Cerebellar contributions moving, sensing, and learning

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Rehabilitation:
Neural control of movement

~ 600 muscles
~ 200 bones
> 80 joints (arms, legs)

1-3 degrees of freedom per joint.
Multiple muscles cross each joint.
Biarticular muscles.
Non-linear force generators
Mechanical interactions

Imperfect sensors (vision, proprioception).
Slow sensors.
Cross modal integration.

Movements must be:
- fast, accurate, smooth.
- adaptable.
- relatively ‘automatic’.
- learnable.
Objectives

1. Describe a possible mechanism of cerebellar ataxia.

2. Describe why cerebellar damage will affect active proprioception but not passive proprioception.

3. Describe how non-invasive brain stimulation can alter motor adaptation in walking.

4. Best rehabilitation strategies for people with cerebellar disorders?

5. Use of cerebellum-dependent adaptation to help rehabilitation of people with cerebral damage from stroke.
Lesions of the cerebellum

**Ataxia** (Greek, from a- + tassein to put in order)
“incoordination of movement”

dysmetria (hypermetria or hypometria)
abnormal path of movement
action tremor
gait ataxia
oculomotor deficits

cerebellum influences movement through projections to other motor structures.
Deficit in countering interaction torques.
(analysis of torques; single jointed movements less impaired than multijointed).

A. Control  B. Carotid

C. Fast-acccurate  D. Slow-acccurate

Bastian, Martin, Keating and Thach Journal of Neurophysiology 1996

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Forward model?

“Some three decades ago David Robinson proposed that endpoint accuracy of saccades is possible because the brain incorporates an internal feedback process through the cerebellum that monitors the motor commands and corrects them online (Robinson 1975)…”

From Shadmehr et al. 2010 Ann Rev Neuro.
A fast reach can be 300-500 ms!

“...the cerebellum may be a forward model that uses an efferent copy to predict consequences of motor commands and to correct the movement as it is being generated...” Shadmehr et al. 2010 Ann Rev Neuro.

This would theoretically affect proprioception, but only during active movement.

“Sensory prediction errors” drive learning [adaptation]. Mismatch between the predicted and actual consequences of motor commands.
Variability

Is there a bias, what kind, and can we correct it?

Multijoint more impaired than single joint movements.

Single joint more tractable to model.

<table>
<thead>
<tr>
<th>Kinarm robot, BKin</th>
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<table>
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<tr>
<th>ICARS</th>
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<td>11</td>
<td>47 M</td>
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For group mean ± standard deviation
*Multiple system atrophy patient included for comparison but not included in statistical analysis
modeling a mismatch in brain versus plant dynamics reproduces cerebellar trajectories.
More fundamental than just interaction torque compensation.

Mismatch between forward model in cerebellum and actual limb inertia.

We can replicate cerebellar subject behavior by creating a mismatch in control dynamics (inertia) and using simulation.

We can improve accuracy by altering cerebellar subject limb inertia in the right direction with a robot. Increasing and decreasing!

This does not correct trial to trial variability.
Variability

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**Active movement improves proprioceptive discrimination** Paillard and Brouillon 1968;

? Peripheral mechanism-- Active movement increases muscle spindle sensitivity (gamma motor neuron drive)?

? Central mechanism-- Forward model can be used to predict where a motor command will take you. This can be used with peripheral information to give better estimate?

Do cerebellar patients show this benefit?  Can we distinguish these two mechanisms?
3 tasks: 
Passive- Robot moves arm.

Active- You move your arm.

Active complex (unpredictable)-You move your arm but encounter unpredictable resistances.

?? look like active--peripheral mechanism
?? look like passive -- forward model mechanism
No active proprioceptive benefit in
1) cerebellar patients or
2) controls when they cannot predict dynamics.

Suggests central forward model mechanism
and not peripheral muscle spindle mechanism.
People with cerebellar damage show motor and sensory deficits consistent with a biased and noisy forward model of limb dynamics.

We can correct the bias for movement control by altering limb (i.e. plant) inertia in a patient specific way.

Proprioceptive deficits for only active movements. Integration of a noisy internal estimate of active limb motion.

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“Sensory prediction errors” drive learning [adaptation]. Mismatch between the predicted and actual consequences of motor commands.

Sensory prediction error is different from target or goal error.
Split-belt treadmill walking

baseline tied belts  adaptation split-belt 3:1  post-adaptation tied belts

The cerebellum is necessary for adaptation

Morton and Bastian, Journal of Neuroscience 2006
Non-invasive stimulation

Transcranial direct current stimulation (tDCS)

- Neuromodulation
  - No action potentials
  - Modulates cortical excitability
  - Effects can last beyond the train of stimulation
- Blocking NMDA receptors (dextromethorphan) prevents persistent effects. - Liebtanz et al. *Brain* 2002
- Mouse slice - direct current + low freq. stim induces NMDA dep. potentiation. This depends on BDNF secretion and TrkB activation. - Fritsch et al. *Neuron* 2010

Wagner, Valero-Cabre, Pascual-Leone 2007 Ann Neurol

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Non-invasive stimulation (tDCS) of the cerebellum can change adaptation rate in neurologically intact people.

Split adaptation

Jayaram, Celnik and Bastian *Journal of Neurophysiology* 2012
Motor learning (adaptation)

• Error driven—sensory prediction errors. No target necessary.
• Split-belt walking adaptation (and reaching, eye movements) depends on the cerebellum.
• Stimulation of the cerebellum in neurologically intact individuals can change learning rate.
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ARTICLES

Intensive coordinative training improves motor performance in degenerative cerebellar disease

W. Ig, PhD
M. Synofzik, MD
O. Berth
S. Brainard
M. Glain, PhD
L. Schöls, MD

Objectives: The cerebellum is known to play a strong functional role in both motor control and motor learning. Hence, the benefit of physiotherapeutic training remains controversial for patients with cerebellar degeneration. In this study, we examined the effectiveness of a 4-week intensive coordinative training in 16 patients with progressive ataxia due to cerebellar degeneration in 120 or degeneration of afferent pathways in 4.

Methods: Effects were assessed by clinical ataxia rating scales, individual goal attainment scores, and quantitative movement analysis. Four assessments were performed: 8 weeks before, immediately before, directly after, and 8 weeks after training. To control for variability in disease progression, we used an individual control design, where performance changes with and without training were compared.

Results: Significant improvements in motor performance and reduction of ataxia symptoms were observed in clinical scores after training and were sustained at follow-up assessment. Patients with predominant cerebellar ataxia revealed more distinct improvement than patients with afferent ataxia in several aspects of gait-like velocity, lateral sway, and intralimb coordination. Consistently, patients with cerebellar but without afferent ataxia, the regulation of balance in static and dynamic balance tasks improved significantly.

Conclusions: In patients with cerebellar ataxia, coordinative training improves motor performance and reduces ataxia symptoms, enabling them to achieve personally meaningful goals in everyday life. Training effects were more distinct for patients whose afferent pathways were not affected. For both groups, continuous training seems crucial for stabilizing improvements and should become routine care.

Level of evidence: This study provides Class III evidence that coordinative training improves motor performance and reduces ataxia symptoms in patients with progressive cerebellar ataxia.
E1 (exam 1)  8 weeks before training
E2  first day of 4 week intensive training of balance and gait.
E3 last day of training- start home prog.
E4 8 weeks later.

<table>
<thead>
<tr>
<th>Code</th>
<th>Name</th>
<th>Gender</th>
<th>Condition</th>
<th>Outcome 1</th>
<th>Outcome 2</th>
<th>Outcome 3</th>
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Ataxia was clinically assessed at the 4 examinations E1-E4 using the scale for the assessment and rating of ataxia (SARA) as primary outcome measure. SARA covers a range from 0 (no ataxia) to 40 (most severe ataxia). In addition, scores of the International Cooperative Ataxia Rating Scale (ICARS) are provided. In the patient column, "C" indicates individuals with predominantly cerebellar ataxia while "A" indicates patients with ataxia and tremor. For training: (yes) vs (no) categorization whether patients performed other physiotherapeutic training before intervention. Post training: (yes) vs (no) categorization based on interviews, assessing whether patients performed daily training after intervention.

IDCA = idiopathic cerebellar ataxia; SCA 6 = spinocerebellar ataxia type 6; ADCA = autosomal dominant cerebellar ataxia; SCA 2 = spinocerebellar ataxia type 2; SASSA - sensory ataxia neuropathy with dystone and ophthalmoplegia caused by mutations in the polymerase gamma gene (POLG); SN - sensory neuropathy; FA - Friedrich ataxia.
Ilg et al., Neurology 2009.

Improved walking and balance after intense outpatient balance program.

No additional gains seen with follow-on home exercise program.

People with cerebellar and sensory ataxia (e.g. Friedreich) did not improve.
Far, far away in another country... another group wanted to understand if people with cerebellar damage could benefit at all, even a little, from extended practice. If so, then maybe there is an intact learning mechanism that they can use to improve their movement control. Such a mechanism would perhaps depend on another part of the brain.

6 week home exercise program for people with cerebellar damage.

Table 1. Subject characteristics at baseline and exercise log summary

<table>
<thead>
<tr>
<th>Subject</th>
<th>Diagnosis</th>
<th>Sex</th>
<th>Age (y)</th>
<th>ICARS (total)</th>
<th>Exercise Duration (days)</th>
<th>Exercise Intensity (%)</th>
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<td>40</td>
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</tbody>
</table>

Mean±SD: 7M/7F 52±11 39±15 23±1 47±20

*SAOA, sporadic adult onset ataxia; FAOA, familial adult onset ataxia; SCA 3,5,6,8,17 spinocerebellar ataxia type, subject 14 ataxia due to 2 hygromas with anterior lobe atrophy.
Exercise: balance (sitting, standing, walking) and endurance

- Trunk circles
- Trunk rotation
- Toe touch
Standing

- Weight shifts in all directions, stable surface, eyes closed, foam.
- Changing base of support, stable surface, eyes closed, foam.
- Stepping on steps, stable surface, foam.

Walking

- Tandem, head turns, braiding, backwards etc.

Endurance

Rated difficulty of exercise - 0% no confidence to 100% complete confidence in maintaining balance.

Tests that were not directly part of the training improved.
Participants who rated the exercise as more challenging improved the most.

Balance training can improve walking performance and balance tests.

- generalized to tests that were not trained.
- retained 1+ months after.
- possible with both outpatient therapy and a home exercise program.

- Benefit correlates with challenge. Harder seems better (to a point).
- How and what are they learning?
time scales of learning movement

- strategic, declarative learning (minutes)
- use dependent learning (Hebbian) (hours)
- reinforcement learning (days)
- motor adaptation (weeks)
- sensory adaptation (months)
- years

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Are any brain regions important for split belt adaptation?

Adults and kids with cerebral damage **do adapt**.
Reisman, Silver, Wityk, and Bastian, Brain 2007.
Choi, Vining, Reisman and Bastian, Brain 2009.
and transfer to over ground walking.
Reisman, Wityk, Silver and Bastian, NNR 2009.
and improve symmetry with long-term training.
Reisman, Mclean, Bastian JNPT 2010
Reisman, Mclean, Keller, Bastian, NNR in press.

People with cerebellar damage **do not adapt**.

(3) Brain regions

**Split-belt perturbation must exacerbate limp.**
*This pushes subjects to learn to correct it.*
During adaptation, to exacerbate limp:

Put the leg that takes the smaller step on the **fast belt**
**bigger step on the slow belt.**

(3) Brain regions

Understand the deficit to avoid training the wrong way.
4 weeks of training in individuals with stroke

- **Baseline**
- **Post-training**
- **1 month follow-up**

- **Paretic**
- **Non-paretic**

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**Split-belt walking adaptation**

Depends on the cerebellum, thus individuals with cerebral stroke can benefit in short term.

Can help individuals with stroke improve symmetry long term (4 weeks; testing 3 months).
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These guys did the work
Darcy Reisman
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James Finley
Julia Choi
Susanne Morton
Gowri Jayaram
Erin Vasudevan
Katie Amenabar
Nasir Bhanpuri
Jen Keller

Hopkins Collaborators
Pablo Celink
Kathy Zaczkowski
Reza Shadmehr
John Krakauer
Robert Wityk
Ken Silver
Patti Vining

Outside Collaborators
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Jaynie Yang
Allison Okamura

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Kristin Musselman
Alex Vazquez
Heidi Weeks
Gowri Jayaram
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Andy Long
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