Genetics And Neural Plasticity After Stroke

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Disclosures

Dr. Cramer has served as a consultant for MicroTransponder, Dart Neuroscience, and Toyama.

"Genetic variation, stress, and functional outcomes after stroke rehabilitation"

R01-NR015591

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Genetics And Neural Plasticity After Stroke

Genetic variation

Measures of neural plasticity

Studies of genetic polymorphisms related to stroke recovery

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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 [*Sickle cell disease*]
- 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 expression not dependent on primary gene sequence

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

Interaction with experience

Approaches to studying genetic association

--Candidate gene approach, examine key genes

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

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

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

Stroke Genetics Network (SiGN)

Meschia et al, Stroke 2013;44:2694-2702

Stroke Genetics Network (SiGN)

Stroke Genetics Network (SiGN) Study

Design and Rationale for a Genome-Wide Association Study of Ischemic Stroke Subtypes

James F. Meschia, MD; Donna K. Arnett, PhD; Hakan Ay, MD; Robert D. Brown Jr, MD; Oscar R. Benavente, MD; John W. Cole, MD, MS; Paul I.W. de Bakker, PhD; Martin Dichgans, MD; Kimberly F. Doheny, PhD; Myriam Fornage, PhD; Raji P. Grewal, MD; Katrina Gwinn, MD; Christina Jern, MD; Jordi Jimenez Conde, MD, PhD; Julie A. Johnson, PharmD; Katarina Jood, MD; Cathy C. Laurie, PhD; Jin-Moo Lee, MD, PhD; Arne Lindgren, MD; Hugh S. Markus, FRCP; Patrick F. McArdle, PhD; Leslie A. McClure, PhD; Braxton D. Mitchell, PhD; Reinhold Schmidt, MD; Kathryn M. Rexrode, MD; Stephen S. Rich, PhD; Jonathan Rosand, MD, MSc; Peter M. Rothwell, MD; Tatjana Rundek, MD; Ralph L. Sacco, MD; Pankaj Sharma, MD; Alan R. Shuldiner, MD; Agnieszka Slowik, MD; Sylvia Wassertheil-Smoller, PhD; Cathie Sudlow, MD; Vincent N.S. Thijs, MD; Daniel Woo, MD; Bradford B. Worrall, MD, MSc; Ona Wu, PhD; Steven J. Kittner, MD; on behalf of the NINDS SiGN Study

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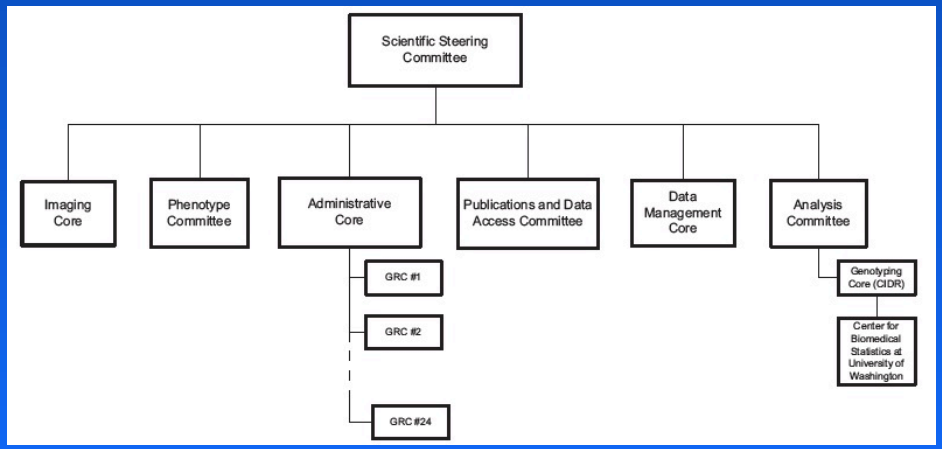

Meschia et al, Stroke 2013;44:2694-2702

Genetic variation

Measures of neural plasticity

Studies of genetic polymorphisms related to stroke recovery

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

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Nudo, Curr Op Nbio, 99; Cramer & Chopp, TINS, 00; Wieloch & Nikolich, Curr Op Nbio 06

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There are also extra-neural processes of interest that affect stroke recovery, e.g., stress, inflammation, metabolism

Nudo, Curr Op Nbio, 99; Cramer & Chopp, TINS, 00; Wieloch & Nikolich, Curr Op Nbio 06

The Volume of the Spleen and Its Correlates after Acute Stroke

Nina L. Chiu, BS,* Brian Kaiser, DO,* Y Vien Nguyen, DO,†
Susan Welbourne, BSN, RN,‡ Chandana Lall, MD,† and Steven C. Cramer, MD*§

Chiu et al, Journal of Stroke and Cerebrovascular Diseases (in press).

Stroke recovery at the bedside

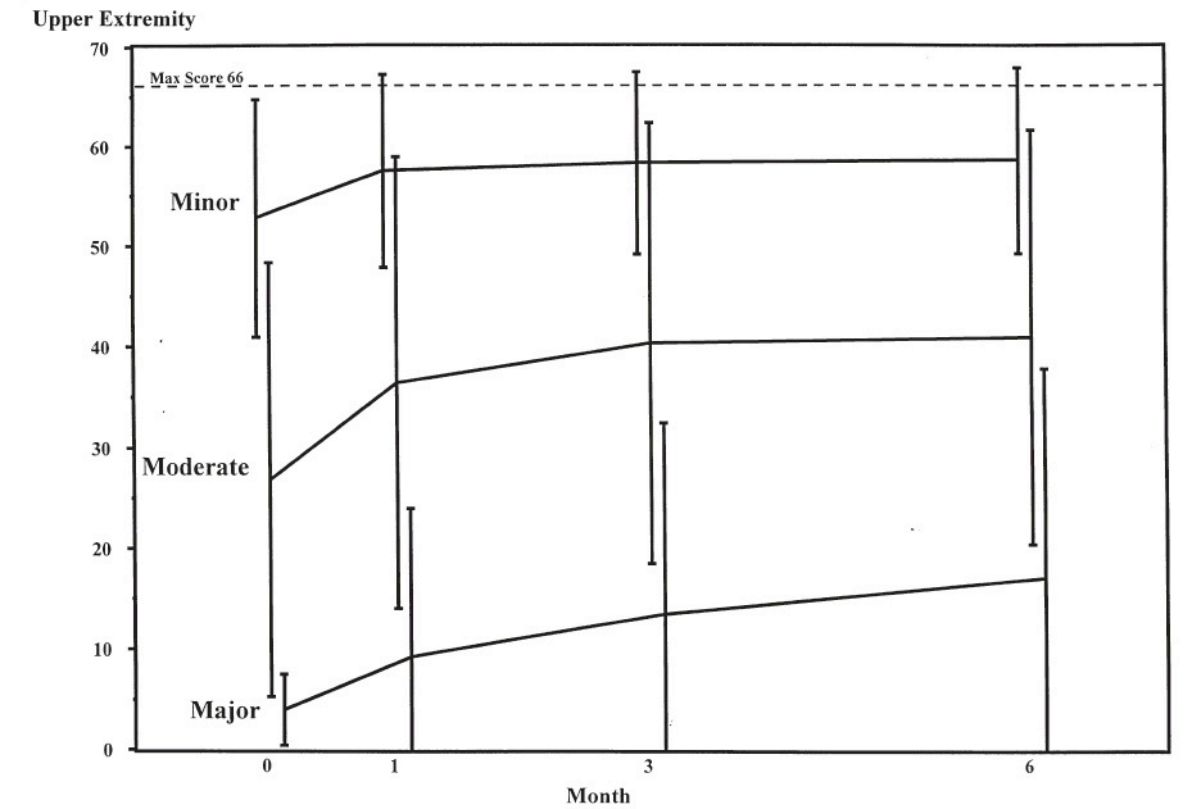

Fig. 2. Plot of means and 1 SD of Fugl-Meyer upper extremity after stroke.

Change in Fugl-Meyer scale over time after stroke

Duncan et al, Neuropharmacology; 39:835-841

A Standardized Approach to Performing the Action Research Arm Test

Nuray Yozbatiran, PT, PhD, Lucy Der-Yeghiaian, MA, OTR/L, and Steven C. Cramer, MD

Yozbatiran et al. Neurorehabil Neural Repair. 2008; 22:78-90.

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A Standardized Approach to the Fugl-Meyer Assessment and Its Implications for Clinical Trials

Neurorehabilitation and
Neural Repair
27(8) 732–741

DOI: 10.1177/1545968313491000
nnr.sagepub.com
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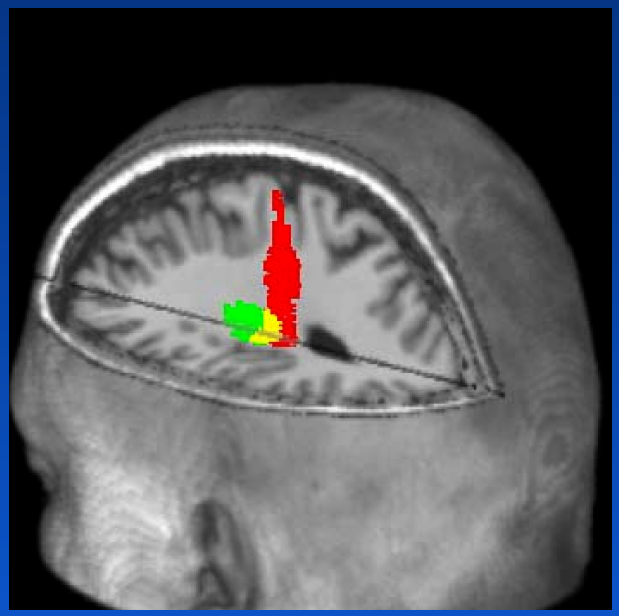
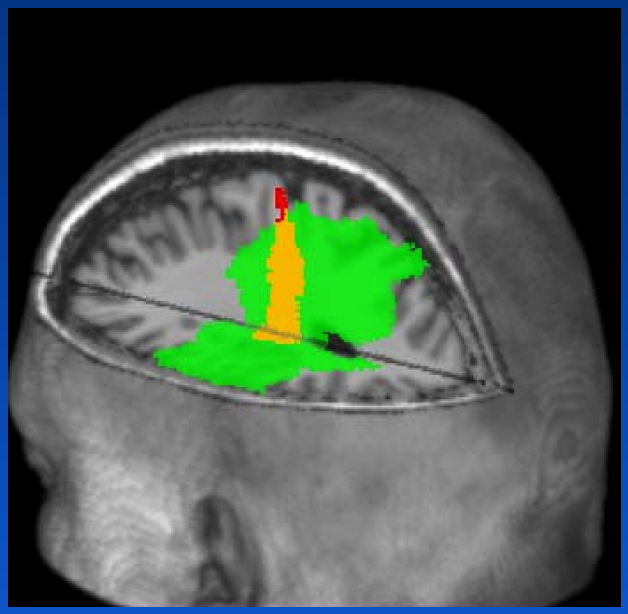
Jill See, MPT[1], Lucy Dodakian, MA[1], Cathy Chou, MPT[1],
Vicky Chan, MSPT[1], Alison McKenzie, PhD[2],
David J. Reinkensmeyer, PhD[1] and Steven C. Cramer, MD[1]

See et al. Neurorehabil Neural Repair. 2013; 27:732-741.

A standardized approach to measuring corticospinal tract injury in a clinical study





Corticospinal tract (M1)--uninjured

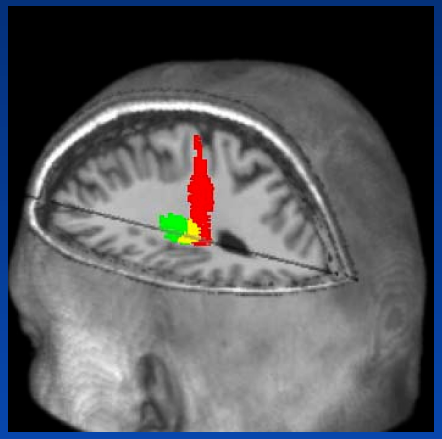
Corticospinal tract (M1)--injured by stroke

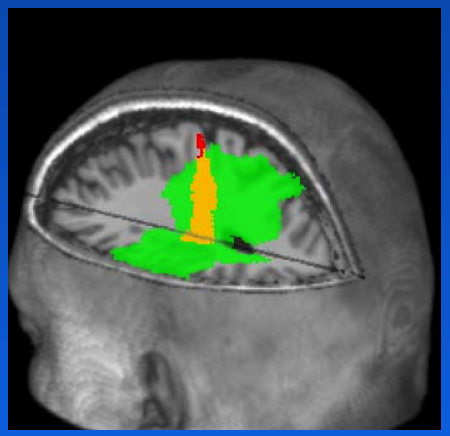
Stroke

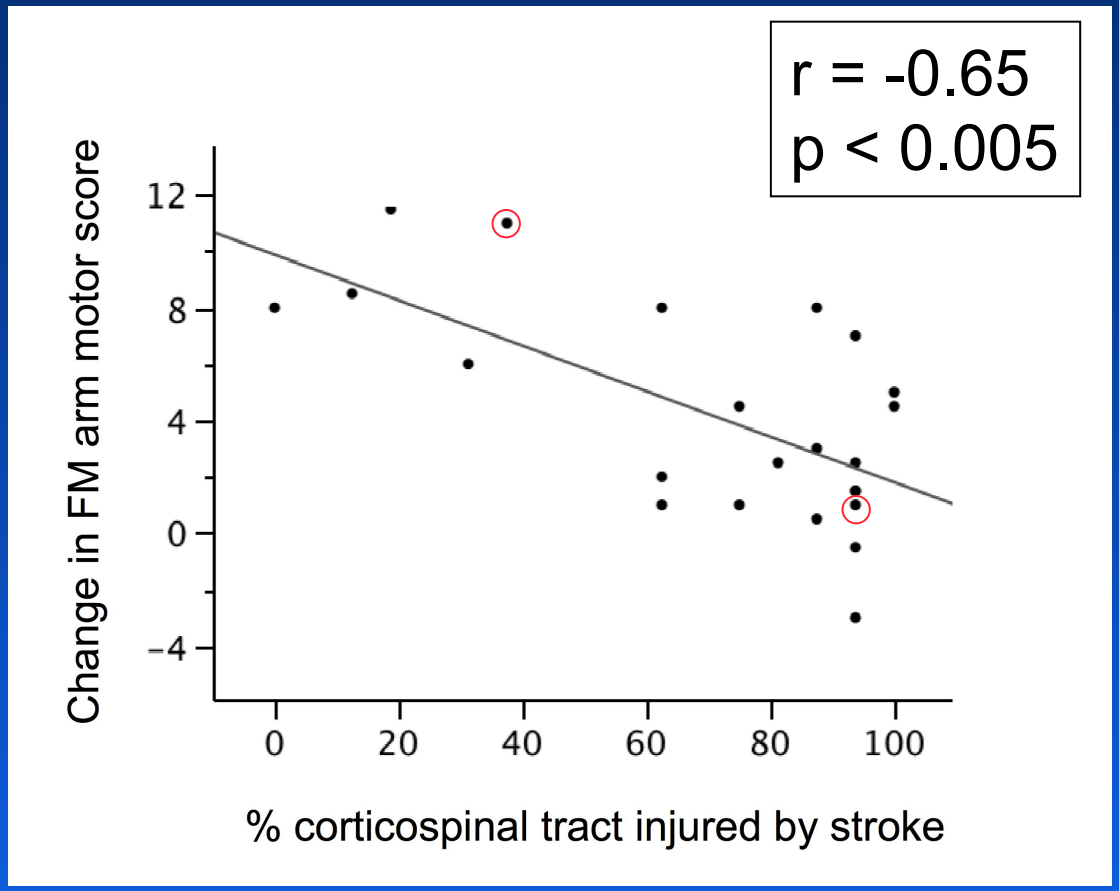
Measuring extent of corticospinal tract injury to stratify patients

Riley et al, Stroke; 2011

A standardized approach to measuring corticospinal tract injury in a clinical study







Extent of corticospinal tract injured predicts treatment response

This measure is a better predictor than infarct volume, baseline behavioral status, or demographic measures (n = 23)

Riley et al, Stroke; 2011

A standardized approach to measuring neurophysiology in a clinical study

Malcolm et al., J Clin Trials 2014, 4:6
http://dx.doi.org/10.4172/2167-0870.1000199

Clinical Trials

Protocol Open Access

Methods for an International Randomized Clinical Trial to Investigate the Effect of Gsk249320 on Motor Cortex Neurophysiology using Transcranial Magnetic Stimulation in Survivors of Stroke

Matt P. Malcolm[1*], Lori Enney[2] and Steven C Cramer[3]

Malcolm et al, J Clin Trials; 2014

Genetic variation

Measures of neural plasticity

Studies of genetic polymorphisms related to stroke recovery

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

Transl Stroke Res. 2016 Apr 25. [Epub ahead of print]

Spontaneous and Therapeutic-Induced Mechanisms of Functional Recovery After Stroke.

Cassidy JM[1], Cramer SC[2,3,4,5].

Why would clinicians study genetics?

Clinicians might study genetics in order to better

- Inform therapeutic decision-making, e.g., Rx choice or Rx dose
- 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:	an endophenotype of brain function and spontaneous stroke recovery
ApoE4 polymorphism:	
Dopamine polygene score:	predicts motor learning, mood, impulsiveness, response to L-Dopa

Genetics and therapeutic decision-making

Persons taking clopidogrel (Plavix) who have CYP2C19 loss-of-function alleles have a higher rate of cardiovascular events compared to those who do not.

Shuldiner et al, JAMA. 2009; 302:849-858
Mega et al, N Engl J Med. 2009; 360:354–362.

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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An endophenotype is a component of a complex phenotype that is more directly related to the underlying genotype.

Examples: OCD symptoms in certain autism spectrum disorder subgroups; or premotor cortex activation in certain Parkinson's-related genotypes.

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 et al, Phys Therapy, 2016

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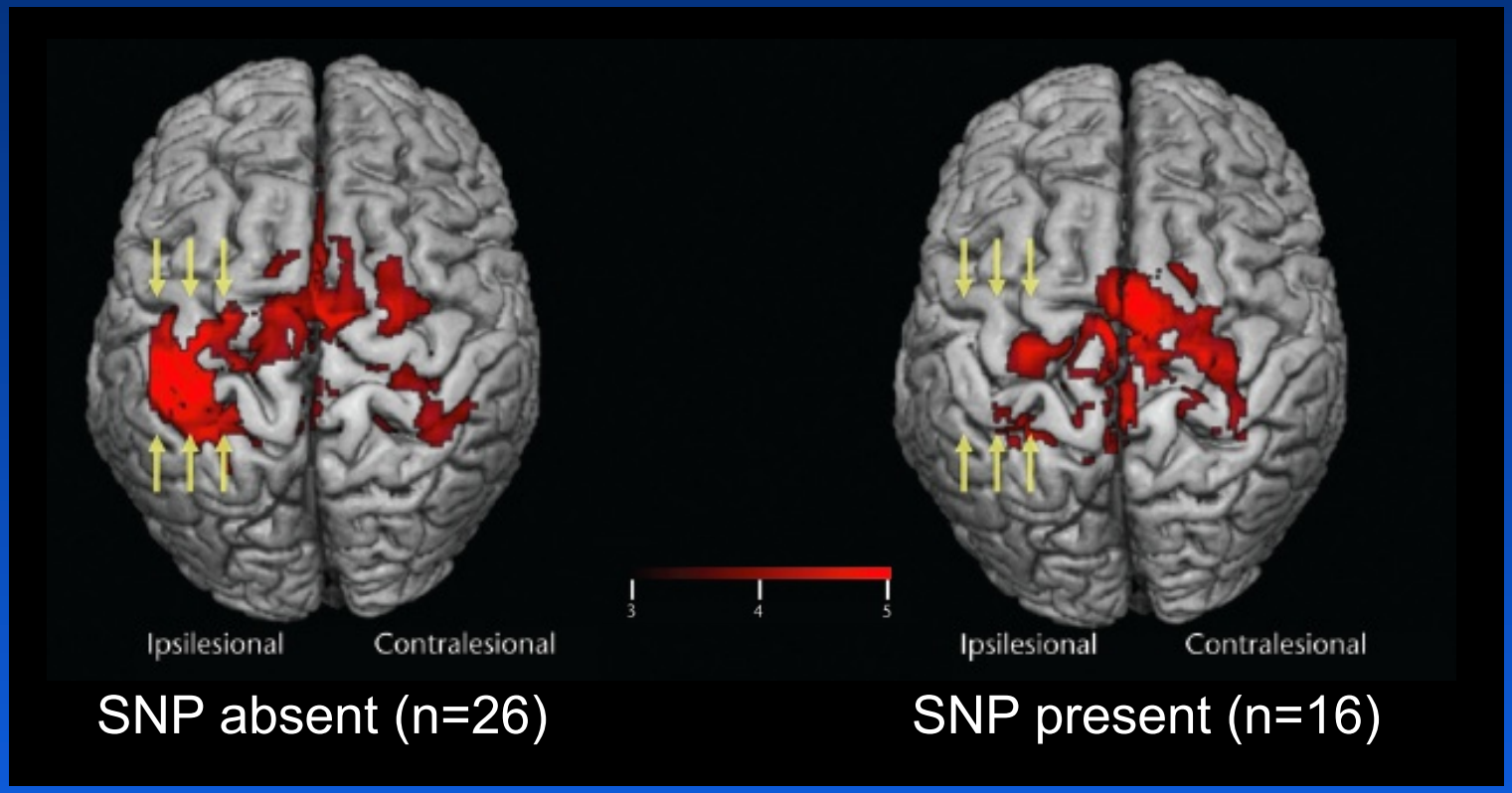

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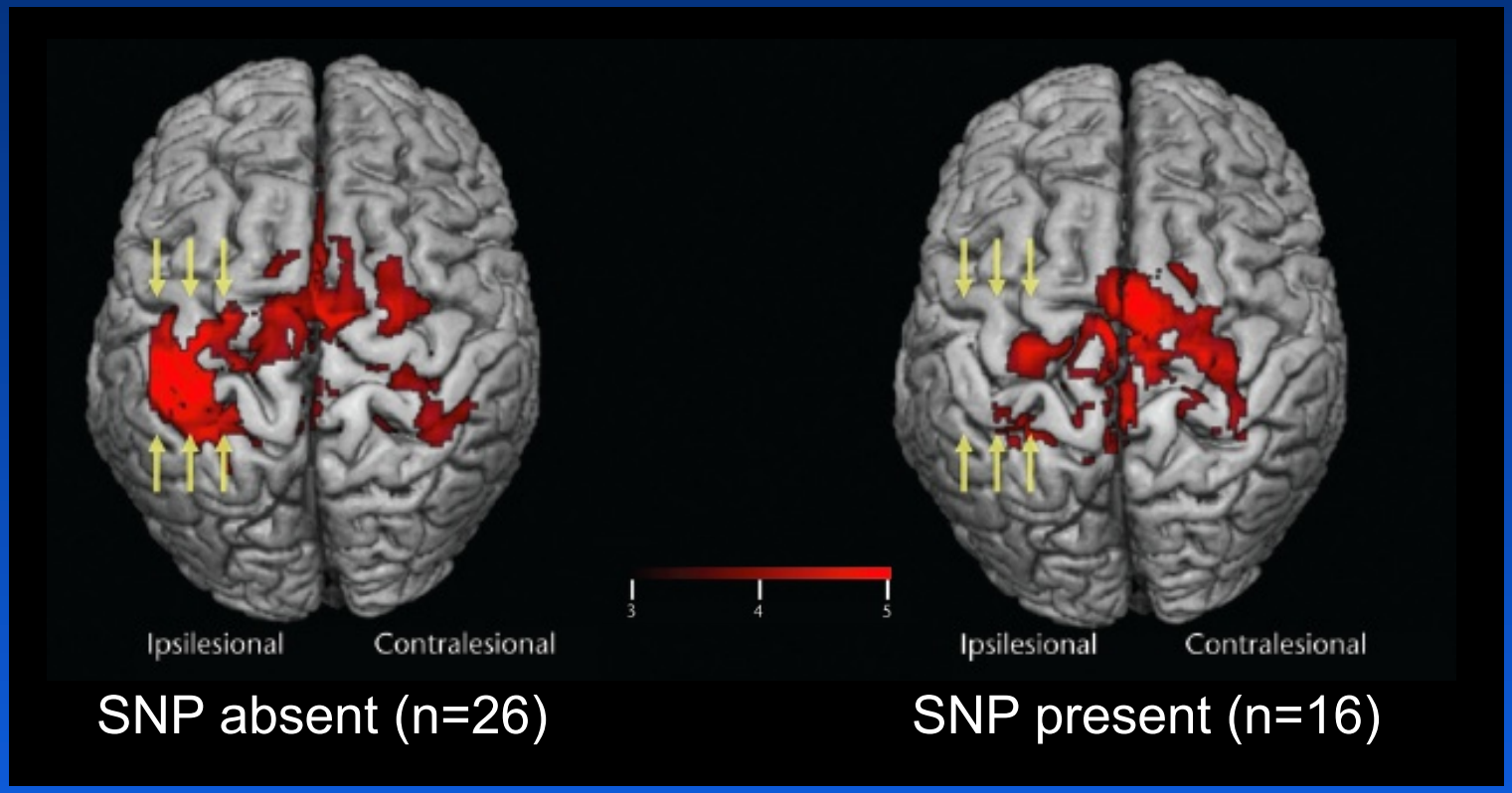
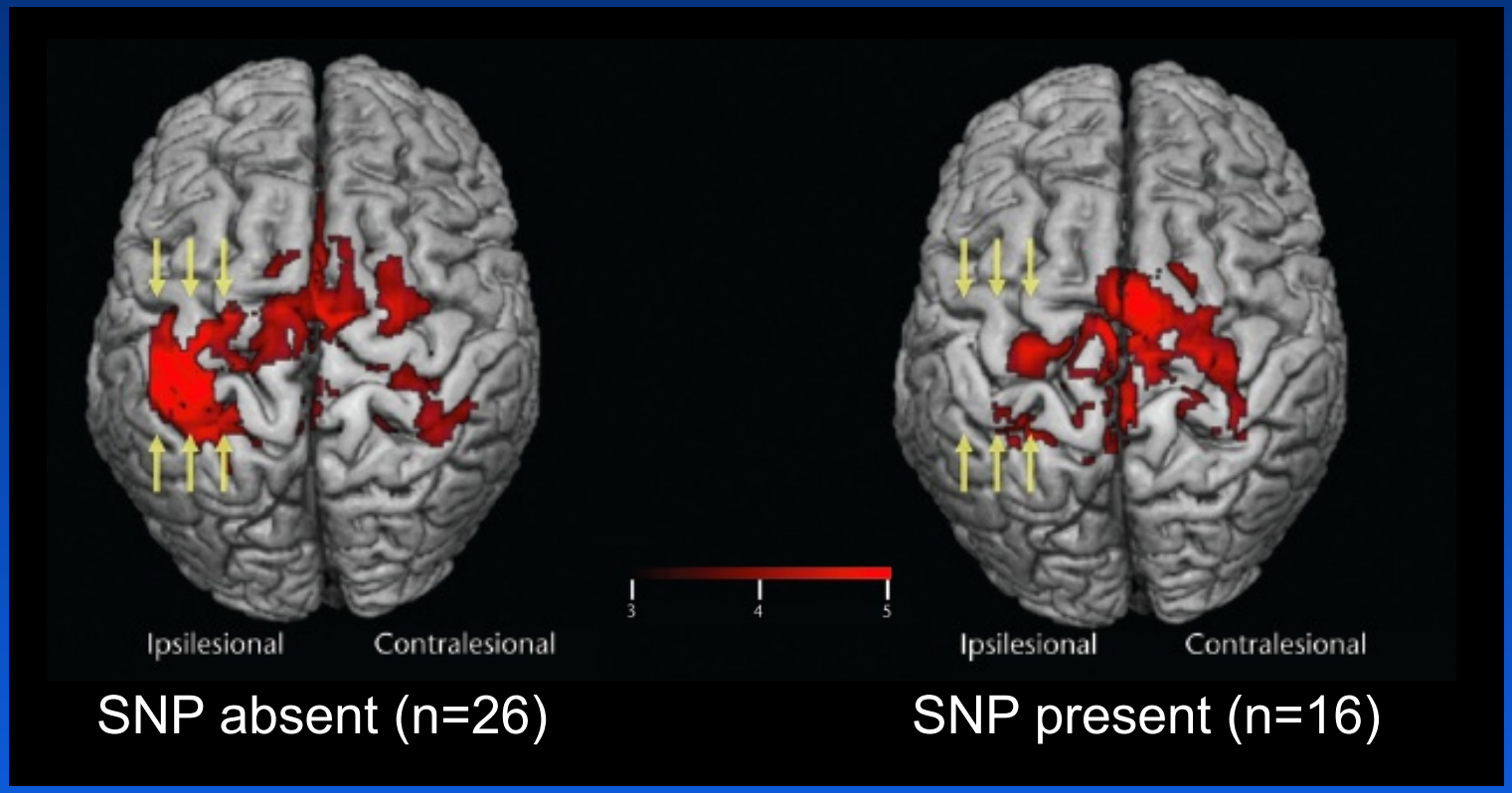


Motor cortex activation varied significantly per BDNF genotype.

Same result as was seen in our prior study of healthy controls
(McHughen et al, Cerebral Cortex 2010; 20:1254-1262)

Kim et al, Phys Therapy, 2016



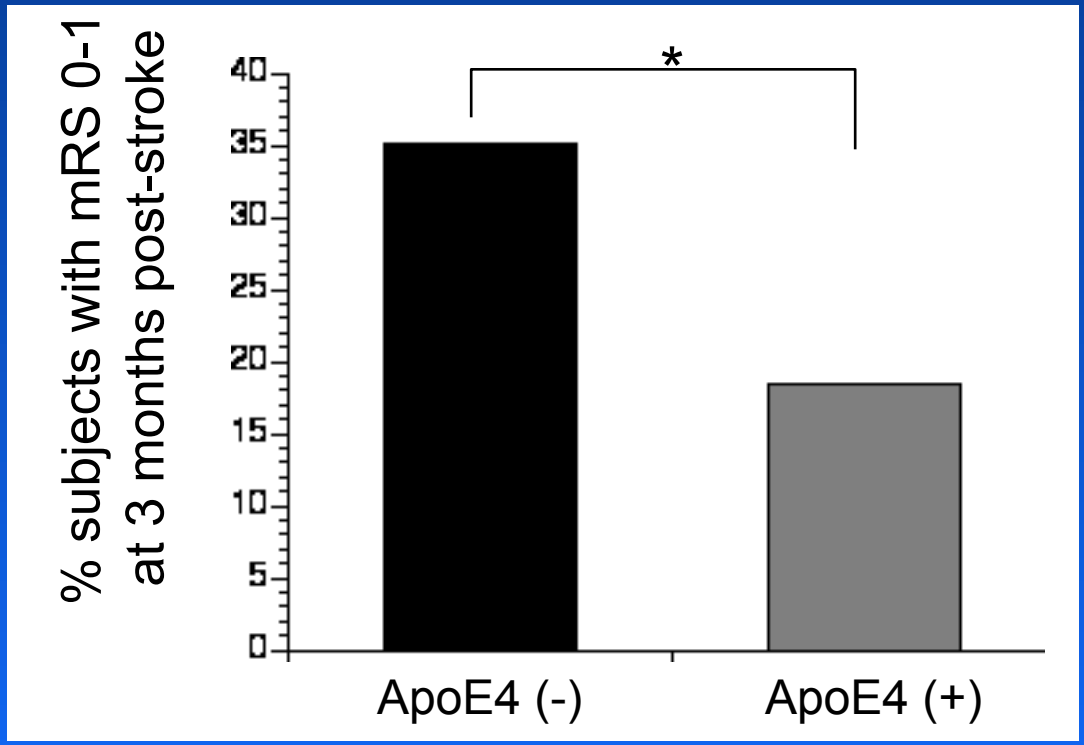
Motor cortex activation varied significantly per BDNF genotype.

But: differences in cortical function not related to baseline FM or to change in FM with therapy (wrong motor task during fMRI?)

Kim et al, Phys Therapy, 2016

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

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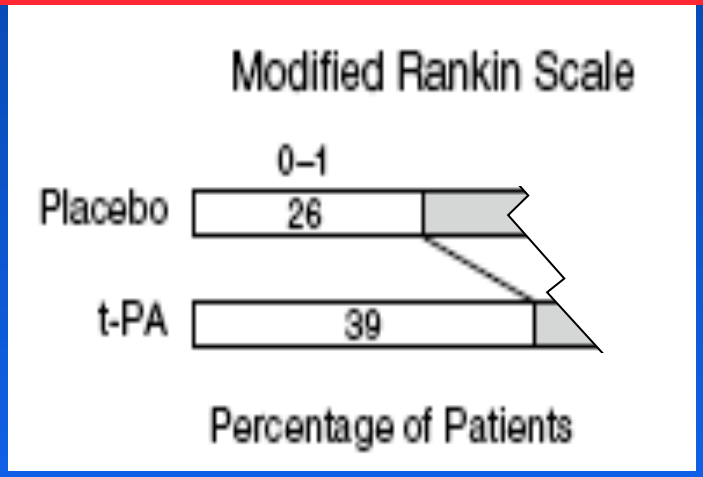
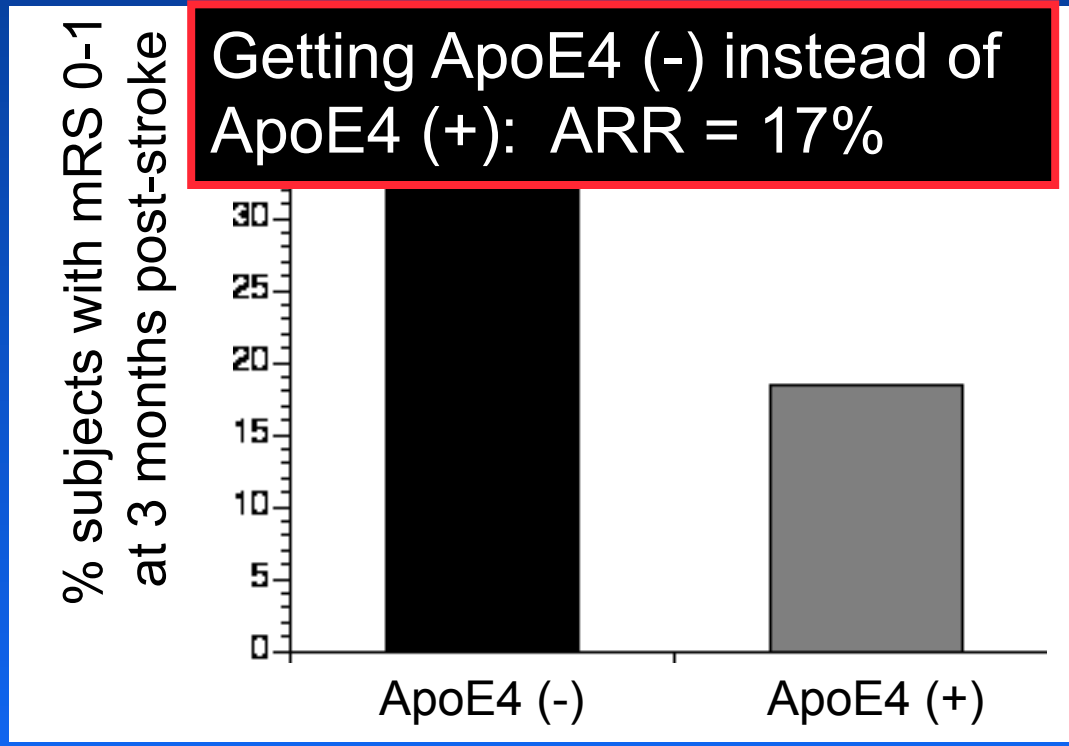
Getting iv tPA instead of placebo: ARR = 13%



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 generally small--ApoE is a major exception

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Thus interest in combining the effect of many genes in polygenic models or panels…that assigns points for the presence of various risk alleles and calculates an overall risk of disease

For example, in a study of 5 SNPs associated with prostate cancer, the investigators expressed the risk of disease associated with the increasing presence of risk alleles:

they found an OR of 1.6 with risk allele at 1 SNP and up to 4.5 with risk alleles at 4 SNPs

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

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

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- --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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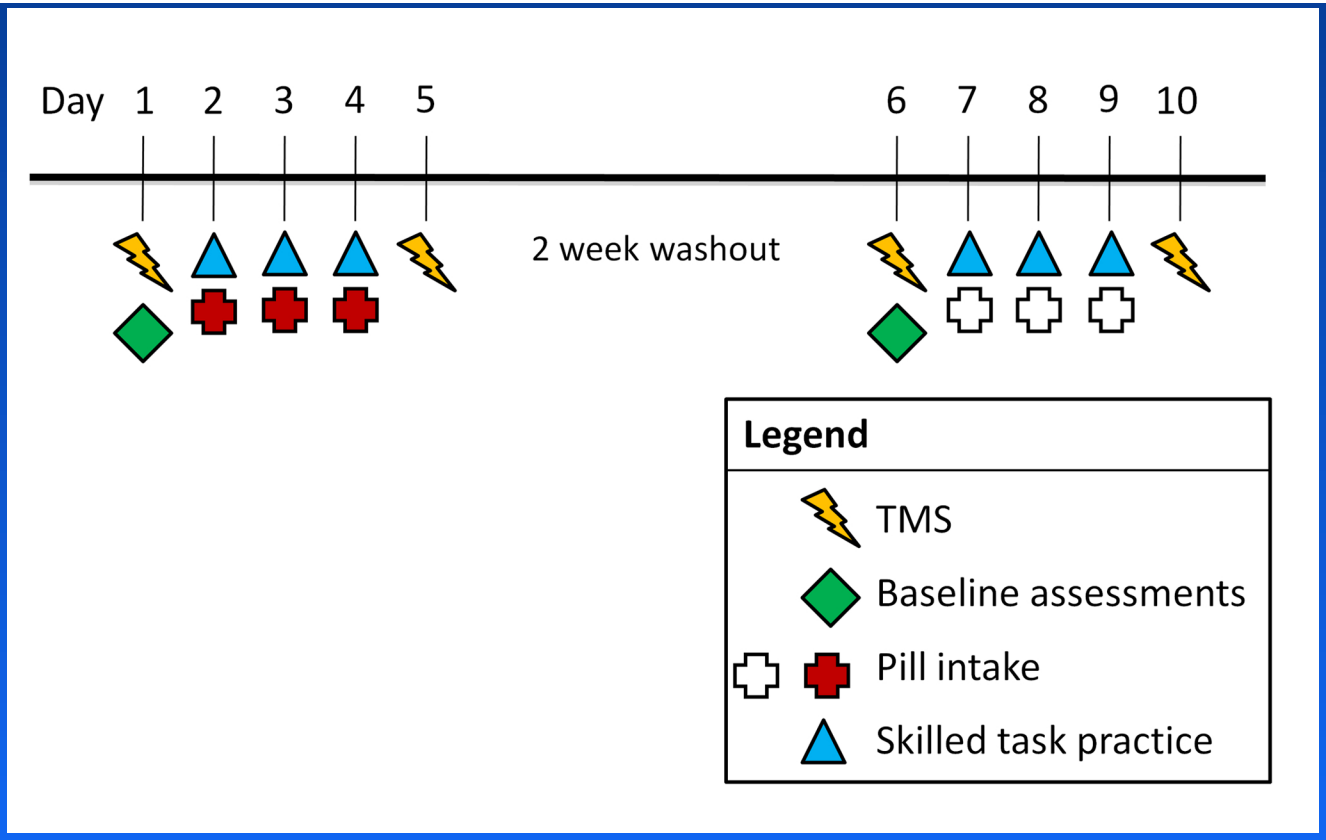
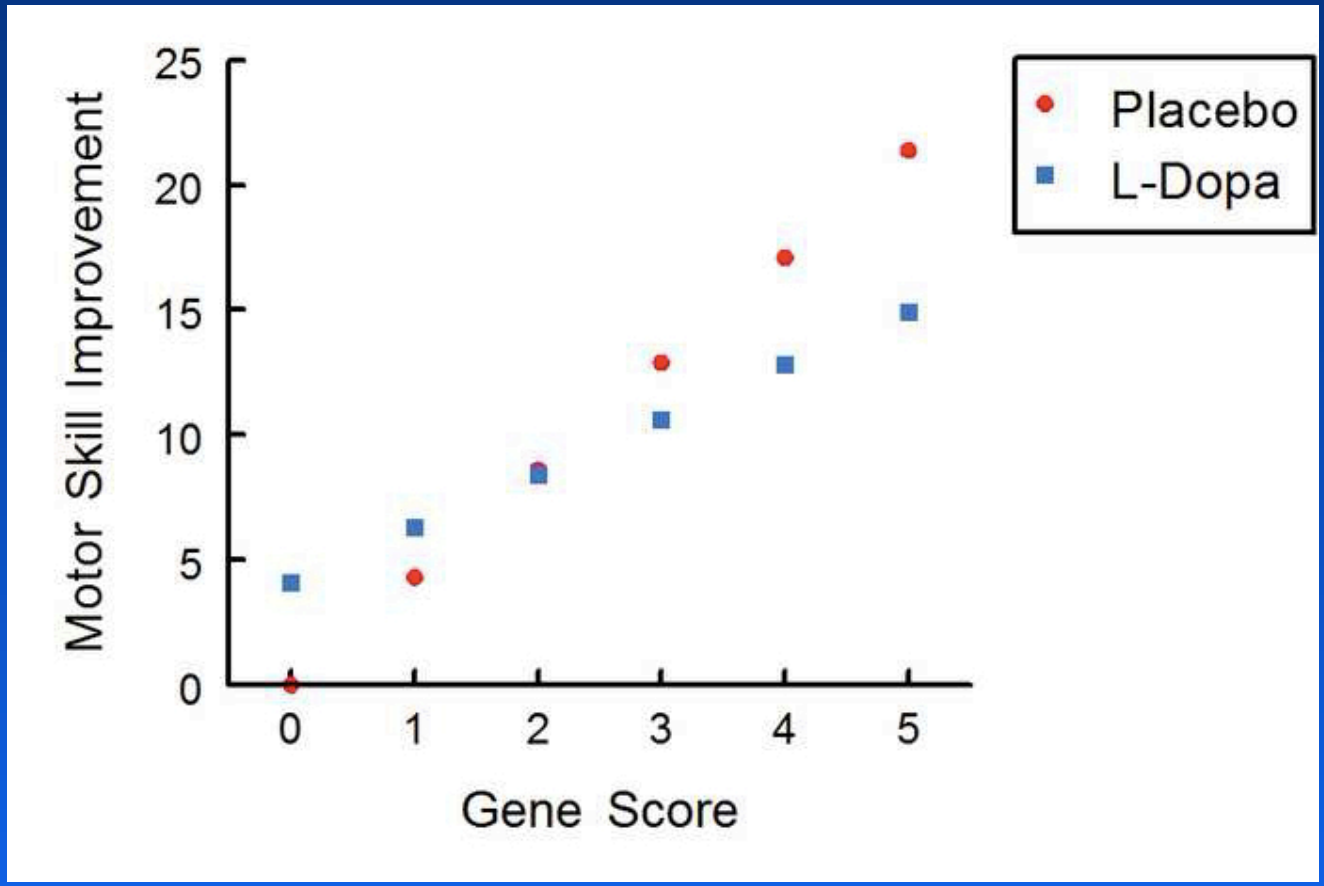


Pearson-Fuhrhop et al PLOS-ONE 2013



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Dopamine gene score

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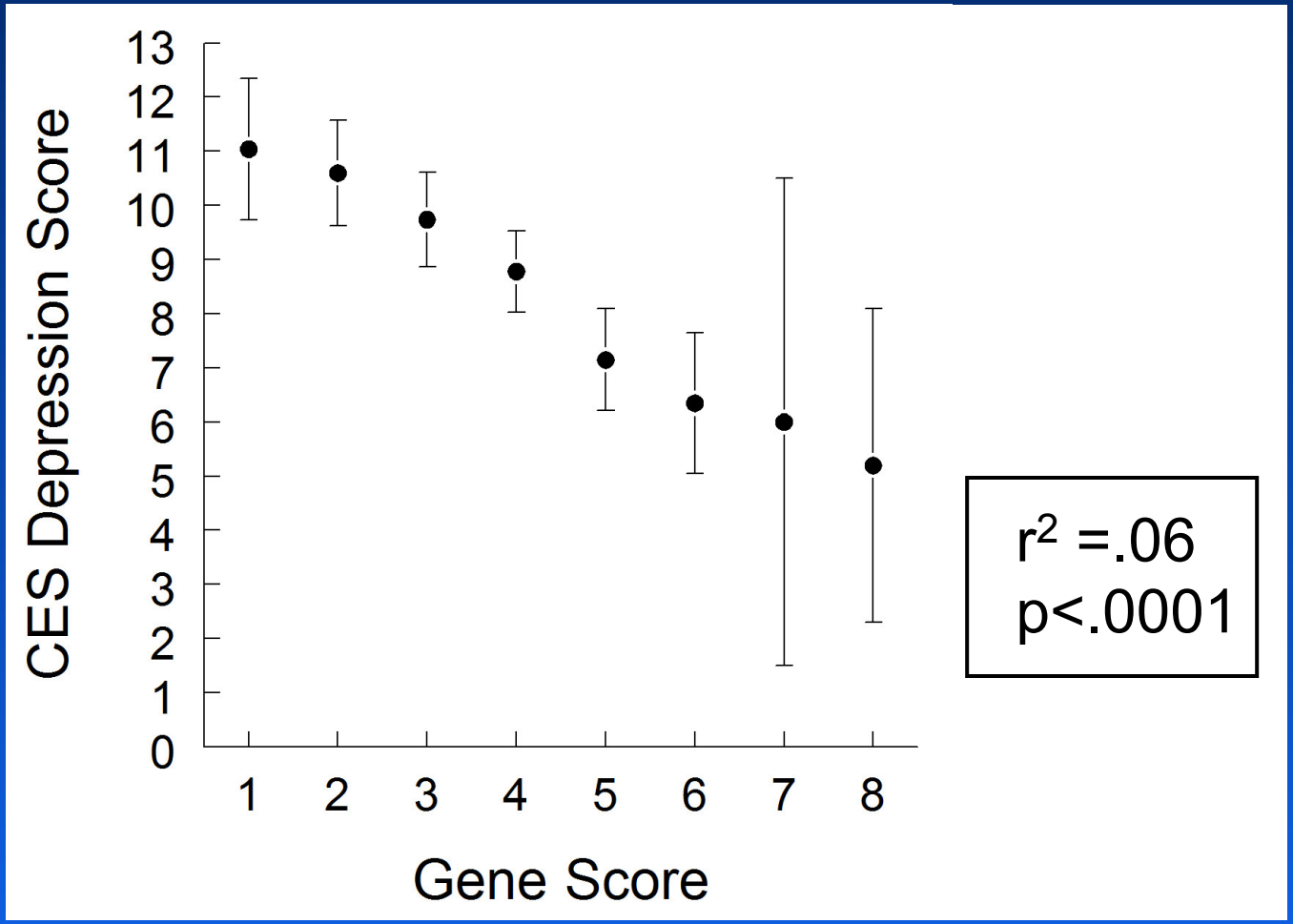
PLOS ONE

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

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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 Cognitive Neuroscience (in press)

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 with trend towards worsened response inhibition.

MacDonald et al, Journal of Cognitive Neuroscience (in press)

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

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