Use of exercise training to reverse age-related changes in neuronal function and skeletal muscle morphology

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Age-induced changes in neuromuscular function:
**Loss of motor neurons, MU reorganization**
Ageing and neuromuscular function

**Spinal motor neurons**
reduced number of motor neurons in the spinal cord

25% average loss of spinal motor neurons (lumbospinal segments L1-S3)
from 20 yrs to 90 yrs of age

Tomlinson & Irving 1977

several subjects > 60 yrs showing ~ 50% less MN's compared to 20-40 yrs old

Tomlinson & Irving 1977

Ageing and neuromuscular function

**Motor Units**
reduced number of excitable (i.e. functioning) MU's observed at 60-70 yrs of age

Brown et al. 1988, Doherty et al. 1993,
Campbell, McComas et al. 1973

Number of excitable MU's in aged subject (60-95 yrs)
~ 1/3 of that observed in younger subjects (1-60 yrs)

Campbell, McComas et al. 1973
Extensor digitorum brevis (n=207, age=3-96 yrs)
AJ McComas: Skeletal muscle - form and function, 1996
Ageing and neuromuscular function

↓ # motor neurons = ↓ # motor units at increasing age

ongoing process of 
**denervation** and **reinnervation**
of skeletal muscle fibers late in life

Vandervoort 2002, McComas 1996

AJ McComas: Skeletal muscle - form and function, 1996
Ageing and neuromuscular function

\( \downarrow \) # motor neurons = \( \downarrow \) # motor units at increasing age

ongoing process of denervation and reinnervation of skeletal muscle fibers late in life

evidenced by
- histological findings of fiber type grouping
- elevated coexpression of MHC isoforms
- preferential atrophy of type II muscle fibers
- very large MUAPs, indicating \( \uparrow \) innervation ratio

Vandervoort 2002, McComas 1996

Age-induced changes in neuromuscular function:

**Loss of muscle mass with aging: sarcopenia**

Picture courtesy Paolo Caserotti
Institute of Sports Science and Clinical Biomechanics
University of Southern Denmark
Loss of muscle mass with aging: sarcopenia

Reduced muscle cross-sectional area (↓ 40% between the age of 20 and 80 yrs)

The decline seems to start in early adulthood and accelerate after the age of 50 years

↑ content of non-contractile tissue such as intramuscular fat and connective tissue

Vandervoort, Muscle & Nerve 25, 2002
McNeill et al, J Appl Physiol 102, 2007
Parise & Yarasheski, Curr Opin Clin Nutr Metab Care, 2000

Sarcopenia (loss of muscle mass)

Sarcopenia is significantly associated with a
- 3-4 times greater risk of physical disability
- 2-3 times greater risk of balance abnormality
- 2-3 times greater risk of falls

Baungartner RN 1998, 1999

In frail elderly persons with advanced sarcopenia but without circulatory or pulmonary diseases, muscle weakness is typically more limiting for daily functioning than aerobic fitness.
Elderly male subjects (70-75 yrs) show ~40% fewer muscle fibers than young subjects (19-30 yrs)
VL muscle, Lexell et al. 1983

Very old male subjects (>80 yrs) ~60% fewer fibers compared to young subjects
VL muscle, Lexell et al. 1988

Reduction in muscle fiber size with aging

Young subject (31 yrs) Old subject (79 yrs)

VL muscle
Jesper L. Andersen, CMRC
### Age-related reductions in skeletal muscle fiber size

<table>
<thead>
<tr>
<th>Study</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Percent reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larsson et al., Acta Physiol.</td>
<td>M</td>
<td>22-65</td>
<td>1  &lt;&lt; 25</td>
</tr>
<tr>
<td>Scand. 103, 1978</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essen-Gustavsson and Borges,</td>
<td>M</td>
<td>20-70</td>
<td>15  ≈ 19</td>
</tr>
<tr>
<td>Acta Physiol. Scand. 126, 1986</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>84, 1988</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hakkinen et al. J. Gerontol.</td>
<td>M</td>
<td>15-83</td>
<td>1  &lt;&lt; 29</td>
</tr>
<tr>
<td>53B, 1998</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiatarone Singh et al. Am. J.</td>
<td>M, F</td>
<td>72-98</td>
<td>+7  &lt;&lt; 60</td>
</tr>
<tr>
<td>Physiol. 277, 1999</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hikida et al. J. Gerontol. 55</td>
<td>M</td>
<td>58-78</td>
<td>24  &lt;&lt; 40</td>
</tr>
<tr>
<td>2000</td>
<td></td>
<td></td>
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</table>

### Neuronal and Muscular changes induced by Ageing

- **Motor Unit remodeling**
  - ↓ Motor unit number
  - ↓ # Spinal motor neurons
  - ↑ Motor unit size
  - ↑ innervation ratio (# fibers/neuron)

- **Reduced muscle mass** ('sarcopenia')
  - ↓ cross sectional area
  - ↓ Total muscle fiber number
  - ↓ Muscle fiber size (pref. type II)

- **↓ Muscle strength/power**
Age-induced changes in neuromuscular function:

**Impairments in mechanical muscle function**

Isometric muscle strength

- Is preserved to ~50-60 yrs of age (cross sectional data)
- Decreases at a rate of 1-1.5% per year from 60-65th year
- Substantial individual differences!

Spirduso, Physical dimensions of aging, 1995
Vandervoort & McComas 1986
Spirduso 1995

**Decreased Muscular Strength With Aging**

**CROSS-SECTIONAL DATA**

**Isometric muscle strength**

- Is preserved to ~50-60 yrs of age (cross sectional data)
- Decreases at a rate of 1-1.5%
- Substantial individual differences!

Vandervoort & McComas 1986
Spirduso 1995
Decreased Muscular Strength and Power with Aging

Decreased maximal muscle force and contractile power from > 65 years

- Loss of strength: 1.5% per year
- Loss of power: 3.5% per year

Young & Skelton, Int. J. Sports Med. 15, 1994

Muscle function in elite master weightlifters

Trained (closed circles) and untrained (open circles) individuals demonstrated similar age-related decline rate in peak power (1.3% vs 1.2% per year, respectively)

Trained (closed circles) and untrained (open circles) individuals demonstrated similar age-related decline rate in peak power (1.3% vs 1.2% per year, respectively)

Pearson, Harridge et al.

Is maximal muscle power important in elderly individuals?  
YES!
Functional performance in the elderly is influenced by maximal mechanical muscle power.

![Graph showing correlation between leg extensor power and stair-climbing speed, walking speed, and chair-rising speed for men and women.](image)

**Bassey et al., 1992**
*Nursing Home residents*

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**Aging**

- loss of motorneurones
- loss of muscle fibers
- muscle fiber atrophy

\[\downarrow\]

- reduced muscle strength, RFD and Power

\[\downarrow\]

- Impaired function in tasks of daily living (stair walking, rising from chair, etc.)
Aging

loss of motorneurones
loss of muscle fibers
muscle fiber atrophy

\[ \downarrow \]

reduced muscle strength, RFD and Power

Impaired function in tasks of daily living
(stair walking, rising from chair, etc)

Aging & strength training
**Aging**
- loss of motorneurones
- loss of muscle fibers
- muscle fiber atrophy

\[ \downarrow \]
- reduced muscle strength, RFD and Power

**Aging & strength training**
- muscle fiber hypertrophy
- improved neuromuscular function

\[ \downarrow \]
- Marked gains in muscle strength, RFD, Power
- improved function in everyday activities

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**Age-induced changes in neuromuscular function:**

**Adaptive alterations in neuromuscular function with strength/power training**
### Percentage increases in Muscle Size (CSA) and Maximal Muscle Strength (MVC) with Strength Training in old vs young adults

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<thead>
<tr>
<th>Population</th>
<th>Training Duration (weeks)</th>
<th>ΔMVC (%)</th>
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<td>24</td>
<td>26.8</td>
<td>0.16</td>
<td>6.8</td>
<td>0.04</td>
<td>Häkkinen 1985</td>
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<td>Young adults</td>
<td>12</td>
<td>15.0</td>
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<td>5.7</td>
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<td>Jones &amp; Rutherford 1987</td>
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<td>24</td>
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<td>0.11</td>
<td>Narici 1996</td>
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Aagaard et al., J Physiol 2001

Narici et al., J Musculoskel Neron Interact 2004

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<td>0.11</td>
<td>Narici 1996</td>
</tr>
<tr>
<td>Elderly (65-81 yrs)</td>
<td>16</td>
<td>19.0</td>
<td>0.17</td>
<td>7.4</td>
<td>0.07</td>
<td>Ferri 2003</td>
</tr>
<tr>
<td>Elderly (60-72 yrs)</td>
<td>12</td>
<td>16.7</td>
<td>0.20</td>
<td>9.3</td>
<td>0.11</td>
<td>Frontera 1988</td>
</tr>
<tr>
<td>Elderly (61 yrs)</td>
<td>10</td>
<td>17.0</td>
<td>0.25</td>
<td>9</td>
<td>0.12</td>
<td>Häkkinen 1998</td>
</tr>
<tr>
<td>Elderly (85-97 yrs)</td>
<td>12</td>
<td>37</td>
<td>0.44</td>
<td>10</td>
<td>0.11</td>
<td>Harridge 1999</td>
</tr>
</tbody>
</table>

Narici et al., J Musculoskel Neron Interact 2004
Heavy-resistance strength training also induces muscle fiber hypertrophy in the very old (85-98 yrs, mean age 89 ± 3 yrs)

Loading 80% 1RM, 3/week, 12 weeks

Muscle fibre CSA

- Type 1
- Type 2

Before | After | Before | After

Results

- Type IIa fibre CSA: ↑ 22% *
- Quadriceps muscle CSA: ↑ 10% *
- Quadriceps strength: ↑ 40-45% *
- Chair rising time (5 reps): 30% faster *
- Maximal walking speed: 25% faster *

* p<0.05

85+ year old discharged geriatric patients
12 weeks of resistance exercise
knee ext. 3 x weekly, 3 x 8 rep, >70% 1 RM

**Increases in muscle fibre size in older individuals following high-intensity dynamic leg strength training. Based on biopsy samples obtained from vastus lateralis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontera et al., J. Appl. Physiol. 64, 1988</td>
<td>34</td>
<td>≈ 26</td>
</tr>
<tr>
<td>Charett et al., J. Appl. Physiol. 70, 1991</td>
<td>7</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>Grimby et al., J. Appl. Physiol. 73, 1992</td>
<td>8</td>
<td>≈ 5</td>
</tr>
<tr>
<td>Häkkinen et al. J. Gerontol. 53B, 1998</td>
<td>23</td>
<td>≈ 27</td>
</tr>
<tr>
<td>Fiatarone-Singh et al. Am. J. Physiol. 277, 1999</td>
<td>5</td>
<td>&gt; -12</td>
</tr>
<tr>
<td>Hunter et al., J. Appl. Physiol. 86, 1999</td>
<td>14</td>
<td>&lt; 23</td>
</tr>
<tr>
<td>Hikida et al. J. Gerontol. 55, 2000</td>
<td>46</td>
<td>≈ 43</td>
</tr>
</tbody>
</table>

**Muscle fiber size increase (%)**

**Changes in explosive muscle strength**
**(rate of force development, RFD)**
**induced by strength training in the elderly**
**RFD** Rapid force capacity ['explosive muscle strength']

Maximal rate of force development (RFD) in elderly vs young individuals

Contractile RFD is substantially reduced in healthy aging individuals compared to young individuals

**Aagaard et al, J Appl Physiol 2002**
RFD Rapid force capacity

Effects of resistance training on RFD in the elderly?

Rate of Force Development (RFD)

\[ RFD = \frac{\Delta \text{Force}}{\Delta \text{Time}} \]

Maximal Explosive Muscle Strength

1000 2000 3000 4000 5000

0 0.2 0.4 0.6 0.8

Time (seconds)

Force (N)

RFD explosive-type heavy-resistance training seems to be safe and well tolerated by healthy women in the eighth decade of life and elicits adaptive neuropeptide changes in selected physiological variables that are commonly associated with the risk of falls and disability in aged individuals.

Muscle power, which is the product of contractile force and movement velocity, is a stronger predictor of functional motor performance, incidence of falling and self-reported functional status than maximal muscle strength in community-dwelling old adults (Feldman et al., 2000; Skelet et al., 2002). Furthermore, lower limb muscle power declines at a faster rate than in the elderly, which is related to the number of active sarcomeres in series (Edgerton et al., 1984; Kramer & Newton, 2000). Thus, maximal muscle power depends on the muscle morphology (e.g. physiological muscle cross-sectional area, muscle fiber pennation angle, muscle fiber length, fiber-type composition) and neuromuscular activation properties (discussed below), and it
Explosive-type strength/power training in the old (60 yrs) and the very old (80 yrs)

Subjects
Mean age 62.7 (SD 2.2) and 81.8 (SD 2.7) yrs
n = 20 + 20 con  n = 12 + 13 con

Duration, frequency of training
12 weeks, twice a week

Familiarisation period
2 wks with lower training loads (50% 1RM), and reduced movement velocity

Progressive load adjustment:
Every two weeks with a new estimated 1RM (5-RM test)

Exercises (bilateral)
Horizontal leg press, knee extension, calf rise, incline leg press, leg curl - slow ECC, rapid (max acc) CON actions

Exercise intensity and reps
75-80% 1RM loads, 8-10 reps, 4 sets each exercise
Explosive-type strength/power training in the old and the very old

Static leg extensor MVC and RFD

Unilateral isometric leg press test device

Paolo Caserotti
Explosive-type strength/power training in the old and the very old ⇒ marked increases in rapid force capacity (RFD)

Contractile Rate of Force Development
Leg Press MVC; 0-200 ms

- TG60 (n=20)
- CG60 (n=20)
- TG80 (n=12)
- CG80 (n=13)

60 yrs old

Diff = 43%
p < 0.001

80 yrs old

P<0.05 within-group changes


Explosive-type strength/power training in the old and the very old ⇒ marked increases in rapid force capacity (RFD)

Contractile Rate of Force Development
Leg Press MVC; 0-200 ms

- TG60 (n=20)
- CG60 (n=20)
- TG80 (n=12)
- CG80 (n=13)

60 yrs old

Diff = 43%
p < 0.001

80 yrs old

Diff = 15%
n.s.

P<0.05 within-group changes

Explosive-type HRST in 80 yr old
↓ 20 years younger!

Explosive-type strength/power training in the old and the very old
⇒ marked increases in MVC, RFD and power


<table>
<thead>
<tr>
<th>TG 60</th>
<th>TG80</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVC (maximal strength)</td>
<td>+22%*</td>
</tr>
<tr>
<td>RFD (rapid force capacity)</td>
<td>+18%*</td>
</tr>
<tr>
<td>SSC muscle power (CMJ force plate)</td>
<td>+5%*</td>
</tr>
<tr>
<td>1-legged muscle power (Power rig)</td>
<td>+12%*</td>
</tr>
</tbody>
</table>

* pre vs post (p<0.05)

RFD Contractile Rate of Force Development
Elderly subjects (60-86 years) - hip replacement patients (n=11)
Pre and Post 12 wks unilateral resistance training - Affected Limb

RFD = Δ Force Moment / Δ Time

Training induced changes in explosive muscle strength (RFD)
Adaptive responses in aged individuals

Heavy-resistance strength training

Concurrent increases in maximal RFD and neuromuscular activity (iEMG) in elderly individuals

Häkkinen & Häkkinen 1995 (age 50, 70 yrs, gender F, M)
Häkkinen et al. 1998 (age 40, 60 yrs, gender F, M)
Häkkinen et al. 2001 (age 63 yrs, gender F)
Suetta et al. 2004 (post hip replacement surgery, 60-86 yrs)
Barry et al. 2005 (age 60-79 yrs, gender F, M)

Training induced changes in explosive muscle strength (RFD)
Adaptive responses in aged individuals

Heavy-resistance strength training

Concurrent increases in maximal RFD and neuromuscular activity (iEMG) in elderly individuals

Functional consequences
- enhanced acceleration
- elevated maximal movement velocity
- elevated muscle force & power during rapid movements
- reduced risk of falls
Influence of neuromuscular activity on RFD

Rapid force capacity (RFD) is strongly influenced by the magnitude of neuromuscular activity at onset of contraction.

\[ \text{RFD} = \frac{\Delta \text{Moment}}{\Delta \text{time}} \]

Very high firing rates of spinal motorneurons increases the maximal Rate of Force Development

De Haan, Exp Physiol 1998 (rat GM, in situ)
Elevated motorneuron firing rates leads to increases in the maximal Rate of Force Development

De Haan, Exp Physiol 1998 (rat GM, in situ)
What is the effect of strength/power training on maximal MN firing frequency in old adults?

**UNTRAINED STATE:**
Maximal motorneuron firing frequency recorded during MVC is reduced in elderly vs young subjects

Ageing and neuromuscular function

Motorneuron firing frequency

Effects of strength/power training on maximal MN firing rate...

A

MVC Force

B

MN firing rate

Kamen & Knight, J Gerontol 2004
Graph modified from Duchateau, Semmler, Enoka, J Appl Physiol 2006
Ageing and neuromuscular function

Motorneuron firing frequency

Effects of strength/power training on maximal MN firing rate...

Strength training induce changes in maximal motorneuron firing frequency in young and old individuals

Strength/power training

↓

↑ motorneuron firing rate (at 100% MVC) in both young and old subjects

Patten et al. 1999 (old, young), 2001 (young)
Van Cutsem et al. 1998 (young), Kamen & Knight 2004 (old, young)
Christie & Kamen 2010 (old, young)

Furthermore, after strength training maximal motorneuron firing rate did not differ between old and young subjects

Patten et al. 1999, Kamen & Knight 2004, Christie & Kamen 2010
Effects of strength training in frail elderly patients

Well, does the need exist?

Often, severe muscle atrophy is observed in elderly patients...
Strength training is the only exercise modality known to effectively increase muscle mass

YES!
Effects of strength training in frail elderly patients

Does it lead to improved functional capacity?

YES!
Rehabilitation from elective Hip replacement Surgery by use of Strength Training

Strength Training protocol

Strength exercises - heavy loads
unilateral heavy-resistance strength training - Affected Limb

Knee-extension
Leg-press

wks 1: 3 sets x 10 reps (50% 1RM ~20RM load), wks 2-4: 3x12 (65% 1RM ~15RM),
wks 5-6: 4x10 (70% 1RM ~12RM), wks 7-8: 5x8 (80% 1RM ~8RM),
wks 9-10: 4x8 (80% 1RM ~8RM), wks 11-12: 3x8 (80% 1RM ~8RM)


Rehabilitation from elective Hip replacement Surgery by use of Strength Training

Changes in anatomical Muscle Cross Sectional Area (CT-scanning)

Pre-training
Post-training

PRE training
POST training

Suetta, Aagaard et al, J Appl Physiol 2004
Rehabilitation from elective Hip replacement Surgery by use of Strength Training

**Changes in anatomical Muscle Cross Sectional Area**
(CT-scanning)

- **CSA (mm²)**: Bar graphs showing changes in CSA from Pre, 5wk, and 12wk for Standard Rehab (SR), Electro Stimulation (ES), and Strength Training (ST). The graphs indicate significant changes with * symbols for ES and ST conditions.

- **ST**: The graph shows a significant increase in CSA for ST compared to SR.

Rehabilitation from elective Hip replacement Surgery by use of Strength Training

**Changes in maximal muscle strength**
(isometric MVC)

- **Isometric strength 60°**: A bar graph showing isometric strength improvement for RT (resistance training), ES (electrical stimulation), and SR (standard rehabilitation) from Pre, 5wk, and 12wk.

- **Torque (Nm)**: The graph shows significant increases for ES (+24%) and decreases for SR (-22%) compared to Pre.

- **Suett, Aagaard et al, J Appl Physiol 2004**

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* 12 wk > pre (p<0.05); # 5 wk < pre,12 wk (p<0.05)
Rehabilitation from elective Hip replacement Surgery by use of Strength Training

Changes in Functional Capacity

Max 10m walk speed

Pre 5w 12w

Speed of Chair-rising x 5

Pre 5w 12w

Suetta, Aagaard, Kjaer et al, JAGS 2004

Rehabilitation from elective Hip replacement Surgery by use of Strength Training

Does training-induced gains in rapid force capacity RFD result in improved functional performance?
Does training-induced gains in rapid force capacity RFD result in improved functional performance? **YES!**

### Rehabilitation from elective Hip replacement Surgery by use of Strength Training

- **Training-induced changes in maximum walking speed vs RFD**
- \( r=0.79, p<0.005 \)

- **Impaired fine motor control with aging**
  - **Effects of resistance training**
  - **Force steadiness**
  - **Submaximal force steadiness**
  - A measurement of the fluctuations in force during isometric or dynamic muscle contraction
  - **Target force vs Produced force**
  - \( SD(\text{force}) \)
  - 20% MVC force

---

**Suetta, Aagaard, Kjaer et al, J Appl Physiol 2004**

**Tracy & Enoka 2002, Hortobagyi et al. 2001**

**courtesy P Caserotti**
Impaired fine motor control with aging
Effects of resistance training

Force steadiness
Greater force error, less steady muscle forces (↑SD) during submaximal constant-force motor tasks in elderly compared to young subjects
Tracy & Enoka 2002, Hortobagyi et al. 2001

Potential mechanisms: age related changes in
- MU size and firing rate variability Tracy & Enoka 2002, Barry & Enoka 2007
- MU synchronization Patten & Kamen 1996
- Antagonist coactivation Enoka 1997

tracking of 25-N target force during 5-sec slow-speed eccentric quadriceps contraction (15°/s)
post 10 familiarization trials
Hortobagyi et al. 2001
Impaired fine motor control with aging
Effects of resistance training

Effects of strength training in elderly
- improved force accuracy
  - force error 30-60% reduced
- improved force steadiness
  - SD 20-40% reduced

Hortobagyi et al. 2001
Impaired fine motor control with aging
Effects of resistance training

Effects of resistance training in elderly

▼ Improved force steadiness
   reduced SD(force)

▼ Improved force accuracy

= Improved fine motor control

Hortobagyi et al, J Gerontol 56A 2001
Tracy, Enoka et al, JAP 96, 2004
Tracy & Enoka, MSSE 38, 2006

SUMMARY  Effects of strength/power training on
neuromuscular function and muscle size in the elderly
SUMMARY Effects of strength/power training on neuromuscular function and muscle size in the elderly

**Strength and Power properties**
- ▲ dynamic muscle strength, ▲ isometric muscle strength  
- ▲ muscle power  
- ▲ rapid force capacity (rate of force development: RFD)  
- ▲ EMG amplitude and rate of EMG rise  
- ▲ maximal motor neuron firing frequency  
  Patten 1999, Kamen & Knight 2004, Christie & Kamen 2010
- ▲ improved force steadiness, enhanced fine motor control  
  Hortobagyi 2001, Tracy 2004, Tracy & Enoka 2006
- ▲ single muscle fiber CSA, ▲ whole muscle CSA  
- ▲ myogenic satellite cell activation  
  MacKey 2007, Petrella 2008
- ▲ muscle fiber pennation angle, ▲ tendon stiffness  
  Reeves 2003, Reeves 2006, Suetta 2008

**Neural factors**

**Muscular factors**

Effects of aging on muscle and neural function - influence of training

**OVERALL CONCLUSION**

The age-related loss in muscle mass and the concurrent decrease in maximal muscle strength, rapid force capacity (RFD) and power can be slowed or reversed by training (strength training!)

Likewise, the age-related impairment in neural function can be effectively compensated by training (strength training)

!! ALSO the case in frail elderly patients !!
OVERALL EFFECT OF STRENGTH/POWER TRAINING IN THE ELDERLY?

Strength/Power TRAINING
↓
Adaptive changes in muscle size and neuromuscular function
↓
improved function in ADL (activities of daily living)


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Charlotte Suetta  Michael Kjær
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Ulrik Frandsen  Peter Krstrup
Niels Ørtenblad  Lis Puggaard

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Institute of Sports Medicine Copenhagen, University of Copenhagen