?
- What is the basis of your recommendations?
- What are your goals for the recommendations?
  - Cardiovascular benefit
  - Neurological benefit
The Problem with Exercise in MS: Uhthoff’s Phenomena

- Uhthoff’s clinical phenomena (1889).
- **Transient visual** changes associated with exercise or hot bath.
- Initial mechanism was unknown
- Core temperature-dependent decrease in conduction along demyelinated axons

Still an active area of investigation

- Worsening number or intensity of sensory symptoms in 40% of MS patients after exercise
  - 85% normalize in 30 minutes (Smith RM, 2006 APMR 87:723)
Reproducible Effects of heat on physical functioning in MS (Romberg, 2012)

- 23 heat sensitive MS participants, 19 controls
- Mean age 42.3, EDSS 2.9
- Heat exposure in dry Finnish sauna 35-40 min
- Examined at 1-hour and 1-day later
  - Upper limb: Grip and 9 Hole peg test
  - Lower limb: timed-walk, sit-to-stand, frontal reach
Change in core body temperature
0.2°C in controls, 0.5 °C (0.9 °F) in MS

**Fig. 1.** Core body temperature (mean, SD) of subjects with MS and healthy cont before the heat exposure, immediately after the heat exposure and 1 hour after heat exposure.
Effects of heat stress on physical functioning in persons with MS (Romberg, 2012)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Time point</th>
<th>MS subjects</th>
<th>Healthy controls</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immediately after heat exposure</td>
<td>0.4 (0.2 to 0.6)</td>
<td>-0.1 (-0.3 to 0.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>1 hour after heat exposure</td>
<td>0.2 (0.0 to 0.3)</td>
<td>-0.1 (-0.3 to 0.1)</td>
<td>0.06</td>
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<tr>
<td></td>
<td>1 day after heat exposure</td>
<td>-0.1 (-0.2 to 0.1)</td>
<td>-0.1 (-0.3 to 0.1)</td>
<td>0.69</td>
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<tr>
<td>TWT (s)</td>
<td></td>
<td>2.0 (0.9 to 3.0)</td>
<td>-0.4 (-1.6 to 0.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>FTSST (s)</td>
<td>Immediately after heat exposure</td>
<td>-0.1 (-1.1 to 1.0)</td>
<td>-0.6 (-1.8 to 0.5)</td>
<td>0.45</td>
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<td></td>
<td>1 hour after heat exposure</td>
<td>-0.7 (-1.8 to 0.4)</td>
<td>-0.5 (-1.7 to 0.7)</td>
<td>0.78</td>
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<tr>
<td></td>
<td>1 day after heat exposure</td>
<td>-1.8 (-3.1 to -0.4)</td>
<td>1.1 (-0.4 to 2.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>FRT (cm)</td>
<td>Immediately after heat exposure</td>
<td>-1.0 (-2.4 to 0.3)</td>
<td>0.5 (-1.0 to 2.0)</td>
<td>0.14</td>
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<tr>
<td></td>
<td>1 hour after heat exposure</td>
<td>-0.2 (-1.6 to 1.2)</td>
<td>0.6 (-0.9 to 2.4)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

TWT = Timed 7.62 m walk test; FTSST = Five-Times-Sit-to-Stand-Test; FRT = Functional Reach Test.

* P-value for group-by-time interaction.
Sauna experiment results

- MS showed significantly higher core body temperature than controls following heat stress. **Selective sensitivity**
  - Impaired sweating
- Heat affected **Lower Extremity** (walking and balance) more than Upper Extremity (grip, 9HPT)
  - Poorer immediately after heat
  - Nearly back to baseline at 1 hour
  - Baseline in 1 day
Modeling Uhthoff’s phenomenon in MS with internuclear ophthalmoparesis (Davis, 2008)

- **Neurophysiologic model** for object findings of temperature-related reversible changes in axonal conduction in MS
  - Internuclear ophthalmoparesis (INO)
  - Versional disconjugacy index (VDI)
  - First pass amplitude (FPA)

- Changes in core body temperature **0.8 Degrees** (heating and cooling) are associated with **stereotypic decay** and **restoration** in axonal conduction mechanisms
Figure 2: Velocity versinal dysconjugacy index (velocity-VDI) and first-pass amplitude versinal dysconjugacy index (FPA)

(A) Velocity-VDI, (B) FPA for individuals with clinically diagnosed multiple sclerosis (MS) and chronic unilateral or bilateral internuclear ophthalmoparesis (INO) (MS-INO), individuals with clinically diagnosed MS and no evidence of INO (MS-CON), and healthy age-/gender-matched controls (CON) during normothermic baseline (Baseline), peak whole-body heating (Heating), and the end of whole-body cooling (Cooling). Velocity-VDI in MS-INO was significantly different from MS-CON (p < 0.001) and CON subjects (p < 0.001). Velocity-VDI following Heating was significantly higher than during Baseline in MS-INO (p < 0.001). Similarly, velocity-VDI following Cooling was significantly lower than peak Heating in MS-INO patients (p < 0.001) but not different from Baseline (p = 0.20). This observation suggests that physiologic recovery from a thermal heat stress-induced conduction deficit in the MLF is reversible and even potentially mitigated by active cooling. The FPA in MS-INO was significantly different from MS-CON (p < 0.001) and CON (p < 0.001). FPA following Heating was significantly higher than during Baseline in MS-INO (p < 0.001). FPA following Cooling was significantly lower than during Heating in MS-INO (p < 0.001) but not different from Baseline (p = 1.00).
In 2011, what does the overall (meta-analysis) data say about exercise effects on MS
Meta-Analysis on the Effect of Exercise on Walking in MS (Snook and Motl 2009)

- 22 articles, 600 participants
- Overall effect size: 0.19 (IFN 0.20 for reducing progression 2 yrs)
- Larger effects with supervised exercise (0.32), less than 3 months (0.28), and mixed samples of RR and PP (0.52).
Can we trace exercise effects down from the system and behavioral level to the tissue, cellular and molecular level
Exercise as a disease modifying intervention for multiple sclerosis

Insight from animal models
Effect of exercise on progression, severity and relapses in EAE

- Monophasic and chronic relapsing EAE
- 10 days of exercise (60-120 min)
  - No exacerbations of disease
  - Delayed Disease \textit{onset} for CR-EAE
- 2 days of intensive exercise (250-300 min/day)
  - Decreased \textit{severity} of disease
- Moderate exercise for 5 days. No effect
- Mice with opportunity to self-exercise (Rossi, 2009)
  - Less severe neurological deficits

(Le-Page et al 1994)
Effect of Exercise on EAE Severity

**Fig. 1.** Effects of exercise on EAE-induced motor deficits. A. The graph shows that the severity of EAE-induced clinical disturbances was attenuated in both acute and chronic phases of EAE in exercising mice ($n = 10$ mice for both groups, $p < 0.05$ at each time point starting from 12 dpi). The animals were randomly allocated to the two experimental groups the same day. B. EAE mice reared in cages equipped with a wheel with blocked movement developed motor deficits that were similar to those seen in mice in standard cages ($n = 10$ mice for both groups, $p > 0.05$ at each dpi). The animals were randomly allocated to the two experimental groups the same day.
In EAE exercise is a disease modifying intervention

- Affects behavioral **onset, severity** and **relapses**
- Affects neuronal structure
- Definition of intensity was not clear
- Some cases more intense was more beneficial
- Other cases moderate also had an effect
Exercise on CNS function

Cognition
Exercise & Cognition: Older Adults

- **Meta-analyses** show an effect size ranging from 0.48 - 0.59
- Fitness training **increased performance** 0.5 SD on average, regardless of cognitive task, training method, or subjects’ characteristics
- Large effects seen for:
  - aerobic and aerobic + resistance training
  - training sessions **30 min** or more
  - interventions lasting **6 months** or more
- Domains such as:
  - simple reaction time, information processing speed, attention, learning and memory, and executive control tasks
    (Colcombe, 2003; Heyn, 2004; Smith, 2010)
Effect sizes demonstrated across all cognitive domains

- Simple reaction time
- Processing speed,
- Attention
- Learning and memory
- Executive control tasks

(Colcombe, 2003)
Effect of Rehabilitation on MS Cognition

- Cognitive impairment affects 43-65% patents with MS
  - ex. slowed mental processing, memory deficits
- Extensive data on cognitive benefits of exercise in older adults
- Limited data examining the effect of exercise on cognition in MS

Cross sectional studies
- Aerobic fitness (measured by VO2peak) has been shown to be correlated with PASAT score (Prakash et al., 2010; Sandroff, 2011)

2 intervention studies
- Oken, 2004. n=69 Home Yoga, class bicycle, waitlist control.
  - 6 months, no longitudinal change for cognition
- Romberg, 2005. n=95. Home-based progressive resistance training or waitlist control.
  - 6 months No change PASAT.
- Null findings (low intensity exercise? / Unsupervised home-based routine?)
Exercise on brain structure

Changes in Gray and White Matter
Map of gray matter showing regions that shrink with age. Clusters with largest peaks are evident in the frontal/prefrontal cortex (BAs 46/9,6), parietal cortex (BAs 40,21,5) and temporal cortex (BAs 21,38).

Map of gray matter revealing regions that show preservation with cardiovascular fitness. Clusters with largest peaks are in frontal/prefrontal cortex (BAs 46,9,6), parietal cortex (BA 40) and temporal cortex (BAs 21,22,38).

Map of white matter showing greatest age-related changes in the anterior white matter tracts and the more posterior tracts in the parietal lobes.

Map of white matter showing regions of relative preservation from age-related decline with fitness. Most regions that show age-related decline also show sparing with fitness.

Aerobic exercise increases brain volume
Elderly adults (Colcombe 2006)

- N=59, age 60-79
- **Aerobic training versus toning and stretching**
- Aerobic target 60-70% of HR reserve
- 6 months
- Three one-hour training sessions per week for 6 months
- Aerobic fitness affects cerebral white matter integrity
Changes in exercise group relative to stretching control group

**Blue**: Gray matter increases relative to control
**Yellow**: White matter volume increase relative to control
Change in anterior cingulate, SMA, medial frontal cortex, anterior WM Areas with daily functional roles. Atrophy associated with decline ADLs

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**Figure 1.** Regions showing a significant increase in volume for older adults who participated in an aerobic fitness training program, compared to nonaerobic (stretching and toning) control older adults. A and B, Neurologically oriented axial slices through the brain, at +2 and +34 mm, respectively, in stereotaxic space. C, Sagittal slice 2 mm to the right of the midline of the brain. **Blue regions**: Gray matter volume was increased for aerobic exercisers, relative to nonaerobic controls. **Yellow regions**: White matter volume was increased for aerobic exercisers, relative to controls. (See also Table 2.)
Largest changes were in the frontal lobe,
- Anterior cingulate gyrus
- Supplementary motor cortex, middle frontal gyrus
- Right inferior frontal gyrus and the left superior temporal lobe
- Anterior white matter tracts

All are areas known to affect daily function. Atrophy is associated with significant decline in memory, processing.

27-42% risk reduction for brain volume loss compared to toning/stretching

No change to aerobic training for young adults
Cardiorespiratory Fitness: A predictor of cortical plasticity in MS (Prakash, 2007)

- 24 RR MS participants (EDSS ± 2.61)
- Peak oxygen consumption (VO2peak) correlated with fMRI with PVSAT (visual version)
- Cardiorespiratory fitness positively correlated with right IFG/MFG and negatively correlated with ACC
- High-fit, greater % signal change than low-fit in right Interior frontal gyrus//middle frontal gyrus
- Low-fit participants recruited significantly more ACC activation (need for greater top-down inhibition)
- Hi-fit, greater functional recruitment of task-related areas than low-fit (greater cognitive reserve)
Cardiorespiratory Fitness: A predictor of cortical plasticity in MS (Prakash, 2007)

Figure 1. Activation in frontal, parietal, temporal and occipital lobes during performance of the PVSAT collapsed across all participants.

Fig. 2. Average % signal change in ACC and rt IFG/MFG in high-fit and low-fit participants along with standard error bars.
Fitness associated with preserved gray matter and white matter integrity in MS (Prakash, 2010)

- Preserved gray matter (yellow)
- Greater integrity of white matter (green)
- Both were associated with greater processing speed

Fig. 3 – Represents regions of GM loss (displayed in yellow) and FA reductions (displayed in green) in MS participants that are preserved with higher levels of cardiorespiratory fitness. Partial volume estimates in the GM structures and FA values in the white matter tracts correlated positively with fitness levels.
Exercise effects on the cellular environment and neuronal structure

Neurotrophic factors
Mechanisms: Neurotrophic factors

- **Nerve growth factor (NGF)**
  - Role in preventing neural death, favoring recovery process, neural regeneration, and remyelination

- **Brain-derived neurotrophic factor (BDNF)**
  - Necessary for long-term potentiation (long-term memory formation), and for the growth and survival of new neurons; can enhance brain plasticity

Single session of Aerobic Training Effects on BDNF and NGF

- Serum levels of NGF and BDNF
- 48 MS patients and 20 controls
- Before and after
- One 30 min bicycle session BDNF and NGF level rise by 30 mins

(Gold et al. 2003)
Resting Circulating BDNF is lower in MS: 8 week cycle ergometry study

- 30 minutes cycle ergometry at 60% VO2 max, 3 times per week
- 11 RRMS, EDSS 0-5.5, 11 controls

Exercise-induced BDNF change

- 0, 4 weeks, 8 weeks
- MS and Control are different across all timepoints
- Equilibration of BDNF over time as “novelty” of the stimuli diminishes
- 30min at 60% VO2 max is a **sufficient dose**, change of resting level conc
- Source of BDNF not clear, muscle, schwann cell
- Peripheral clearance with uptake by ? Muscle or CNS
Exercise Effect on Neuronal structure ...Back to animal models

- C57BL MOG EAE
- Exercise=running wheel
- Day 20 and 50 post
- All spine count along 100um dendrite length, 33/26/34, p< 0.01
- ? Independent effect of exercise on EAE
- Inflammatory infiltrate appeared the same
- Mechanism: exercise activate striatal dopamine, DA D2 Receptors, cannabinoid system

Golgi stained striatum
Rossi S (2008)
Revisiting electrophysiological stress on demyelinated axons

Electrically Active Axons Degenerate When Exposed to Nitric Oxide

Kenneth J. Smith, PhD, Raju Kapoor, DM, FRCP, Susan M. Hall, DSc, and Meirion Davies, BSc

- Are there any theoretical risks with intense activity?
- Axonal degeneration and neuronal loss are concerns
- Nitric oxide, high levels at inflammatory sites
- NO can impair mitochondrial function; complexes (I-IV) are abnormal in MS (Mahad 2008)
- Energy deficiency within axons and neurons creates virtual hypoxia and increases their susceptibility to excitotoxicity
Virtual chronic hypoxia in demyelination injury versus stroke (Trapp and Stys 2009)

Figure 3: Virtual hypoxia in multiple sclerosis lesions: imbalance of energy supply versus demand
The proposed modes of damage to axons during acute ischaemia (eg, stroke) versus chronic demyelination are
**Figure 5: Cascade of events leading to axoglial damage during states of energy deprivation**

White matter is dependent on a continuous supply of oxygen and glucose as well as ATP, which is taken up by axons and/or lactate (lactate) supplied by astrocytes. Reduction in energy supply leads to failure of ATP-dependent pumps, such as the \(Na^+K^+\) and \(Ca^{++}\) ATPases, including those located on the axoplasmic reticulum (AR), the axonal equivalent of endoplasmic reticulum. Axonal \(Na^+\) accumulates via non-inactivating (ie, not fully closed) \(Na^+\) channels and, with \(K^+\) loss through \(K^+\) channels (3) and depolarisation, stimulates the \(Na^+/Ca^{++}\) exchanger (NCX) to operate in the reverse \(Ca^{++}\) import mode. (1) Axonal \(Ca^{++}\) also accumulates by release of internal \(Ca^{++}\) stores, through an excitation-contraction coupling-like mechanism (L-type \(Ca^{++}\) channel activation of nyanode receptors [RyR]; see main text), which itself is modulated by GluR6 kainate receptors and neuronal nitric oxide (NO) synthase (nNOS)-derived NO. Insoluble triphosphate (IP3), generated by activation of group I metabotropic glutamate receptors (mGluR1; 2) and GluR5 kainate receptors (KAR; 4), acts via phospholipase C (PLC) to release \(Ca^{++}\) via IP3-activated receptors (IP3R) on the AR. Direct \(Ca^{++}\) entry through voltage-gated \(L\)-type and \(N\)-type \(Ca^{++}\) channels (1,4), and through axonal GluR4 AMPA receptors (AMPAR; 3), is also likely. \(Ca^{++}\) admitted via AMPARs acts in a cardiac-type \(Ca^{++}\)-induced \(Ca^{++}\) release to cause further \(Ca^{++}\) efflux from the AR via RyR type 2 (3). (2) The rise in \([Na^+]i\), coupled with depolarisation, also promotes glutamate (glu) and glycine (gly) release through reverse \(Na^+\)-dependent glutamate and glycine transporters (gluT and glyT), leading to glial and axonal injury by activation of AMPA/kainate receptors, and in the case of oligodendrocytes, NMDA receptors (NMDAR). NMDAR activation leads to \(Ca^{++}\)-dependent myelin and oligodendrocyte injury. Together, these pathways produce damaging increases in axonal \(Ca^{++}\), which in turn lead to an overactivation of various \(Ca^{++}\)-dependent enzyme systems (4). One of these is NO synthase (NOS), which generates NO and, indirectly, production of its reactive metabolite peroxynitrite (ONOO\(^{-}\))

This will adversely affect many structures, including mitochondria, thereby worsening the axon's energy deficit (see main text). G=protein. KCC=K/Cl cotransporter. NF=neurofilament. PAD2=peptidylarginine deiminase type 2. PDZ=postsynaptic density/disc large/zona occludens. PKC=protein kinase C.
Experiment Design/Method

- Rat spinal roots
- Exposed to Nitric Oxide (physiological levels)
- Electrical stimuli applied ranging in frequency (1-100Hz)
1Hz, quite and normal appearing

100 Hz, ovoid formation, axonolysis, wallerian degeneration
Results/ Interpretation

- Independently, neither NO or electrical stimuli cause degeneration
- However, with dual exposure, degeneration occurred after 2 hours of NO
- Not on human data, circumstantial evidence
- More relevant question may be the vulnerability of demyelinated axons
- Suggests minimizing electrical impulse activity during active CNS inflammation
Summary

- General population (and MS) is generally too sedentary
- Data (with limitations) to date suggests exercise is beneficial
  - Cardiovascular fitness, reduction of risk for comorbidities
- Exercise affects disease course in EAE
- Exercise associated with
  - Improved cognition
  - Gray matter volume
  - White matter connectivity
  - Production of neurotrophic factors, greater dendrite spines
- Increasing in core temperature affecting neurologic function, particularly the lower extremities, reversible
- Theoretical vulnerability of chronically hypoxic axons, not reversible

- Review of **116 papers**, analyzed 25 papers, 9 abstracts. Only interventions on resistance, endurance, combined.
- No solid evidence for specific recommendations. **Composite** using ACSM recommendations below
- Resistance: Yes, machines 2-3 days a week, 8-10 reps, 1-4 sets, 4-8 exercises
- Endurance: Yes, Bicycle ergometry, arm-leg ergometry, aquatic and treadmill
  - 2-3 days a week, 50-70% VO2 max, or 60-80% max HR
  - 10-40 minutes
- Combined resistance and endurance: Not clear
- **CMSC:** Similar as AHA, ACSM except allowances for individual disability or exercise tolerance (150 min moderate or 60 min/week vigorous) (Vollmer et al., 2012, *Int J MS Care* 14:2)
Balanced intensity/duration Model for neurological and cardiovascular goals

- Intensity:
  - 6 MET
  - 4 MET

- Duration:
  - 20min
  - 30min

- Cardiovascular
- Neurological
Extrapolated Recommendation for both cardiovascular and neurological benefit

- Balance between **enough for benefit**, but **not enough** for additional **risks**

- 2-3 days a week of resistance or endurance exercise, 10-30 min, rotate for **novelty** 4-8 weeks

- Avoid exercise that increase core temperature (0.8 deg)

- Training intensity resulting in declining performance is reason for caution

- Ask about exercise. **Exercise as vital sign** (minutes/week) Robert Sallis MD, Kaiser Permanente,
  - **Days of week** engage in moderate or greater, and **minutes/day**
  - Less than150min of exercise is flagged
THANK YOU

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