Connecting musicality with other traits

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@CrunchyNeuroSci

June 19, 2019

KNAW Master Class on Musicality and Genomics
Amsterdam

VANDERBILT UNIVERSITY MEDICAL CENTER

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It all started with rhythm and grammar…

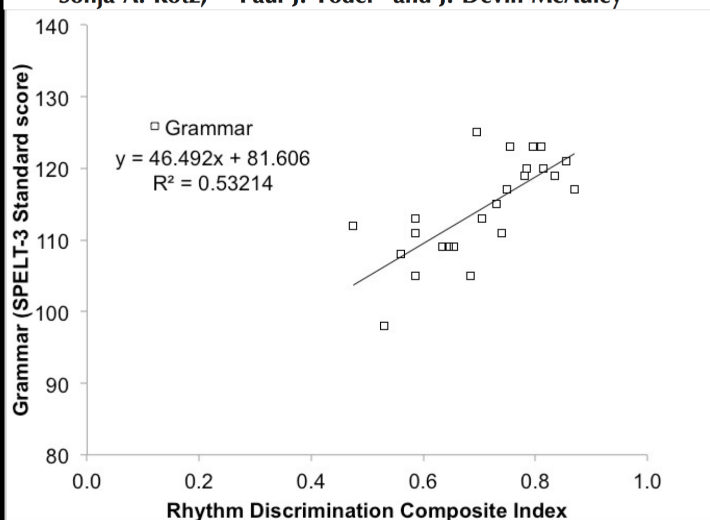
Developmental Science

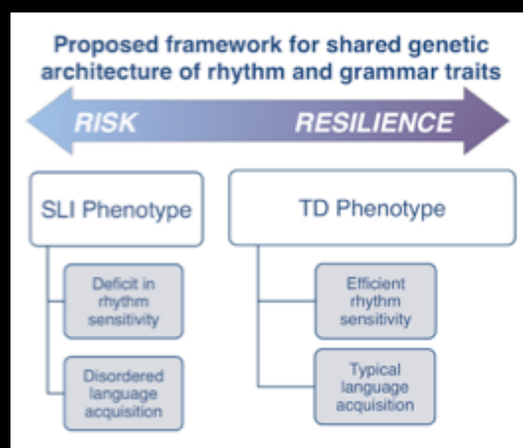
Developmental Science 18:4 (2015), pp 635–644 DOI: 10.1111/desc.12230

SHORT REPORT

Musical rhythm discrimination explains individual differences in grammar skills in children

Reyna L. Gordon,[1] Carolyn M. Shivers,[1] Elizabeth A. Wieland,[2] Sonja A. Kotz,[3,4] Paul J. Yoder[1] and J. Devin McAuley[5]





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Individual differences in language and music abilities

- Emerging evidence for plasticity effects of music training
- But… associations between language and music are present in young children before formal music training
    - shared neural resources for language and music

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"Influence" of music training

Psychophysiology, 41 (2004), 341–349. Blackwell Publishing Inc. Printed in the USA.

DOI: 10.1111/1469-8986.00172.x

The music of speech: Music training facilitates pitch processing in both music and la

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Musician Children Detect Pitch Violations in Both Music and Language Better than Nonmusician Children: Behavioral and Electrophysiological Approaches

Cyrille Magne[1,2], Daniele Schön[1,2], and Mireille Besson[1,2]

Abstract

■ The idea that extensive musical training can influence processing in cognitive domains other than music has re-

guage. Moreover, the greatest differences in the ERPs of musician and nonmusician children were also found for the ...gruity: whereas for musician children, early neg- ...nents developed in music and late positive com-

From Notes to Vowels: Neural Correlations between Musical Training and Speech Processing

Iliza M. Butera
Neuroscience Graduate Program, Vanderbilt University, Nashville, Tennessee 37232
Review of Bidelman and Alain

...ted Neuroplasticity ...nteract Age-Related Declines in Categorical Vowel Perception

Gavin M. Bidelman[1,2] and Claude Alain[3,4,5]

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Music and language expertise: what drives the underlying biology?

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *The Neurosciences and Music V*

Music training and speech perception: a gene–environment interaction

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PNAS

Inherent auditory skills rather than formal music training shape the neural encoding of speech

Kelsey Mankel[a,b] and Gavin M. Bidelman[a,b,c,1]

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Edited by Dale Purves, Duke University, Durham, NC, and approved November 6, 2018 (received for review July 9, 2018)

Musical training is associated with a myriad of neuroplastic changes in the brain, including more robust and efficient neural processing of

event-related potentials (ERPs) and fMRI show differential speech activity in musicians at cortical levels of the nervous system

- Shared neural resources for language and music may be partially genetic, rather than expertise transfer effects

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…jumping into the deep end…

- Genotype children in participating in our rhythm & grammar study?
  - Initial plan: single SNP on *ANKK1* involved in grammar and timing? (Wong et al, 2013; Wiener et al, 2014)
  - Instead: we needed to look more broadly across the genome!
    - Larger goals:
      - Is human communication built in part on biological architecture for rhythm? (Fitch, 2017).
      - How is the genetic basis of rhythm related to health and disease?

Reyna learning genetics…

NIH K18DC017383

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Nancy Cox, PhD

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… but then we needed…

- *…large sample sizes to conduct Genome-Wide Association Studies (GWAS) on rhythm & grammar*

  - Leverage big data: combine other findings from the literature with new data/new analyses from large-scale biobanks?

  - Musical GWAS groundwork in large samples are needed (see review by Gingras, Honing, Peretz, Trainor & Fisher, 2015)

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Lessons learned

- Look to twin studies to see if your trait is heritable
- Be skeptical of candidate gene studies for which the candidate genes did not originally come from a well-powered GWAS

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Genetics of rhythm

- Twin studies: Musical rhythm ability is moderately heritable (Ullen et al, 2014) , and correlates with IQ (Ullén et al., 2014; Mosing et al., 2016)
  - Who pursues music training? Music training and musical practice are heritable, too! (Mosing et al, 2014; Butkovic et al, 2015)
- suggestive molecular genetic evidence calls for large GWAS sample (Oikkonen et al., 2015; Wiener et al., 2011; 2014)
- Goals of current study:
  - Large-scale genome-wide interrogation on self-reported rhythm phenotype *("Can you clap in time with a musical Beat?")*, collaboration with 23andMe
    - Does rhythm share genetic architecture with other traits?

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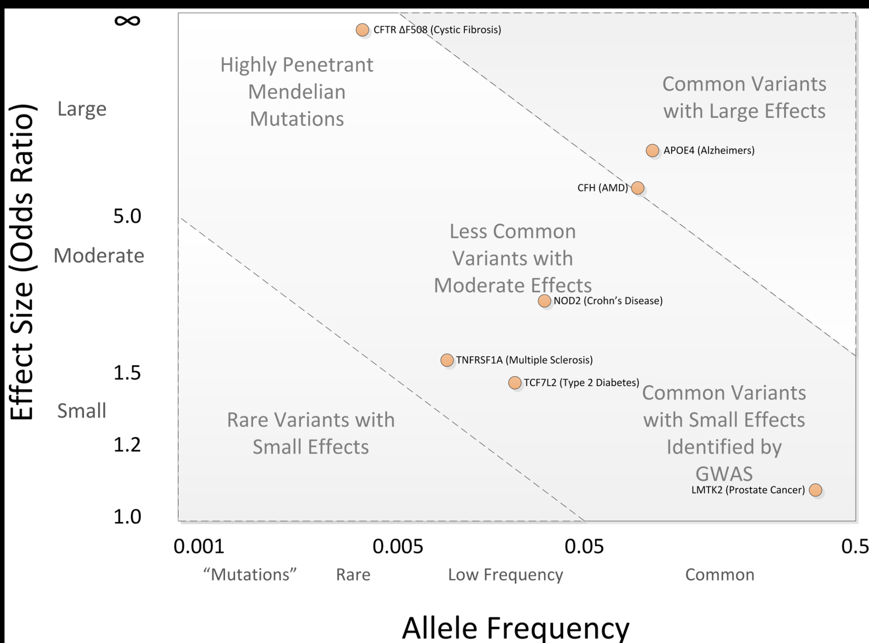
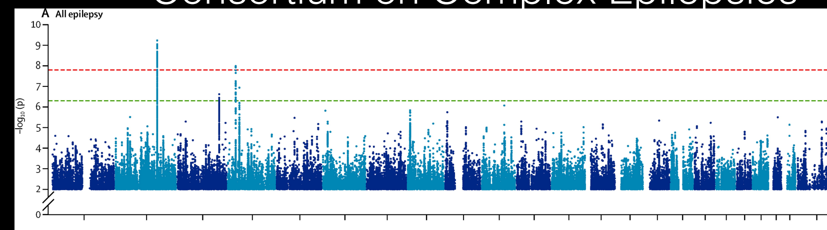
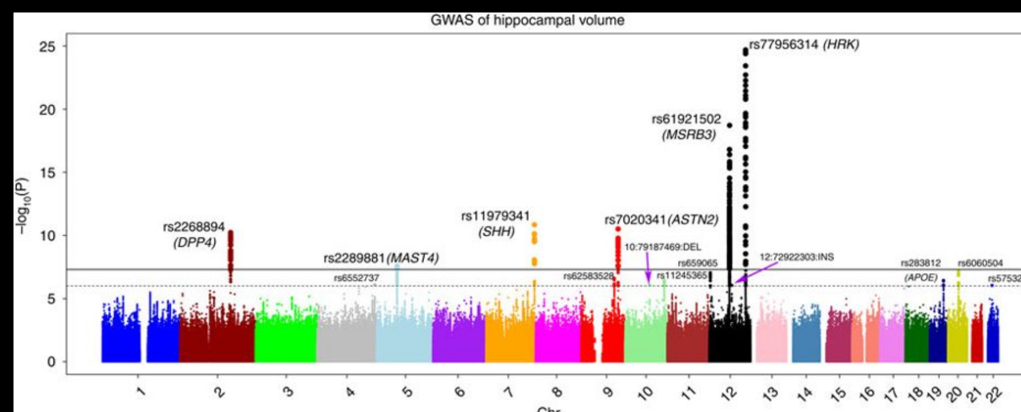
Genome-Wide Association Study

GWAS allows us to compare associations of genetic markers with phenotypic traits (e.g., rhythm scores, or disease vs healthy control…) from strategically measured “markers” (SNPs) across the genome



International League Against Epilepsy Consortium on Complex Epilepsies





Hibar et al, 2017

An Introduction to Genome-Wide Association Studies: GWAS for Dummies

A. G. Uitterlinden, PhD[1]

good starting place for learning about GWAS

GWAS study design

Question: *Can you clap in time with a musical beat?*

Yes N=555,660
No N= 51,165
Total: N=606,825

23andMe research participants of European ancestry


Maria Niarchou

Niarchou, Sathirapongsasuti, Jacoby, 23andMe research team, McAuley, Bell, Mosing, MacArthur, Straub, Creanza, Ullén, Capra, Hinds, Davis, & Gordon, *in preparation*


Lea Davis

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DP2HD098859 NIH Director's New Innovator award

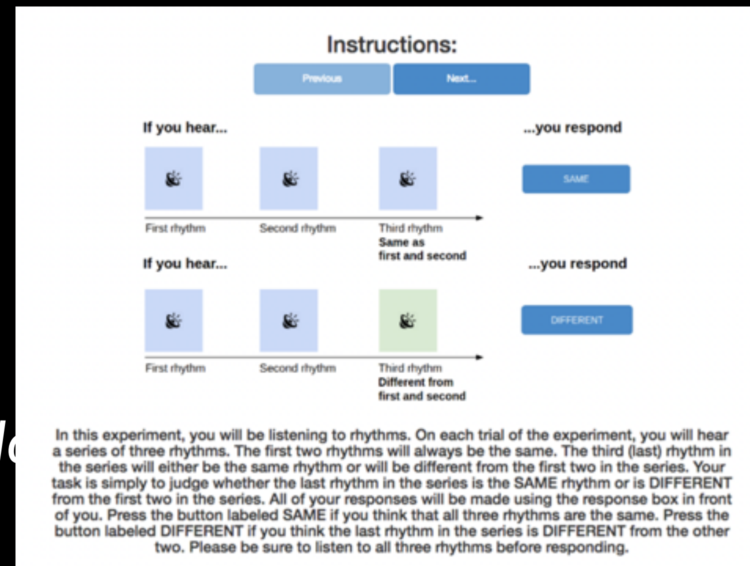
Phenotype validation study

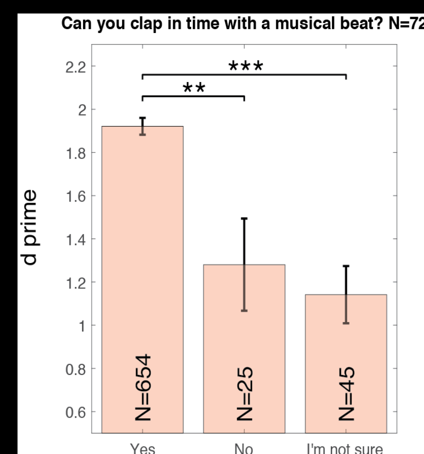
Internet-based - Amazon Mechanical Turk (separate sample)
N=724 (mean age =36 years, F=333)

Self-report:
Can you clap in time with a musical beat? (Yes, N
I’m not sure)

Rhythm discrimination test:
Rhythm perception test based on Grahn & Brett (2007).
8 practice + 32 unique trials

“Yes” responders => better rhythm perception
t(677)=3.148 *p*=0.002, Cohen’s d=0.64





Nori Jacoby + Eammon Bell

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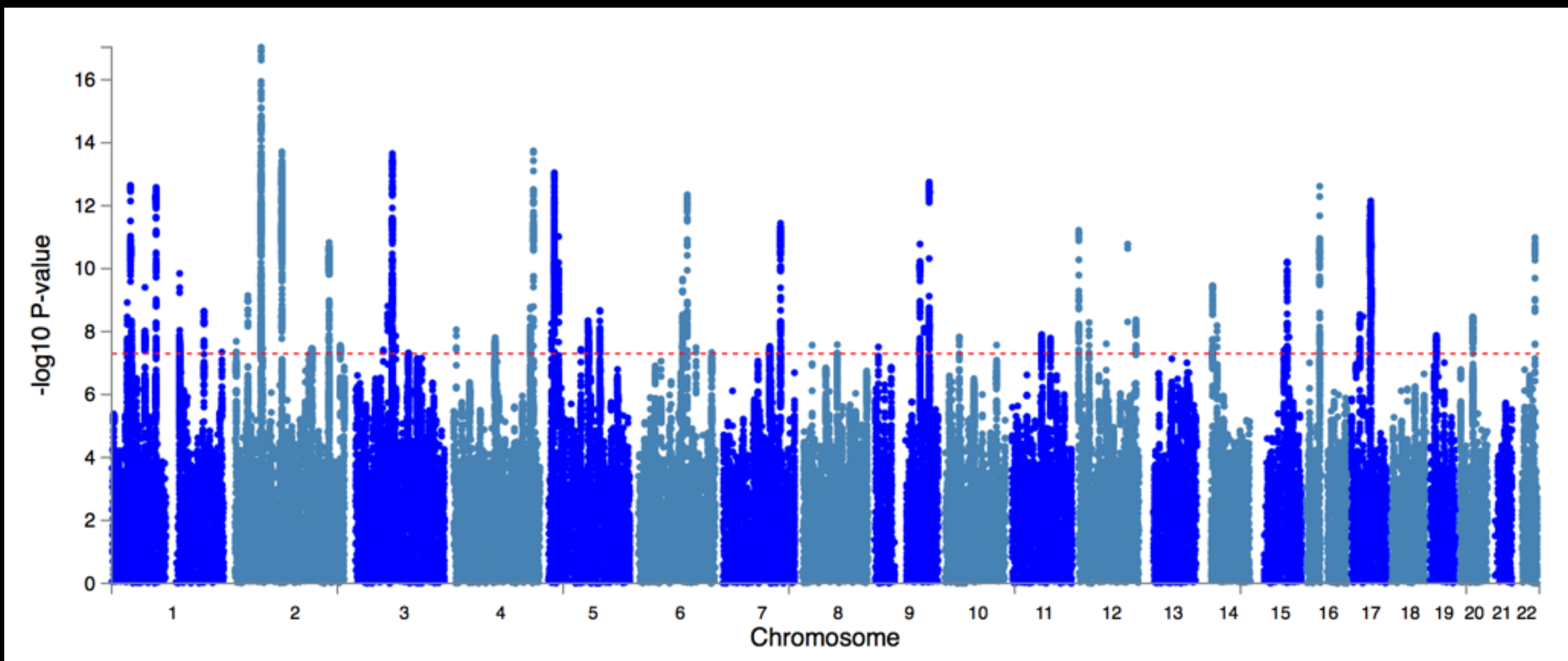
GWAS results: do common genetic variants account for variability in our rhythm trait? Yes!

68 independent loci - genome-wide significance ($p<5 \times 10^{-8}$).

Observed SNP-heritability = 5% computed w/ LD-score regression



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Does our rhythm phenotype share genetic architecture with other traits?

- exploratory investigation of other traits in LDHub (genetic correlations)
- control for known GWAS markers of IQ/EA (conditional analyses)

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Utilizing genetic correlations

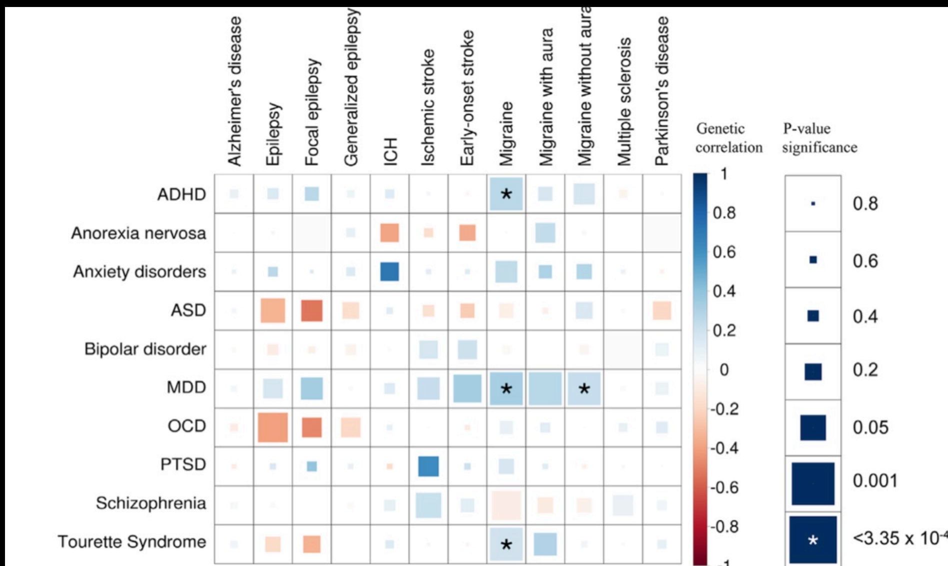
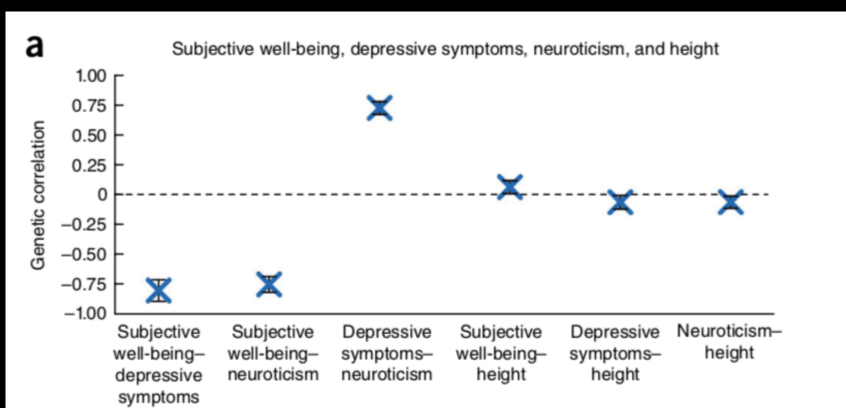


Fig. 3. Genetic correlations across neurological and psychiatric phenotypes. The color of each box indicates the magnitude of the correlation, and the size of the box indicates its significance (LDSC), with significant correlations filling each square completely. Asterisks indicate genetic correlations that are significantly different from zero after Bonferroni correction.

Anttila, Brainstorm Consortium et al, 2018



Okbay et al., 2016, Nature Genetics

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Exploration of Genetic Correlations

- **Genetic Correlations tested against all traits in LD Hub**
- Rhythm is associated with:
  - *faster processing speed*
  - *hand grip strength*
  - *chronotype (being an evening person)*
  - *tinnitus*

neural efficiency/cognition

motor function

musician/musical environment?

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Lessons learned

- Many interesting analyses are possible from group-level summary statistics
  - check out FUMA http://fuma.ctglab.nl and LDHub http://ldsc.broadinstitute.org/ldhub/
- You can look at genetic correlations between traits from *separate samples!*

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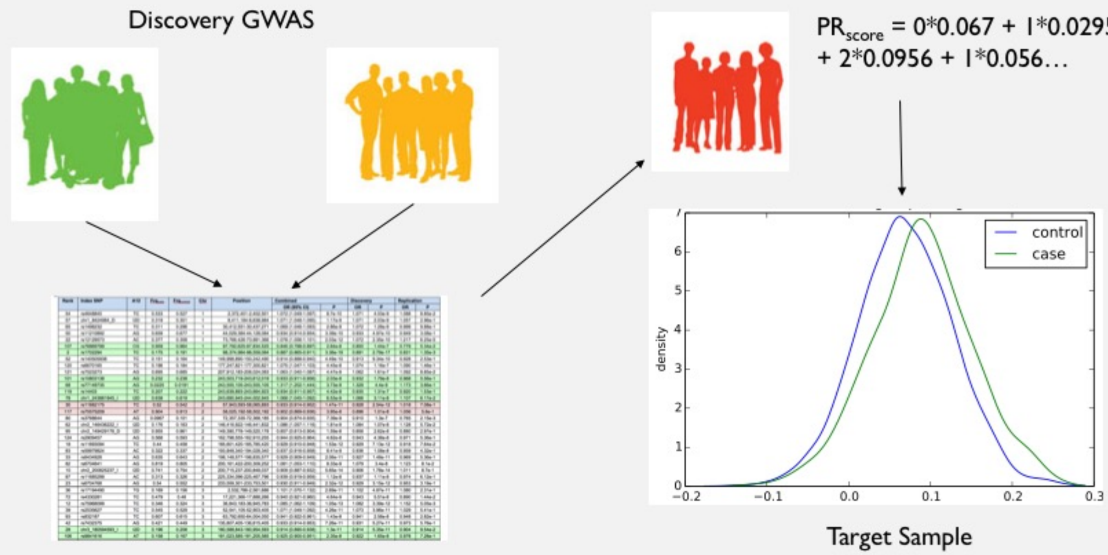
Health & BioVU

POLYGENIC SCORE ANALYSIS



STRUCTURE OF THE VANDERBILT EHR AND BIOBANK

The Synthetic Derivative
A de-identified and continuously-updated image of the EMR (>2.9 M individuals)

BioVU
- DNA samples available: >270,000
- Plasma collection underway

Redeposited genotypes
- Subjects with GWAS data: >109,000
- Subjects with any genotyping: >120,000

- Median length of EHR is ~1 year, max is 20 years
- Tertiary care center: ascertainment for sicker people
- Music City: ascertainment for musicians
- Median length of EHR for genotyped BioVU subjects is ~10 years
- Average age of BioVU is 58

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What can genomic analyses tell us about the basis for this trait?

- Large-scale GWAS yielded 68 genomic loci associated with self-reported rhythm ability
  - many loci previously linked to behavioral, cognitive, and neurological traits + 23 novel loci
- enrichment of rhythm heritability in gene expression in brain tissue
  - *consistent with auditory-motor networks underlying rhythm*
- Genetic correlations and polygenic risk score analyses generate hypotheses for future genetic (and epidemiological!) work on *rhythm + cognition, motor abilities, sleep, & mental health*

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Genetics of DLD

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Specific language impairment

- *(Selective) deficit in communication/language skills where nonverbal ability is normal; Grammar and vocabulary are particularly affected.*
    - also known as **developmental language disorder**
    - long-term academic, economic, and social consequences - late talking that never catches up, also struggle with reading
    - example: "our cat looks very smaller"
- **Children with SLI struggle with complex sentences**

sentence repetition task:

[prompt]: *That's the ladybug that Christina saw on the grass*

child: "The ladybug sink into the grass."

~~Specific~~ Language Impairment

- Their deficits are not restricted to language! They also struggle with:
  - the nuances of speech rhythm
  - singing
  - recognizing melodies
  - tapping to the beat and perceiving differences in musical rhythms

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Automated **P**henotyping **T**ool for identifying **DLD** cases in health-systems data (**APT-DLD** phenotyping algorithm)

Goal: *Large-scale cohort identification of developmental language disorder in existing Electronic Health Record Databases*

Rachana Nitin

Courtney Walters

Step 1: Broad search criteria

ICD-9 codes	ICD-10 codes
315.39 (Other developmental speech or language disorder) ICD9 code 315.32 (Mixed receptive-expressive language disorder) ICD9 code 315.31 (Expressive language disorder)	F80.89 (Other developmental disorders of speech and language) F80.1 (Expressive language disorder) F80.2 (Mixed receptive-expressive language disorder)

Exclude records with hearing loss, ID, known syndromes

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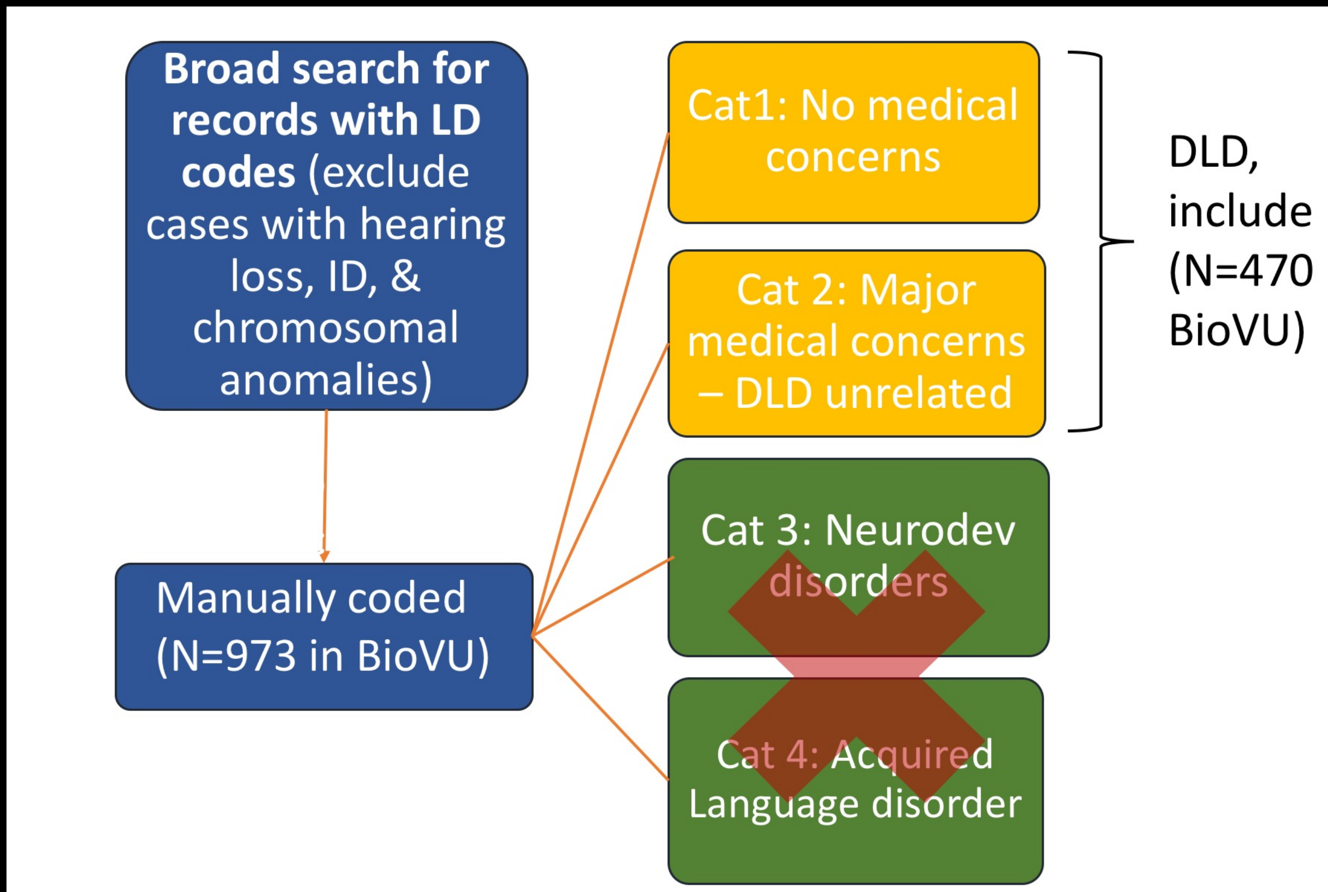
APT-DLD algorithm



Automated **P**henotyping **T**ool for identifying **DLD** cases in health-systems data

Walters, Nitin, Margulis, Boorom, Davis, Below, Cox, Camarata & Gordon, in preparation

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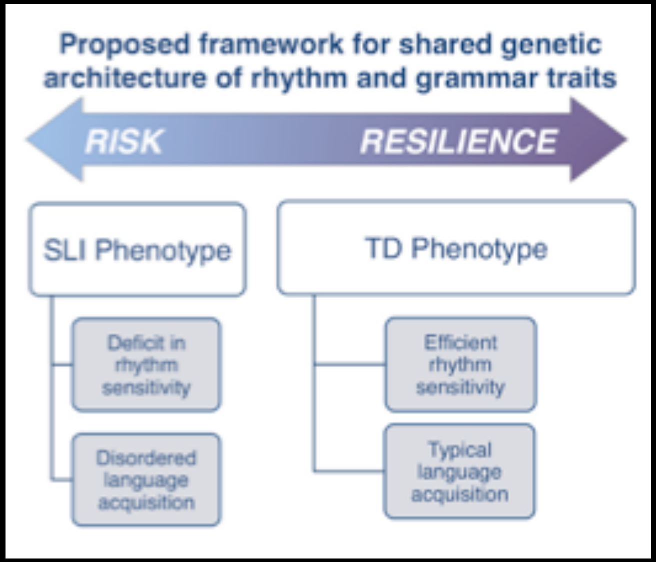
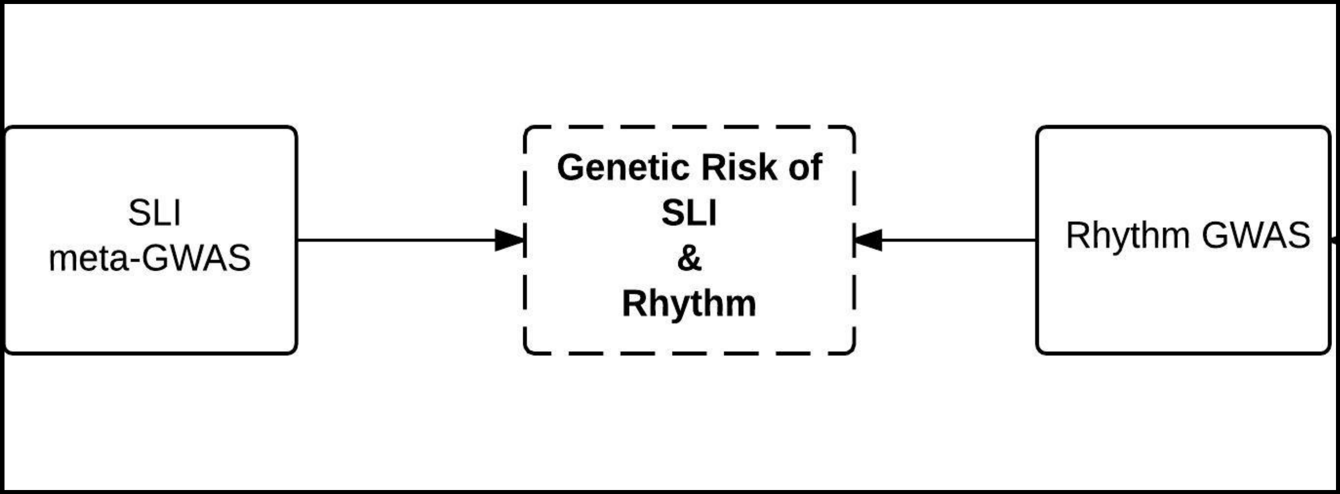
Can genetic markers of rhythm risk predict DLD?

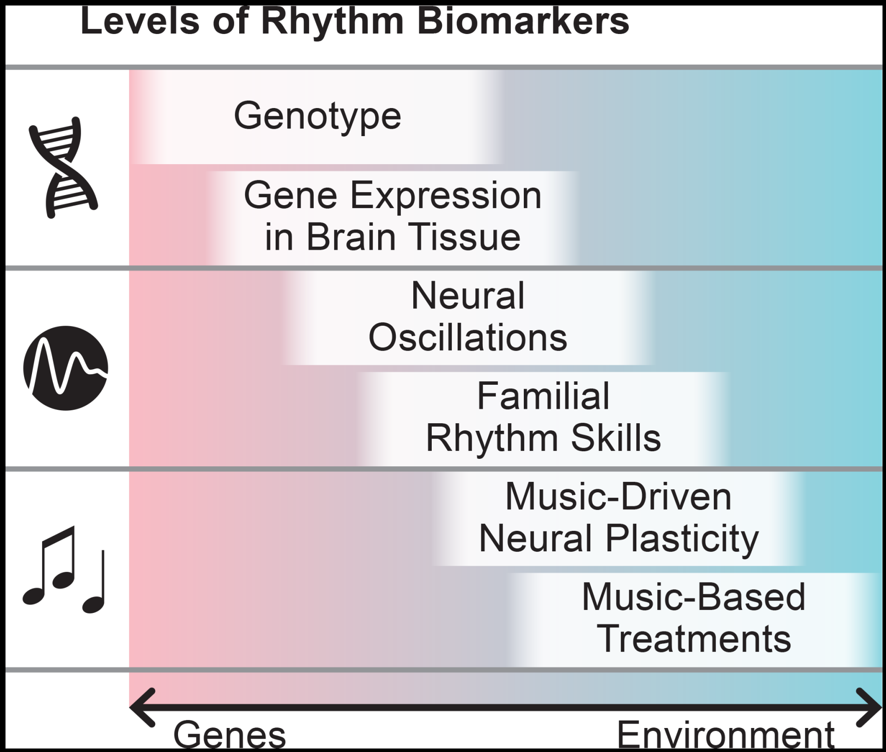
- Polygenic risk score and genetic correlation approaches
- Shared genetic architecture?





Innovations in rhythm and grammar

What can we predict about an individual person's language based on a combination of genetic, neural, and behavioral rhythm biomarkers?



DP2HD098859 NIH Director's New Innovator award

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(surprising) Things I've learned

- **Sample size/power** is key. Look for cohorts that are already genotyped!
  - Also simplify phenotype data collection (can your phenotype be reduced to *one* question?)
  - International consortia and data sharing bring awesome collaborative opportunities
- You can look at **genetic correlations** between traits from *separate samples!*
- Most traits of interest are ***polygenic*** - involve small contributions of *many* genetics markers. There is no single "gene for rhythm"!

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Wisdom from Nancy…

- **Cross-disciplinary** collaborations and training
- **Diversity** of populations, scientific backgrounds, life experiences
- **Numbers**: no one group can ascertain or learn enough on their own. Competition is out, collaboration is in!

Nancy Cox, PhD

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Future directions for rhythm genomics in large cohorts

- Explore neural endophenotypes in more depth (especially gene expression in subcortical areas)
- Deeper phenotyping:
  - Objective music perception & production phenotyping - *listening games*
- GWAS on groups of non-European ancestry
- Explore relationship with genetics of speech/language
- Explore relationships with sleep/chronotype

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Resources for learning best genomic approaches

- **Reading**
  - Uittenlinden, 2016, Seminars in Reproductive Medicine (GWAS for dummies)
  - Special issue of Psychonomic Bulletin & Review 2017 on language evolution
  - Deriziotis & Fisher, 2017, Trends in Genetics (Speech & Language: Translating the Genome)
  - Thompson et al, 2017, NeuroImage (ENIGMA and the individual)
  - Solovieff et al, 2013, Nature Reviews Genetics (Pleiotropy and complex traits)
- **Workshops**
  - International Statistical Genetics Workshop, Boulder, Colorado https://www.colorado.edu/ibg/workshop
  - Cognomics 2019 https://www.mpi.nl/events/cognomics-conference-2019-bridging-gaps and Brain Imaging Genetics (2020?)
  - Cold Spring Harbor Genetics and Neurobiology of Language workshop

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Uma & Giri Peters

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Acknowledgements

23andMe

Fah Sathirapongsasuti, Liz Noblin, and the 23andMe Research Team

Vanderbilt Music Cognition Lab
Rhythm & Grammar team
Rachana Nitin, CJ Walters, Kate Margulis

Vanderbilt Bill Wilkerson Center
Stephen Camarata

Vanderbilt Genetics Institute
Piper Below, Lauren Petty, Don Hucks

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R01DC016977 - NIDCD

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NIDCD National Institute on Deafness and Other Communication Disorders

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Trans-Institutional Programs

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Special thanks to:
KNAW for sponsoring the Master Class & Colloquium

Henkjan Honing, Simon Fisher, and Bruno Gingras

Nashville MUSIC CITY




Thank you for your attention!

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