Brain Repair After Stroke

Steven C. Cramer, MD

Professor, Depts. Neurology, Anatomy & Neurobiology, and PM&R
Associate Director, Institute for Clinical & Translational Science
Co-PI, NIH StrokeNet (Recovery & Rehabilitation)

University of California, Irvine

Disclosures

Dr. Cramer serves as a consultant for MicroTransponder, Dart Neuroscience, Neurolutions, Regenera, Abbvie, SanBio, and TRCare.

Main points

- Spontaneous recovery after stroke
- Therapies to improve recovery--brain repair
- Variability in response to restorative stroke therapies

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Molecular and cellular events underlying stroke recovery

Ipsilesional changes

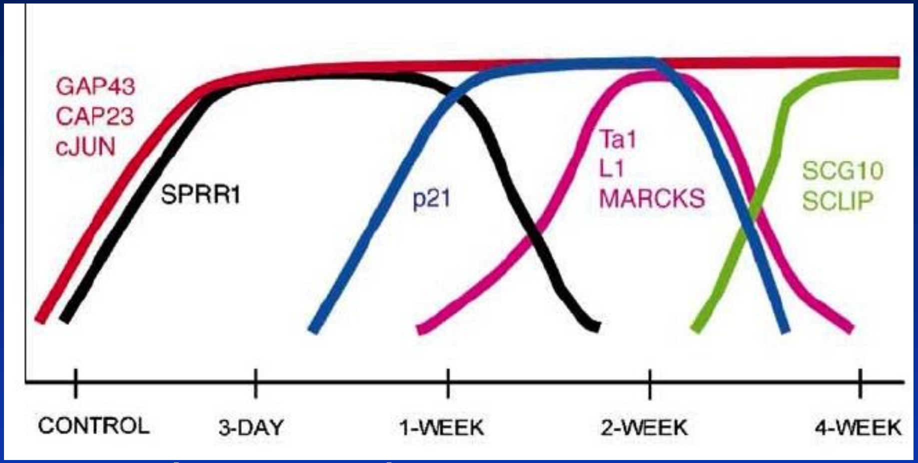
- ↑ inflammatory markers
- ↑ growth-associated proteins
- ↑ cell cycle proteins
- ↑ growth factors
- GABA receptor downregulation
- ↑ NMDA receptor binding
- angiogenesis
- hyperexcitabil'y & facil'n of LTP
- synaptogenesis
- ↑ dendrite branching/spine density
- ↑ neuronal sprouting
- extracellular matrix remodelling
- ↑ cortical thickness

Contralesional changes

- ↑ inflammatory markers
- ↑ growth-associated proteins
- GABA rcpt'r downregulation
- ↑ NMDA receptor binding
- neuronal hyperexcitability
- ↑ dendrite br/spine density
- synaptogenesis
- ↑ cortical thickness

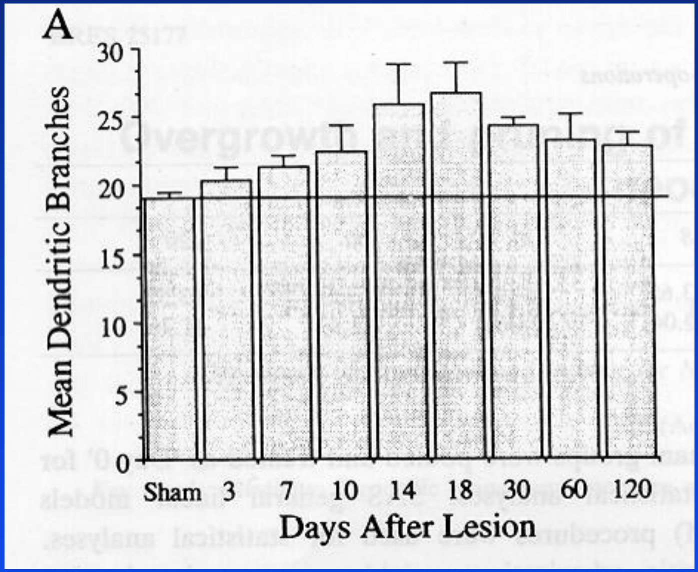
Nudo Curr Op Nbio '99, Cramer/Chopp TINS '00, Wieloch/Nikolich Curr Op Nbio '06, Carmichael Ann Neur '17

Molecular/cellular changes: temporal course



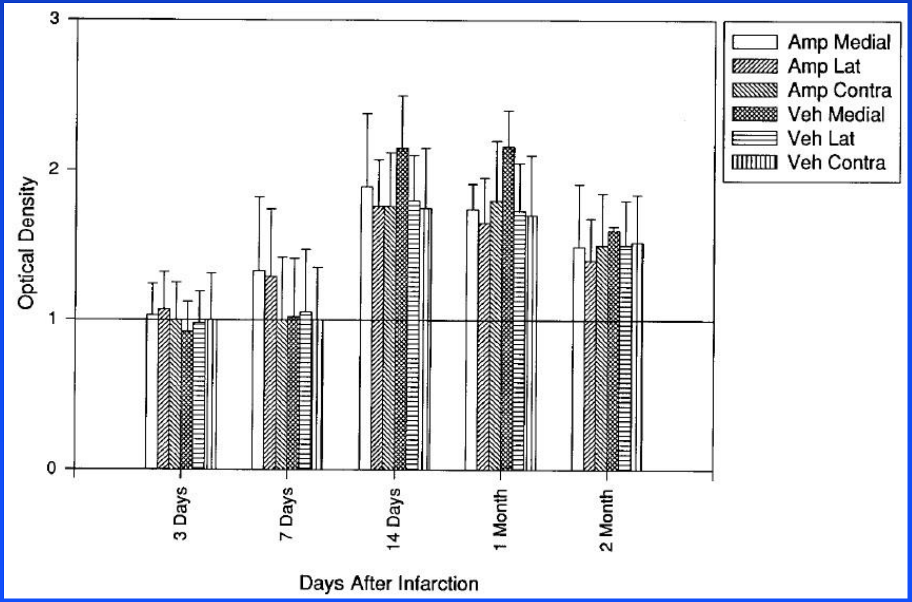
Growth-promoting genes

Li & Carmichael, Neurobiol Dis; 23:362



Increased dendrite branches

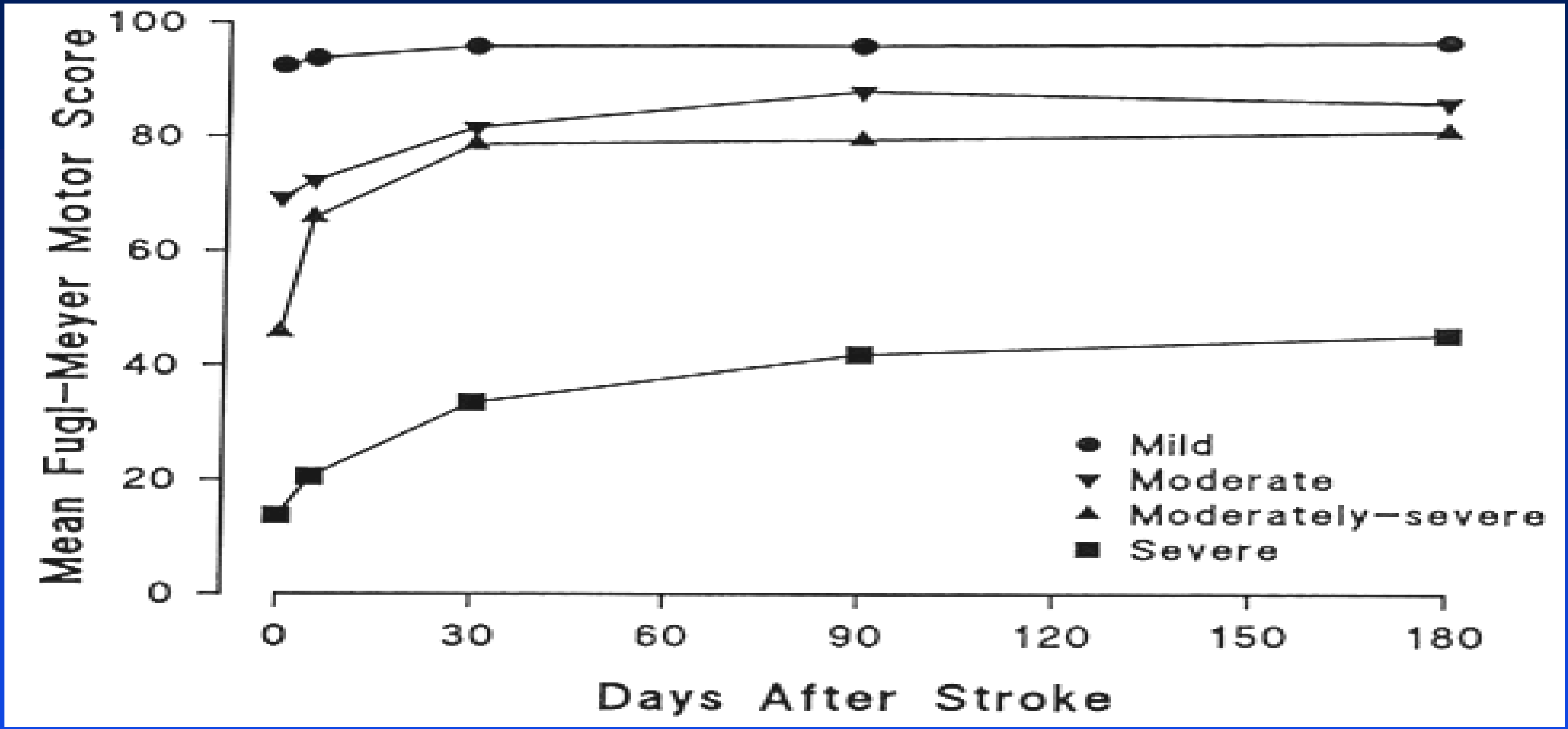
Jones & Schallert, Brain Res 581:156



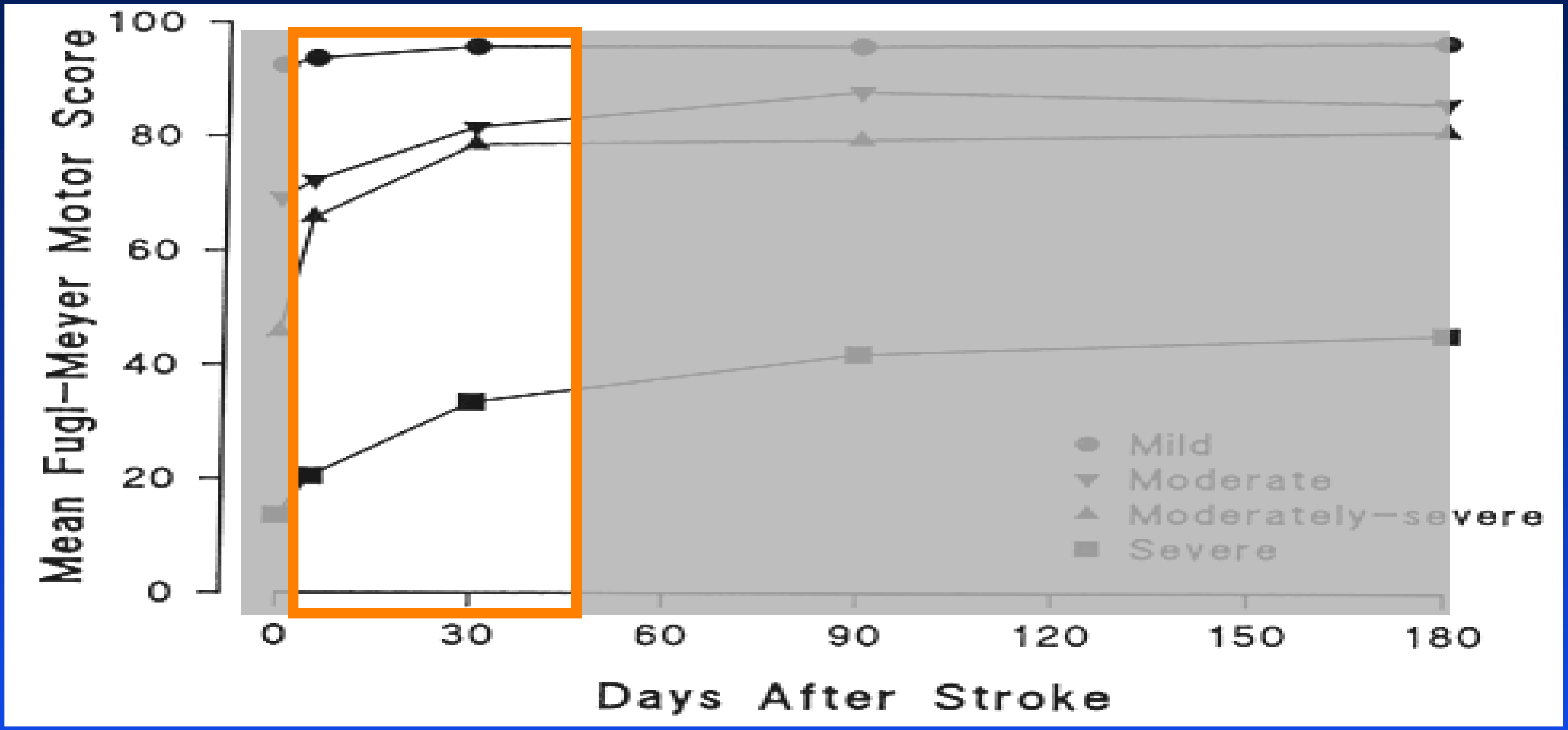
Increased synaptogenesis

Stroemer et al, Stroke; 29:2381

Molecular/cellular changes: temporal course



Molecular/cellular changes: temporal window



Reperfusion, neuroprotection

Endogenous repair mechanisms at peak

Brain is galvanized for recovery

Neural repair remains accessible, but with dampened magnitude

Main points

- Spontaneous recovery after stroke
- Therapies to improve recovery--brain repair
- Variability in response to restorative stroke therapies

Brain repair: a definition

Brain repair: restoring brain structure or function after injury

Potential human restorative therapies

- **Small molecules** eg, SSRIs, amphetamine, levodopa, niacin, memantine, etc
- **Growth factors** eg, EPO, hCG, G-CSF, b-FGF, OP-1, etc
- **Monoclonal Ab**, other large molecules eg, anti-MAG Ab
- **Stem cells**
- **Brain stimulation** eg, TMS, tDCS, tACS, epidural stim, deep brain stim; vagal nerve stim
- **Telemedicine**
- **Intensive physiotherapy, robotics, other training**
- **Lesion bypass** eg, BCI, nerve transfer
- **Motor imagery, observation, environmental enrichment, other cognitive Rx**

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Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial

François Chollet, Jean Tardy, Jean-François Albucher, Claire Thalamas, Emilie Berard, Catherine Lamy, Yannick Bejot, Sandrine Deltour, Assia Jaillard, Philippe Niclot, Benoit Guillon, Thierry Moulin, Philippe Marque, Jérémie Pariente, Catherine Arnaud, Isabelle Loubinoux

Summary

Background Hemiplegia and hemiparesis are the most common deficits caused by stroke. A few small clinical trials

Lancet Neurol 2011; 10: 123-30

Double-blind, placebo-controlled trial of 118 patients enrolled 5–10 after stroke to 20 mg fluoxetine or placebo QD x 3 mo

Baseline NIHSS = 13, but severe weakness

Primary endpoint outcome: Larger Fugl-Meyer score change with fluoxetine (34 vs. 24 points, $p=0.003$)

Also: significant effect for mRS (% ≤ 2) but not NIHSS (% ≤ 5)

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Unmet need: delivery of large doses of rehab therapy

Motor deficits are a major contributor to post-stroke disability.

Animal studies with favorable plasticity use high rehab doses.

(600 repetitions of pellet retrieval/day, Nudo 1996)

In humans, higher rehab therapy doses may improve outcomes.

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Quantity of rehab therapy often low in humans, however:

(1) financial constraints
(2) patient can’t travel to a rehab therapy provider
(3) shortage of rehabilitation care in some regions
(4) poor patient compliance with assignments
(5) limited dose during stroke rehabilitation

(mean of 32 arm repetitions/session, Lang 2009)

Issues with quantity of rehab therapy after stroke

Observation of Amounts of Movement Practice Provided During Stroke Rehabilitation

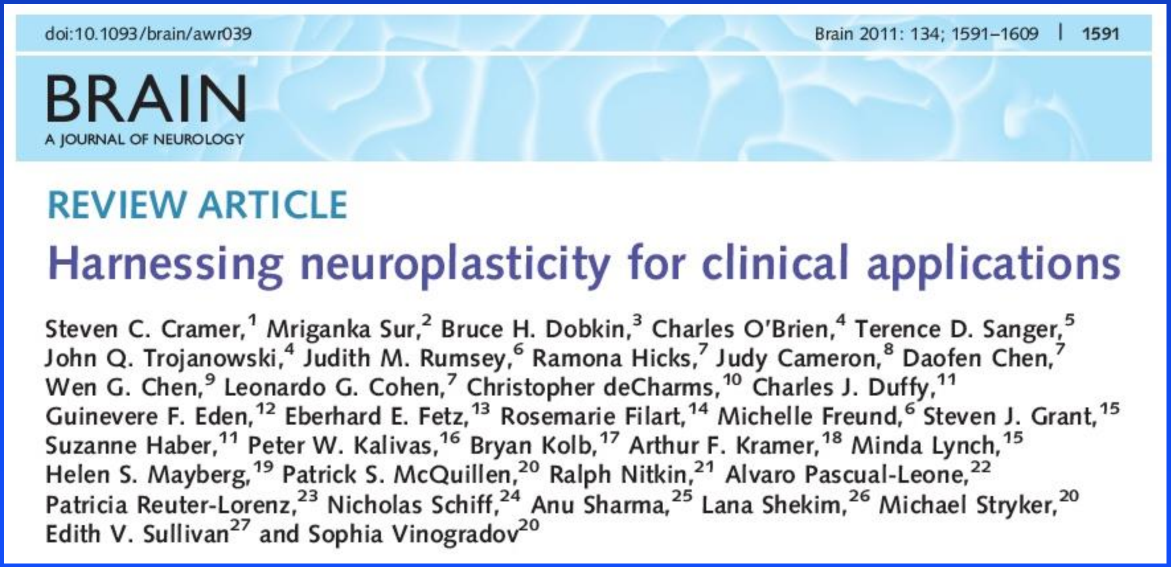
Catherine E. Lang, PT, PhD, Jillian R. MacDonald, DPT, Darcy S. Reisman, PT, PhD, Lara Boyd, PT, PhD, Teresa Jacobson Kimberley, PT, PhD, Sheila M. Schindler-Ivens, PT, PhD, T. George Hornby, PT, PhD, Sandy A. Ross, PT, DPT, Patricia L. Scheets, PT, DPT

During inpatient or outpatient stroke rehabilitation,
the mean # functional UE repetitions per session was 32.

Lang et al Arch PMR 90:1692-1698; 2009

Quality of rehab also important; greater plasticity when a task is

(1) challenging and varied
(2) accompanied by appropriate feedback
(3) motivating and goal-oriented
(4) interesting
(5) environmentally and ecologically relevant



doi:10.1093/brain/awr039 Brain 2011: 134; 1591–1609 | 1591

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

Harnessing neuroplasticity for clinical applications

Steven C. Cramer,[1] Mriganka Sur,[2] Bruce H. Dobkin,[3] Charles O'Brien,[4] Terence D. Sanger,[5] John Q. Trojanowski,[4] Judith M. Rumsey,[6] Ramona Hicks,[7] Judy Cameron,[8] Daofen Chen,[7] Wen G. Chen,[9] Leonardo G. Cohen,[7] Christopher deCharms,[10] Charles J. Duffy,[11] Guinevere F. Eden,[12] Eberhard E. Fetz,[13] Rosemarie Filart,[14] Michelle Freund,[6] Steven J. Grant,[15] Suzanne Haber,[11] Peter W. Kalivas,[16] Bryan Kolb,[17] Arthur F. Kramer,[18] Minda Lynch,[15] Helen S. Mayberg,[19] Patrick S. McQuillen,[20] Ralph Nitkin,[21] Alvaro Pascual-Leone,[22] Patricia Reuter-Lorenz,[23] Nicholas Schiff,[24] Anu Sharma,[25] Lana Shekim,[26] Michael Stryker,[20] Edith V. Sullivan[27] and Sophia Vinogradov[20]

Cramer et al, Brain. 2011;134: 1591-1609.

Quality of rehab also important; greater plasticity when a task is

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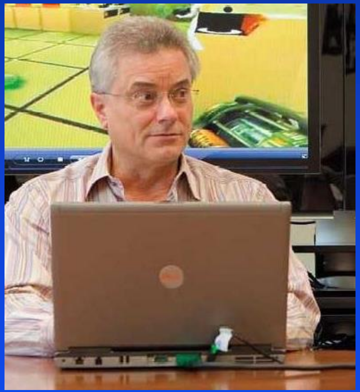
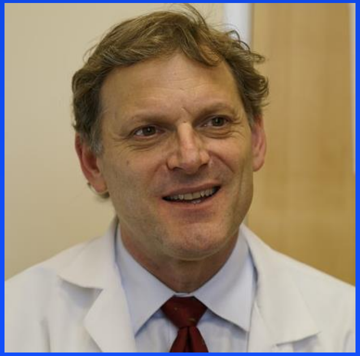
We reasoned that telerehabilitation is ideally suited to efficiently provide a large dose of useful rehab therapy after stroke.

Pilot Study Of Home-Based Telerehabilitation After Stroke

<u>The team includes</u>

Lucy Dodakian, MA, OTR/L
Alison McKenzie, PT, DPT, PhD
Walt Scacchi, PhD
Erin Burke
Renee Augsberger, OTR/L, MHA, C/NDT
Jutta Heckhausen, PhD
Vu Le, MS
Jill See, MPT
Robert Zhou
Steve Cramer, MD




Pilot Study Of Home-Based Telerehabilitation After Stroke

Eligibility

Patients had to be 3-6 months post-stroke; could have mild, moderate, or severe arm weakness (FM score 22-55)

Treatment

We delivered and assembled our system to their home.

Each subject received 28 days of telerehabilitation.

Each day consisted 1 hour that was required and structured, plus 1 optional hour of free play.

Plus 3 videoconferences per week

Dodakian et al, Neurorehab Neural Repair. 2017; 31:923-933

Pilot Study Of Home-Based Telerehabilitation After Stroke

Dodakian et al, Neurorehab Neural Repair. 2017; 31:923-933

Pilot Study Of Home-Based Telerehabilitation After Stroke

Compliance was excellent

Subjects engaged in therapy 329 of 336 (97.9%) assigned days.

Improved arm movement

FM score started at 39±12 (range 23-55),increased by 4.8±3.8 points (p=0.0015); met *clinically important difference* in 6 of 12.

Findings not dependent on computer skills

Computer literacy scores declined with age (r = -0.92, p<0.0001), but were not related to arm motor gains or to home compliance.

Holistic care in parallel

--Daily education increased stroke knowledge by 39% (p=0.001)

--Videoconference screen detected depression in 3/12 patients

--Home BP measurement validated (r = 0.99; p<0.0001)

Dodakian et al, Neurorehab Neural Repair. 2017; 31:923-933

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Average of 24,607 arm repetitions over 28 days

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Telerehabilitation in the Home Versus Therapy In-Clinic for Patients With Stroke

124 subjects with stroke 4-36 weeks prior and arm motor deficits

Randomized at 11 US sites to intensive arm motor therapy
(a) traditional In-Clinic, versus
(b) in-home Telerehabilitation

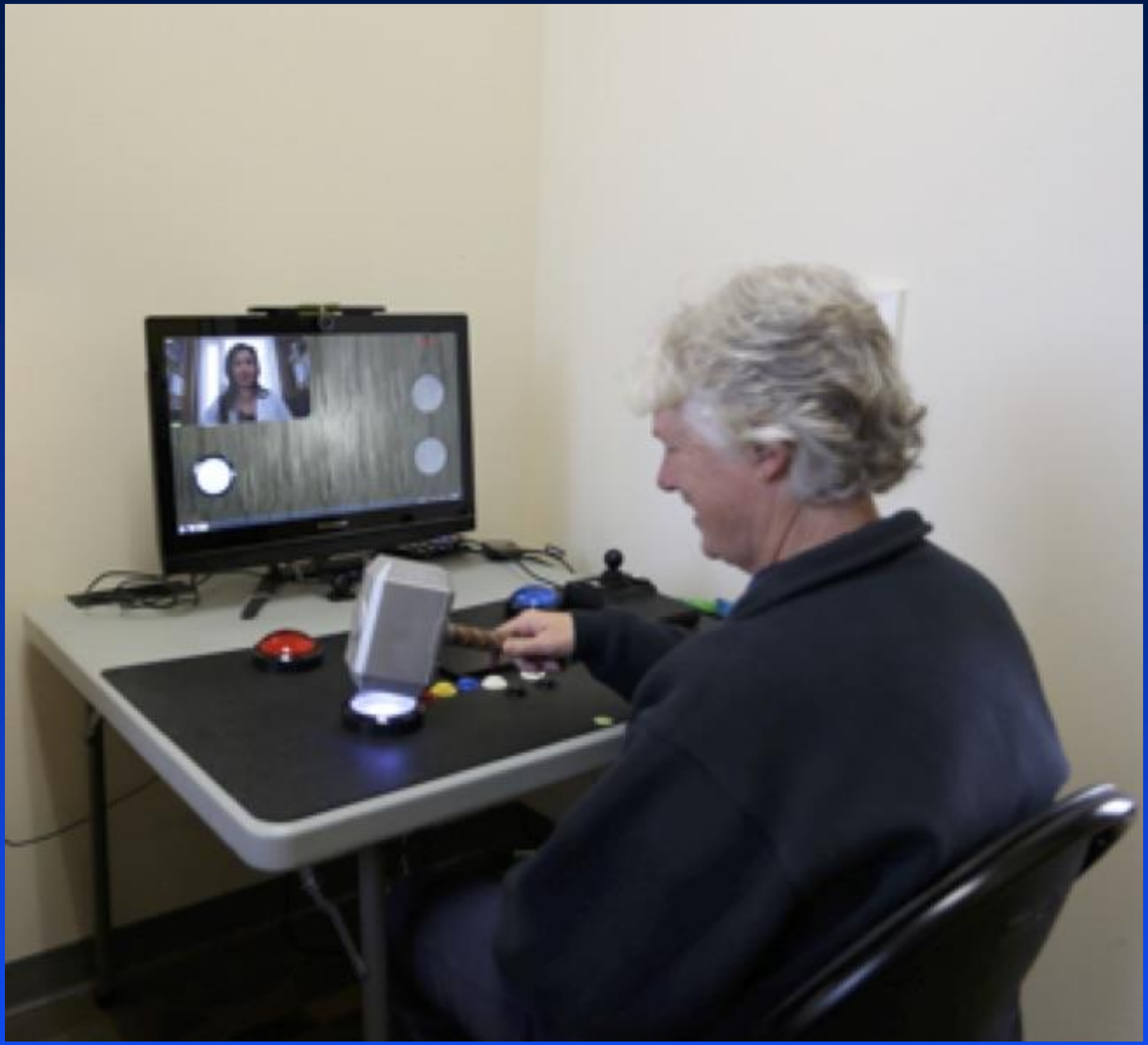
Treatment
36 sessions (18 superv’d, 18 unsuperv’d), 70 min, over 6-8 wk
Intensity, duration, and frequency of therapy matched

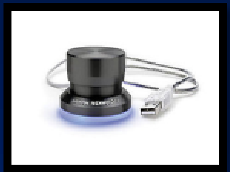
Assessor-blind, randomized, non-inferiority design

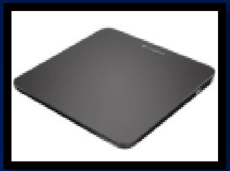
clinicaltrials.gov NCT02360488

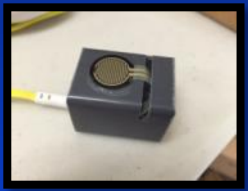
Telerehab Trial

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY









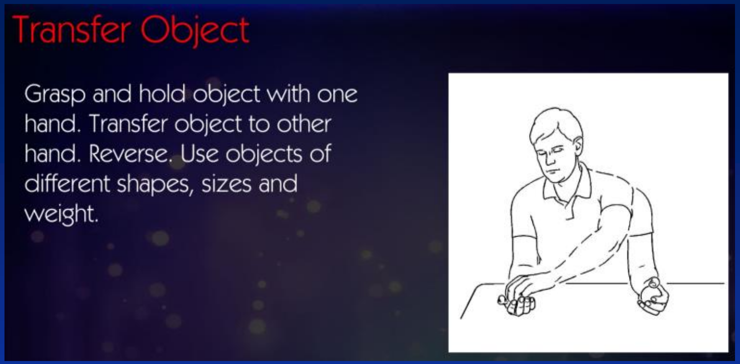
FDA: non-significant risk device study

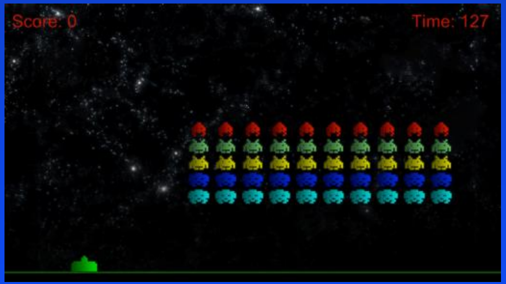
clinicaltrials.gov NCT02360488

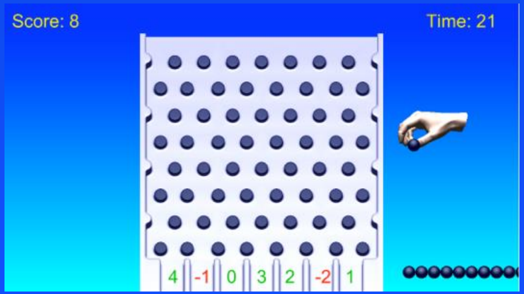
Telerehab Trial

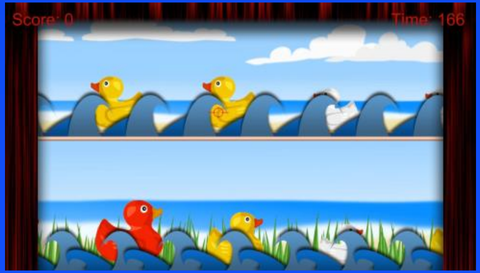
NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

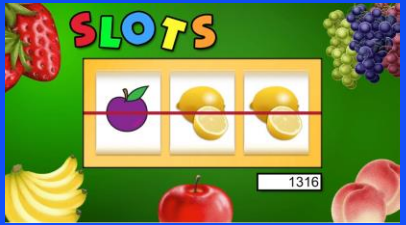
Telerehabilitation











Results

Telerehabilitation in the Home Versus Therapy In-Clinic for Patients With Stroke

University of California, Irvine
Kessler Institute for Rehabilitation
Case Western Reserve University
Burke Medical Research Institute
University of California, San Diego
Brooks Rehabilitation
Northwestern University
University of Washington
Medical University of South Carolina
Harvard University
Emory University

clinicaltrials.gov NCT02360488

Telerehab Trial

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

Main points

- Spontaneous recovery after stroke
- Therapies to improve recovery--brain repair
- Variability in response to restorative stroke therapies

Stroke

Origin:
1250–1300; Middle English *strok*, *strak* (noun), probably continuing Old English strāc

www.dictionary.com

Stratifying Patients With Stroke in Trials That Target Brain Repair

Steven C. Cramer, MD

Abstract*—**A number of therapies are emerging that have the potential to reduce poststroke disability by promoting repair. Careful evaluation of patients with stroke might help distinguish those who are most likely to respond to a restorative therapy from those who lack biological substrate needed to achieve gains. Potential approaches to such stratification are considered, including measures of brain injury or of poststroke brain function. (Stroke*. 2010;41[suppl 1]:S114-S116.**)

- Study power
- Sample size
- Study duration
- Number of sites

Cramer SC. Stroke. 2010

Many factors can affect the outcome after stroke

pre-stroke disability	brain function
genetics	acute stroke interventions
age	time post-stroke
handedness	post-stroke depression
medical co-morbidities	medications (+ and -)
initial and final deficits	caregiver, social factors
injury: location, side, mechanism, volume	quantity, quality, and timing of post-stroke therapy

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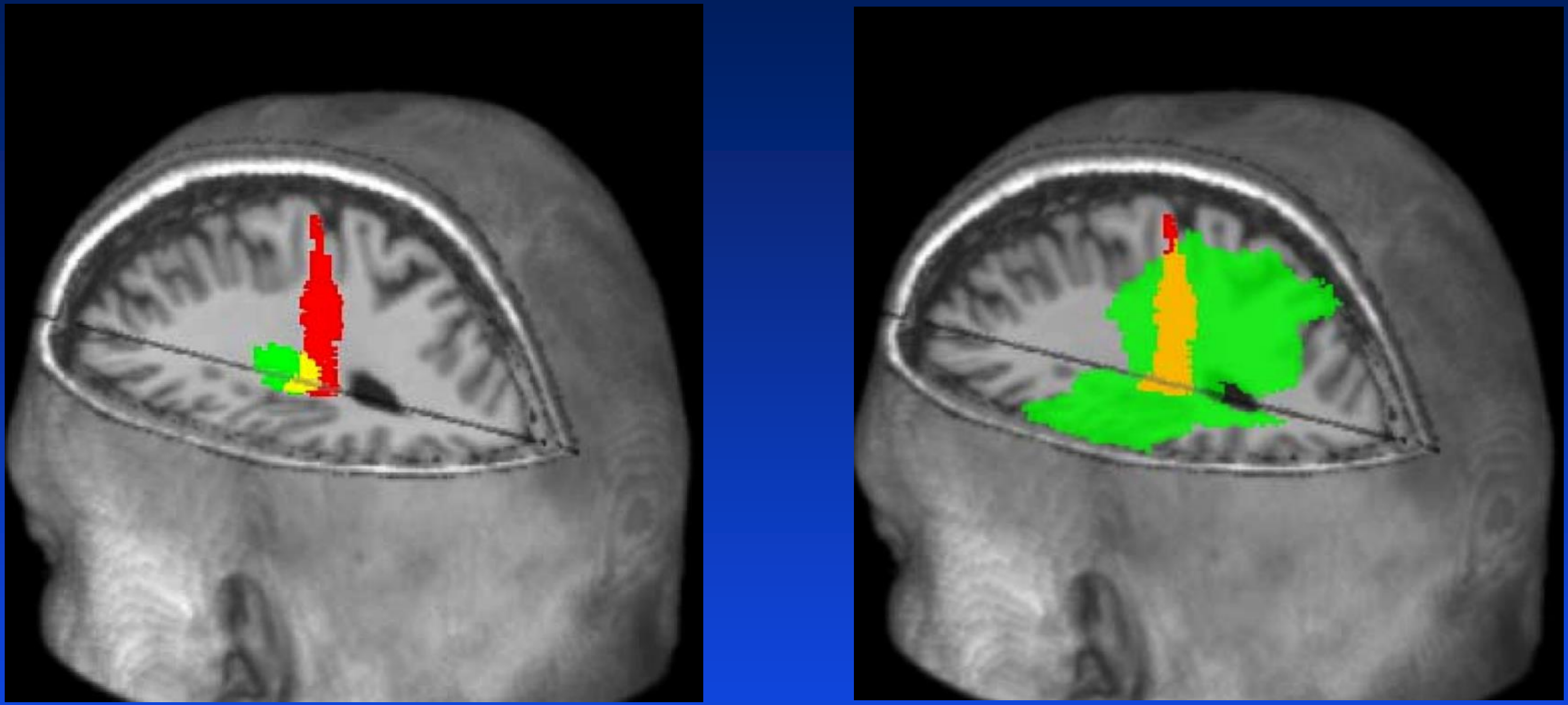
Brain injury predicts gains in a clinical trial



Corticospinal tract (M1)--uninjured

Corticospinal tract (M1)--injured by stroke

Stroke

Measuring extent of corticospinal tract injury to stratify patients

Riley et al, Stroke; 2011

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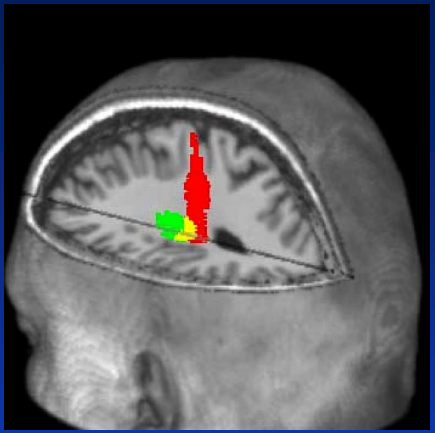
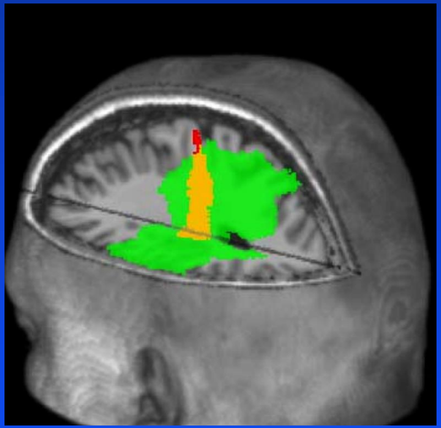
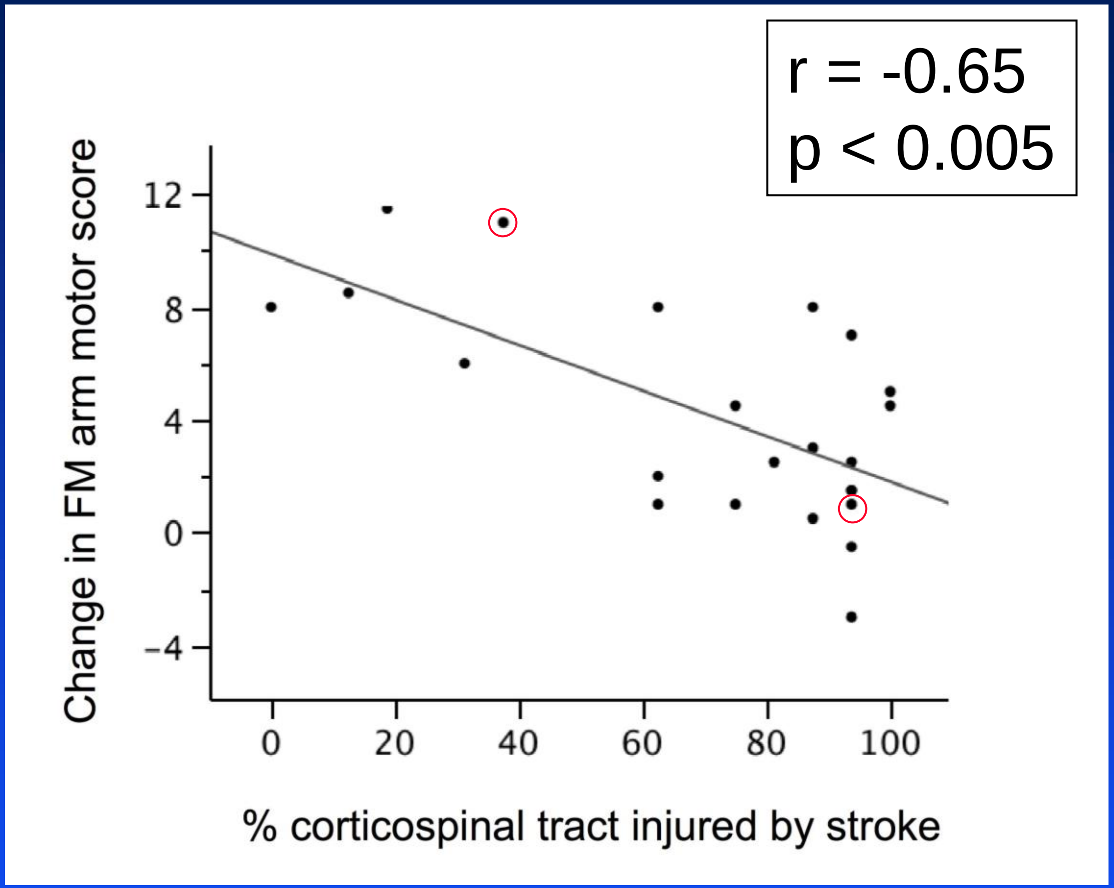






Extent of injury to this key wire bundle predicted treatment gains

(better than global injury, baseline behavior, demographics, etc)

Riley et al, Stroke; 2011

Dense array EEG

256 leads

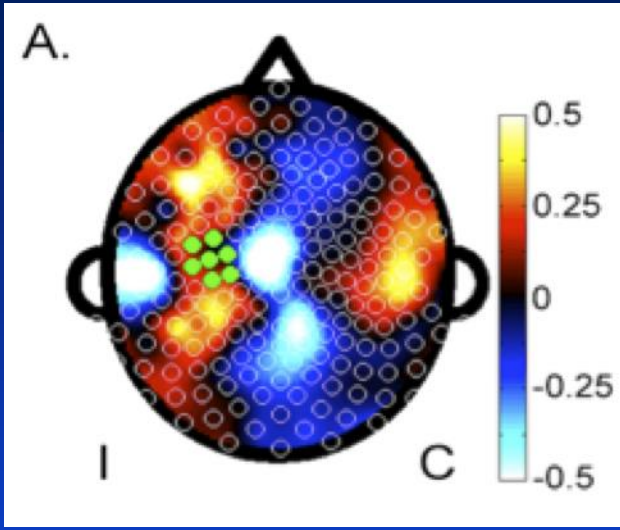
Data collection feasible in ER, ICU, rehab unit, etc

From “hello” to start data collection in 5 minutes

Current methods require only 3 minutes of data collection

Brain function predicts gains from 4 wks telerehabilitation

PLS model predicting UE-FM score change



Wu et al. Brain. 2015; 138:2359-2369.

Brain function predicts gains from 4 wks telerehabilitation

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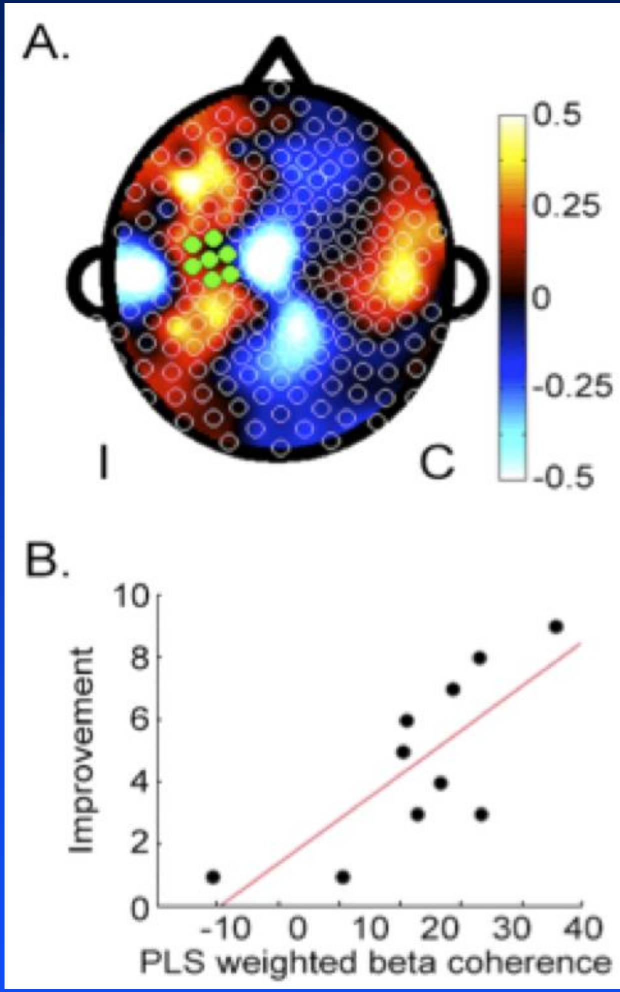
Pattern of β coherence predicts motor gains over subsequent 4 wks



r^2=0.61
p=0.0099

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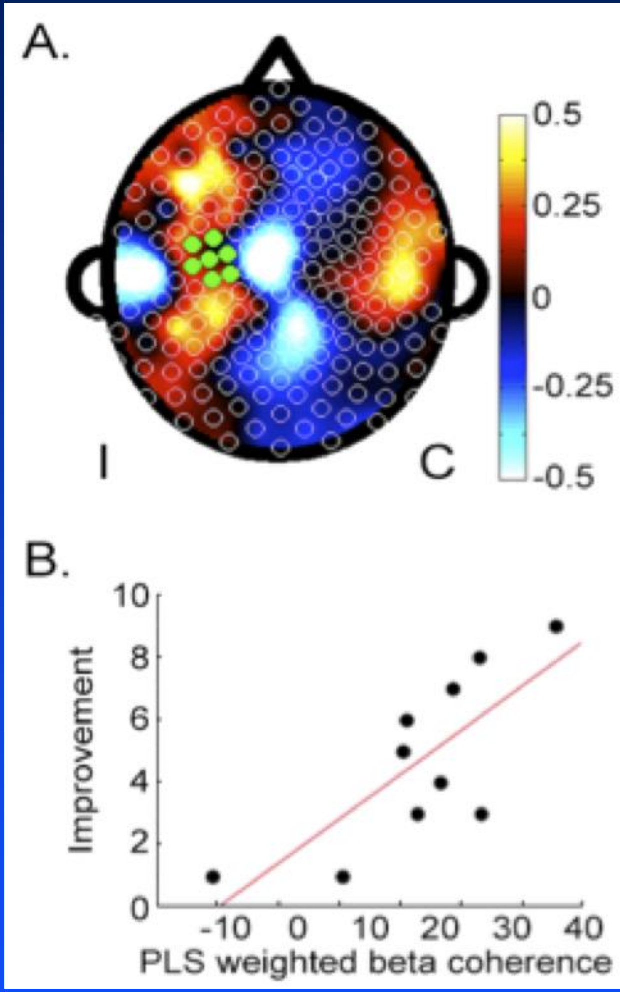

$r^2=0.61$
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3 minutes of resting dense array EEG:
a rapid, inexpensive, easy, bedside, safe test of brain function

Polygene score

Most genetic effects have RR in range of 1.1-1.4; effect of any single gene is generally small--ApoE is a major exception.

Attia et al, JAMA 2009; Zheng et al, NEJM, 2008

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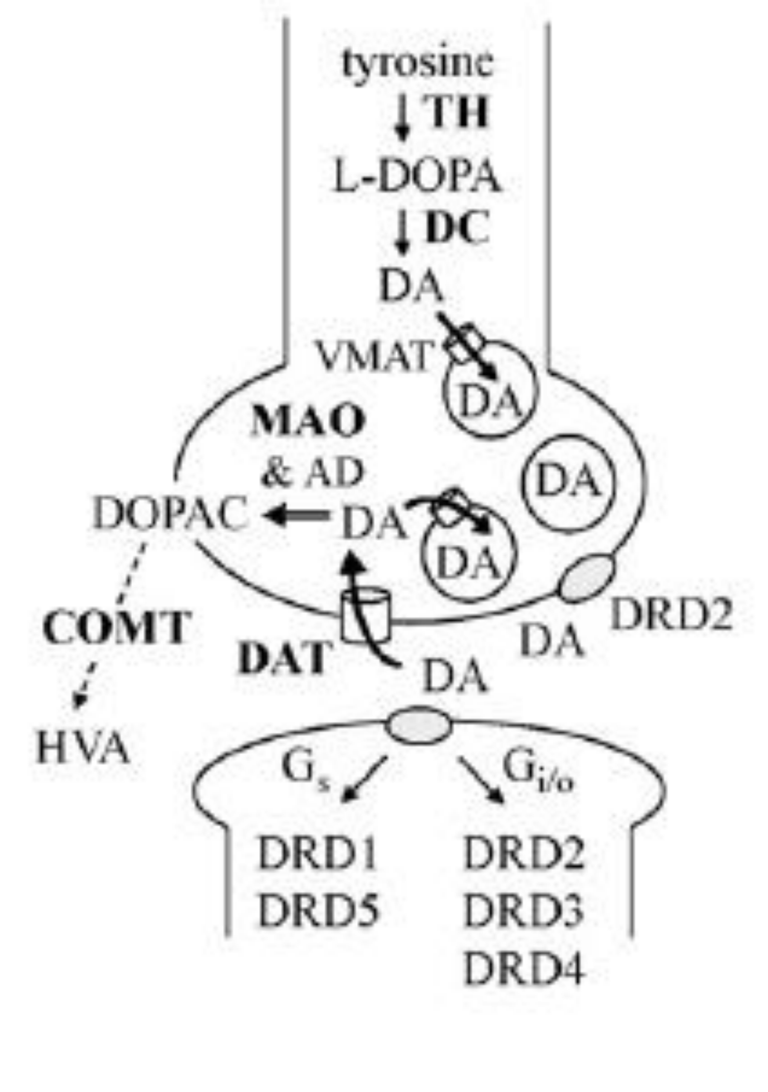
Example: in a study of 5 SNPs associated with prostate cancer, risk of disease associated with increasing # risk alleles:

OR = 1.6 with risk allele at 1 SNP, OR = 4.5 with 4 risk alleles

Attia et al, JAMA 2009; Zheng et al, NEJM, 2008

The many proteins of the dopamine system



Nemoda et al. Neurosci Biobehav Rev 35:1665–1686; 2011

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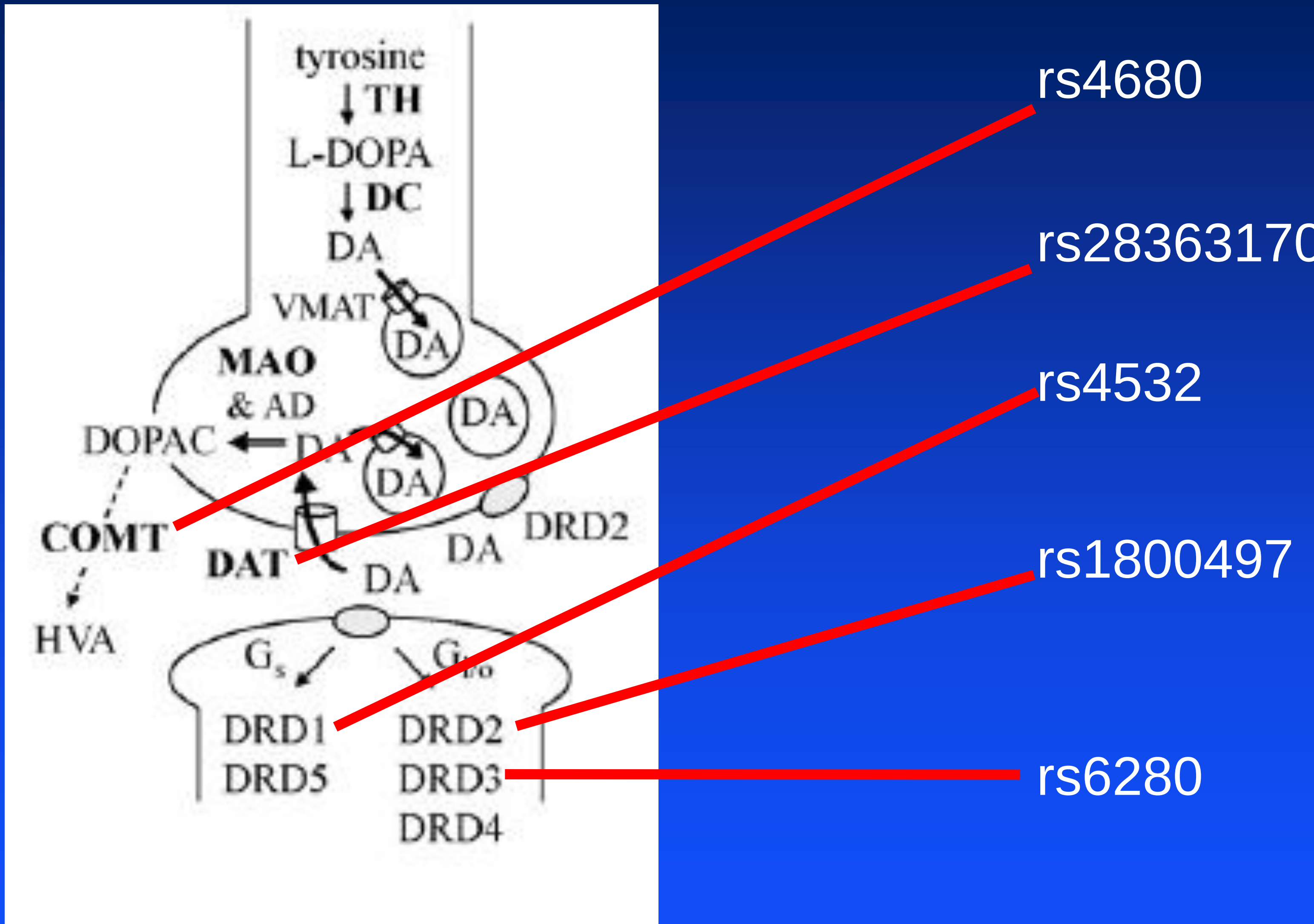

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Dopamine gene score

Constructed a gene score based on the genotype of 5 biologically active polymorphisms related to dopamine

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--less learning
--greater boost in learning with L-Dopa
--more depression
--poorer impulse control, greater improvement with Ropinirole

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PLOS ONE

Genetic Variation in the Human Brain Dopamine System Influences Motor Learning and Its Modulation by L-Dopa

Kristin M. Pearson-Fuhrhop[1], Brian Minton[1], Daniel Acevedo[1], Babak Shahbaba[2], Steven C. Cramer[1,3]*

1 Department of Anatomy & Neurobiology, University of California Irvine, Irvine, California, United States of America, 2 Department of Statistics, University of California Irvine, Irvine, California, United States of America, 3 Department of Neurology, University of California Irvine, Irvine, California, United States of America

Pearson-Fuhrhop et al PLOS-ONE 2013

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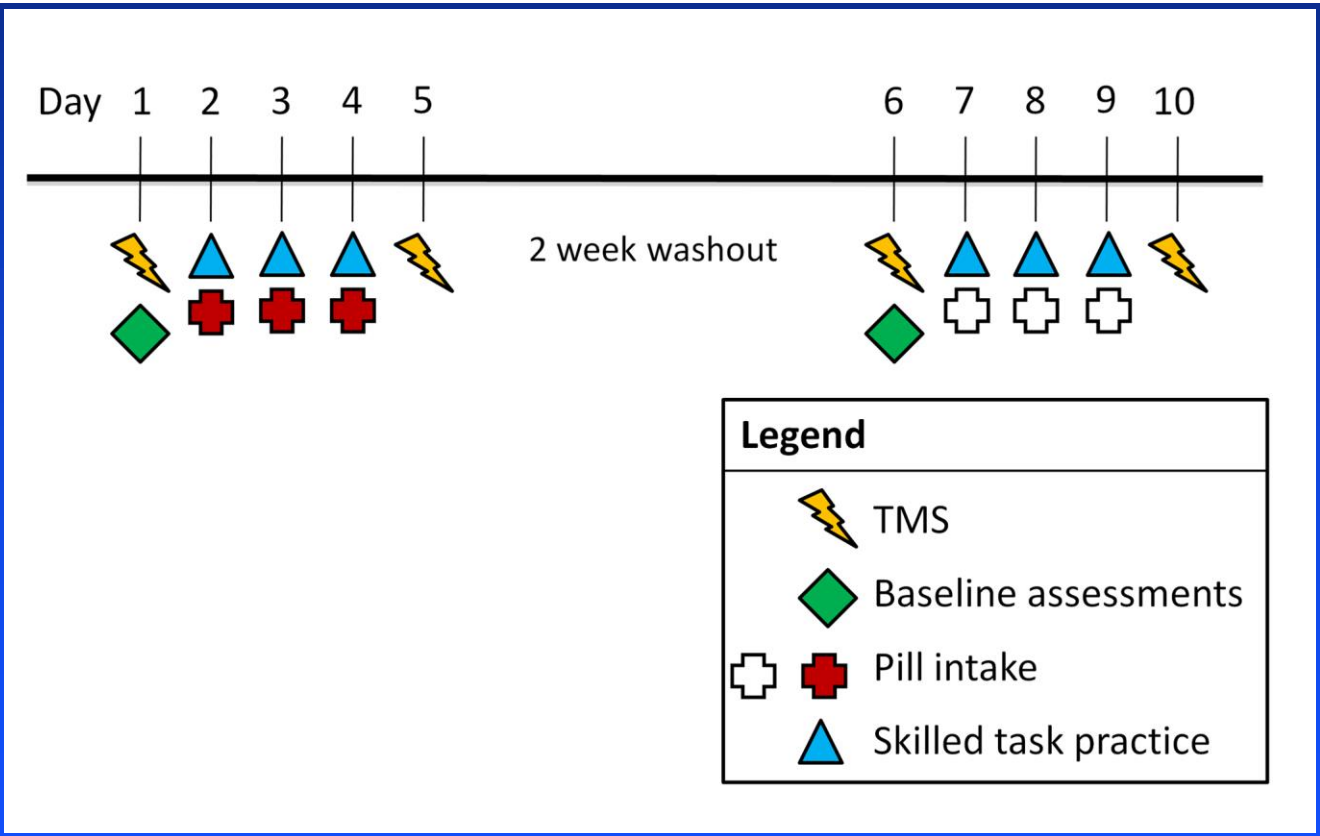
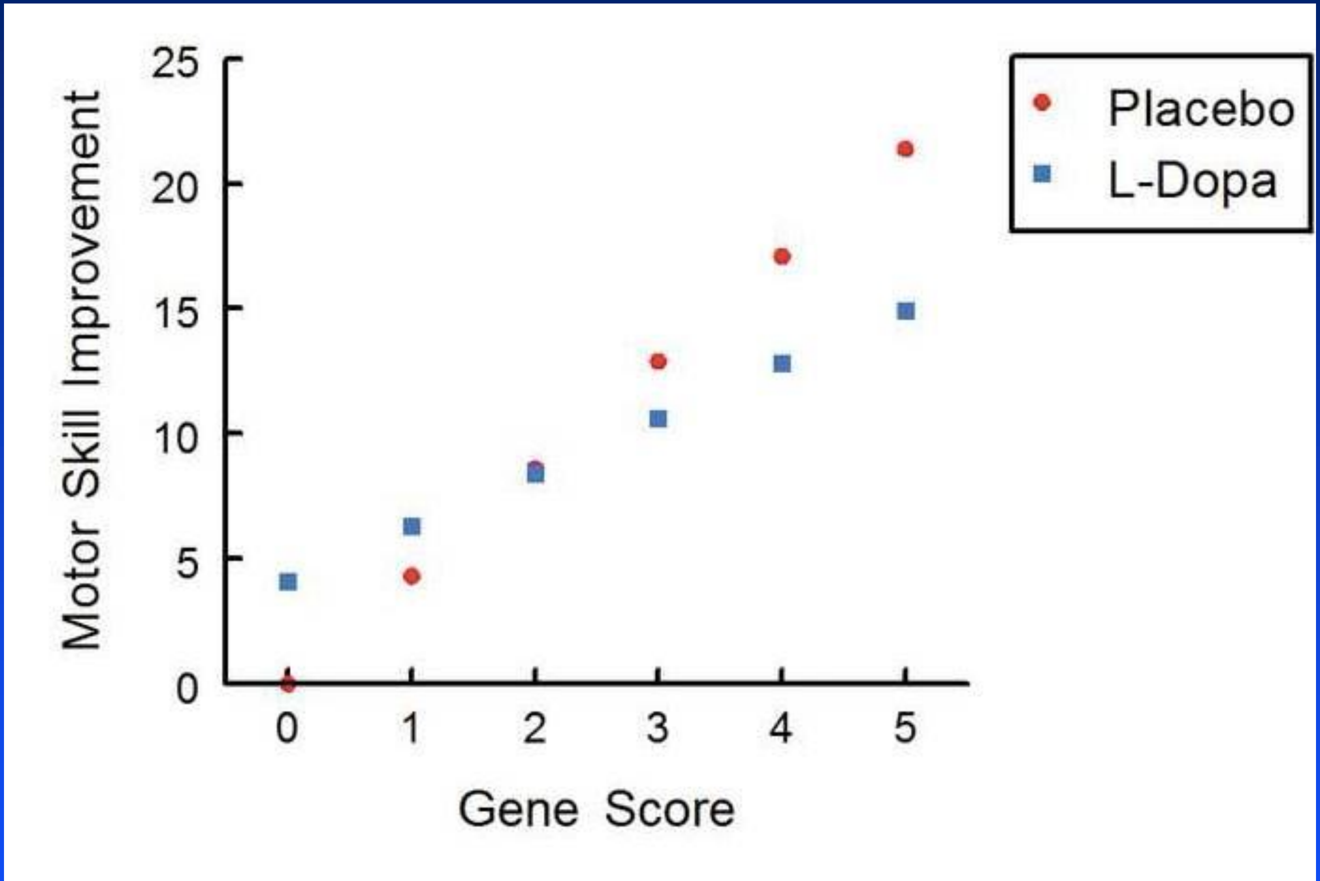


Pearson-Fuhrhop et al PLOS-ONE 2013

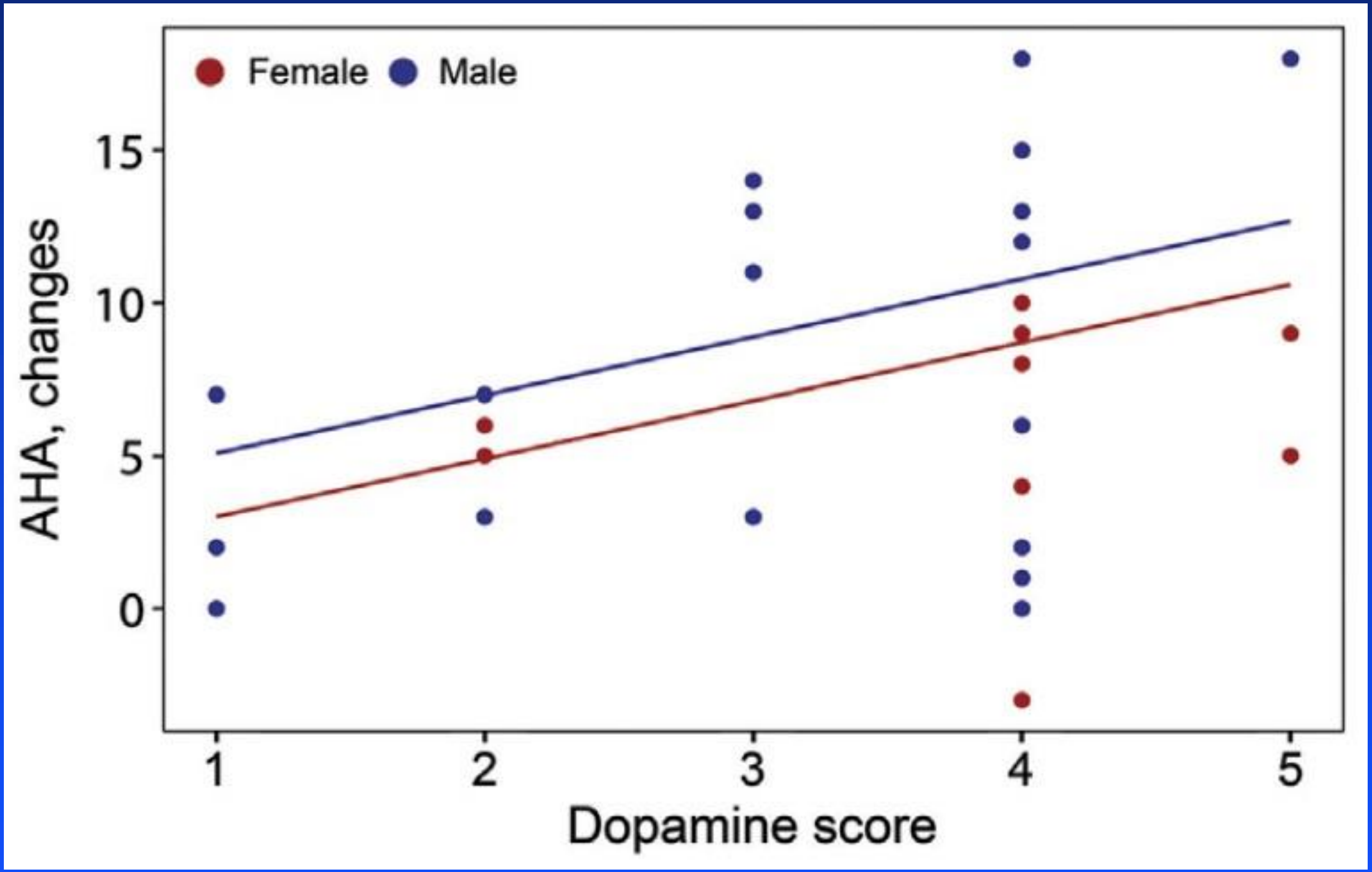


Pearson-Fuhrhop et al PLOS-ONE 2013

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

Rochellys Diaz Heijtz [a], Rita Almeida [a], Ann Christin Eliasson [b], Hans Forssberg [b,*]

[a] *Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden*
[b] *Department of Women's and Children's Health, Karolinska Institutet, Astrid Lindgren Children's Hospital, Stockholm, Sweden*



EBioMedicine 28 (2018) 162-167

Dopamine gene score

Constructed a gene score based on the genotype of 5 biologically active polymorphisms related to dopamine

Hypothesized subjects with lower dopamine neurotransmission would have

--less learning

--greater boost in learning with L-Dopa

--more depression

--poorer impulse control, greater improvement with Ropinirole

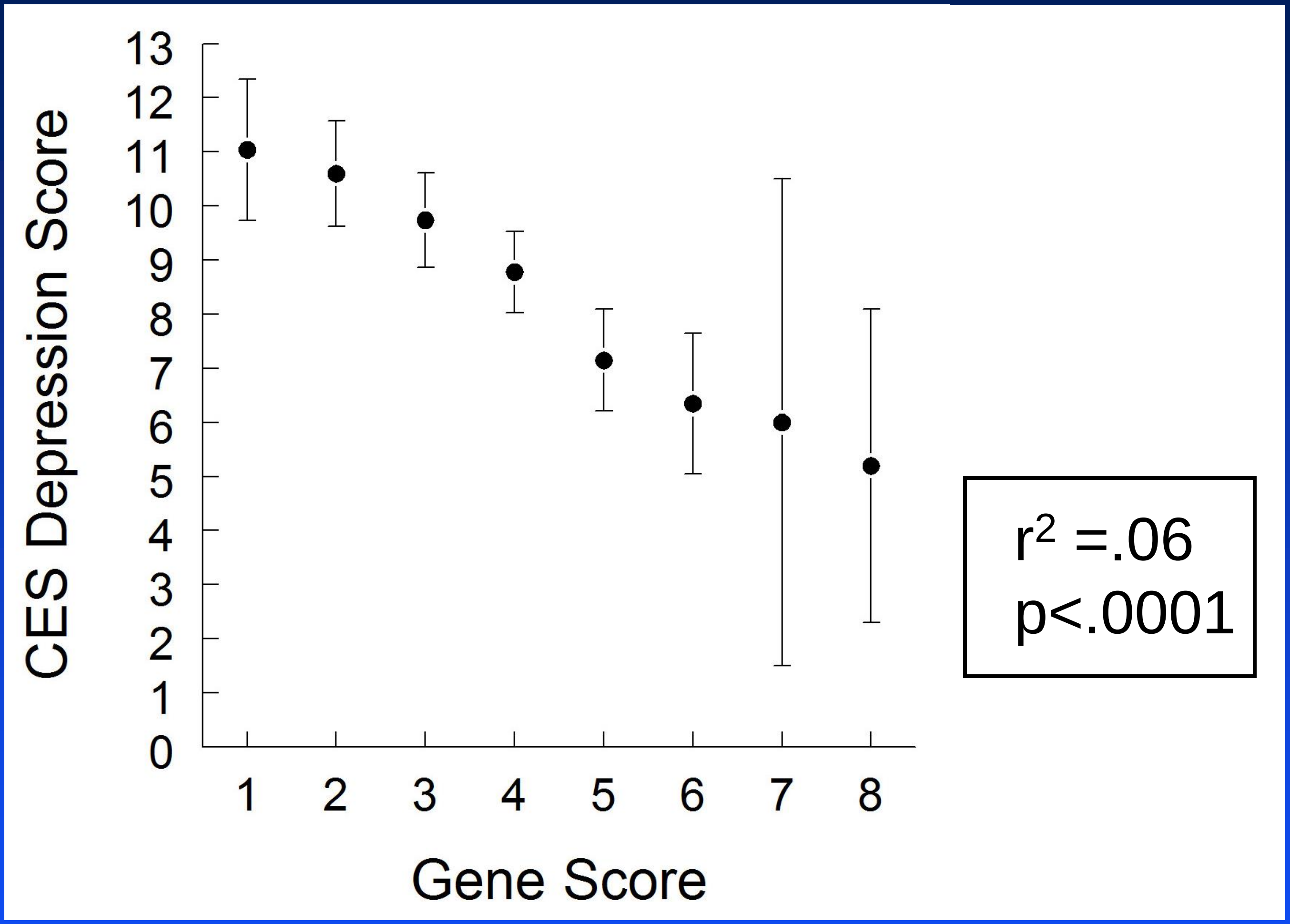
Dopamine gene score

OPEN ACCESS Freely available online PLOS ONE

Dopamine Genetic Risk Score Predicts Depressive Symptoms in Healthy Adults and Adults with Depression

Kristin M. Pearson-Fuhrhop[1], Erin C. Dunn[2,3,4], Sarah Mortero[1], William J. Devan[2], Guido J. Falcone[2], Phil Lee[2,3,4], Avram J. Holmes[3,5], Marisa O. Hollinshead[6], Joshua L. Roffman[3], Jordan W. Smoller[2,3,4], Jonathan Rosand[2,7,8], Steven C. Cramer[1,9*]

Dopamine gene score and depression



Lower dopamine gene scores, i.e. lower dopamine neurotransmission, associated with greater depression scores.

Pearson-Fuhrhop et Dunn et al PLOS-ONE 2014

Main points

- Spontaneous recovery after stroke
- Therapies to improve recovery--brain repair
- Variability in response to restorative stroke therapies

Brain Repair After Stroke

Steven C. Cramer, MD

Professor, Depts. Neurology, Anatomy & Neurobiology, and PM&R
Associate Director, Institute for Clinical & Translational Science
Co-PI, NIH StrokeNet (Recovery & Rehabilitation)

University of California, Irvine