Meaningfulness of mean group results for determining the optimal motor rehabilitation program for an individual child with cerebral palsy

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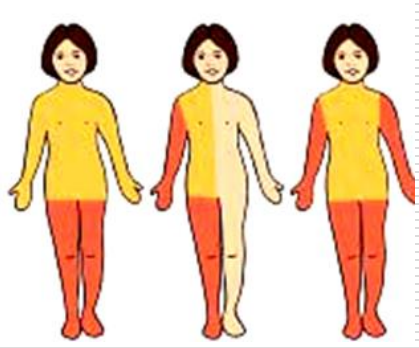
Cerebral Palsy (CP)

- Most common child-onset motor disability
- Group of disorders from early brain insults that vary in type, location, extent, & timing
- Ranges from those who can walk fairly well to those with no independent mobility



Physiotherapy Evidence for CP

- Early 1980s, few treatments and none supported by evidence
- Treatment based on philosophical approaches developed by individuals
- Now many treatments with + mean effects

Narrowing down the list of interventions: which are best?

- Initial studies demonstrated that a given intervention produces + change
  - Lead to long list of possible treatments
- Direct comparison to alternatives: which is better? (RCTs)
  - many "effective" interventions did not show superiority (Dobkin & Duncan, 2013)
- Refining list by strength & consistency of evidence (systematic reviews)

Proven Effective

Preferentially use this approach

Uncertain Effect

Insufficient evidence

No evidence

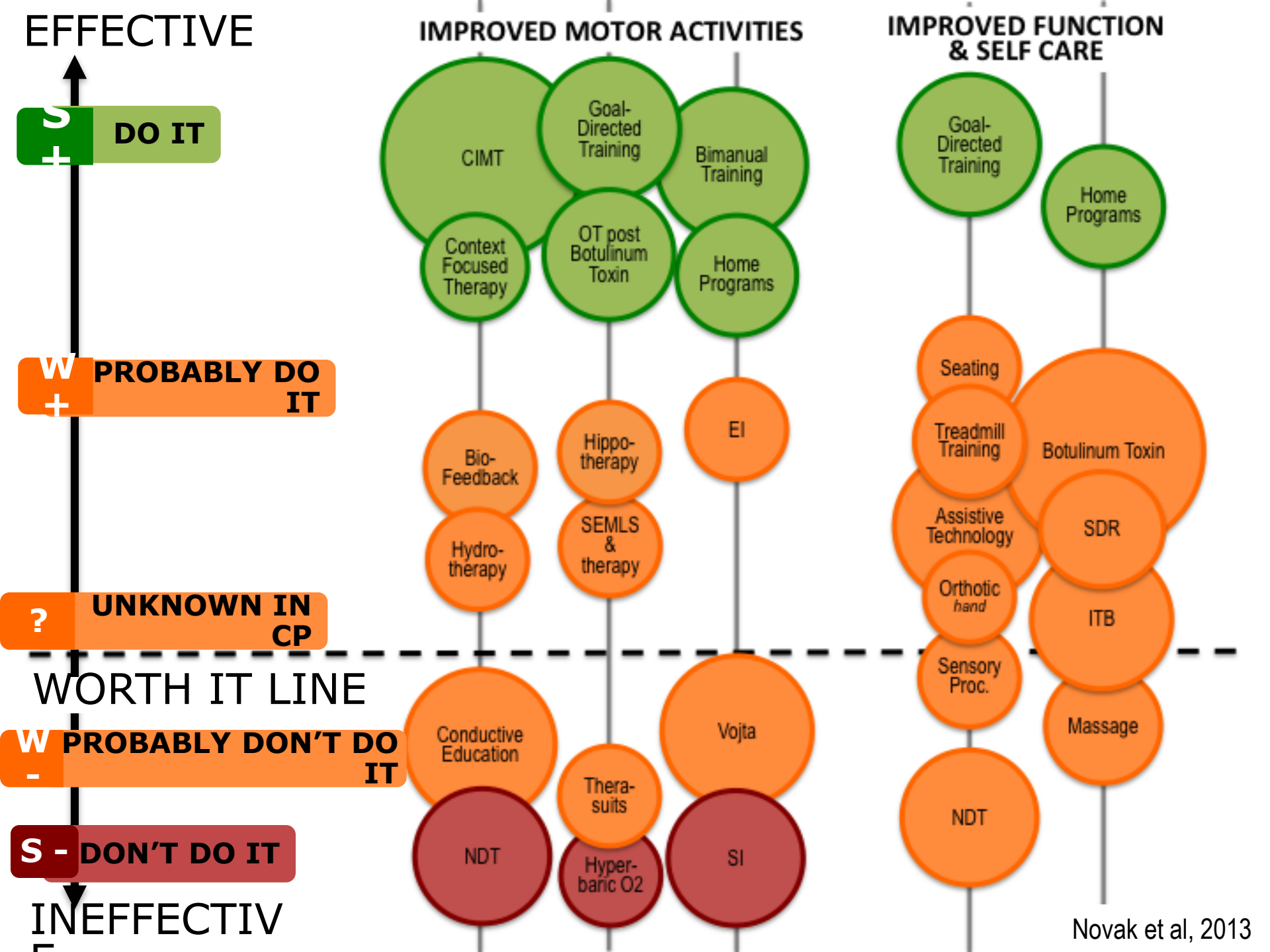
Conflicting evidence

Measure effects. Were goals met?

Proven Ineffective

Do NOT use this approach. Choose alternative

Novak & McIntyre, 2010



Novak et al, 2013

Evidence-Based Practice (EBP)

"Conscientious, explicit & judicious use of current best evidence in making decisions **about the care of individual patients**".

(Sackett, 1996)

Do we have the evidence we need to do this?

Basic Premise of this Talk

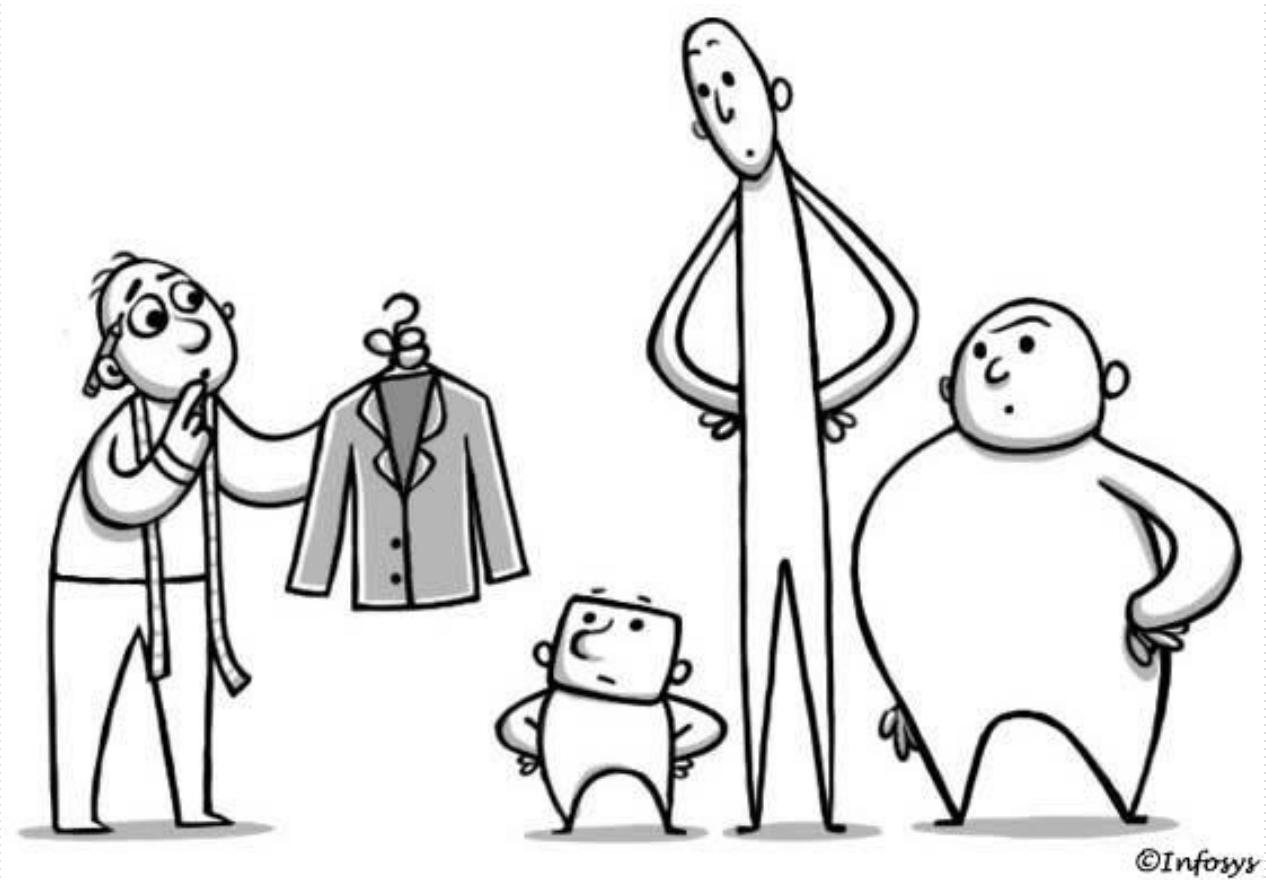
- Group mean data can inform us as to whether a treatment *works*
- Effect sizes can help determine how well a treatment *works*
- This is NOT ENOUGH! We need to better identify sources of individual variation in outcomes (GENETICS) to understand *what works best….for whom?*

Statement of the Problem

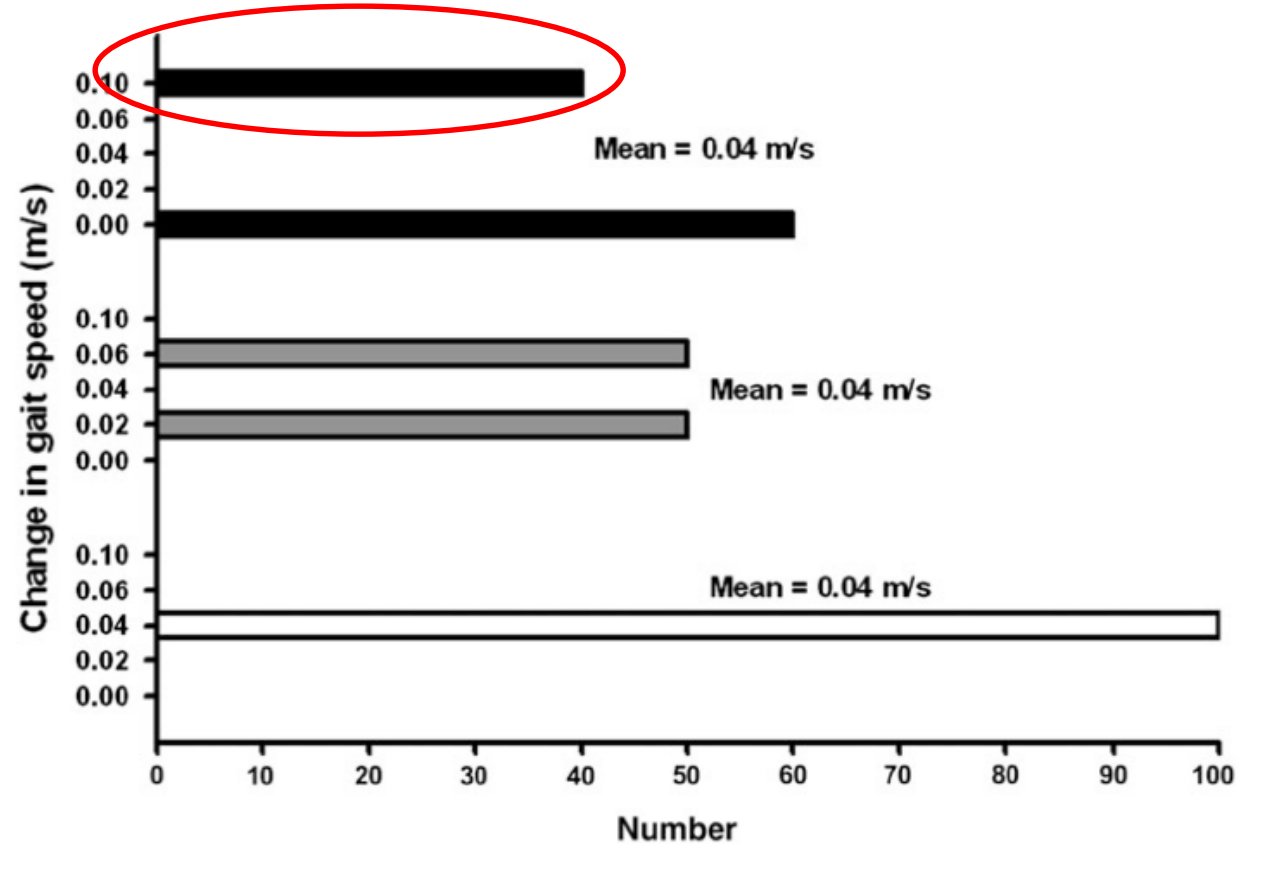
"The vast majority of published studies have emphasized main effects and group differences, while paying little, if any, attention to individual differences. It needs to be recognized that contributions at the level of a group may not fully apply to each member of that group."

Buford, Roberts & Church, 2013

Mean jacket size: No one size fits all!

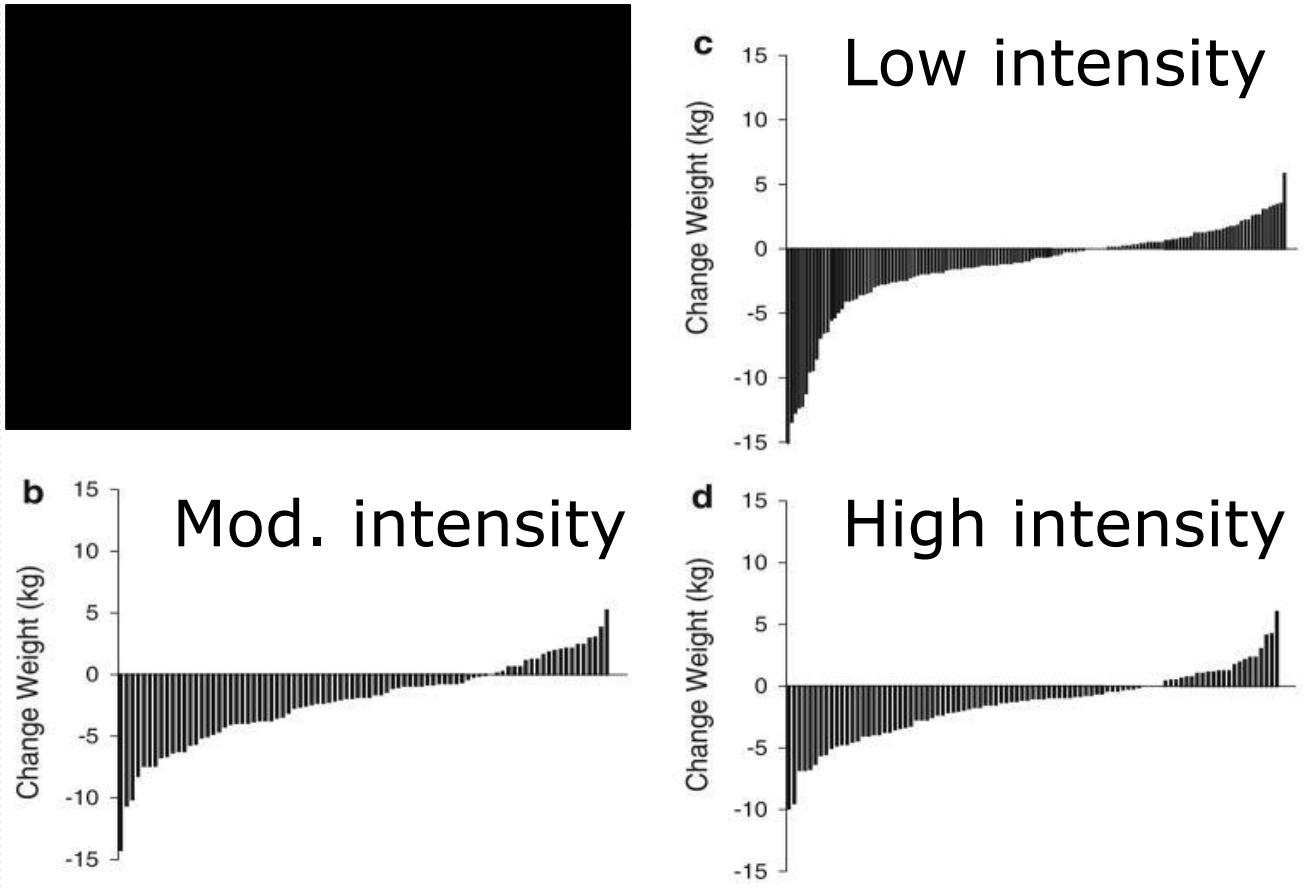


Same Mean - Variable Outcomes



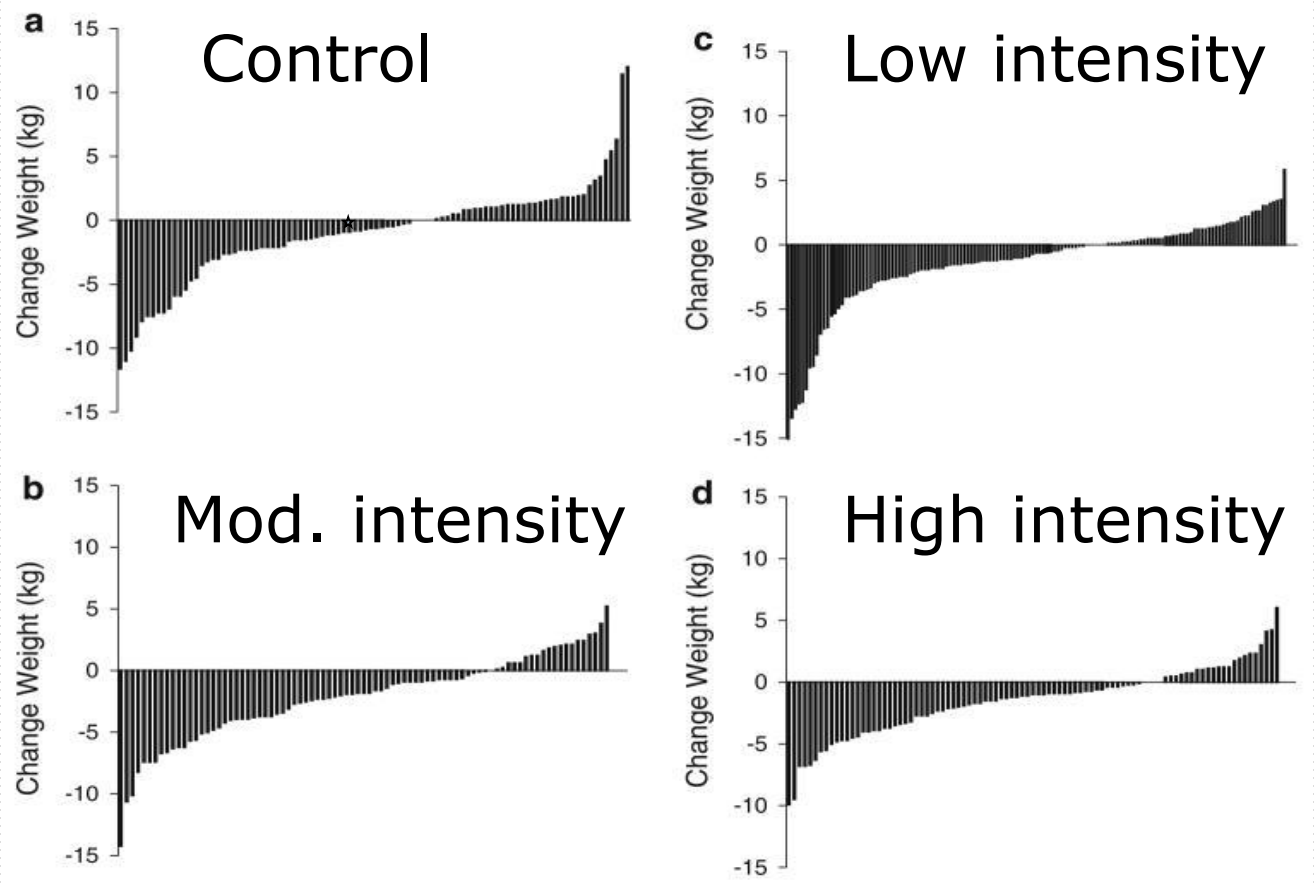
Buford, Roberts & Church, 2013

Individual data example: (n=400+) Weight loss after exercise programs



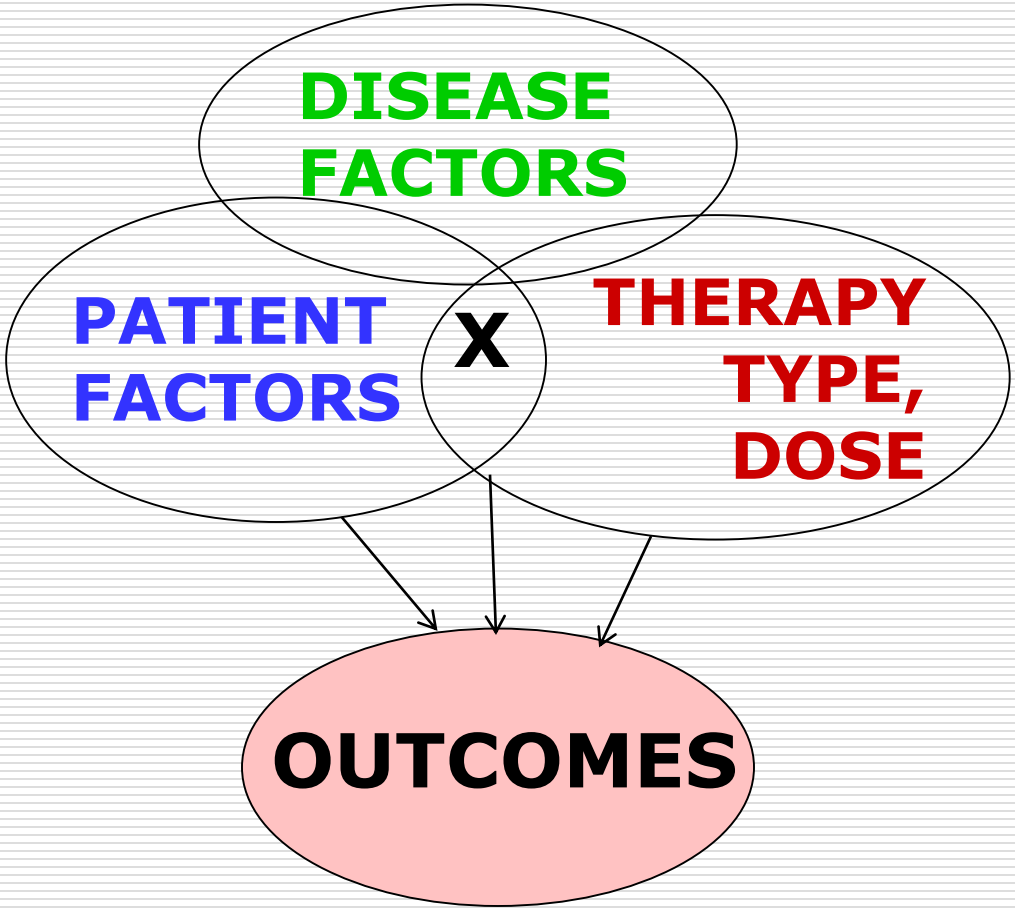
Buford, Roberts & Church, 2013

Weight loss after exercise programs



Buford, Roberts & Church, 2013

Sources of Variability in Outcomes



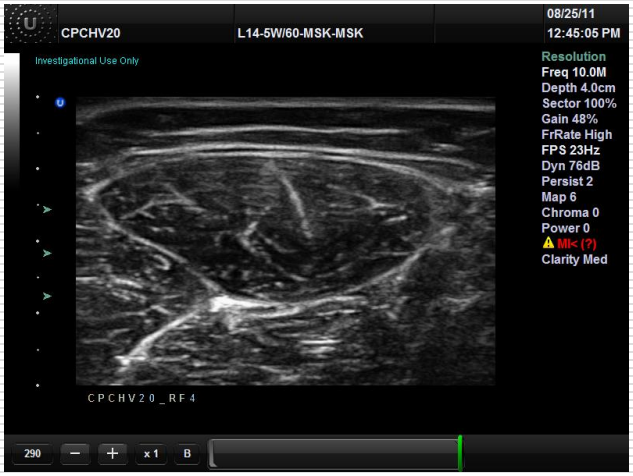
Examples of THERAPY factors

- **Dose:** Many rehabilitation trials do not use sufficient doses to produce clinical change
- Intensive upper limb training protocols (unilateral, bilateral) in CP are equally effective when matched by dose (range of 60-90 hours)
  - Data not as strong for locomotor training: most studies have doses of 20 hours or less

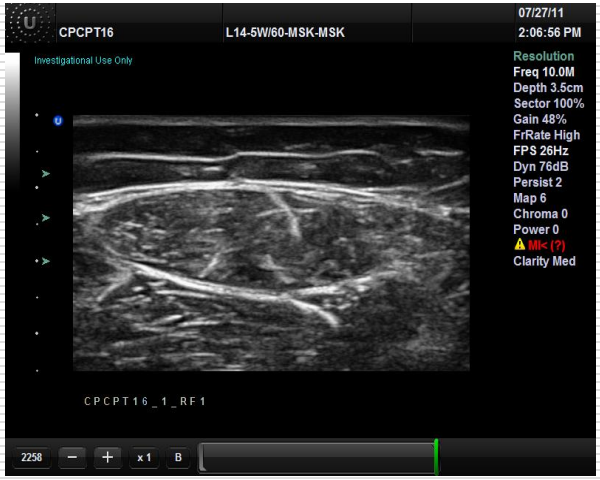
Disease-related Factors

- Factors related to a condition that produce a different response to an intervention than in controls:
  - In CP, muscle integrity (e.g. collagen & fatty infiltration) deteriorates with age & inactivity; leads to poorer response to strength training

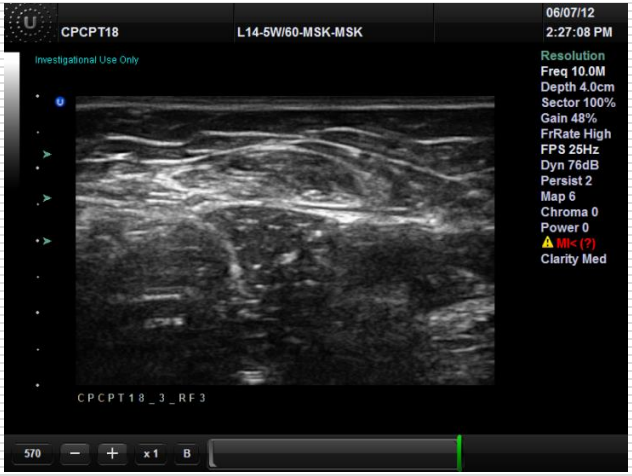
Rectus Femoris Muscle Ultrasound Images in Pre-adolescent Children Matched by Weight



Child without CP



CP GMFCS II



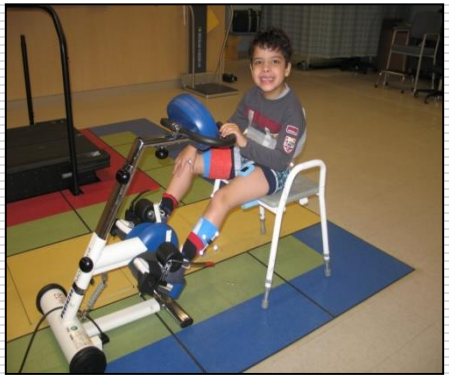
CP GMFCS III

Patient factors

- Age
- Sex
- Mobility Level (GMFCS); hand use (MACS)
- Motivation
- Others?

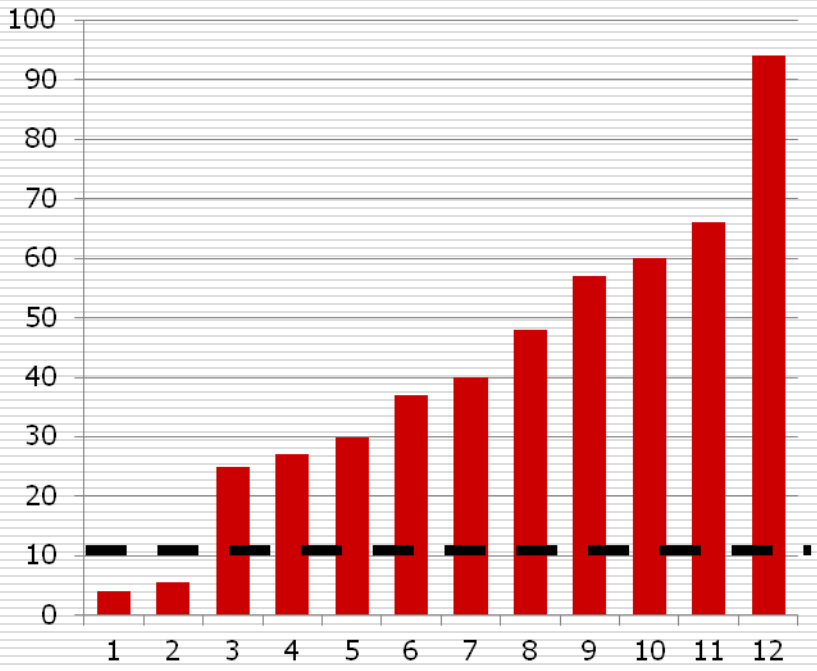
Locomotor Training RCT in CP

- 12 wk rapid resisted leg training (elliptical or computer-assist cycle) to improve reciprocal coordination & gait speed
  - Homogeneous: All preterm with white matter injury, bilateral CP, GMFCS I-III

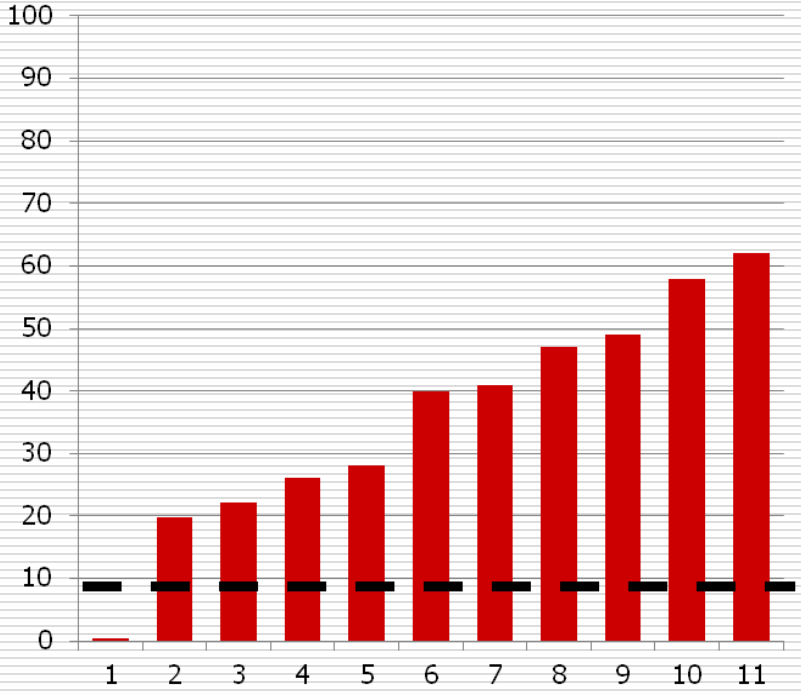


Damiano et al. NNR 2017

Change in cadence (p<0.05)



Cycle



Elliptical

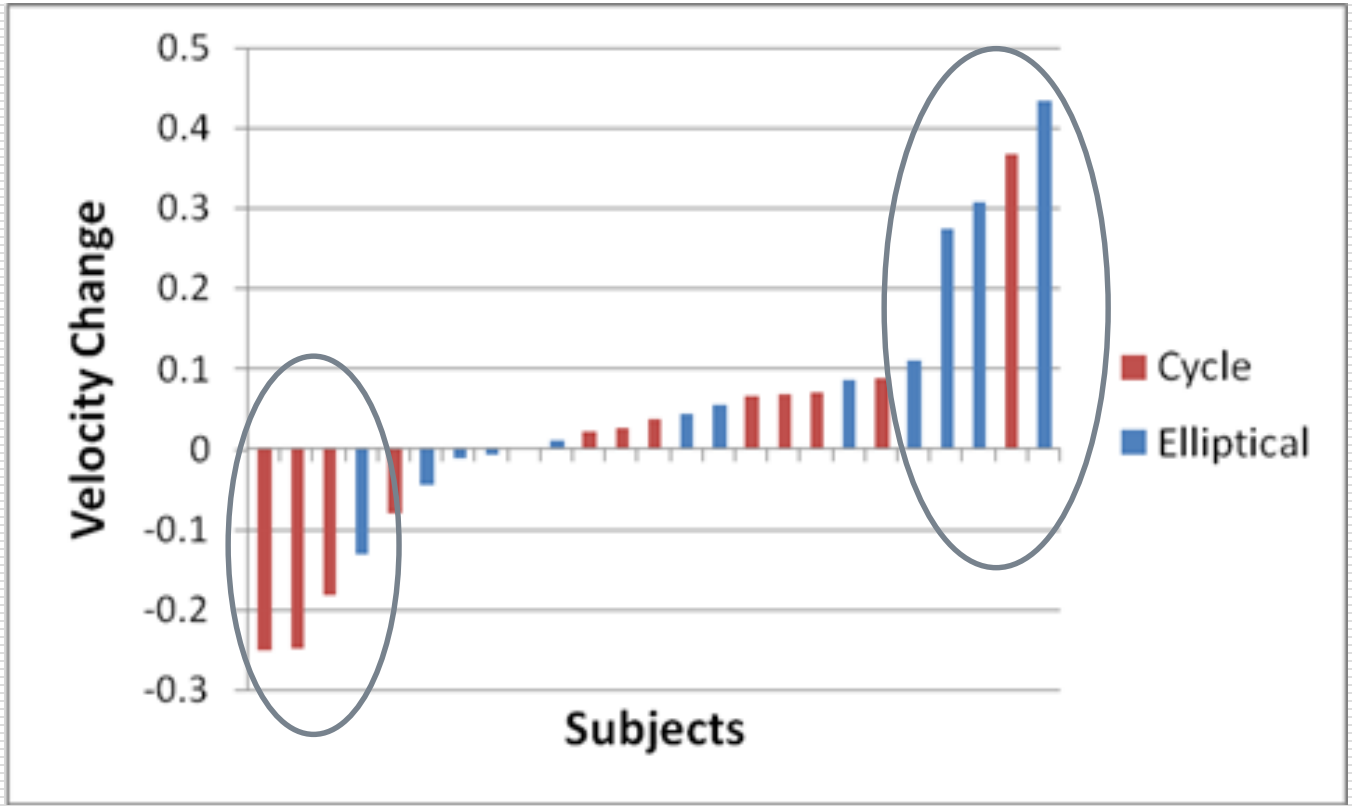
Task Specific Improvement

Mean gait speed values (m/s)

Group	Pre	Post	p
Cycle	0.81	0.81	0.12
Elliptical	0.92	1.01	

- No pre/post change in cycle, no group differences
- +0.09 mean change in elliptical – neither statistically nor clinically significant (0.10 m/s)
- End of story?

Individual Data for Change in Gait Speed



Age or GMFCS level not associated with outcomes

Gait Speed Changes (Elliptical Group)

Predictive factors for CIMT & intense upper limb training in CP

- Best evidence of all treatments in CP
- Consistent + mean response; however, wide variability (@25% are worse)
- No strong predictors of outcomes found:
  - Correlation of age & response inconsistent
    - Response in 4-8yo not different from 9-13
    - 29mos better mean response than 10yo
  - Unlike stroke, hand function not related to response in CP

Eliasson et al, 2014

What other factors are we missing?

Pharmacogenetics & Precision Medicine

- Idea originated @1960 with focus on differential responses to medications
  - No drug 100% efficacious; individual responses can range from benefit to SAEs
  - e.g. Wayfarin (anti-coagulant) doses in Asians for = response are ¼ of that for Caucasians; greater for African-Americans
  - Also wide variability within groups
  - Genetic differences help explain variability (may involve multiple genes)

Genetics and CP?

- Earlier data: @2% of CP a genetic disorder
- 15-40% associated with congenital malformations (McIntyre 2016)
- Multiple genetic factors may interact with environment to cause CP or modify severity of CP as with other disorders, e.g. autism (Moreno-De-Luca, 2012).
- *Little data on effects an individual's genes on treatment outcomes*

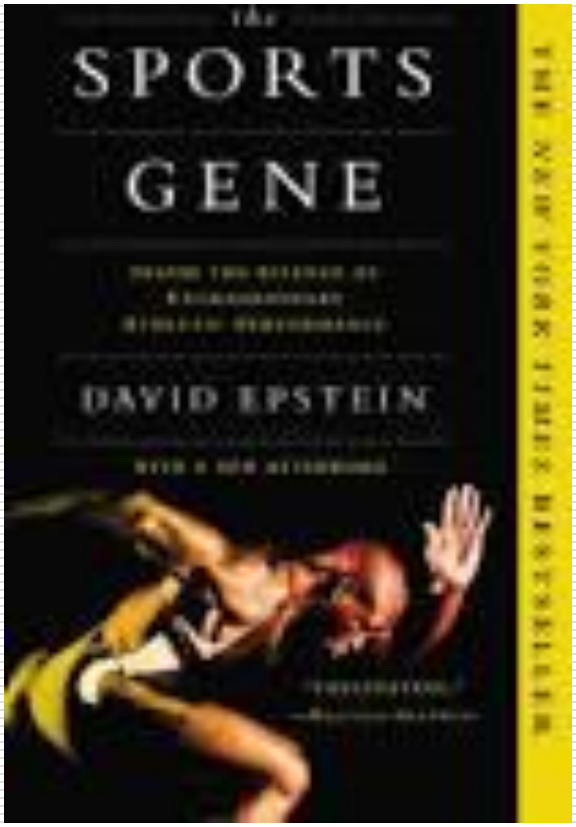
RECENT HEADLINE IN US: Astronauts no longer identical twins!

- One had extended period in space
- Early Reports of 7% DNA change not possible (fake news); still the same.
- Epigenetic changes (gene expression); has also been shown in twins with CP

Exercise as Personalized Medicine
(Buford et al., *Sports Med* 2013)

- Much variability in response to aerobic & resistance training in homogeneous groups of compliant healthy adults:
  - Change in VO_2 max range: 0-100%
  - Elbow flexor strength after 12 wks, 0-250%
  - 16 wk PRE, muscle fiber size change 0-60%
  - Response not binary, but a continuum
  - Genetics, lifestyle, environment, age, disease state all contributing factors

Genes & Extreme Motor Performance



Inside the science of extraordinary athletic performance

Explores the extent to which genes are destiny in different aspects of sports performance

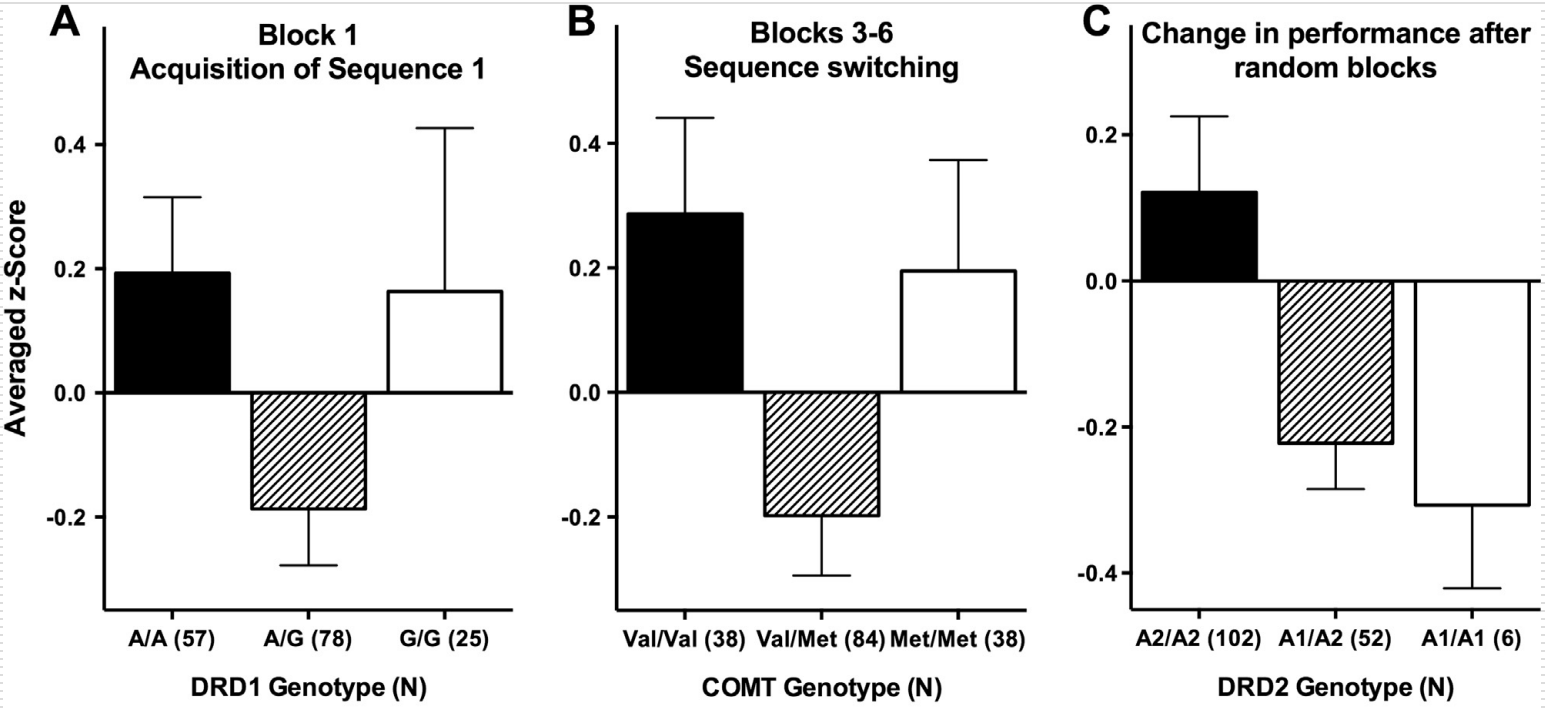
Genetic variability in motor skill training

Genetic variation in motor cortex plasticity

- Identical (9) and fraternal (7) twin pairs tested using paired associative stimulation (electrical stimulation + TMS)
- Cortical excitability (MEPS) up to 30 min.
- Intrapair differences 2X greater in fraternal twins; strong "heritability"
- Conclusion: genetic factors significant contributors to adaptive brain changes

Dopamine Genes & Motor Learning

- Different gene polymorphisms affect different learning aspects in normal population



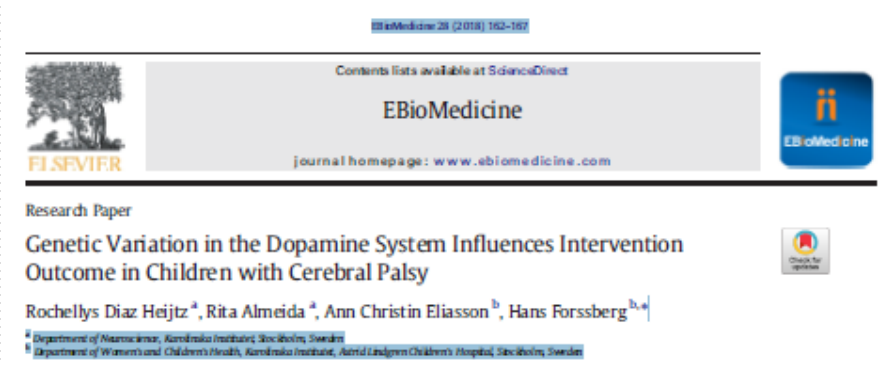
Baetu et al, Neurobiol Learning Memory, 2015

Dopamine (DA) example: Adults

- Genetic variation in DA levels & response
  - RCT 50 adults: 2 wk motor skill training + L-Dopa (Experimental) or placebo (Control) (Pearson-Fuhrhop, 2013)
  - Hypothesis: Levodopa will improve learning
  - NO MEAN DIFFERENCE
  - Calculated gene scores for DA transmission and found interaction. Those w/ higher scores did better on placebo. L-dopa made those w/ lower gene scores better & w/ higher scores worse

CIMT Response & Gene Score

- Dopamine gene scores in 28 children with CP are directly related to CIMT outcomes (higher DA scores did better)



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Research Paper

Genetic Variation in the Dopamine System Influences Intervention Outcome in Children with Cerebral Palsy

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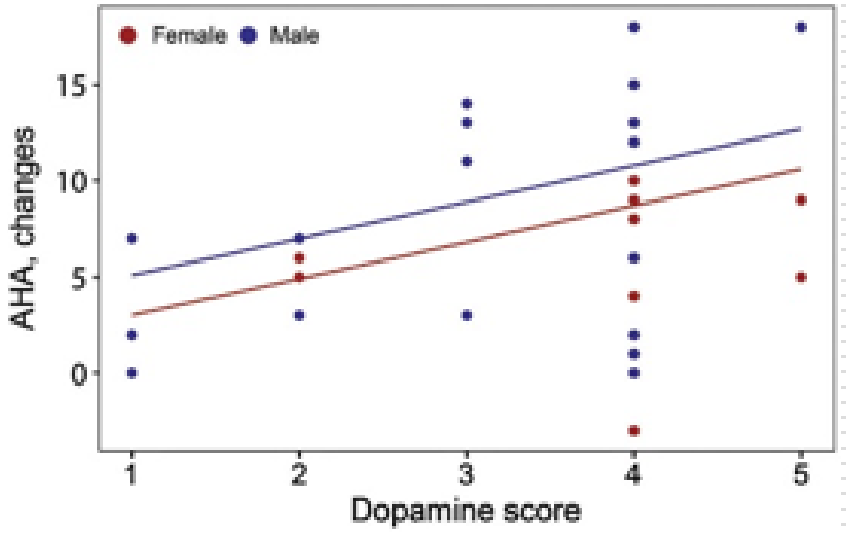


Clinical Implications

- Each patient is different. Do not assume that an "effective" treatment will work on all patients
- Same exercise can have different + effects in different people which may be missed if you are only measuring one outcome
- Many poorer responders may need more time to increase strength, endurance or learn new skill
- Some may benefit from medications, motivation (e.g. reward system, or techniques [TMS, tDCS] that increase cortical excitability, plasticity

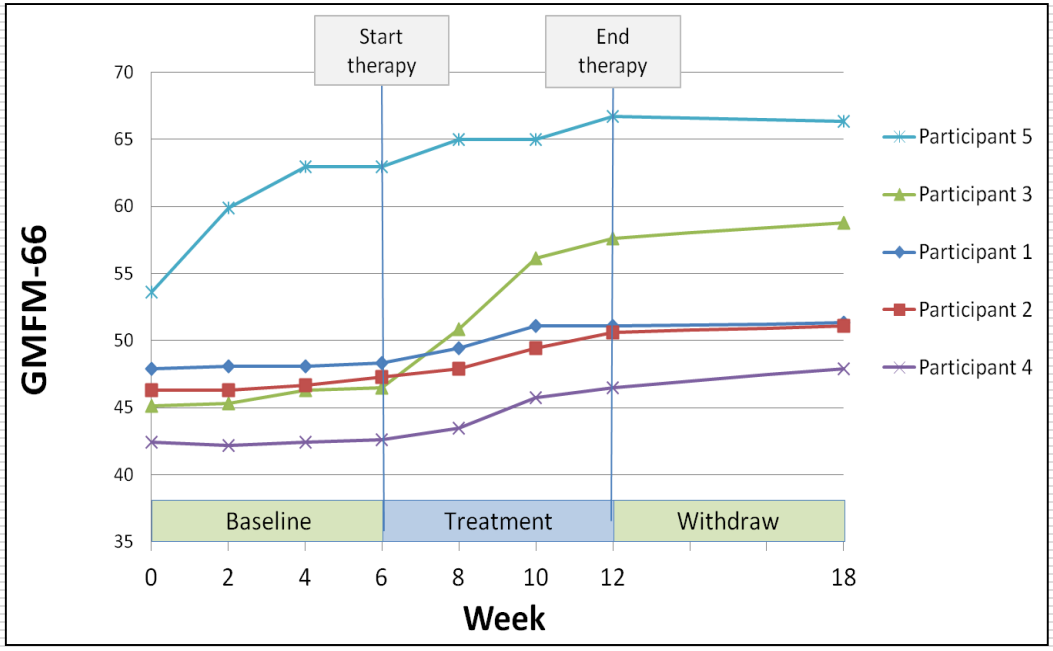
Research implications: More meaningful Mean Group studies

- Greater use of control or comparison groups (many in rehab now using wait-list controls)
- Need adequately powered sample sizes
- Use of confidence intervals and minimal clinically detectable differences helpful (not sufficient)
- Reducing sample variability: reduces individual variability – but also generalizability
- Use correlation or regression to relate patient factors to good/bad outcomes

Need Additional Research Designs

SINGLE SUBJECT DESIGNS, e.g. multiple baselines, can have high internal validity; are gaining greater acceptance in rehabilitation

5 toddlers with CP performed 6 weeks intensive mobility training: 4/5 had significantly greater improvement during therapy (Prosser 2013)



No Device vs. Device

Comparative Effectiveness or Pragmatic Clinical Trials

- Several large scale rehabilitation trials already
  - In contrast to RCTS, exploit variability in patients, treatments, and outcomes
  - Done within clinical care: documents all interventions in large cohort; EMR, point-of-care checklist for therapy; patient-reported outcomes
  - **"What works":** Compares treatments by associations with better or worse outcomes
  - **"For whom":** extensive patient characterization; Links multiple patient characteristics to outcomes to identify better or worse responders

Results in TBI & Stroke (Susan Horn)

- Differences in patient "severity" far better predictor of outcome than type of treatment
- In acute or early rehab, only first several hours of therapy have impact; higher level activities have + association (gait training, functional reaching, talking vs. articulating)
- Recommendations now being implemented in early rehab with + results

" We need a new definition of a clinical trial because it will be impossible to do a separate single trial to answer each question raised by each biomarker and candidate therapy"

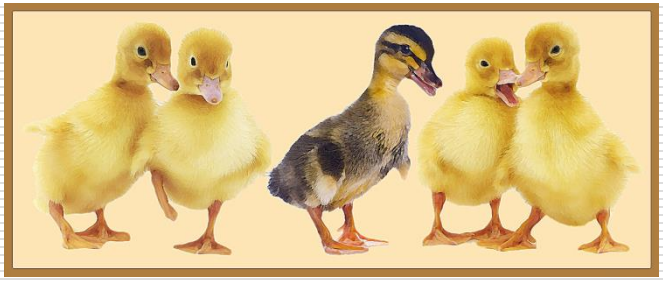
Woodcock, Director of CDER/ FDA

Lessons from Cancer Research

- Large databases "Learn from every patient" based on their characteristics (tumor type), treatments given & associated outcomes
- Subgroups become more refined over time
- Database queried for optimal plan for each new patient whose data then used to refine algorithm

Embrace outliers!

- Most try to ignore or discard them
- National Institutes of Health considers its focus on rare diseases as embracing outliers
  - Francis Collins: Progeria Syndrome; found abnormal protein for target therapy; also found to play a significant role in normal aging



Conclusions:
Moving towards Personalized Rehabilitation

- Mean results (+/-) warrant in depth investigation of individual responses
- Each patient should be an n=1 study throughout clinical treatment
- Explore participation in large research registries or databases
- Potential Benefits for patients & field
  - **Superior outcomes**
  - More efficient: lower cost, less time

"If you have seen one child with CP, you have seen one child (with CP)"