Slide 1

Brain Repair After Stroke

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Slide 2

Disclosures

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

Slide 3

Main points

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

Slide 4

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Slide 5

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

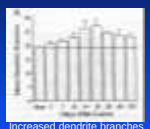
- ↑ inflammatory markers
- ↑ growth-associated proteins
- GABA rept' r downregulation
- ↑ NMDA receptor binding
- neuronal hyperexcitability
- ↑ dendrite br/spine density
- synaptogenesis
- ↑ cortical thickness

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

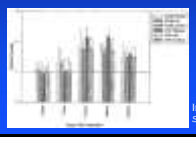
Slide 6

Molecular/cellular changes: temporal course

Growth-promoting genes
Li & Carmichael, Neurobiol Dis, 23:362

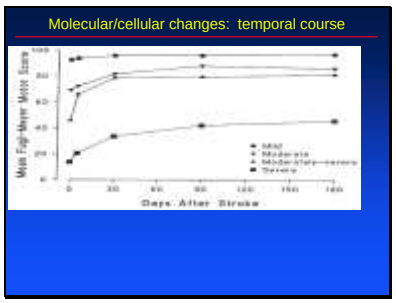


Increased dendrite branches
Jones & Schallert, Brain Res 581:156



Increased synaptogenesis
Stroemer et al, Stroke, 29:2381

Slide 7



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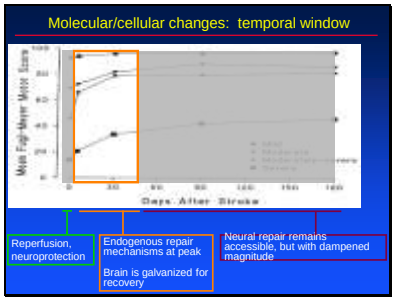

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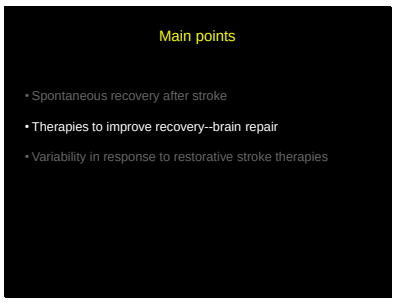

Slide 10

Brain repair: a definition

Brain repair: restoring brain structure or function after injury

Slide 11

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**

Slide 12

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Slide 13


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

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)

Slide 14

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Slide 15

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.

Slide 16

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

In humans, higher rehab therapy doses may improve outcomes.

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)

Slide 17

Issues with quantity of rehab therapy after stroke


Observation of Amounts of Movement Practice Provided During Stroke Rehabilitation

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

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

Slide 18

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

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

Slide 19

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(4) interesting
(5) environmentally and ecologically relevant

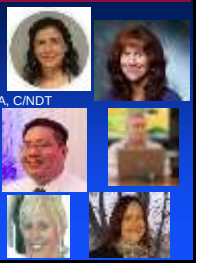
We reasoned that telerehabilitation is ideally suited to efficiently provide a large dose of useful rehab therapy after stroke.

Slide 20

Pilot Study Of Home-Based Telerehabilitation After Stroke

The team includes

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



Slide 21

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.

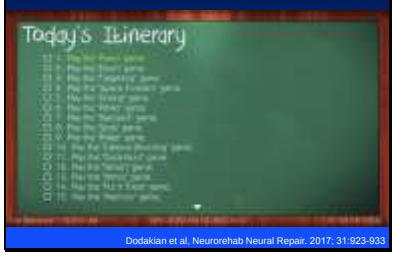
Each day consisted 1 hour that was required and structured, plus 1 optional hour of free play.

Plus 3 videoconferences per week

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

Slide 22

Pilot Study Of Home-Based Telerehabilitation After Stroke



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

Slide 23

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

Slide 24

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Average of 24,607 arm repetitions over 28 days

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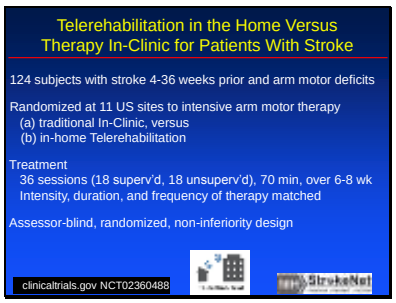
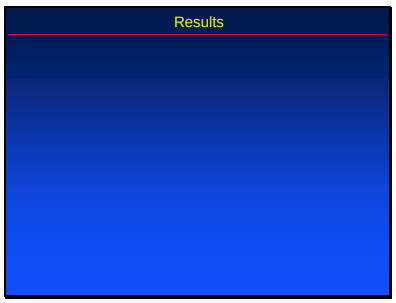
Slide 25



Slide 26

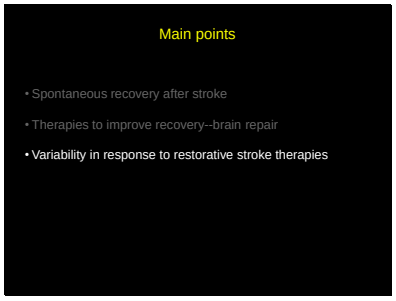
Slide 27

Slide 28



Slide 29

Slide 30



Slide 31

Stroke

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

www.dictionary.com

Slide 32


Stratifying Patients With Stroke in Trials That Target Brain Repair

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

Cramer SC. Stroke. 2010

Slide 33

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

Slide 34

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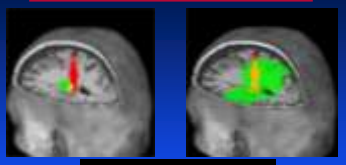
Slide 35

Brain injury predicts gains in a clinical trial

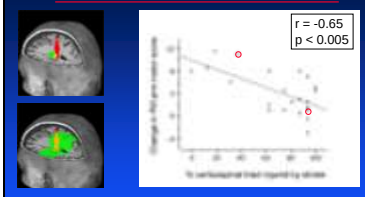


Measuring extent of corticospinal tract injury to stratify patients

Riley et al, Stroke, 2011

Slide 36

Brain injury predicts gains in a clinical trial



Extent of injury to this key wire bundle predicted treatment gains

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

Riley et al, Stroke, 2011

Slide 37

Dense array EEG

256 leads

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

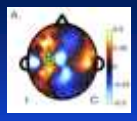
From “hello” to start data collection in 5 minutes

Current methods require only 3 minutes of data collection

Slide 38

Brain function predicts gains from 4 wks telerehabilitation

PLS model predicting
UE-FM score change



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

Slide 39

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PLS model predicting
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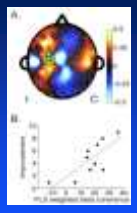
Pattern of β coherence
predicts motor gains
over subsequent 4 wks



r^2=0.61
p=0.0099

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

Slide 40

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PLS model predicting UE-FM score change

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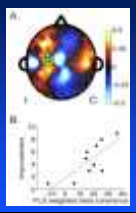
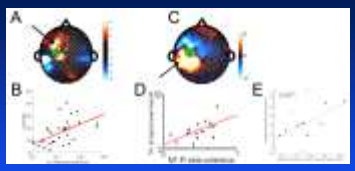


r^2=0.61
p=0.0099

3 minutes of resting dense array EEG:
a rapid, inexpensive, easy, bedside, safe test of brain function

Slide 41

Brain function predicts gains from training



Coherence (20–30 Hz) with L M1 predicts motor learning:

[A-B] after target-directed training in HC (r^2=0.68, whole brain, 0.27 M_1-PMd)
J Neurophysiol. 2018;119:490-498

[C-D] after visuomotor training in HC (r^2=0.81, whole brain, 0.34 M_1-PAR)
[E] chronic stroke (r^2=0.37, M_1-PAR)
Neuroimage. 2014;91:84-90
Front Neurol. 2018 Jul 24;9:597

Slide 42

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

Slide 43

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Thus interest in combining effect of many genes in polygenic models that assign points for the presence of risk alleles and calculates an overall risk of disease

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Slide 44

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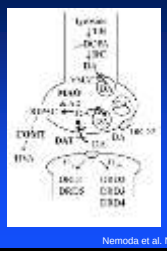
Thus interest in combining effect of many genes in polygenic models that assign points for the presence of risk alleles and calculates an overall risk of disease

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

Slide 45

The many proteins of the dopamine system



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

Slide 46

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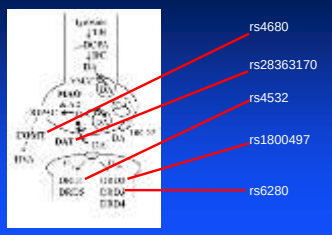

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Slide 47

Dopamine gene score

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

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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

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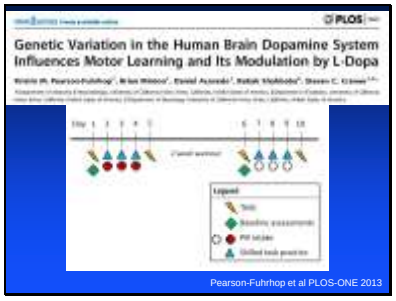
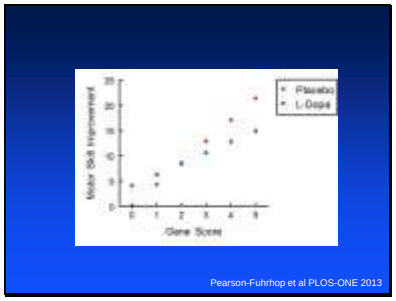
Slide 50

Slide 51

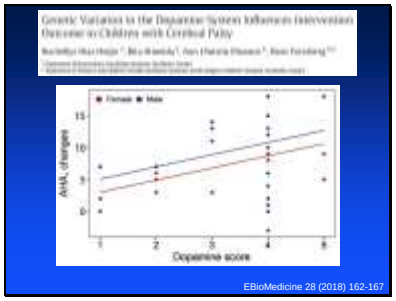


Slide 52



Pearson-Fuhrhop et al PLOS-ONE 2013

Slide 53



EBioMedicine 28 (2018) 162-167

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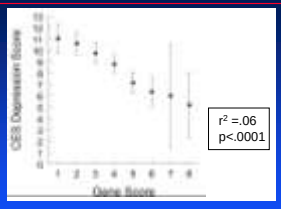
Slide 55

Dopamine gene score

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

Slide 56

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

Slide 57

Main points

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

Slide 58

Brain Repair After Stroke

Steven C. Cramer, MD

Professor, Depts. Neurology, Anatomy & Neurobiology, and PM&R
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