Genomics as an Informational Tool in Neurorehabilitation

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Disclosures

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

Genetics and Stroke Recovery/Rehab

Types of genetic variation

Stroke recovery, neurorehabilitation, and neural plasticity

Genetic variation in relation to recovery, rehab, and plasticity

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Genetics--what are the variables?

Human DNA
- 23 pairs of chromosomes
- ~6.3 billion base pairs
- ~20,000 protein-encoding genes

Alleles
- Different forms of the same gene [*Color blindness*]
- Generally, each person has 2 alleles for a given gene

Classifying genetic variation

Genetic mutation: rare, causes signif functional change [*HD*]

Genetic polymorphism: not rare (frequency ≥ 1%), relatively small effect on behavior or phenotype [*blood type*]

Many types of polymorphism, e.g., single nucleotide polymorphisms (SNP) [*BDNF val^{66}met*], variable number of tandem repeats, insertions/deletions, etc

Numerous classes of genetic variation, e.g., can have translocations of large amounts of DNA, frameshift, copy number variations

Epigenetics: changes in the regulation of gene activity and

Understanding genetic variation via interactions

Interaction with another gene
Epistasis: when the expression of one gene is modified by another gene

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Interaction with chemical state


Genome-Wide Variant by Serum Urate Interaction in Parkinson's Disease

Understanding genetic variation via interactions

Interaction with another gene
Epistasis: when the expression of one gene is modified by another gene

Interaction with chemical state

Interaction with experience


Smoking and Parkinson disease
Evidence for gene-by-smoking interactions


Genome-Wide Variant by Serum Urate Interaction in Parkinson's Disease

Approaches to studying genetic association

--Candidate gene approach, examines key genes

--Genome-wide association study, assesses massive # polymorphisms

--Gene score, examines group of genes across one system

--Many other possible approaches, e.g., exome sequencing, epigenetics, transcriptomic variation

Types of genetic variation

Stroke recovery, neurorehabilitation, and neural plasticity

Genetic variation in relation to recovery, rehab, and plasticity

What is stroke recovery, rehabilitation, and neural plasticity ?

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**

What is stroke recovery, rehabilitation, and neural plasticity ?

Use of these terms is usually far too broad for their measurement to connect with specific gene-based hypotheses.

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Molecular
Systems
Behavior

Cellular & molecular 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

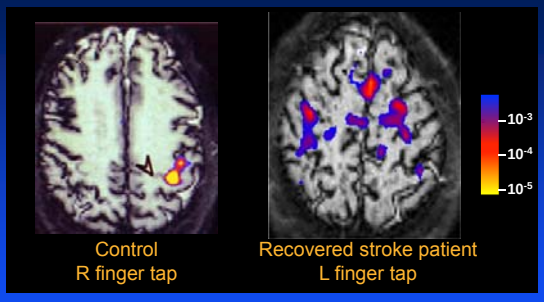
Contralesional changes

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

Molecular
Systems
Behavior

Cramer & Chopp, TINS 00; Wieloch & Nikolich, Curr Op Nbio 06; Carmichael, Ann Neurol 16

Laterality of brain function and stroke recovery



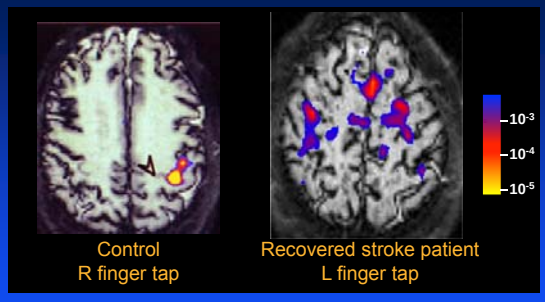
Control
R finger tap

Recovered stroke patient
L finger tap

Molecular
Systems
Behavior

Cramer et al, Stroke. 1997; 28:2518-2527.

Laterality of brain function and stroke recovery



Control
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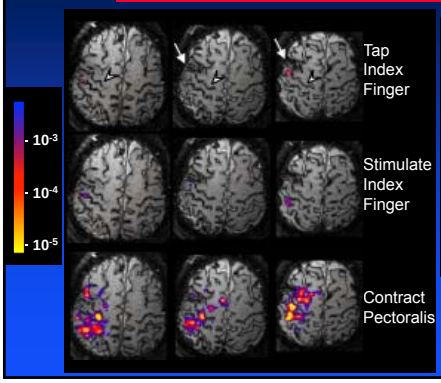
Recovered stroke patient
L finger tap

Less lateralized (more bilaterally organized) with
larger infarct **worse deficits** **over time**
non-dominant side infarct

Cramer et al, Stroke 97; Marshall et al, Stroke 00; Cramer et al, Exp Br Res 05

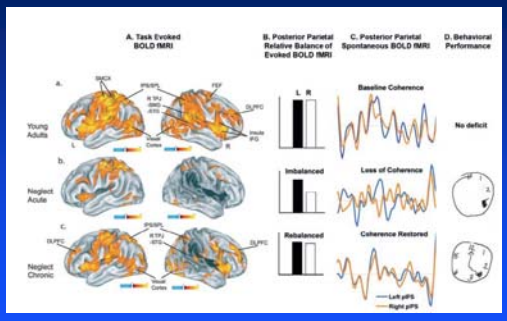
Site of brain activation and stroke recovery:
posterior shift for some tasks



61 y/o RHM 6 mo after R pre-central gyrus embolus

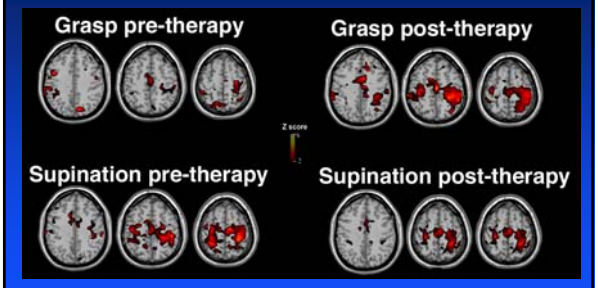
Cramer et al. Stroke. 2000; 31:668-671.

Network activation and spontaneous stroke recovery



Corbetta et al, Nat Neurosci. 2005;8:1603–10

Brain activation and treatment-related stroke recovery



Takahashi et al, Brain 2008

Brain function (EEG) predicts treatment-related recovery

256 leads

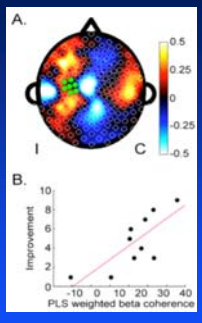
Data collection feasible in ER, ICU, rehab unit, etc

From "hello" to start data collection in 5 minutes

Current methods require only 3 minutes of data collection

Brain function (EEG) predicts treatment-related recovery

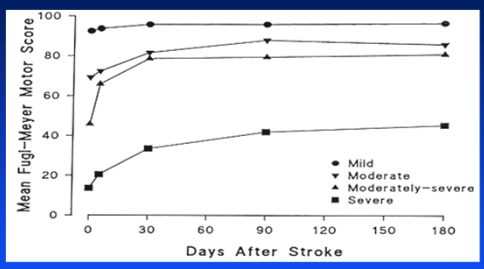
EEG (β coherence) predicted change in Fugl-Meyer score across 4 weeks of telerehab



r^2=0.61
p=0.0099

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

Behavioral recovery after stroke



Duncan et al. *Stroke*. 1992;23:1084-1089

Molecular
Systems
→ Behavior

Behavioral recovery after stroke

The Case for Modality-Specific Outcome Measures in Clinical Trials of Stroke Recovery-Promoting Agents

Steven C. Cramer, MD; Walter J. Koroshetz, MD; Seth P. Finklestein, MD

Stroke. 2007;38:1393-1395.

Types of genetic variation

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REVIEW

The influence of genetic factors on brain plasticity and recovery after neural injury

Kristin M. Pearson-Fuhrhop[a], Erin Burke[a], and Steven C. Cramer[a,b]

Curr Opin Neurol 2012, 25:682-688

Genetics as a molecular window into recovery, its treatment, and stress responses after stroke

Vanessa Juth,[1] E Alison Holman,[1] Michelle K Chan,[1] Steven C Cramer[2]

Juth V, *et al. J Investig Med* 2016;**64**:983–988.

Genetic Variation and Neuroplasticity: Role in Rehabilitation After Stroke

Jill Campbell Stewart, PT, PhD, and Steven C. Cramer, MD

(*JNPT* 2017;41: S17–S23)

Stroke, sTress, RehabilitatiON, and Genetics Study

R01-NR015591 ; scramer@uci.edu

Why would clinicians study genetics?

Clinicians might study genetics in order to better

- Inform therapeutic decision-making, e.g., Rx choice or Rx dose; adverse event risk

Genetics and therapeutic decision-making

Cytochrome P450 enzymes metabolize many drugs; polymorphisms can alter drug levels, e.g., for clopidogrel, codeine, or azathioprine.

Vitamin K epoxide reductase complex reduces vitamin K; SNPs account for 25% of the variance in warfarin dosing.

Stevens Johnson syndrome from carbamazepine is substantially more common with even one copy of certain HLA alleles: B*1502 (Asian populations) and A*3101 (Europeans).

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- Understand biology and pathogenesis of disease
- Estimate individual risk, prognosis, tendencies
- Stratify enrollees in a clinical trial

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BDNF val^{66}met SNP:	endophenotype
ApoE4 polymorphism:	spontaneous stroke recovery
Dopamine polygene score:	predicts motor learning, mood, impulsiveness, response to L-Dopa

Why would clinicians study genetics?

Stroke Recovery Genetics

Arne Lindgren, MD, PhD; Jane Maguire, RN, PhD

Stroke. 2016;47:2427-2434

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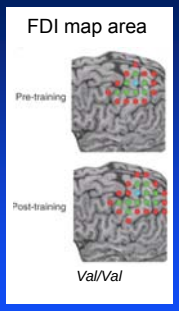
Genetics of motor cortex plasticity



Kleim et al, 2006; *Nat Neurosci*

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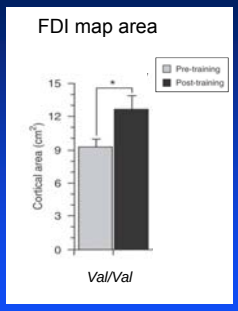

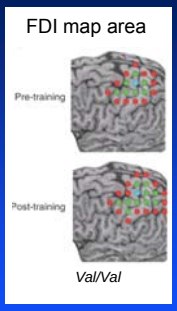

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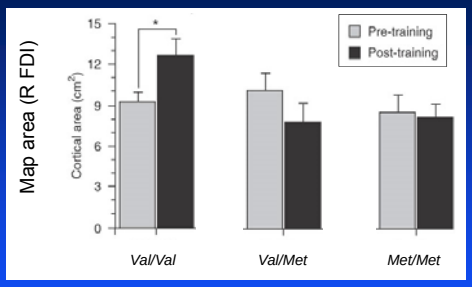
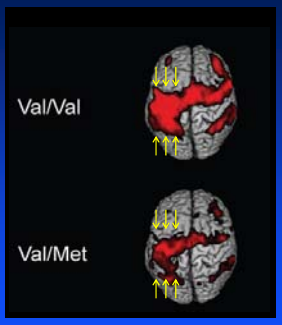


val[66]met BDNF polymorphism associated with reduced short-term, activity-dependent motor cortex plasticity

Kleim et al, 2006; *Nat Neurosci*

BDNF val[66]met polymorphism and motor activation



Healthy control subjects

McHughen SA, Rodriguez PF, Kleim JA, Kleim ED, Marchal Crespo L, Procaccio V, Cramer SC. BDNF val[66]met polymorphism influences motor system function in the human brain. *Cereb Cortex*. 2010;20:1254-1262

BDNF Val[66]Met Polymorphism Is Related to Motor System Function After Stroke

Dae Yul Kim, Erin B. Quinlan, Robert Gramer, Steven C. Cramer

42 patients with chronic stroke received arm motor robot therapy

Kim DY, Quinlan EB, Gramer R, Cramer SC. BDNF val[66]met polymorphism is related to motor system function after stroke. *Phys Ther*. 2016;96:533-539

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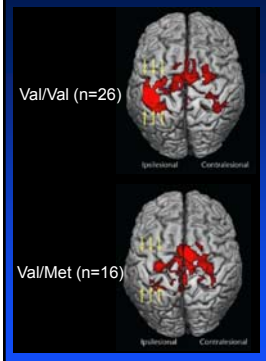

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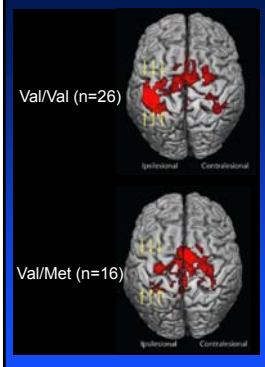
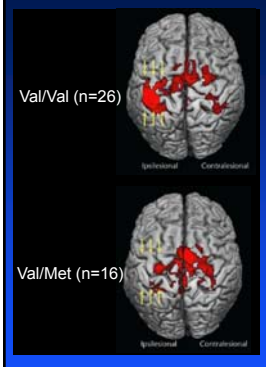


Motor cortex activation varied significantly per BDNF genotype.

Same result as was seen in our prior study of healthy controls.

Kim DY, Quinlan EB, Gramer R, Cramer SC. BDNF val[66]met polymorphism is related to motor system function after stroke. *Phys Ther*. 2016;96:533-539



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But: differences in cortical function not related to baseline FM or to change in FM with therapy

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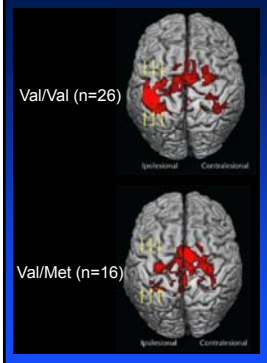

Motor cortex activation varied significantly per BDNF genotype.

But: differences in cortical function not related to baseline FM or to change in FM with therapy

--other compensatory process?

--wrong motor task during fMRI?

--endophenotype?

Kim DY, Quinlan EB, Gramer R, Cramer SC. BDNF val^{66}met polymorphism is related to motor system function after stroke. *Phys Ther*. 2016;96:533-539

Endophenotype

Endophenotype: a measurement (behavioral, imaging, biochemical, etc) linked to a genotype that is useful for distinguishing biological subgroups that look the same clinically.

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Examples:

Decreased pre-symptomatic hippocampal volume in certain genetic forms of Alzheimer's disease

Increased error-related negativity (an EEG measure of cingulate activity following an error) in subjects with OCD

Increased pre-symptomatic activation and connectivity in premotor cortex of certain genetic forms of Parkinson's disease

Imaging Endophenotypes of Stroke as a Target for Genetic Studies

Xueqiu Jian, PhD; Myriam Fornage, PhD

"Endophenotypes are typically quantitative and lie in the causal pathway to the disease but are closer to the gene action than the clinical phenotype…"

Variants in specific genes have been associated with several imaging endophenotypes of

--white matter hyperintensities
--covert brain infarcts by MRI
--Virchow-Robin spaces
--cerebral microbleeds
--carotid intima/media thickness
--atrial fibrillation

Stroke. 2018;49:1557-1562.

Genetic factors & brain atrophy after stroke

Genetic variation has been associated with differences in brain atrophy in many settings—is this true after stroke?

^^ Winstein et al. JAMA. 2016; 315:571-581.

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Volume of the ventricles and the brain were measured in stroke survivors enrolled in ICARE trial.^^

Brain atrophy expressed as the Ventricle-Brain Ratio (VBR).

VBR was then examined in relation to the two genotypes of interest, BDNF val^{66}met and ApoE ε4.

^^ Winstein et al. JAMA. 2016; 315:571-581.

Genetic factors & brain atrophy after stroke

n=127 (61 with MRI and 66 with a CT scan).

Scans acquired 5 ± 11 days post-stroke.

The BDNF val^{66}met genotype was present in 23/127 subjects; ApoE ε4, in 41/127; both were in HW equilibrium.

Mean ventricle volume=30.8 cc; brain volume=1,166 cc; and VBR=0.027

Genetic factors and brain atrophy after stroke

VBR as a function of
- BDNF val^{66}met carrier status, p=0.014
- ApoE ε4 carrier status, p=0.53

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Mean VBR increases 1.97-fold (97%) when the BDNF val^{66}met polymorphism is present compared to absent.

Mean VBR not associated with baseline behavior (WMFT, p=0.50) or its change over 12 months (p=0.47).

Genetic factors and brain atrophy after stroke

BDNF val^{66}met polymorphism assoc with 97% greater atrophy.

But BDNF val^{66}met not related to behavior at enrollment or 12 month change.

Suggests VBR is an endophenotype for val^{66}met status

Genetic factors and brain atrophy after stroke

BDNF val^{66}met polymorphism assoc with 97% greater atrophy.

But BDNF val^{66}met not related to behavior at enrollment or 12 month change.

Suggests VBR is an endophenotype for val^{66}met status.

VBR association with atrophy but not behavior might reflect short time interval examined, no measure of brain function (reserve); younger group enrolled, or that patients had mild-mod deficits.

Insights into biology of inter-subject differences in brain anatomy after stroke might inform restorative therapy and clinical trials.

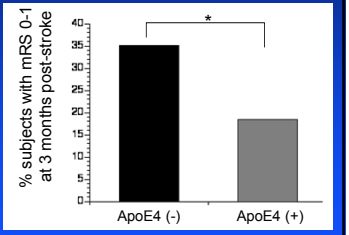
BDNF val^{66}met SNP: endophenotype

ApoE4 polymorphism: ← spontaneous stroke recovery

Dopamine polygene score: predicts motor learning, mood, impulsiveness, response to L-Dopa

Genotype predicts gains in a clinical trial

Among 241 subjects in the GAIN trials
% subjects with min/no disability *(modified Rankin Scale score 0-1)* was lower when the ApoE4 genotype present (*p = 0.01)



Cramer and Procaccio, Eur J Neurol. 2012; 19:718-724.

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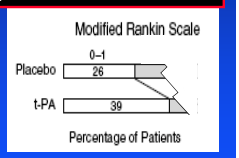
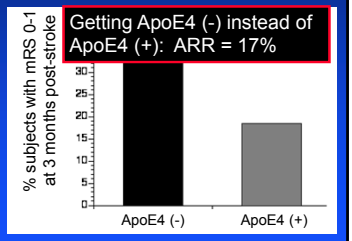
Getting iv tPA instead of placebo: ARR = 13%



NINDS tPA trial; NEJM, 1995

Getting ApoE4 (-) instead of ApoE4 (+): ARR = 17%



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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.

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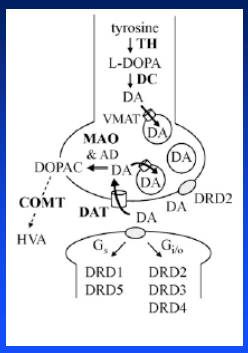
Example: in a study of 5 SNPs associated with prostate cancer, risk of disease associated with increasing # risk alleles:
OR = 1.6 with risk allele at 1 SNP, OR = 4.5 with 4 risk alleles

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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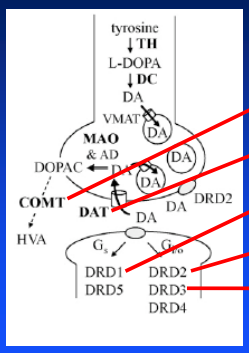

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--greater boost in learning with L-Dopa
--more depression
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Genetic Variation in the Human Brain Dopamine System Influences Motor Learning and Its Modulation by L-Dopa

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

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Pearson-Fuhrhop et al PLOS-ONE 2013

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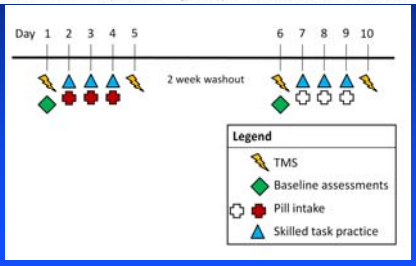

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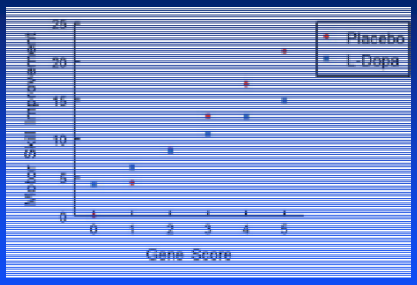

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Genetic Variation in the Dopamine System Influences Intervention Outcome in Children with Cerebral Palsy

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

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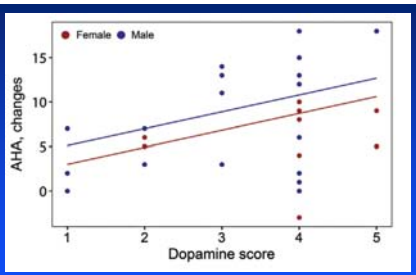
[b] Department of Women's and Children's Health, Karolinska Institutet, Astrid Lindgren Children's Hospital, Stockholm, Sweden



Hand training for 2hr/day x 2 mo in 33 children with cerebral palsy
Gains in Assisting Hand Assessment scores varied by gene score

Diaz Heijtz et al, EBioMedicine 28 (2018) 162–167

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

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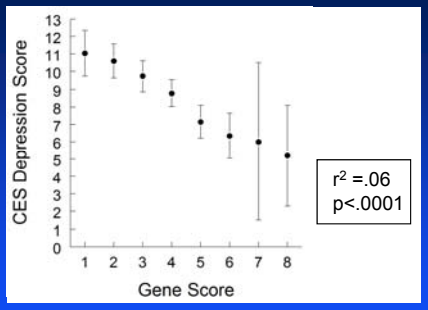
Dopamine Genetic Risk Score Predicts Depressive Symptoms in Healthy Adults and Adults with Depression

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



r^2 =.06
p<.0001

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

Pearson-Fuhrhop et al PLOS-ONE 2014

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 Profiling to Predict Impulse Control and Effects of Dopamine Agonist Ropinirole

Hayley J. MacDonald[1], Cathy M. Stinear[1], April Ren[1], James P. Coxon[2], Justin Kao[3], Lorraine Macdonald[3], Barry Snow[3], Steven C. Cramer[4], and Winston D. Byblow[1]

MacDonald et al, Journal of Cogn Neurosci. 2016; 28:909-919.

Dopamine Gene Profiling to Predict Impulse Control and Effects of Dopamine Agonist Ropinirole

Hayley J. MacDonald[1], Cathy M. Stinear[1], April Ren[1], James P. Coxon[2], Justin Kao[3], Lorraine Macdonald[3], Barry Snow[3], Steven C. Cramer[4], and Winston D. Byblow[1]

On placebo: lower dopamine gene scores (lower dopamine neurotransmission) associated with poorer impulse control.

On the dopamine agonist Ropinirole: lower dopamine gene scores showed improved response inhibition, while higher gene scores had trend towards worsened response inhibition.

MacDonald et al, Journal of Cogn Neurosci. 2016; 28:909-919.

Moving forward

On the one hand, large consortia, big questions, big data.
- --Always with precise definitions and measures of phenotype

On the other hand, continue targeted studies of candidate genes.
- --Esp those with highest therapeutic implications
- --Need mechanistic insights, biomarkers that capture repair events of interest to optimize hypothesis testing

Stroke, sTress, RehabilitatiON, and Genetics Study

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Types of genetic variation

Stroke recovery, neurorehabilitation, and neural plasticity

Genetic variation in relation to recovery, rehab, and plasticity

Genomics as an Informational Tool in Neurorehabilitation

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