

Fred w Sabb  
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to Advance Diagnosis and Treatment of Neurodevelopmental Disorders

## HARNESSING THE POWER OF THE INTERNET

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### Outline

Overarching objectives for this talk

- Knowledge Representation
  - How can we understand/store/build consensus about biomedical knowledge?
- Knowledge Acquisition
  - How can we acquire/measure/capture this knowledge?
- Knowledge Dissemination
  - How can we share it with colleagues and the public?

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### Definitions

How I will use the following terms...

- Tech Terms
  - Nodes and edges – terms for the entities and their relationships in a graph model
  - Open Source – free! Ok, not quite, but ability to work on the source documents
  - Latent Construct – not measured/observed but inferred from the data
- Genetic Terms
  - Heritability – percentage of inheritance for a particular phenotype
  - Genotype/phenotype – genetic constitution/how that's expressed
  - Categorical vs. Dimensional models for phenotypes (e.g. Tall vs. 6'2" in height)
- Cognition Terms
  - Cognitive control ( or executive function) - 'a system that controls and manages other cognitive processes' -wikipedia
  - Task Switching - the ability to switch from one task to another (cost)
  - Response Inhibition – the ability to overcome a prepotent response (interference)
  - Working Memory – the ability to hold in mind and manipulate information (load/delay)

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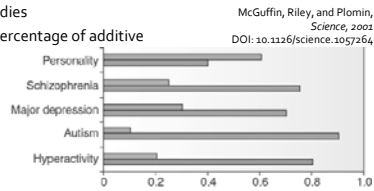
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## Biology, Biomarkers, and Genetics

The goal is to improve diagnosis, intervene earlier, and find/implement better treatments

### Web-Content

- ▶ Flash-based cognitive tests of Stop-Signal and Spatial Working Memory designed from CIDAR-TRECC
- **In order to make progress in these areas we need to improve biological validity of phenotypes** Freimer and Sabatti, *Nature Genetics*, 2009
- There is strong evidence that mental illness is under genetic control
  - Based on Twin Studies
  - Green bars show percentage of additive genetic influence




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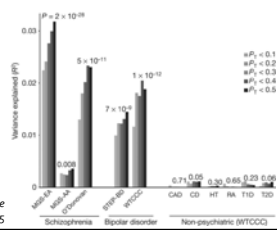
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## Biology, Biomarkers, and Genetics

The goal is to improve diagnosis, intervene earlier, and find/implement better treatments

- Current genetic associations for these major mental illnesses have been very disappointing
- A recent study by the ISC:
  - Thousands of case/controls
  - No significant genes for SCZ, BP
  - 100s of genes that cross both
  - All explain little bits of variation



The International Schizophrenia Consortium *Nature* 460, 2-5 (2009) doi:10.1038/nature08185

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## Why so little success?

Categories and Continua

- There is no empirical evidence for natural boundaries between major syndromes; the categorical approach is fundamentally flawed (Cloninger 1999)
- Most sciences start with a categorical classification of their subject matter but often replace this with dimensions as more accurate measurement becomes possible (Hempel 1961)
- Little evidence for a category of ADHD or SCZ or BP...
  - This doesn't necessarily mean its not reliably diagnosed
  - But might preclude us from finding biological underpinnings
  - Lets go back to the height example...

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## Implications

How to tackle the current genetic story

- Unlikely to be one 'bad' gene, but 100s of risk genes
- Much of the risk is present at birth, but environment plays a major role too, and we expect research will find new treatments to overcome genetic risks
- Looking across thousands of genes, some that pose risk, some protective, will help us create a "genetic profile" for each person
- The genetic profile will help us figure out the right mix of treatments, including medications and behavioral treatments, that are best for each person

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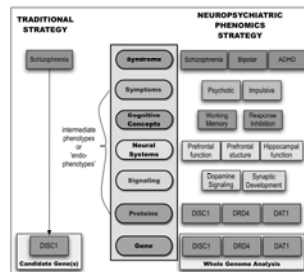
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## Neuropsychiatric Phenomics

A new perspective on tackling the genetics

- Phenomics is a novel approach to understanding the relationship between gene and behavior
  - Rather than the traditional strategy that examines a single diagnostic category, phenomics embraces the complex interactions between numerous phenotypes



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## Towards Personalized Medicine

The future of medicine

- There's no panacea
- We need targeted, individualized treatments
  - If DNA is unique like a fingerprint, how can one treatment work for even a majority?
- That will only come through really good characterization/assessment
  - There are countless variables to characterize (i.e. the 'phenome')

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## What does this have to do with the Internet?!

Science is complex, technology can help us

- Science is becoming more and more collaborative
  - Technology reduces the barriers (e.g. skype)
- The next generation of scientists will embrace technology in unprecedented ways
  - We will be the last generation that didn't grow up with the Web
- Most Neuropsychological tests were developed prior to widely available computers
  - NP test development process rooted in print publishing model
  - Print publishing of all kinds is rapidly being displaced by digital media

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## So where are we?

The end of the background...

- Sample Characteristics to date
  - Over 600 people have been enrolled and consented in this
  - ~~We know biology and biological validity is important~~
    - 143 parent-child pairs have completed at least two blocks of Spatial WM online, and 133 pairs have completed Stop-Signal.
  - ~~We know biology is complex~~
    - 53.8% of children are female, 73% of parents are female
    - Our lack of success continually reinforces this point
    - Children are 13.4 years old, on average (parents are 38.8 years old)
  - Technology is capable of helping
    - Myriad examples of this (email/ wikipedia/google/skype)
- How do we tackle the largest problems in biomedicine?

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## Knowledge Representation

Digest/Understand/Model/Build consensus

- How do we currently represent knowledge
  - Pubmed?
  - Box and Arrow models?
- Why build consensus?
  - Collaboration is necessary
- How do we build consensus?
  - Start with organization...

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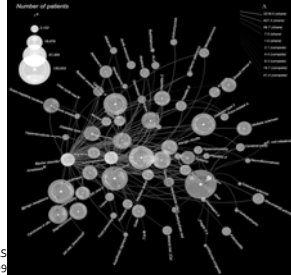
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## Why develop a Knowledgebase?

The power of Informatics

- Lots of information everywhere, little organization
- Especially at the levels of neural systems and above
- Rzhetsky mined a hospital records system



Rzhetsky A et al. PNAS  
2007;104:11694-11699

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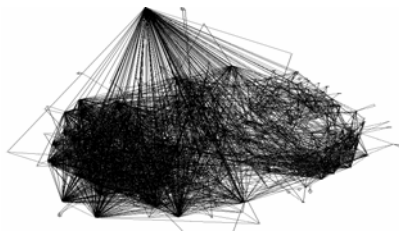
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## Informatics Simplifies Everything

Courtesy of Bob Bilder

- Phenomics KB – 2006\_02\_06 w/ ~600 nodes, 4200 edges
- Diagnoses, Symptoms, Cognitive\_phenotypes, Neuroanatomy, Neuroscience\_genes



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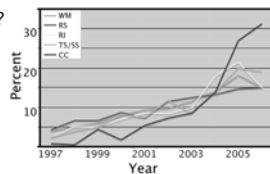
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## A working example: Cognitive Control

Sabb et al, 2008, Molecular Psychiatry

- Cognitive Control is well-studied multifactorial latent construct implicated in almost every mental illness
  - Beyond that, its open for debate...
  - What are the components?
  - What's the biological basis?



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## PubAtlas

Free Literature 'BLAST search' at <http://pubatlas.org>

[Stop Signal RT Histogram](#)

- Type in a list of terms
- PubAtlas does pair-wise search through pubmed



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## PubAtlas vs. PubMed alone

Literature 'BLAST search'

- What's the association between different cognitive control components and ADHD...what about fMRI?



Term	Count
"ADHD"	9255
"response selection"	826
"response inhibition"	1327
"working memory"	11369
"task switching"	517
"cognitive control"	1231
"test" AND ("kiss" OR "kissdown")	503

Venn Diagram Data:

- ADHD only: 9255
- response selection only: 826
- response inhibition only: 1327
- working memory only: 11369
- task switching only: 517
- cognitive control only: 1231
- test AND ("kiss" OR "kissdown") only: 503
- ADHD & response selection: 12
- ADHD & response inhibition: 21
- ADHD & working memory: 10
- ADHD & task switching: 46
- ADHD & cognitive control: 47
- ADHD & test AND ("kiss" OR "kissdown"): 5
- response selection & response inhibition: 3
- response selection & working memory: 30
- response selection & task switching: 5
- response selection & cognitive control: 26
- response selection & test AND ("kiss" OR "kissdown"): 71
- response inhibition & working memory: 153
- response inhibition & task switching: 15
- response inhibition & cognitive control: 153
- response inhibition & test AND ("kiss" OR "kissdown"): 37
- working memory & task switching: 70
- working memory & cognitive control: 186
- working memory & test AND ("kiss" OR "kissdown"): 37
- task switching & cognitive control: 15
- task switching & test AND ("kiss" OR "kissdown"): 70
- cognitive control & test AND ("kiss" OR "kissdown"): 141
- test AND ("kiss" OR "kissdown") & ADHD: 503

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## PubBrain

Courtesy of Russ Poldrack

Literature-based Brain Mapping

- We don't yet have comprehensive databases for neuroimaging data
- Can we use the published literature to map the brain?



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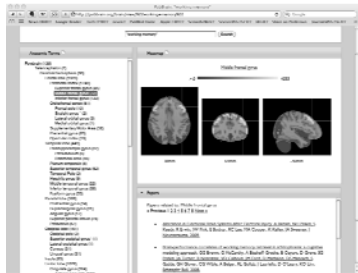
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## PubBrain vs. PubMed alone

Courtesy of Russ Poldrack

A picture is worth a 1000...articles?

- If you want to know what brain regions are important, why not put that on a brain??



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## Literature Wrap-up

Neuropsychiatry is too large a field

- We're developing tools to better organize the literature
  - How can we make progress without knowing where things currently stand?
- This is essential as the literature is too big to digest without getting a technological assist

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## Cognitive Atlas

The next step in organization: Consensus

- After we can digest the literature, we'll see that people use terms in very different ways
  - Are cognitive control and executive function synonyms?
- Debating these points in journals/books takes too long
- The answer is crucial for pushing the field forward in the most efficient way
  - Can a therapeutic intervention that improves Stroop performance help those with ADHD?

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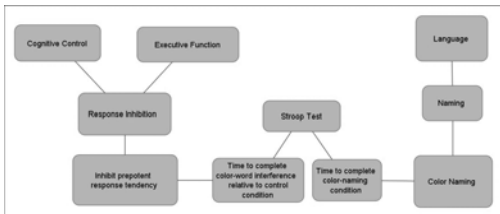
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# Cognitive Atlas

Image courtesy of Bob Blide

Cant we all just get along...?

- Cognitive Atlas allows assertions about the relationships between cognitive terms
  - We know Frontal lobe is part of the Cerebral Cortex
  - How about the Stroop Test? Where does that fit?




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# Phenowiki

What if wikipedia had evidence-based science for clinicians and researchers?

- How do we really get people to agree?
  - Evidence!
- Imagine Wikipedia with access to published data
- This is an active research project in how to design and implement a hybrid wiki/database
  - Needs more input from clinicians/researchers
  - You can input quantitative effect size annotations for key study findings from literature you read
  - Psychometric properties can be input (i.e., test-retest reliability, coefficient alpha)
  - Entire KB can be used for meta-analysis, compared to other findings

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# Wikipedia – Stroop Effect

Surprised Wikipedia has Stroop effect in it?

- Perhaps surprisingly a good article!
- Give History
- Task Modifications
- Clinical implication
- Associated Anatomy




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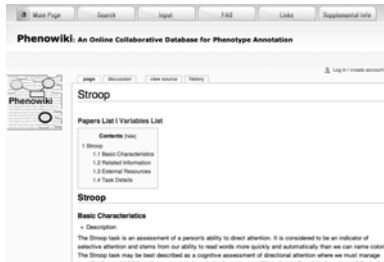
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## Phenowiki – Stroop Effect

Developing a Knowledgebase...

- Descriptions, references, links...and data
  - Correlations
  - Effect sizes
  - Psychometric
  - Validity




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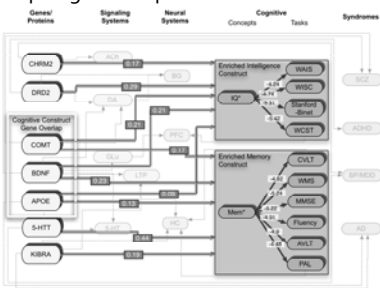
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## Phenowiki- Effect size

Building quantitative models

- Shows the overlap of genes implicated for Memory/Intell



Sabb et al, 2009, Neuroscience

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## APA PsycTEST

Coming in 2011, hopefully

- We're not the only ones!
  - APA is developing a rich database
  - ...but it (probably) wont contain #s

PsycTESTS™ Sample Record	
Test Development Sample Record	Test Evaluation Sample Record
Unique Identifier	2009-1235
Test/Measure Name	Interim Faking Behavior Scale (9m to last)
Test/Measure Acronym	IFB
Purpose	To measure faking behaviors in employment interviews based on a taxonomy developed for these behaviors.
Developer	Falng
Population Group	Human; Male; Female Adult (18 yrs & older) Study 1: 55 Full-year masters of business administration students Study 2: 282 semester undergraduate students Study 3: 189 undergraduate students Study 4: 188 undergraduate students (25% women) Study 5: 58 undergraduate students (25% women) Study 6: 151 undergraduate students (25% women)
Location	USA
Source Document Citation	Strickley, Neil edited Lundström, J., & Carlson, M. A. (2007). Measuring lying in the employment interview: Development and validation of an interview faking behavior scale. <i>Journal of Applied Psychology, 92</i> , 1020-1040.
Relationship of Document to Test/Measure	Document addresses development of test

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## Representation Wrap-up

Tools for better models

- The field is rich and complex, increasingly inter-disciplinary and collaborative
- We need to embrace technology to work together
  - Build models
  - Build consensus
- Push the field forward at a pace that rivals genetic/biological advances

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## Knowledge Acquisition

How can we improve assessment/measurement?

- To find useful biomarkers for assessment and treatment, we must better identify and refine the complex phenotypes/endpoints that underlie neuropsychiatric disorders like ADHD
- Problems achieving this goal arise from the time and cost in recruiting large enough samples to adequately characterize the phenotypes (or endpoints) of interest.

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## BrainTest.org

High-throughput iterative phenotyping platform



BRAIN  
TEST

- Better phenotype definitions will only come with high-throughput iterative & adaptive phenotyping
- A majority of US children use the Internet (60% of all 5-17) and close to 80 percent of those over 15 years of age regularly access the World Wide Web.
  - For example...facebook personality tests get 100k responses....per month!
  - What if we could capture this data!!

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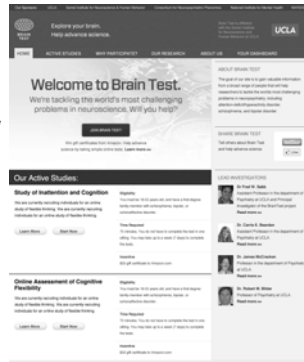
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## BrainTest.org

Acquisition of behavioral data on a new time/size scale

### Web-Content

- ▶ Flash-based cognitive tests of Stop-Signal, Spatial Working Memory, Task Switching, Balloon Analog Risk Task...more under development
- ▶ Mediawiki controlled development for site content and survey construction



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## Why online assessment?

Its time for a paradigm shift!

- Settle those consensus debates?
- Quicker implementation and refinement
- Larger numbers
- Better access to larger population
- Keep pace with genetic discovery
- NP tests need a paradigm shift

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## Potential Pitfalls

The most common concerns...

- Validation of Web-based acquisition is essential. We have several ongoing validation studies that test people on the Web and in the lab.
- Recruitment: Who are these folks who participate?

We believe the challenges are different, but not harder than implementing lab-based studies.

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## Online ADHD cognitive intervention

Still on the design table – application under review

- Attention Training study using C-PAT developed by Shalev demonstrated improved outcome measures in children and adults using a 2 month lab-based training program
  - Multiple sessions with trained staff every week
  - Children showed improved reading comp and parent ratings
- Adapting this for the Web, would allow both:
  - wider dissemination, larger studies
  - greater flexibility/ personalization

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## Acquisition Wrap-up

Using technology to improve assessment

- The technology is ready
  - Continued validation work is needed
- This can allow us to do rapid iterative assessment and targeted cognitive interventions
- This would represent a huge leap towards personalized medicine

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## Dissemination

You don't need to be a couple miles from UCLA to get world-class expertise

- Why is dissemination important?
  - Improve public health information
  - Reach a wider audience
  - Reduce stigma

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## Spread information and reduce stigma

We all have the same genes, the same is bigger than the difference

- If science can coordinate, we can be a powerful voice
- All the mental illnesses are associated with brain function/dysfunction, and thus no more stigmatizing than illness affecting heart, kidney or bone
- If the boundaries across the syndromes are not clear, then we may benefit from studying problems shared across the syndromes, and the overlap of functioning between ill and healthy people

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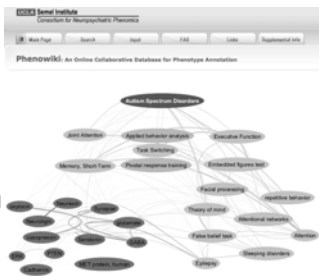
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## Literature Association Model for ASD

PubAtlas-based graph of Literature

- One dissemination project:
  - Our ASD knowledgebase
- Funded by HRSA to coordinate and disseminate treatment/knowledge about ASD



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## Summary – Back to the Objectives...

How'd I do?

- Knowledge Representation
  - How can we understand/store/build consensus about biomedical knowledge?
    - New tools to organize, model, and build consensus
- Knowledge Acquisition
  - How can we acquire/measure/capture this knowledge?
    - A new Web-based platform that can take advantage of the fast pace of bio-behavioral research
- Knowledge Dissemination
  - How can we share it with colleagues and the public?
    - (Almost) everyone has Internet access, so everyone should have access to this information

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