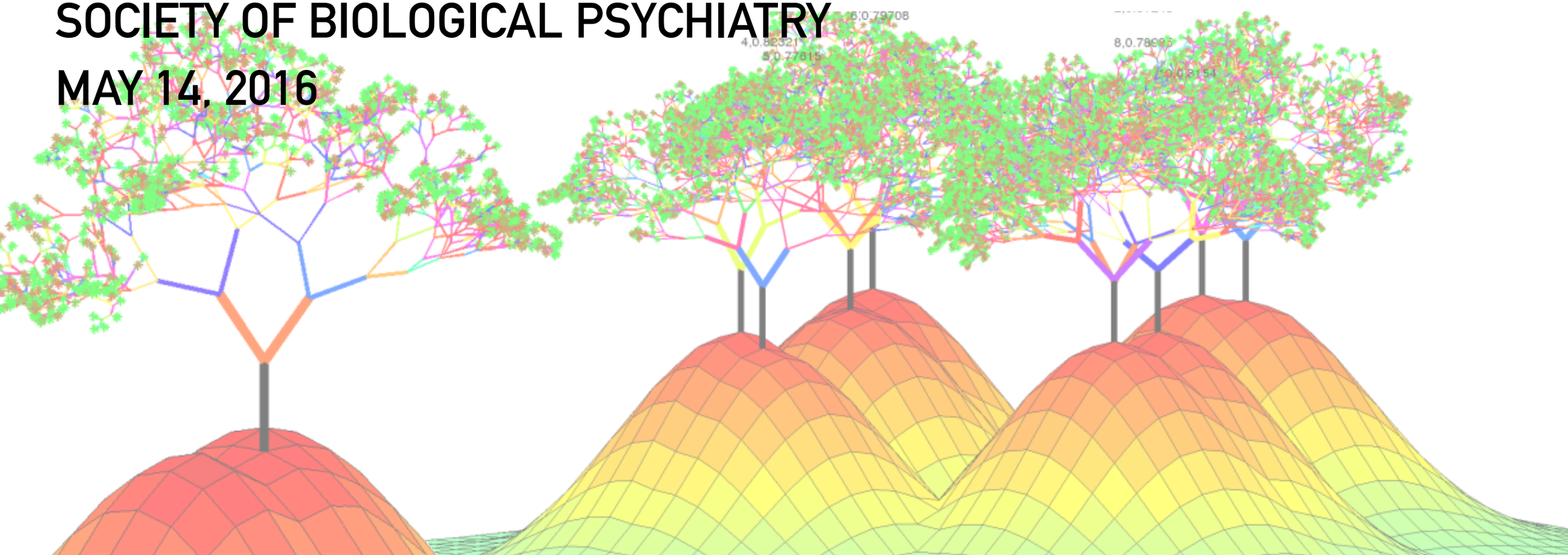
MULTIVARIATE PATTERN ANALYSIS OF GENOTYPE–PHENOTYPE RELATIONSHIPS IN SCHIZOPHRENIA

AMANDA ZHEUTLIN
YALE UNIVERSITY

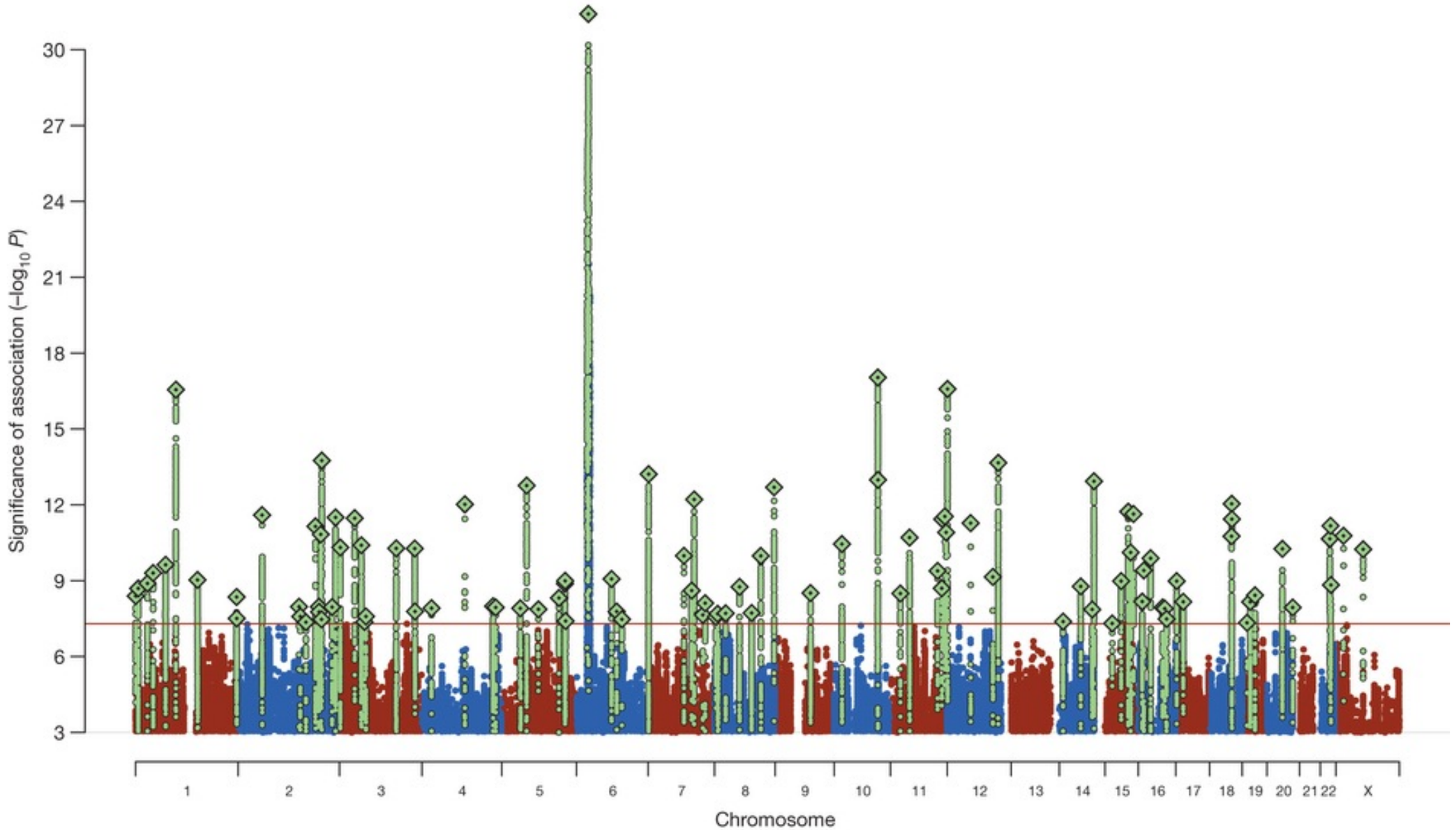
SOCIETY OF BIOLOGICAL PSYCHIATRY
MAY 14, 2016



SCHIZOPHRENIA GENETICS

Ripke et al., 2014, *Nature*

SCHIZOPHRENIA GENETICS



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HOW DO GENES CONFER RISK?

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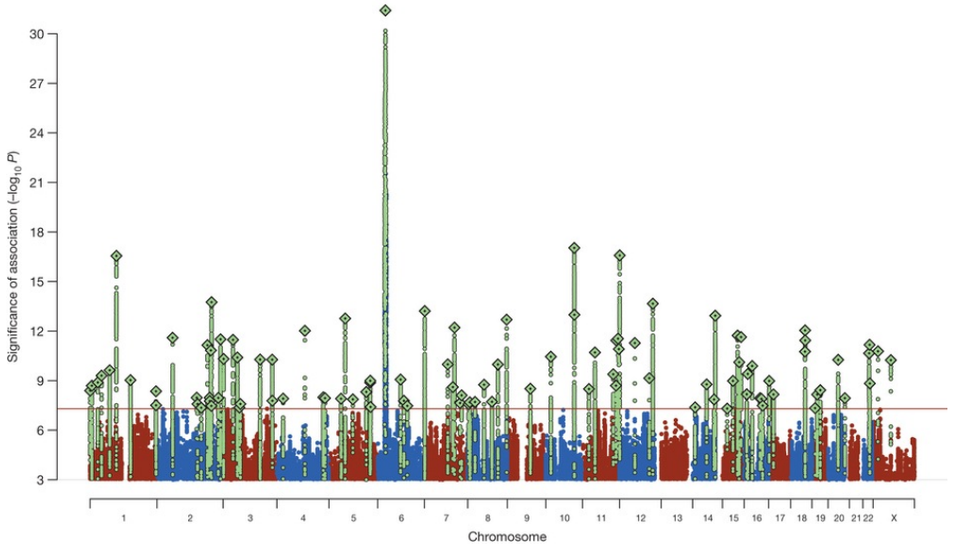

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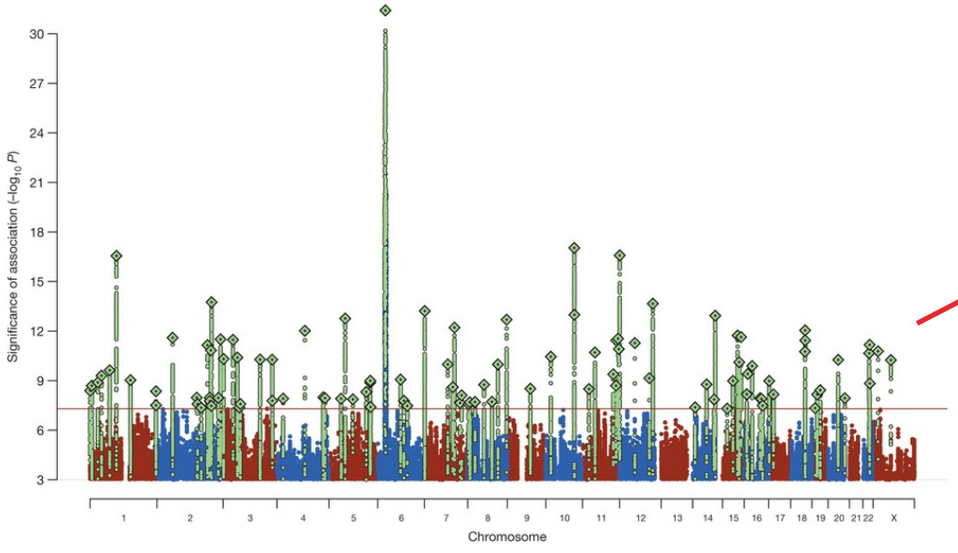

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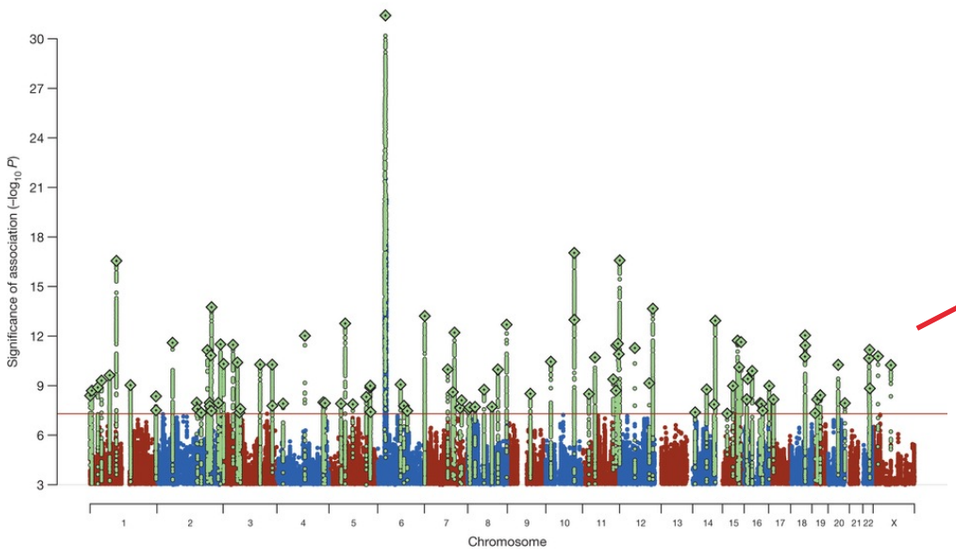

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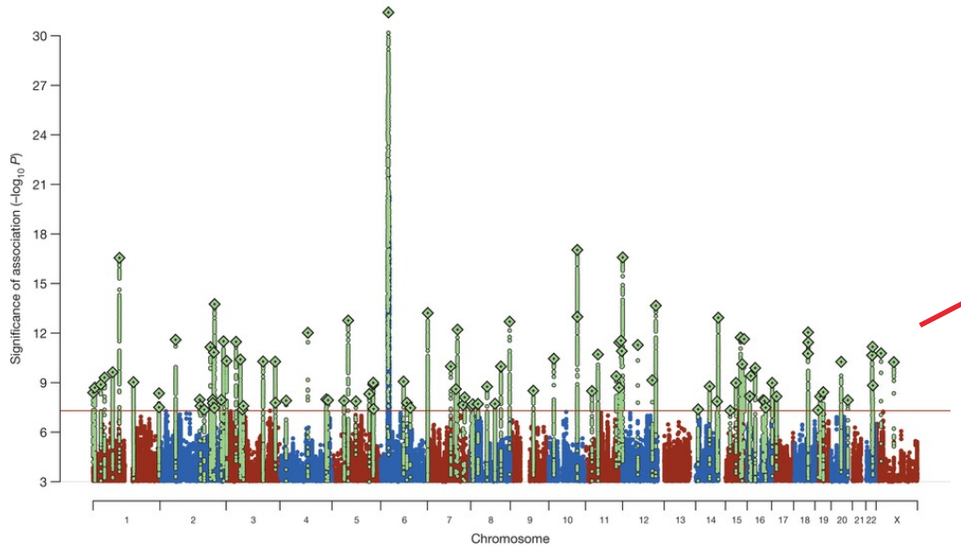

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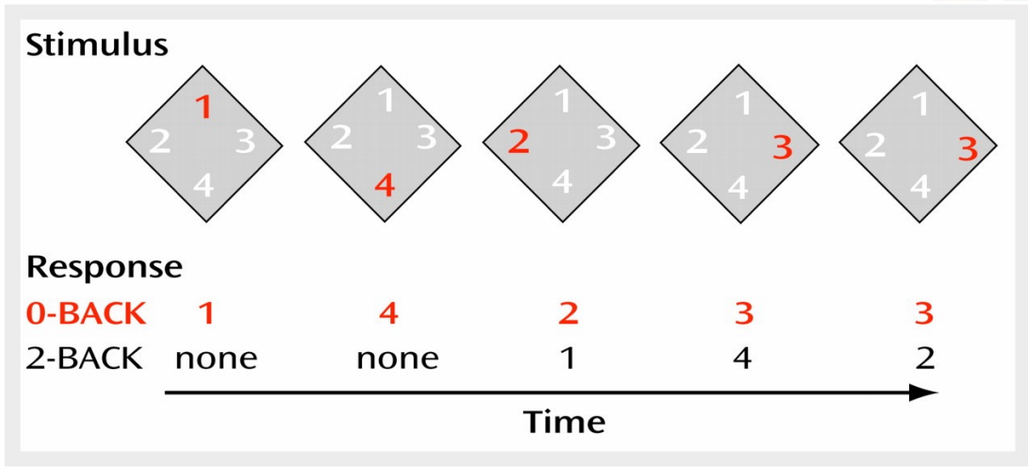

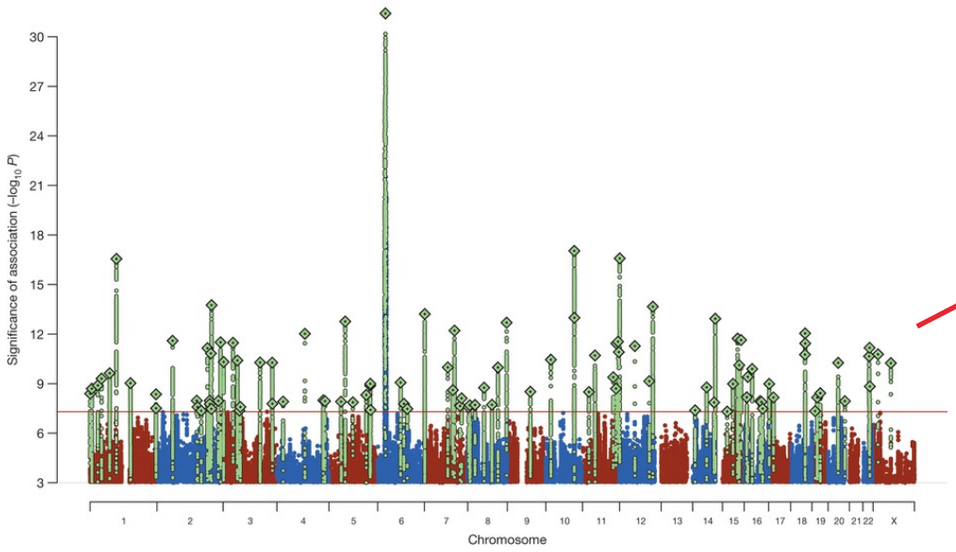

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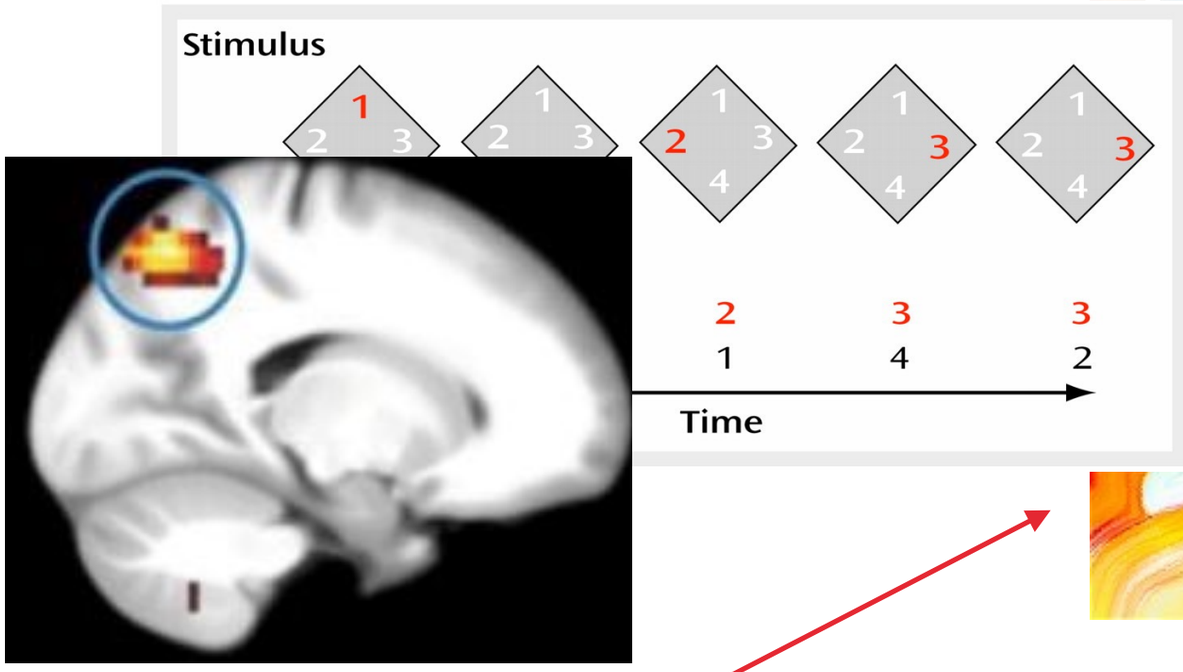

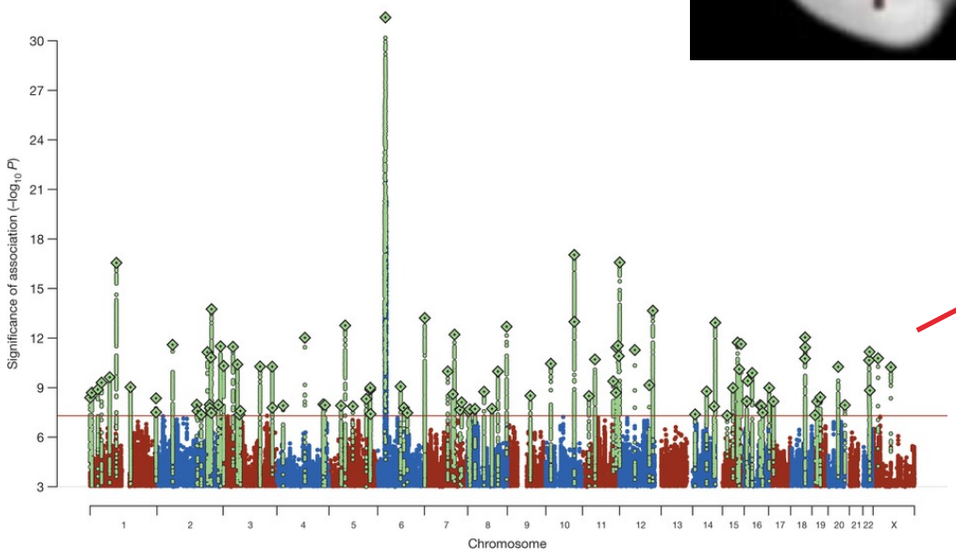

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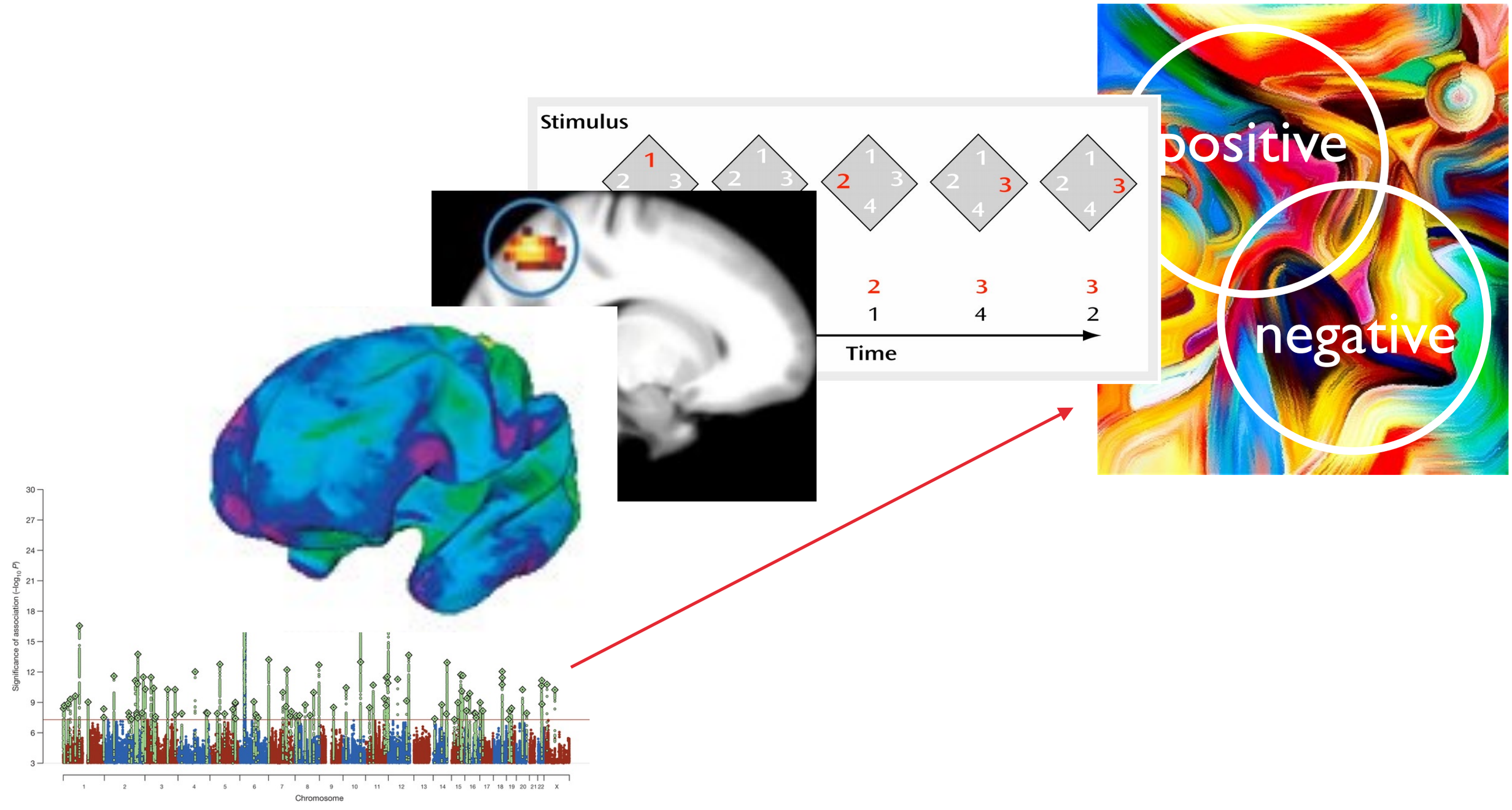

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WHICH GENES CONFER RISK FOR WHAT?

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- Are there differential genotypic effects by phenotype?

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- Are there non-linear effects?

GENOTYPIC PATTERNS

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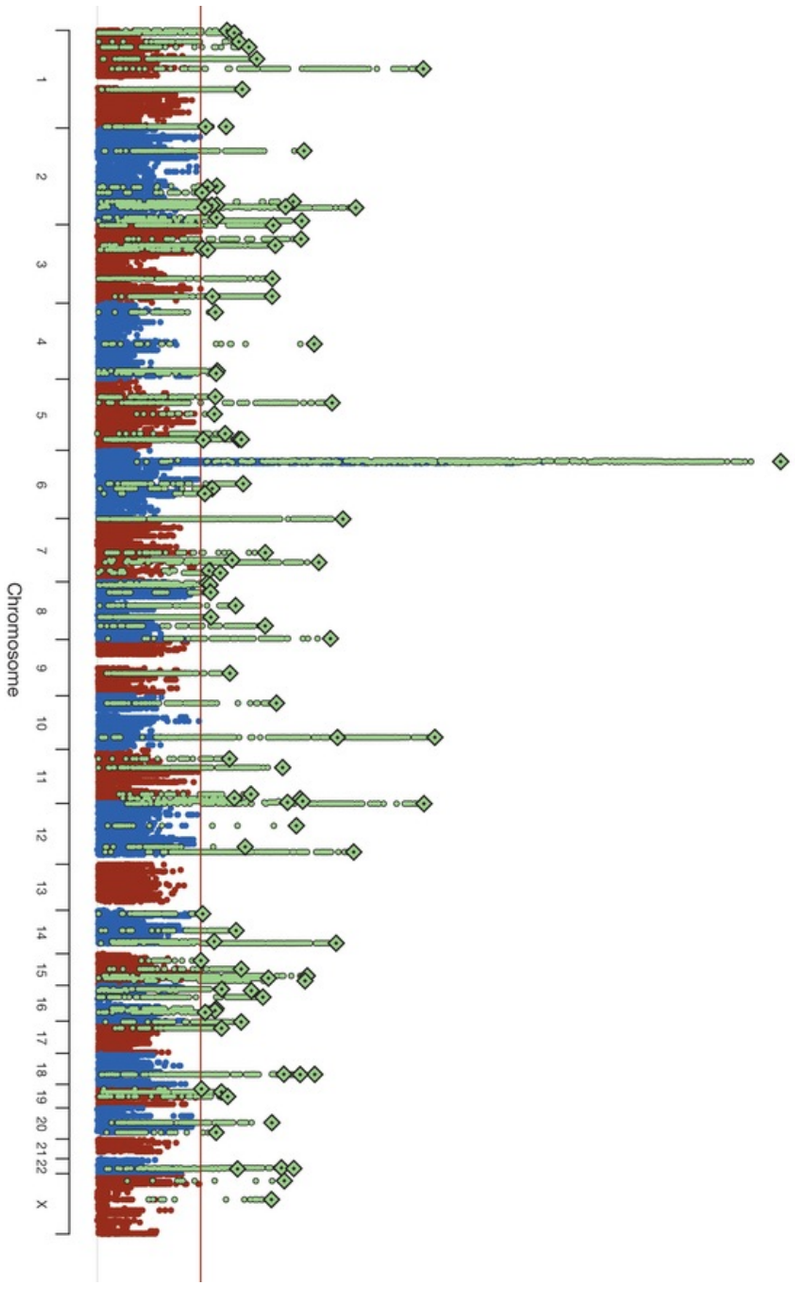

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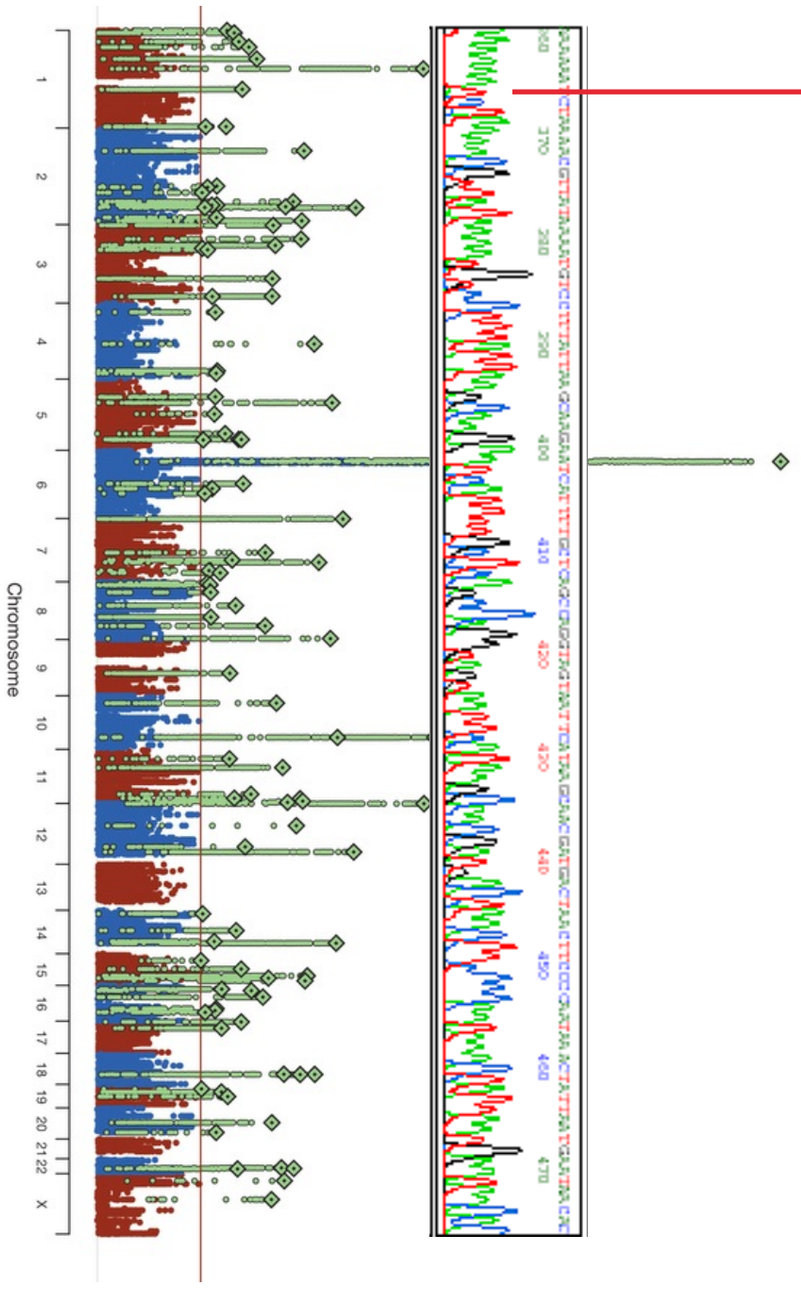

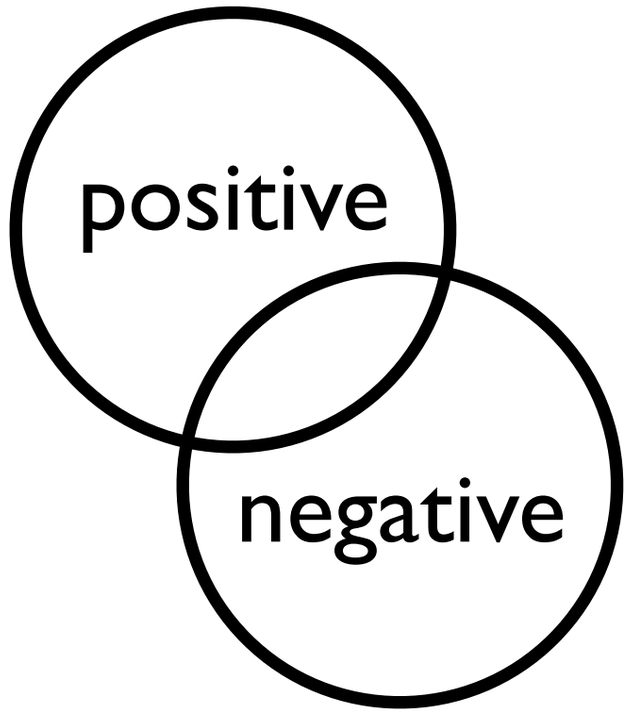

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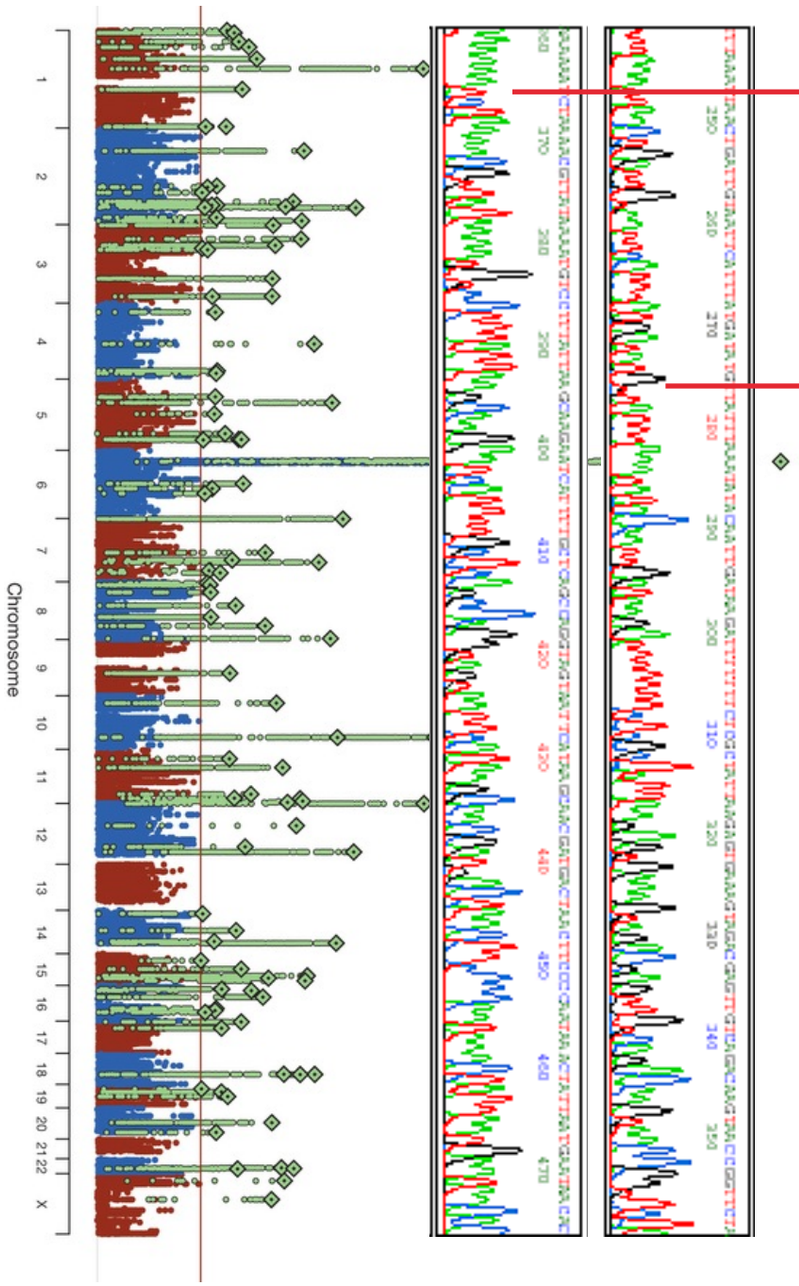

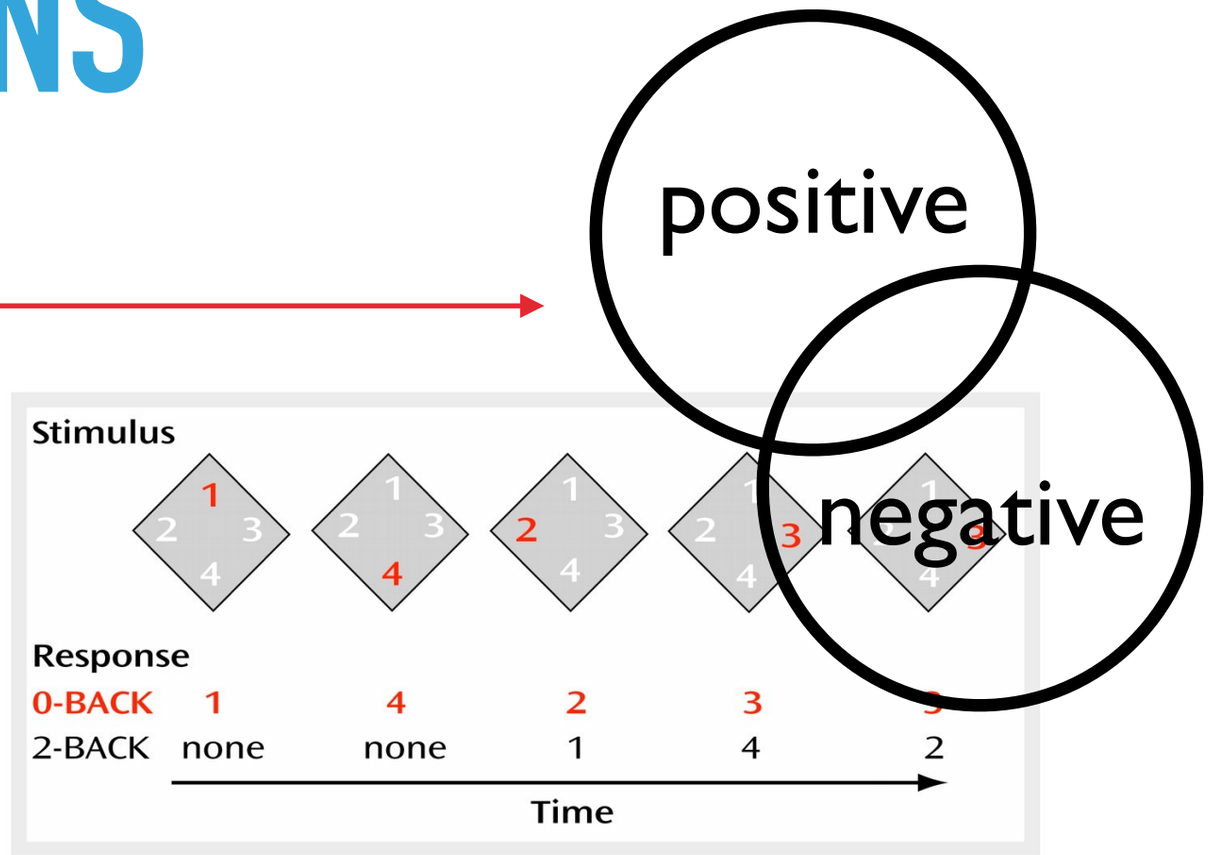

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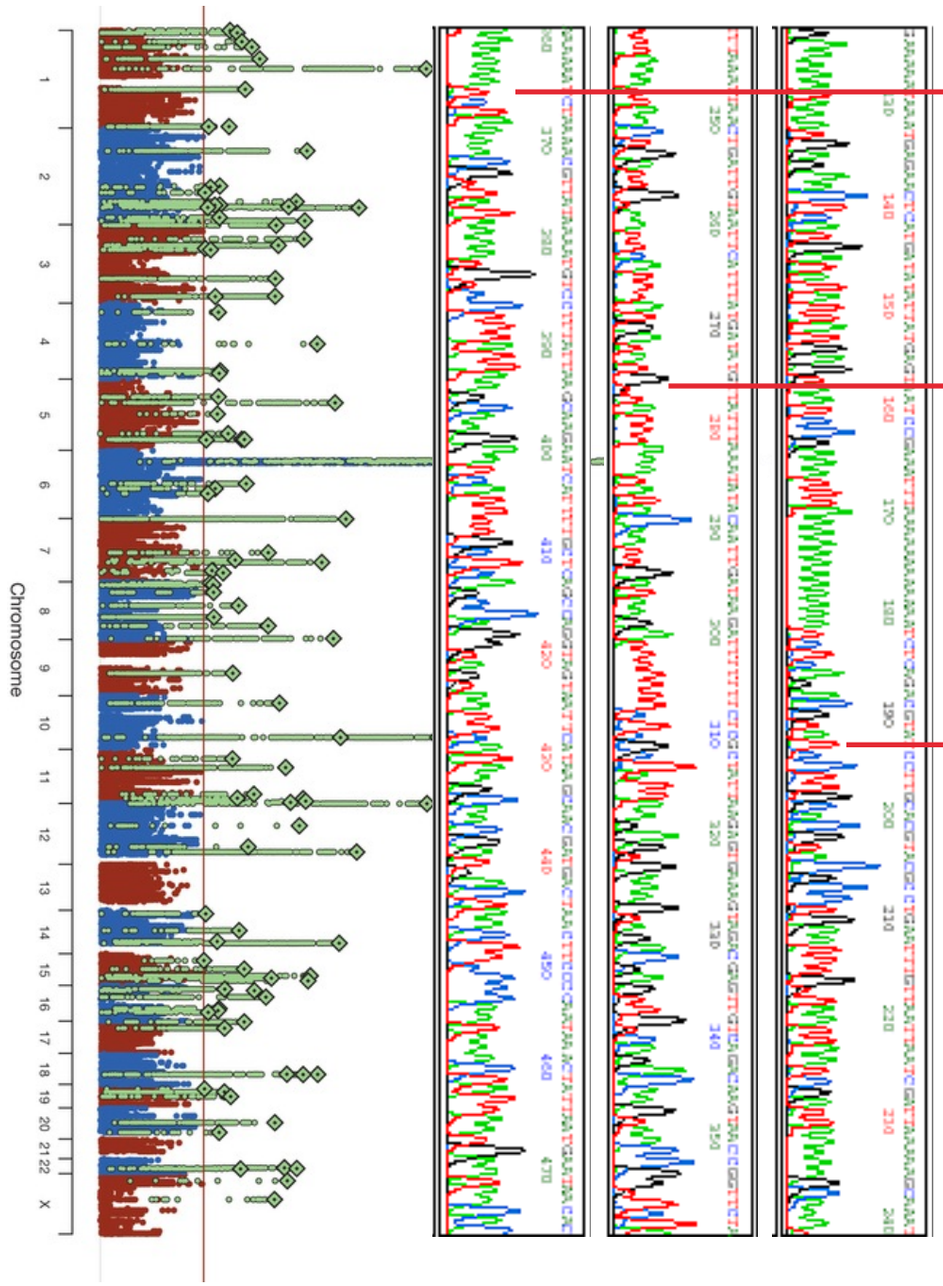
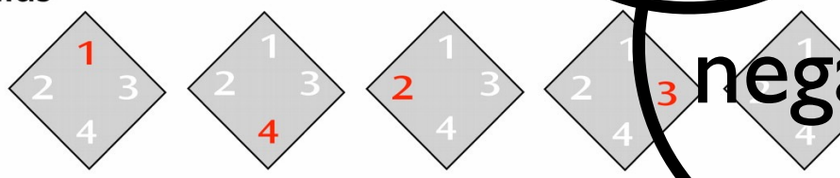


positive

negative

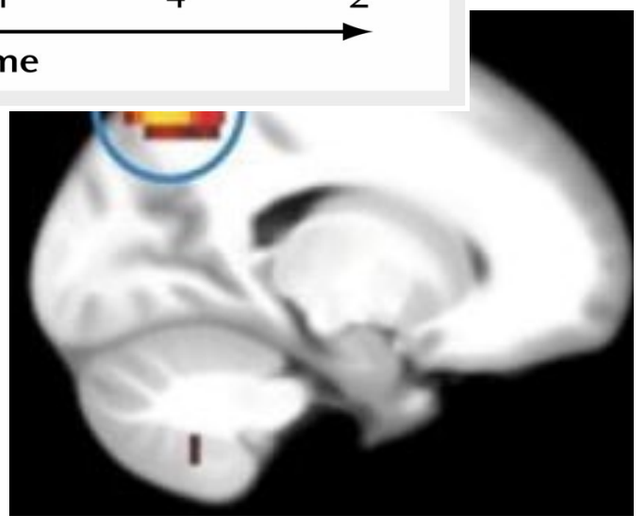
Stimulus



Response

0-BACK	1	4	2	3	3
2-BACK	none	none	1	4	2

Time



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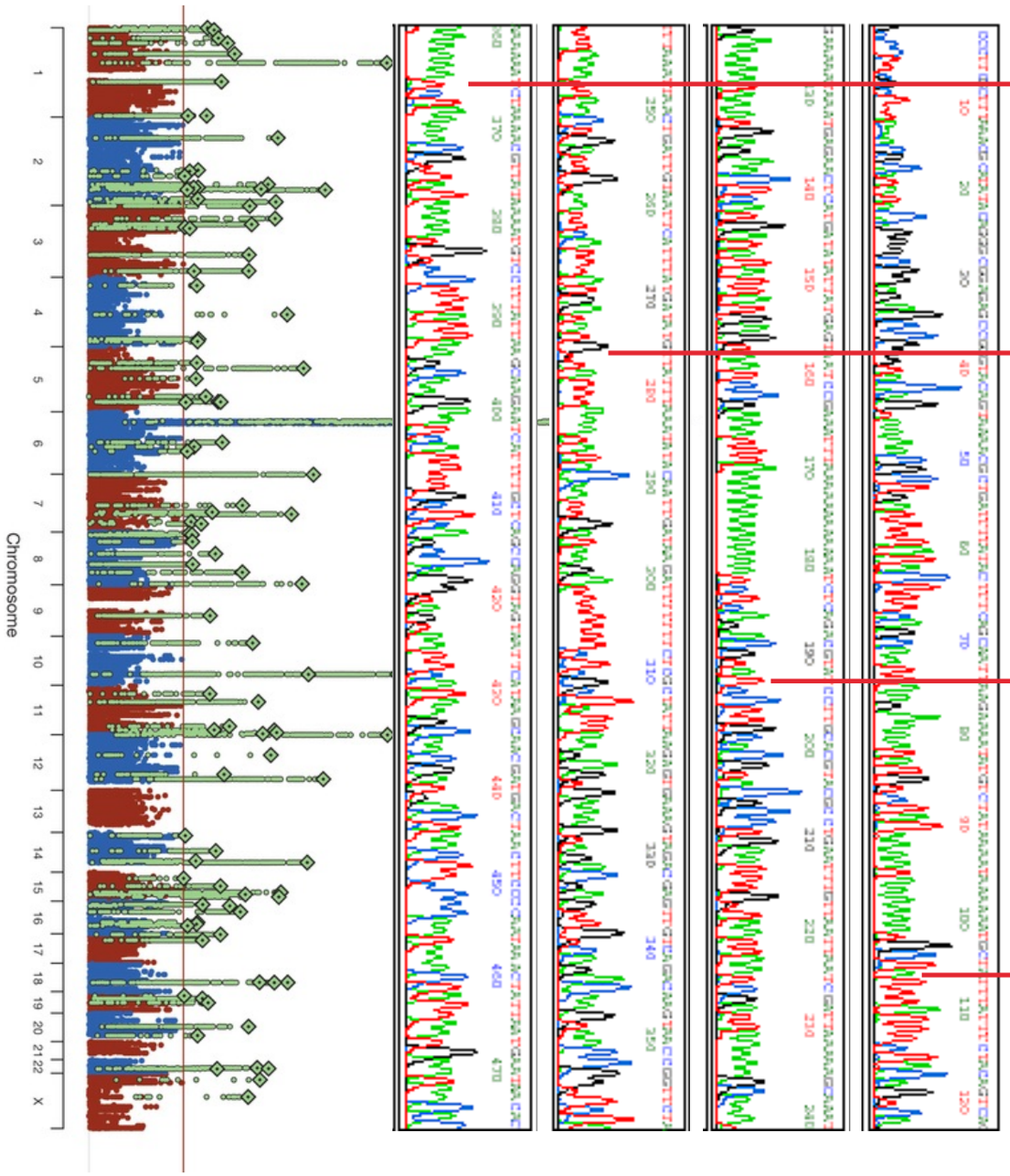

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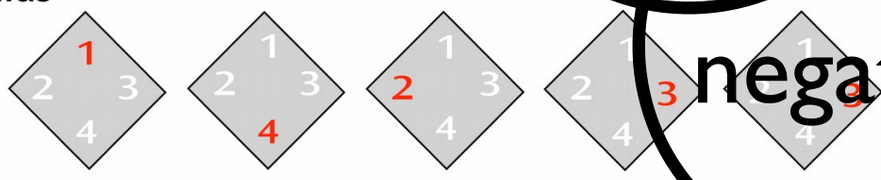

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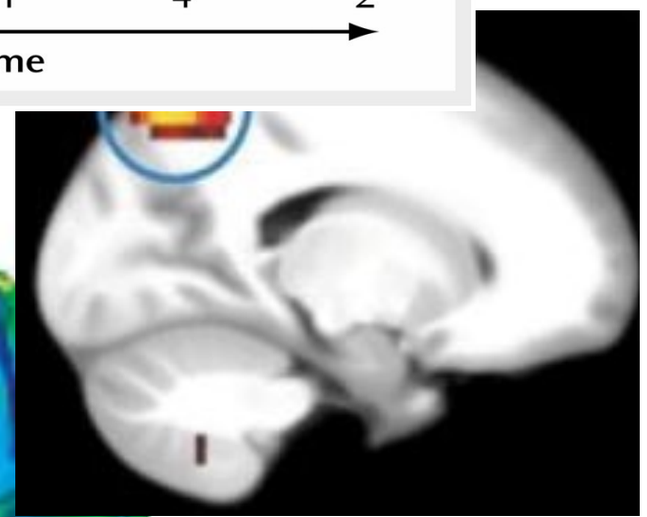

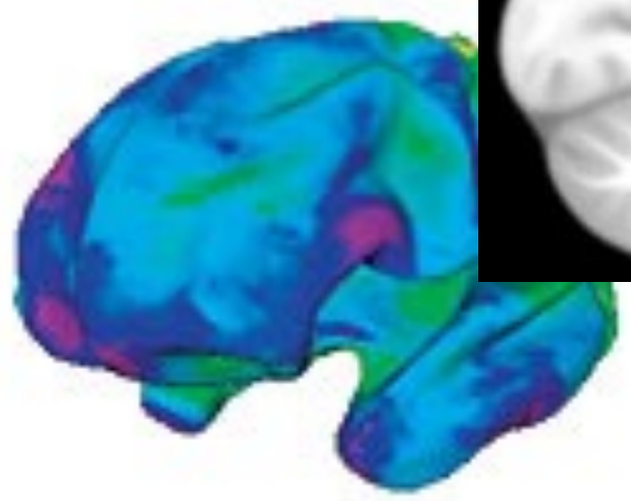

AIMS

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- Proof of principle application of machine learning to genotype-phenotype mapping
  - Schizophrenia-associated variants
  - Cognitive endophenotypes

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  - Schizophrenia-associated variants
  - Cognitive endophenotypes
- Compare this approach to more widely used methods (GLM, polygenic scores) using the same loci and outcomes

GENOTYPES & PHENOTYPES

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- Samples
  - Training: American sample – SZ, BP, ADHD, controls (*N* = 739)
  - Validation: Swedish twin sample – SZ, BP, controls (*N* = 364)

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- Samples
  - Training: American sample – SZ, BP, ADHD, controls (*N* = 739)
  - Validation: Swedish twin sample – SZ, BP, controls (*N* = 364)
- Measures
  - Predictors: 77 of 108 PGC SNPs
  - Outcomes: 6 cognitive measures
    - CVLT, VR I & II, Digit Span, Trail Making Test A, Vocabulary

RANDOM FOREST

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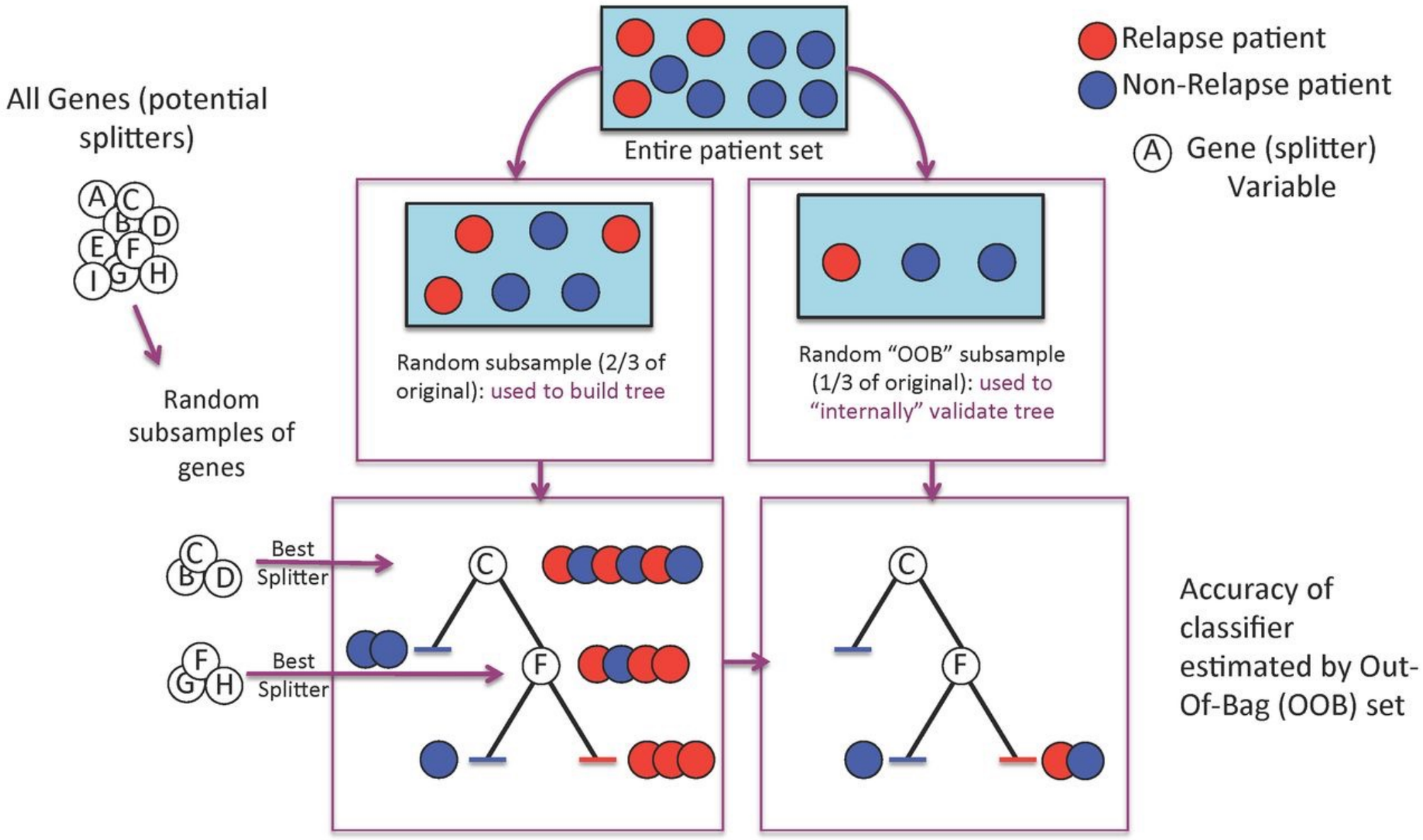

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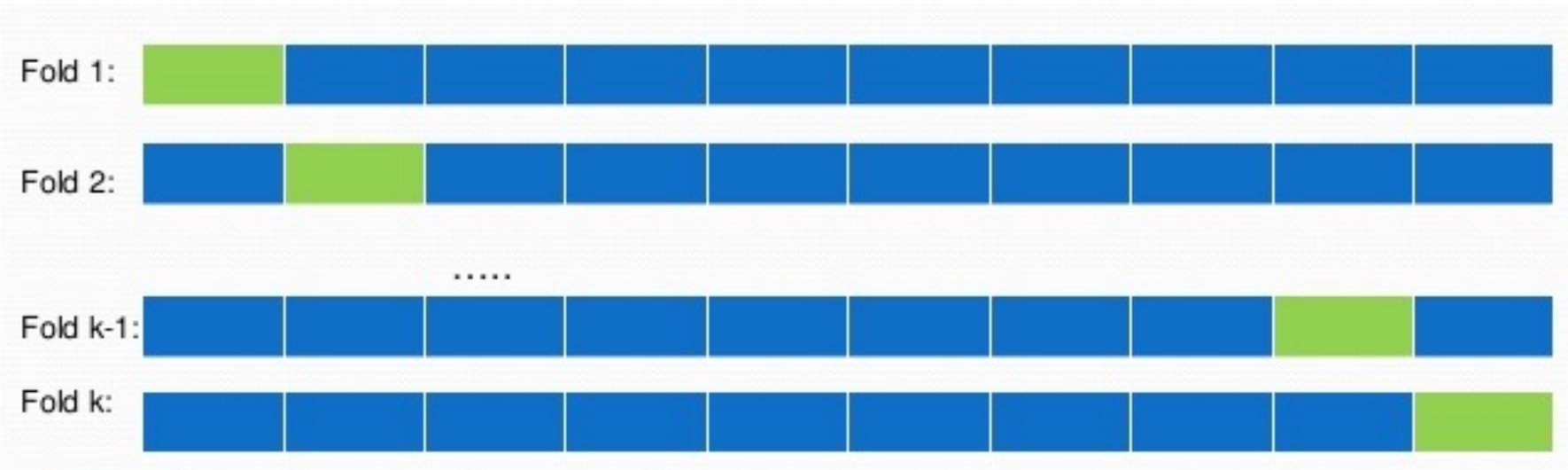

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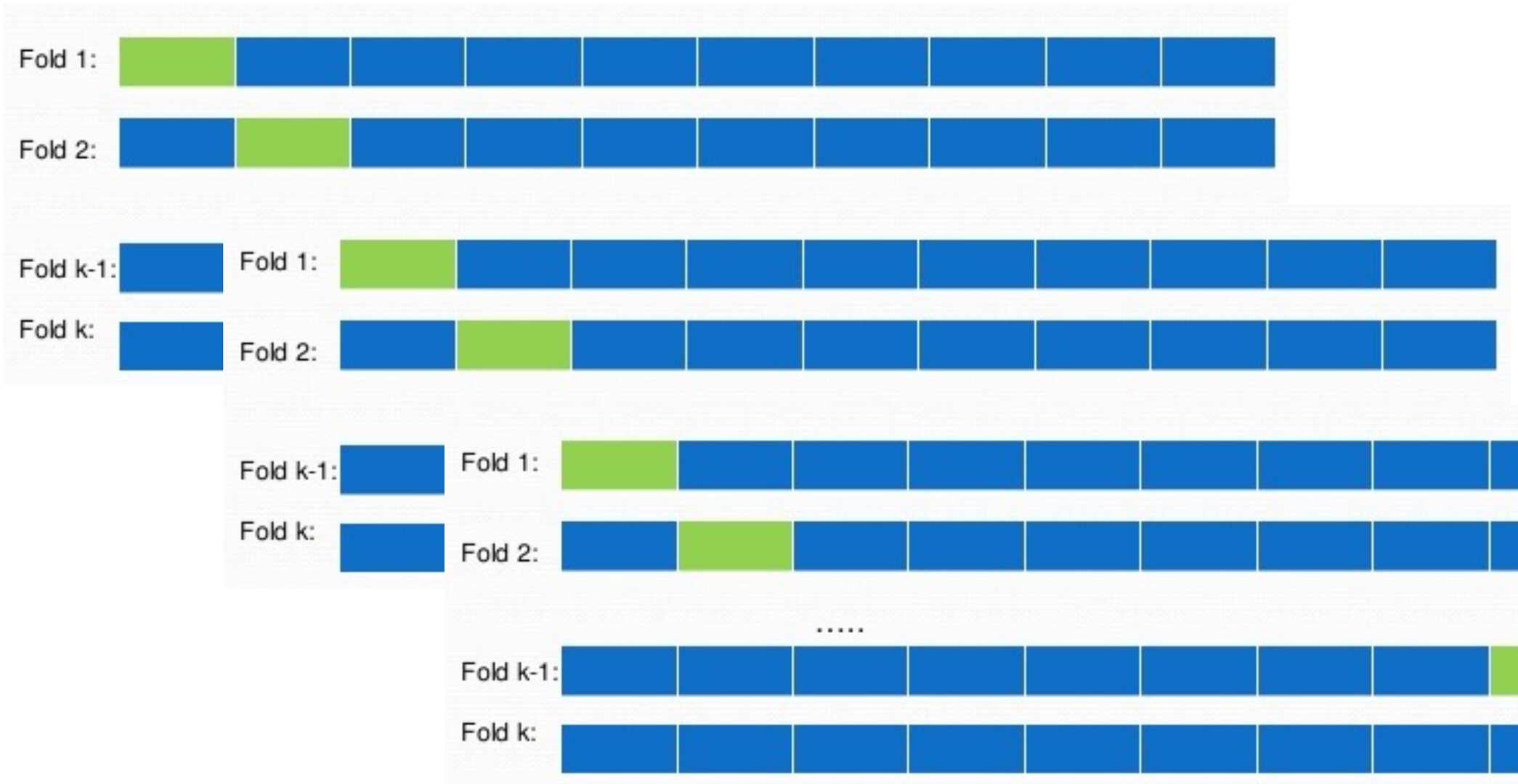

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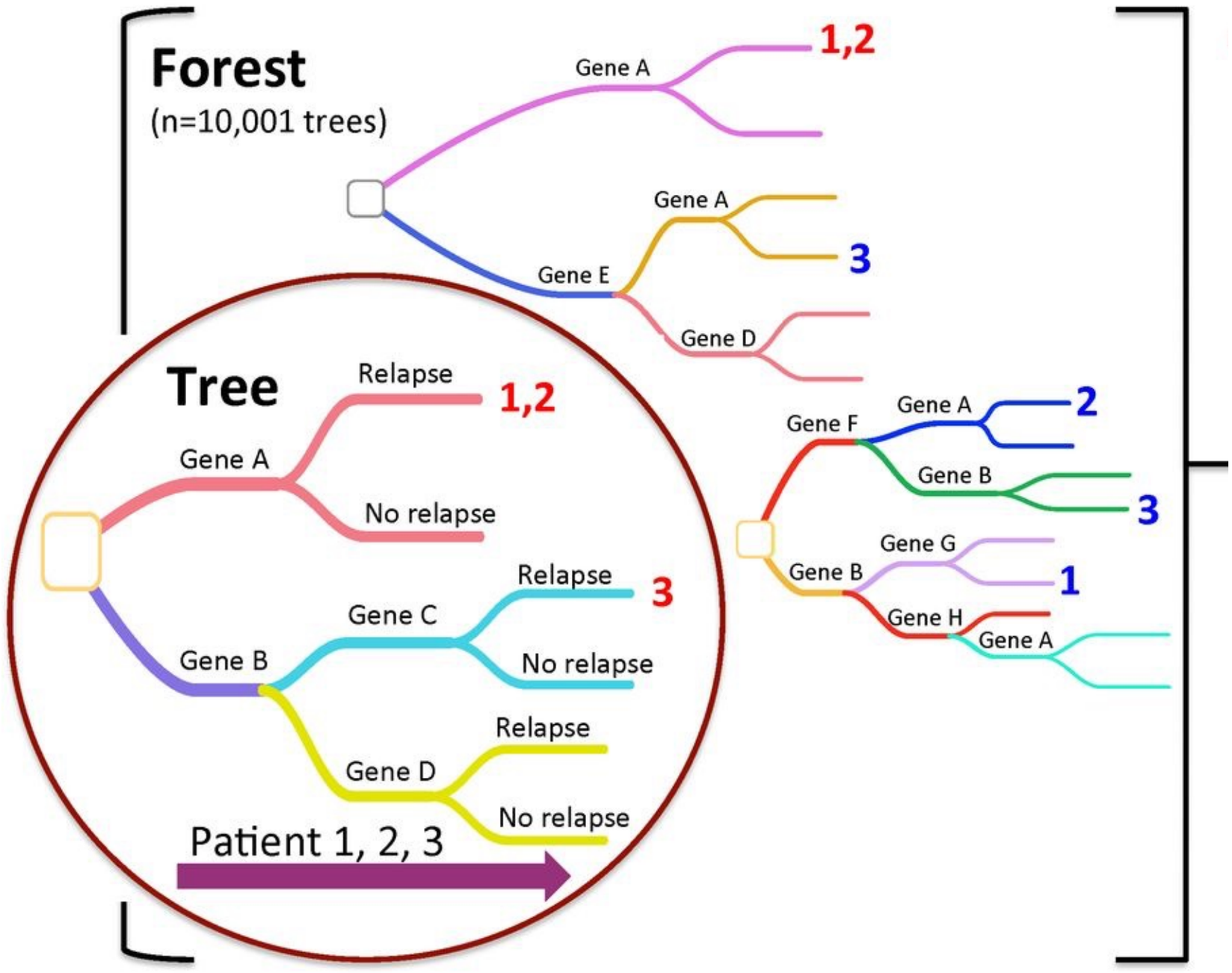
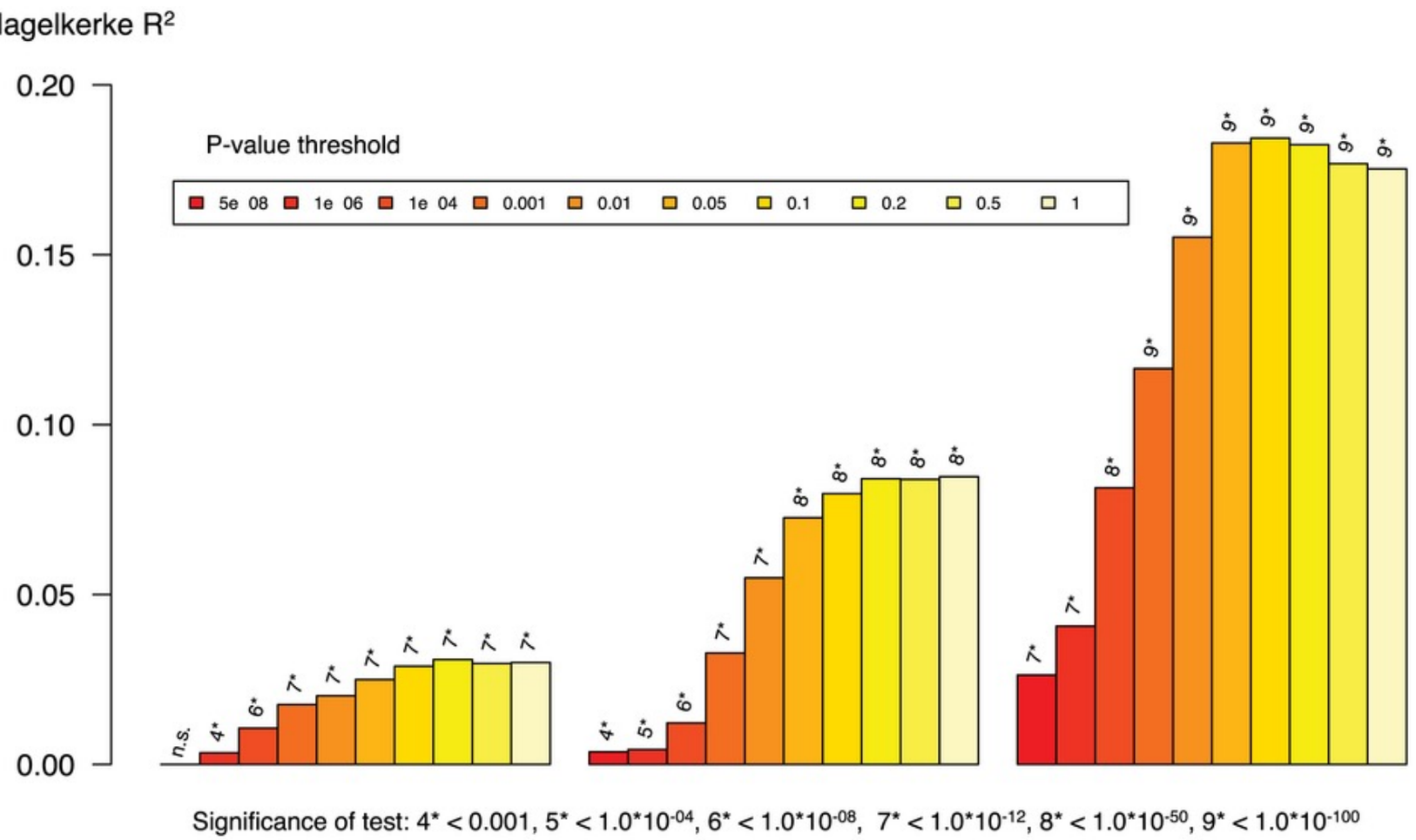


COMPARISON MODELS

- General linear models (GLM)
- Polygenic risk scores (PRS)



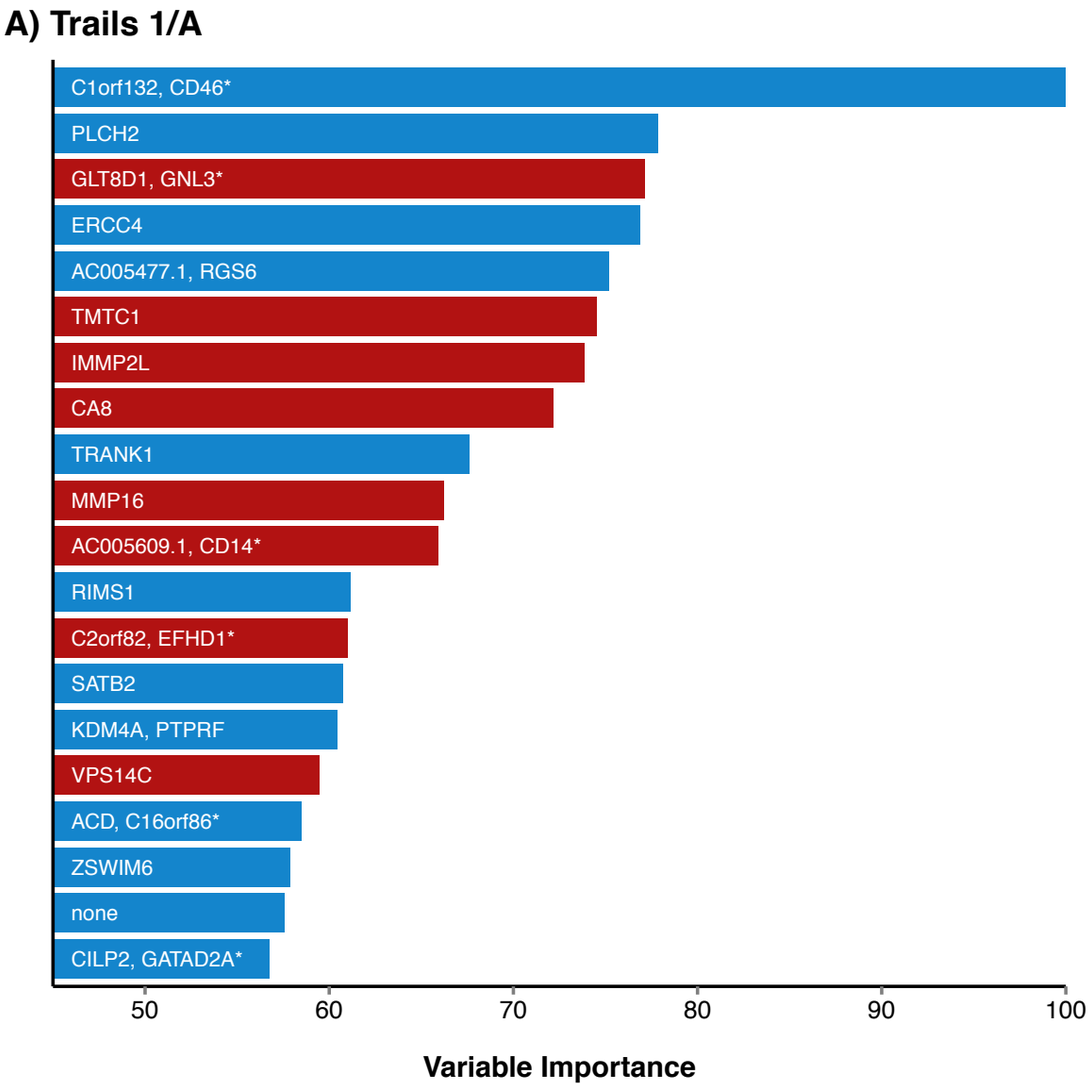
Ripke et al., 2014, *Nature*

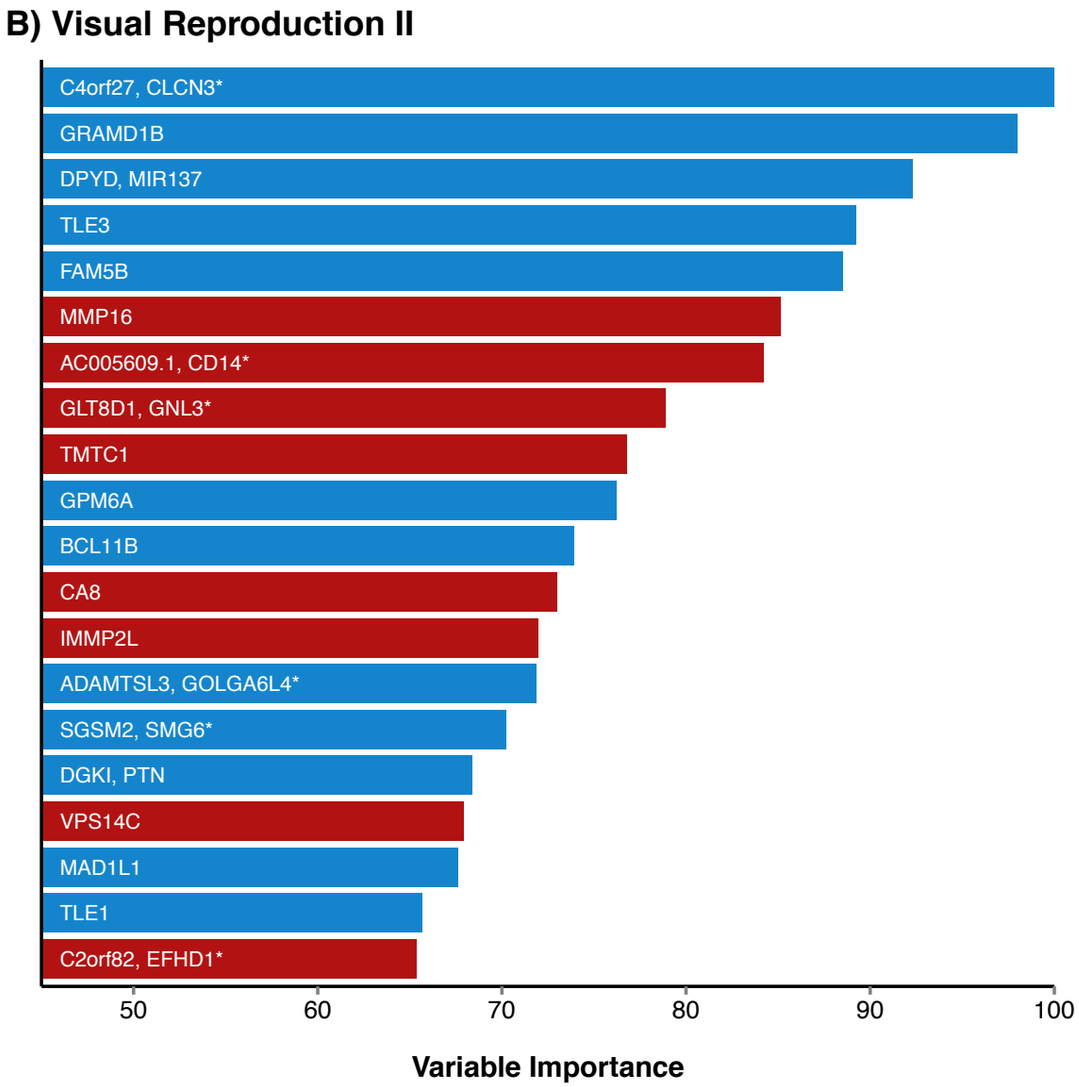
MODEL PERFORMANCE

	American Sample					
	RF		GLM		PRS	
	R^2	p	R^2	p	t	p
CVLT	**0.015**	**< .001**	**0.013**	**.002**	-2.32	.126
Vocabulary	**0.010**	**.005**	**0.017**	**< .001**	-0.75	.683
Trails 1	**0.010**	**.006**	**0.015**	**.001**	-0.16	.871
Digit Span	**0.018**	**.001**	**0.014**	**.001**	-1.45	.444
VR I	**0.012**	**.003**	**0.010**	**.006**	0.98	.654
VR II	**0.013**	**.001**	**0.012**	**.002**	-0.54	.706

	Swedish Sample					
	RF		GLM		PRS	
	t	p	t	p	t	p
CVLT	-0.81	.209	-0.44	.332	-	-
Vocabulary	-0.06	.478	-0.24	.407	-	-
Trails A	**2.86**	**.003**	1.05	.147	-	-
Digit Span	0.15	.440	-0.05	.482	-	-
VR I	-0.55	.291	-0.20	.421	-	-
VR II	**1.76**	**.040**	0.31	.377	-	-

VALIDATED MODELS





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- **Statistical validation:** Random forest outperformed GLM and polygenic risk scores in an independent sample
- **Biological validation:** Random forest models identified calcium ion binding and cell adhesion genes, which have previously been mapped to cognitive impairment in schizophrenia
- **Relevance:** Pattern analysis may be able to identify more specific and generalizable genotype-phenotype associations than standard linear methods

LIMITATIONS

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- PRS typically include 100s - 1000s of variants

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- Relatively small samples

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- Relatively small samples
- Limited by current knowledge of genetic risk variants for schizophrenia

THANK YOU!

Yale University

- Adam Chekroud, MSc
- Ty Cannon, PhD

New Haven VA

- Renato Polimanti, PhD
- Joel Gelernter, MD

UCLA

- Fred Sabb, PhD
- Robert Bilder, PhD
- Nelson Friemer, MD
- Edythe London, PhD

Karolinska Institutet

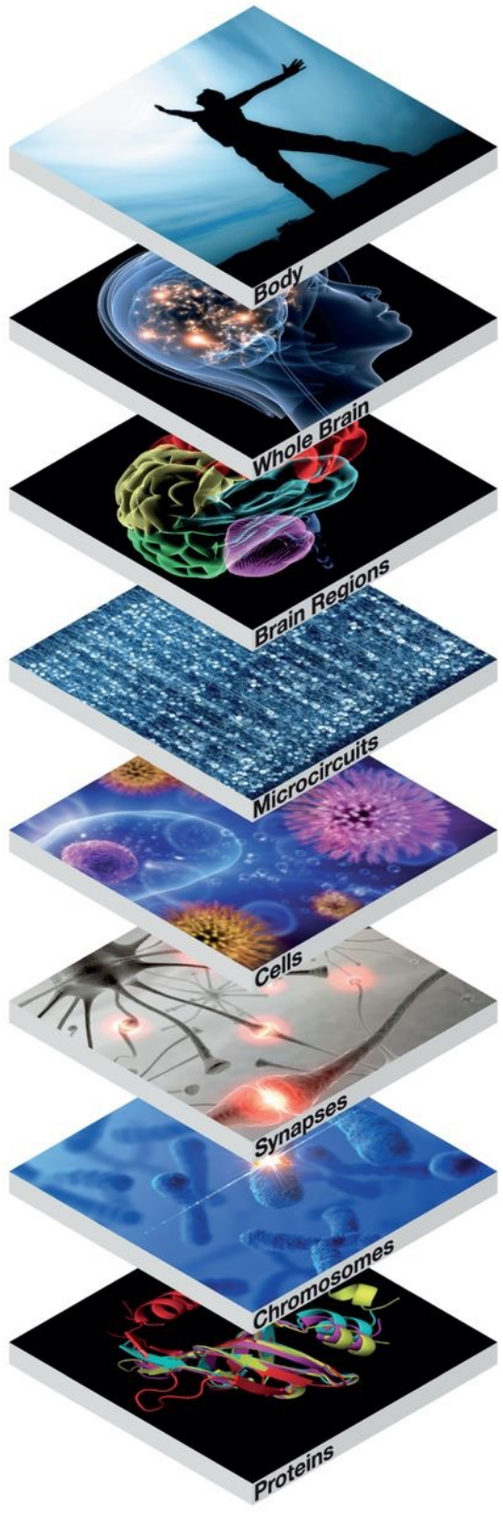
- Christina Hultman, PhD

CLINICAL NEUROSCIENCE LAB

TEXT

SCHIZOPHRENIA

- 1% of global disease burden
- 21 million affected
- $6.8 billion per year



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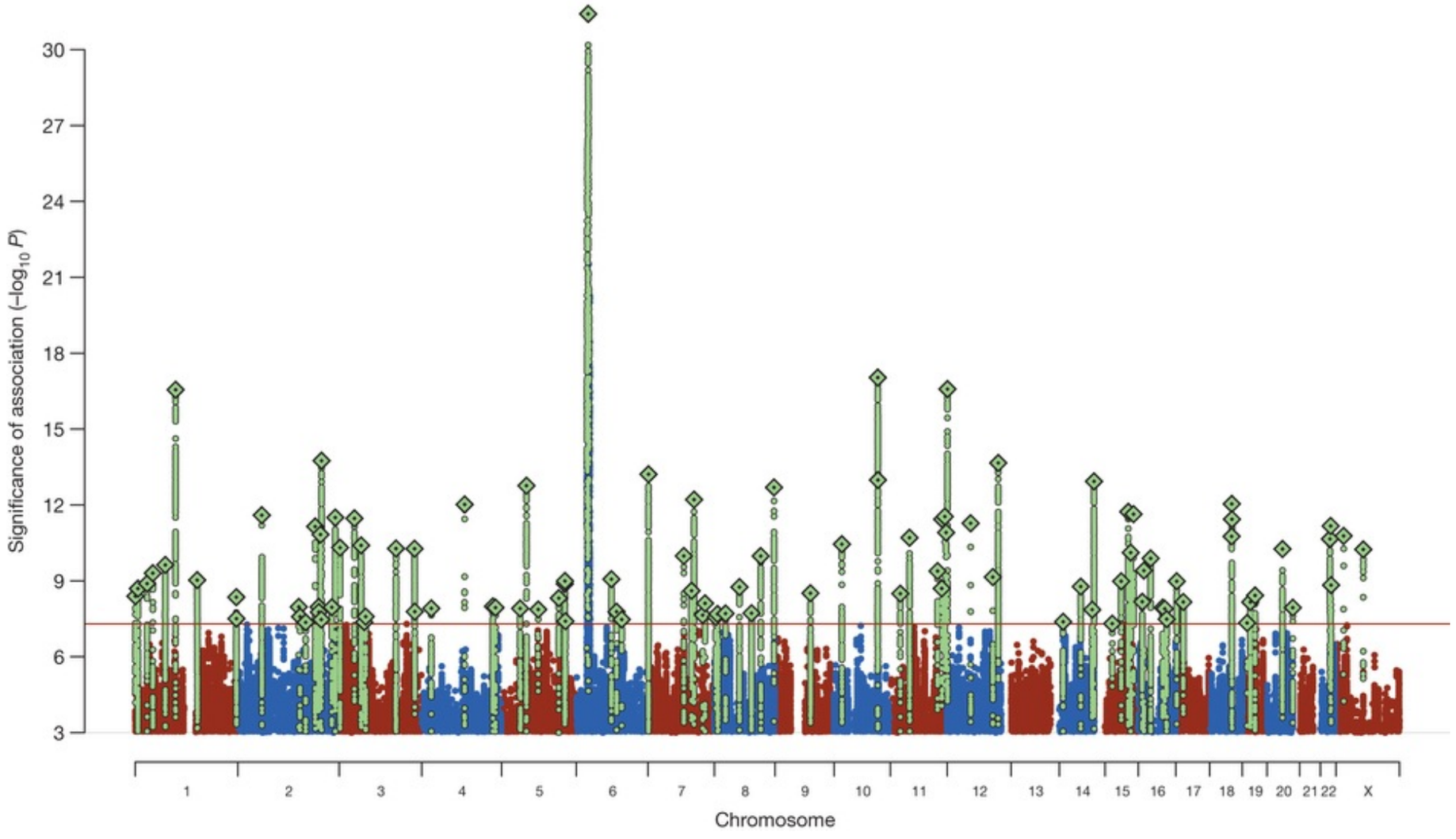

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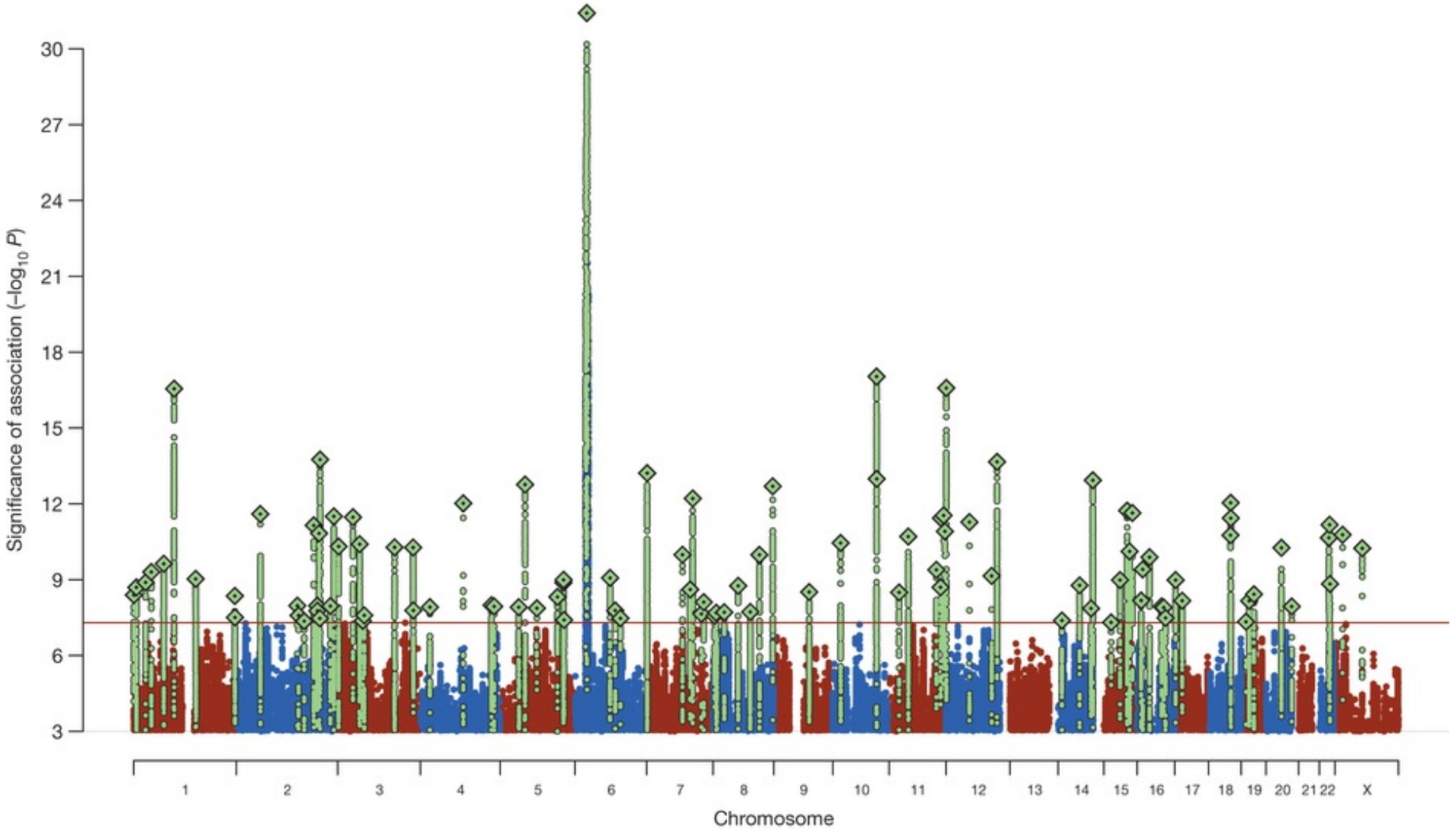

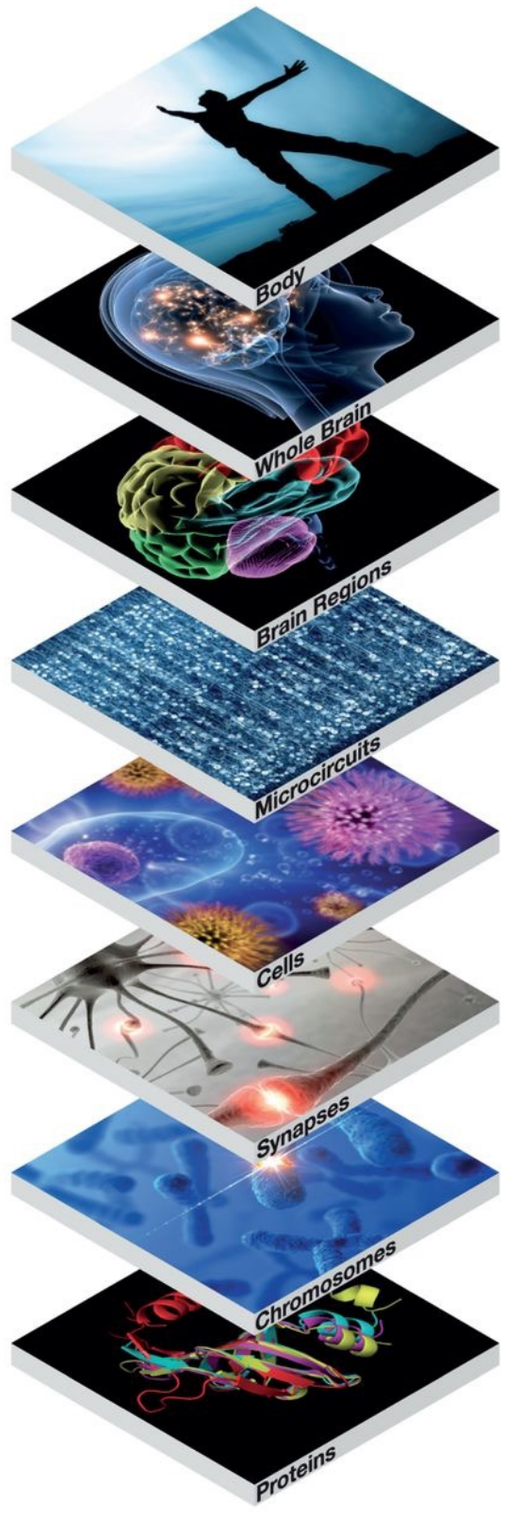

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  - Performance metric = R^2

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- Training and validation
  - 10-fold CV // 3 sets in training sample
  - Performance metric = R^2
- Training model applied without modification to validation sample

DEVELOPMENT OF SCHIZOPHRENIA

Millan et al., 2016, *Nature Rev Drug Discovery*

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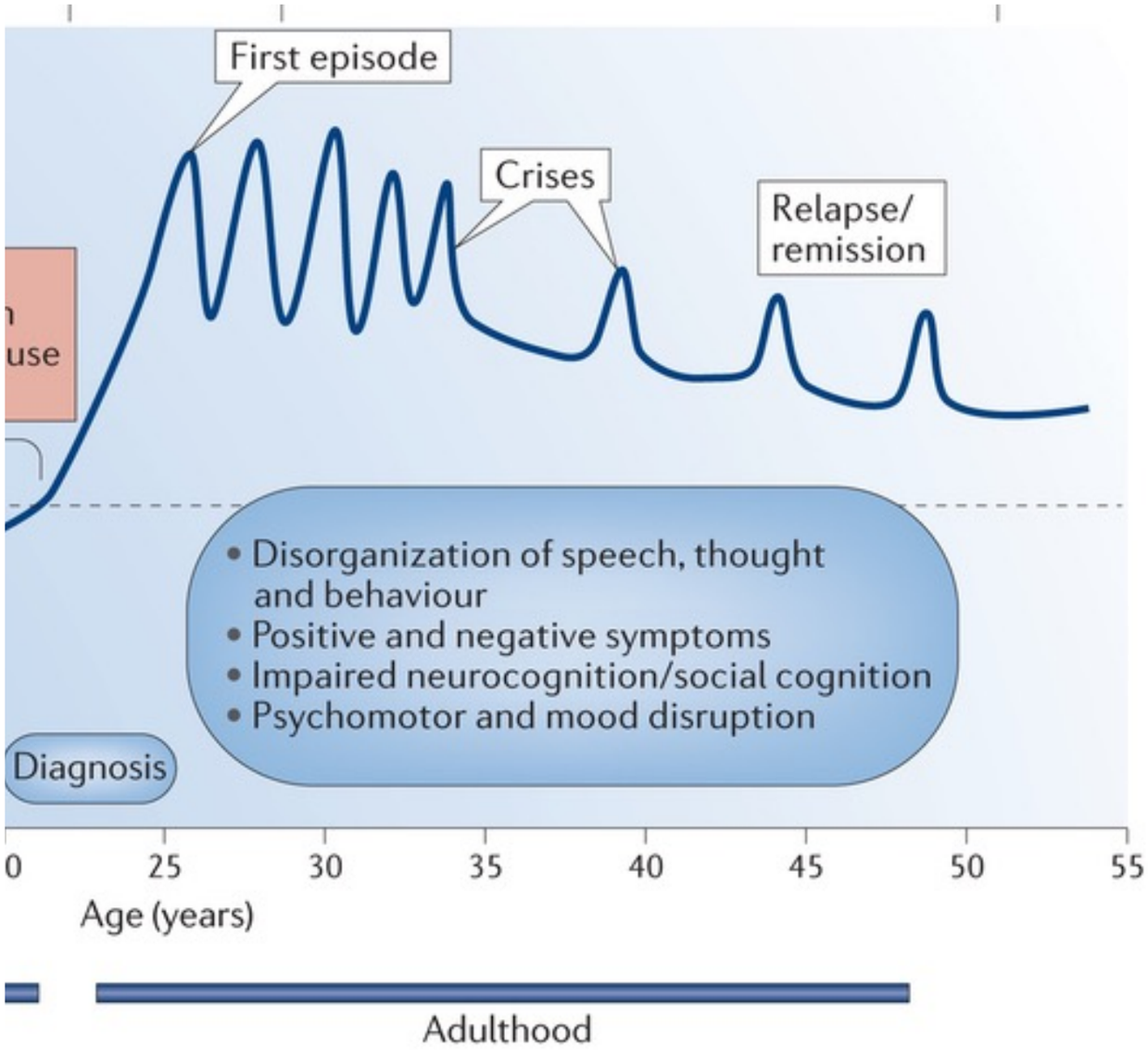

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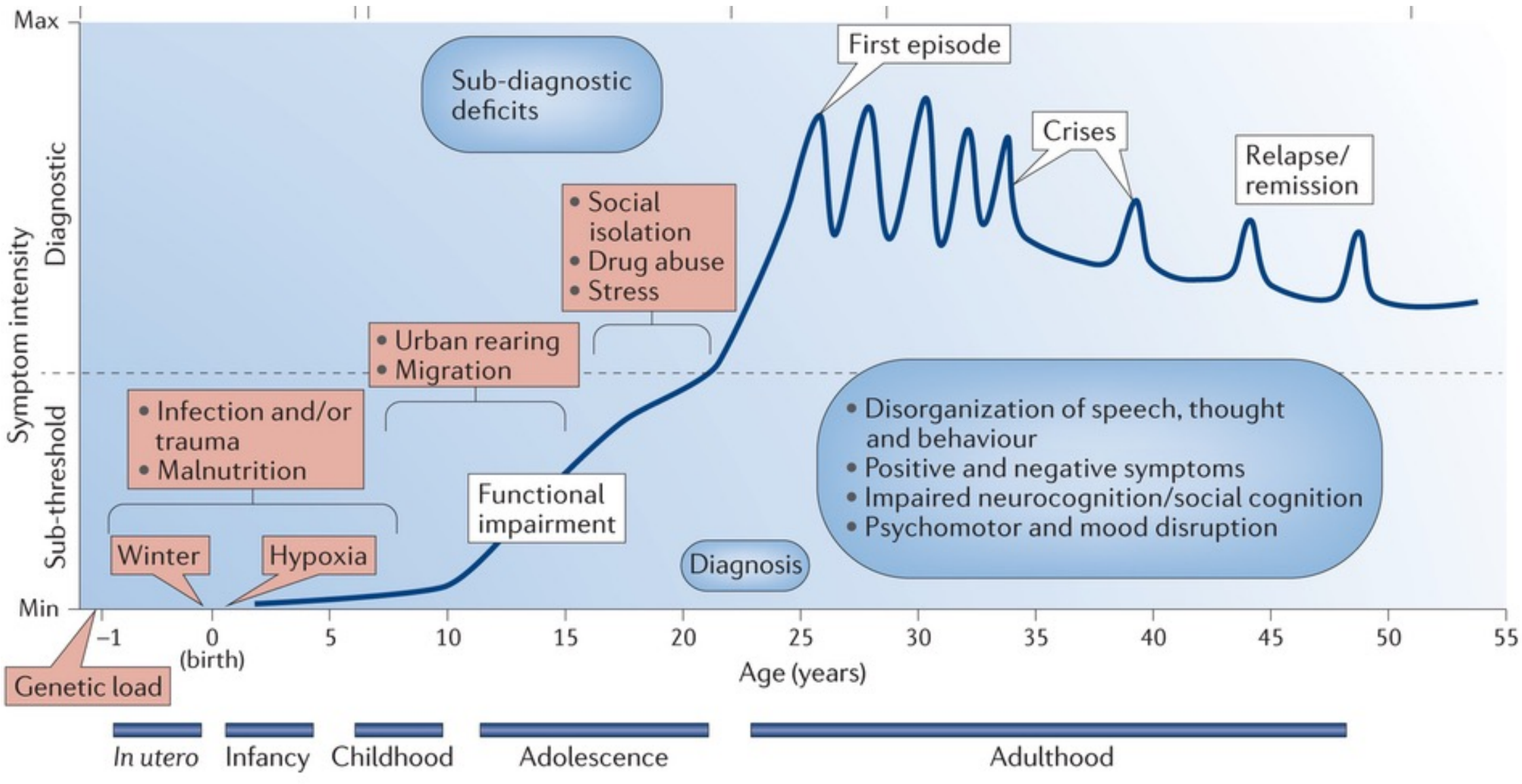

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FROM GENES TO BEHAVIOR

Ripke et al., 2014, *Nature*

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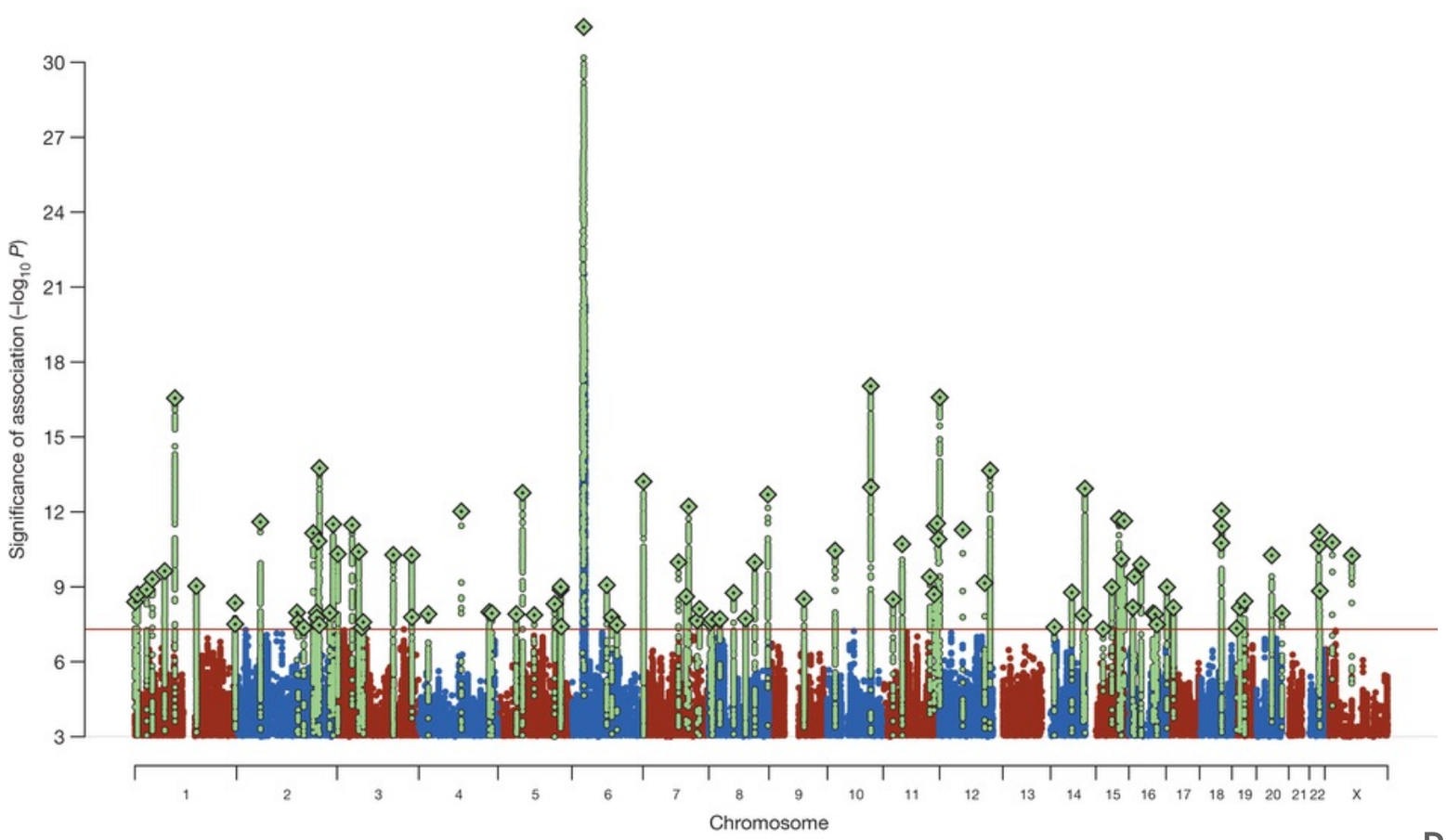

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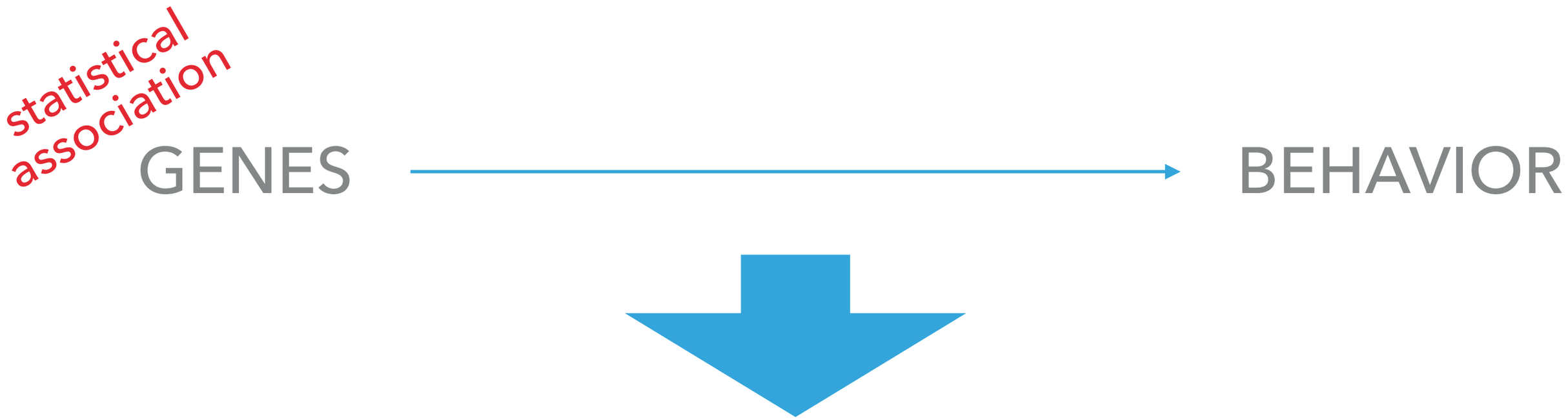
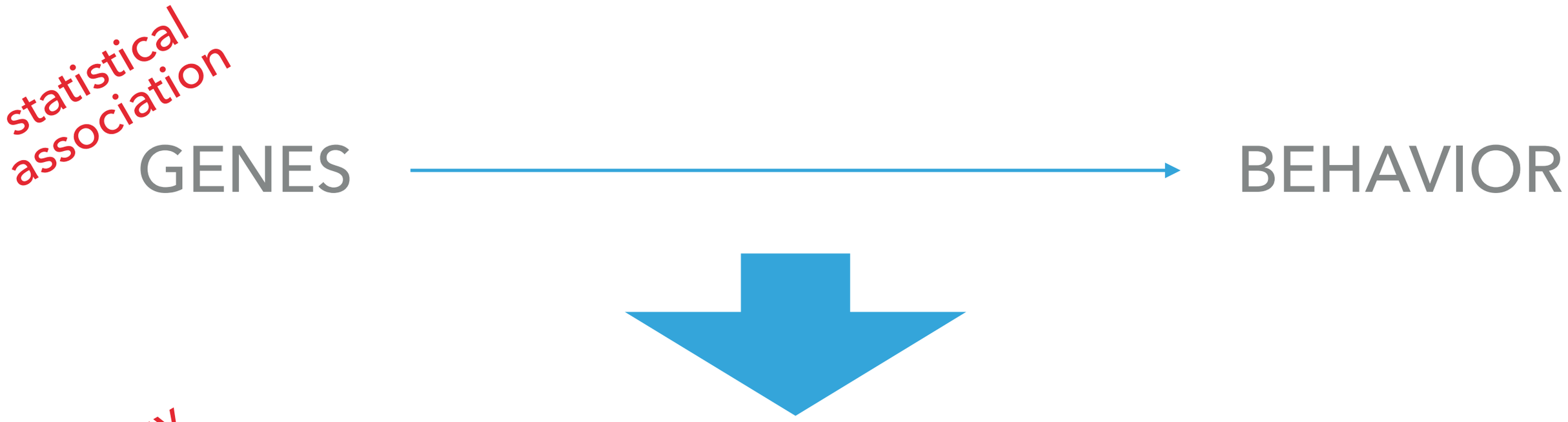


Ripke et al., 2014, *Nature*

FROM GENES TO BEHAVIOR



Ripke et al., 2014, *Nature*

FROM GENES TO BEHAVIOR

statistical association

GENES → BEHAVIOR

biology

GENES → BEHAVIOR

Ripke et al., 2014, *Nature*

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GENES ▸ BEHAVIOR

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GENES ▸ proteins → BEHAVIOR

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GENES ▸ proteins ▸ cells ▸ circuits ▸ networks ▸ BEHAVIOR

Ripke et al., 2014, *Nature*

FUNCTIONAL IMPLICATIONS

Derks et al., 2012, *PLoS One;* Fanous et al., 2012, *AJP;* Martin et al., 2015, *Psych Res;* Lencz et al., 2014, *Mol Psych;* Hatzimanolis et al., 2015, *AJMG B Neuropsych Gen;* Kauppi et al., 2015, *Schizophrenia Bull;* Whalley et al., 2013, *Biol Psych;* van Scheltinga et al., 2013, *Biol Psych;* Heck et al., 2014, *Neuron*

FUNCTIONAL IMPLICATIONS

GENES ▸ proteins ▸ cells ▸ circuits ▸ networks ▸ BEHAVIOR

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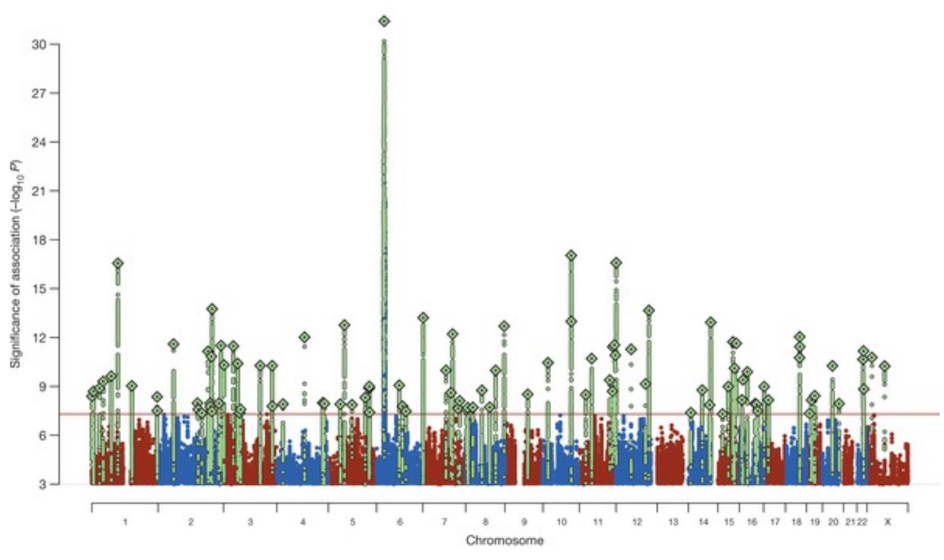
FUNCTIONAL IMPLICATIONS



GENES ▸ proteins ▸ cells ▸ circuits ▸ networks ▸ BEHAVIOR

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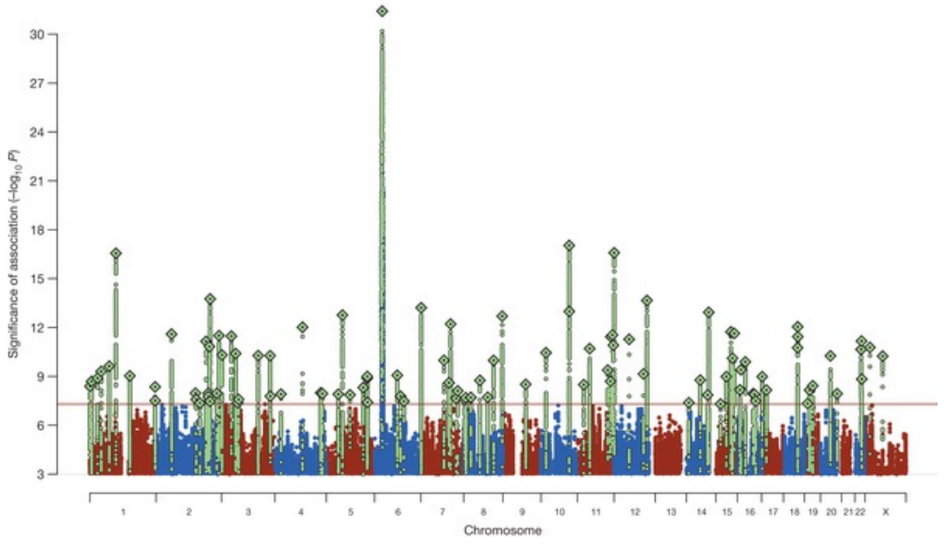
FUNCTIONAL IMPLICATIONS



GENES ▸ proteins ▸ cells ▸ circuits ▸ networks ▸ BEHAVIOR

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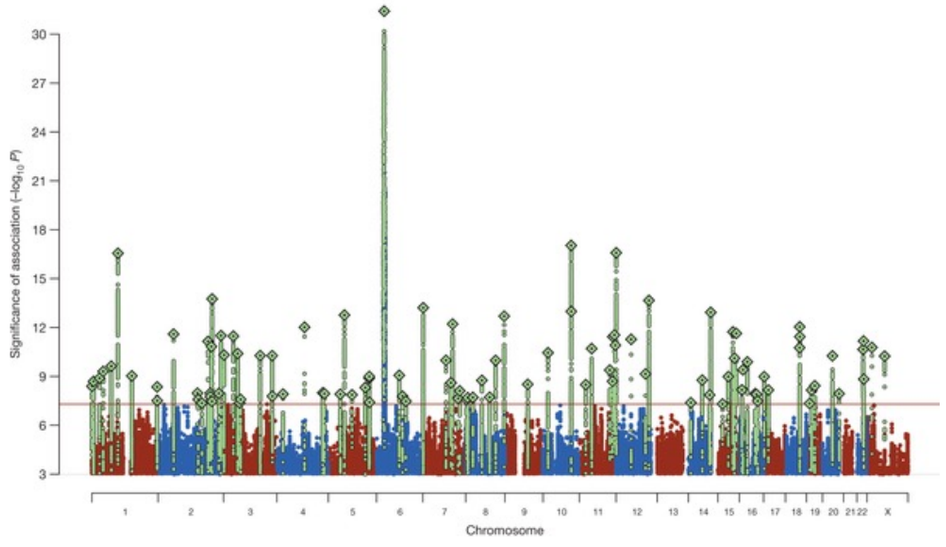
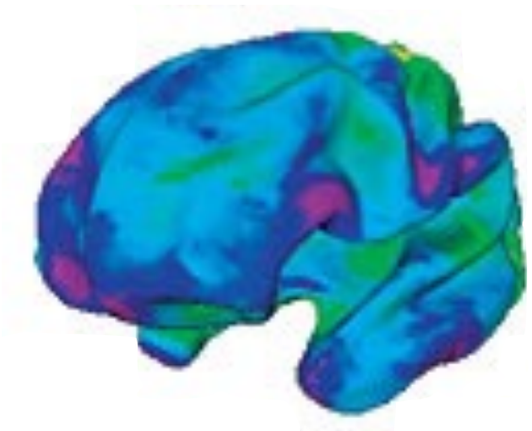
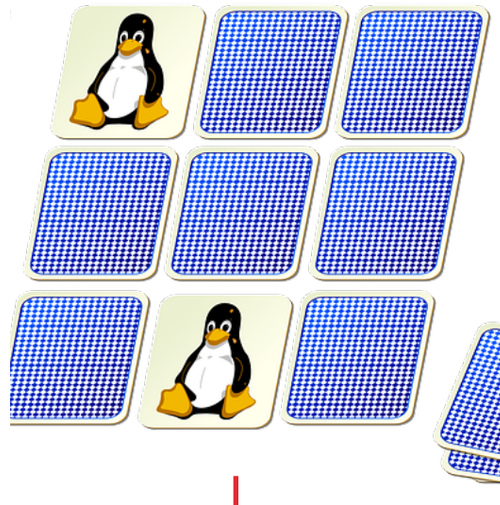
FUNCTIONAL IMPLICATIONS







GENES ▸ proteins ▸ cells ▸ circuits ▸ networks ▸ BEHAVIOR

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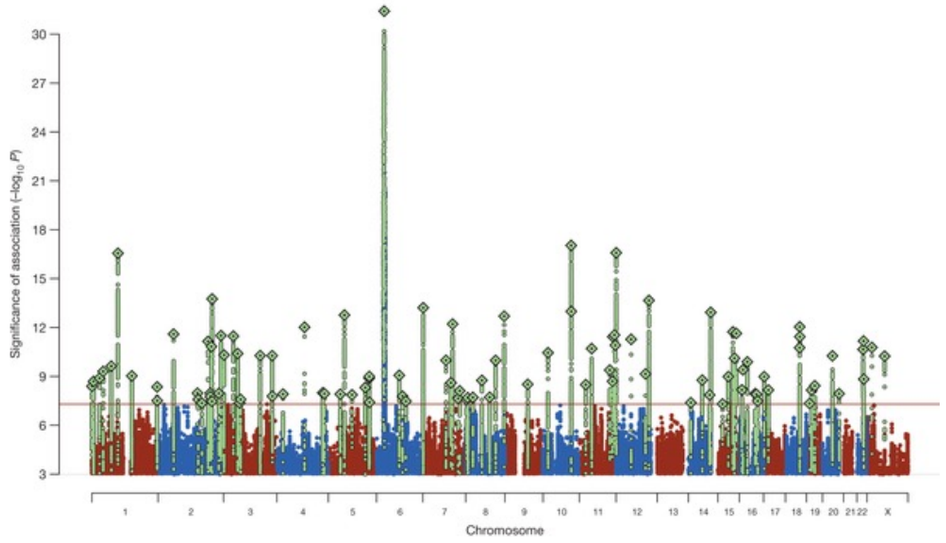
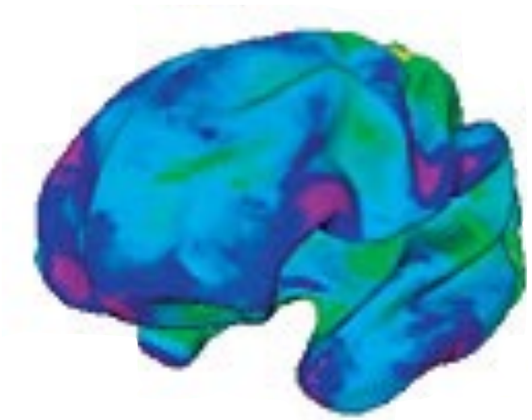
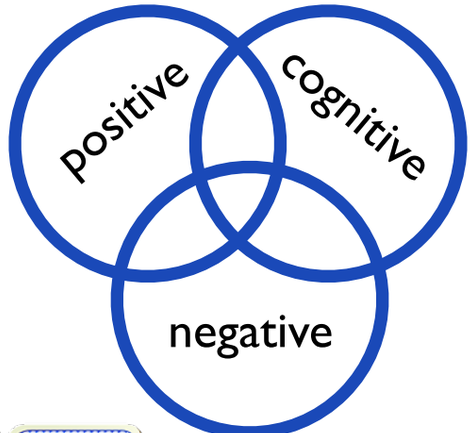
FUNCTIONAL IMPLICATIONS







GENES ▸ proteins ▸ cells ▸ circuits ▸ networks ▸ BEHAVIOR

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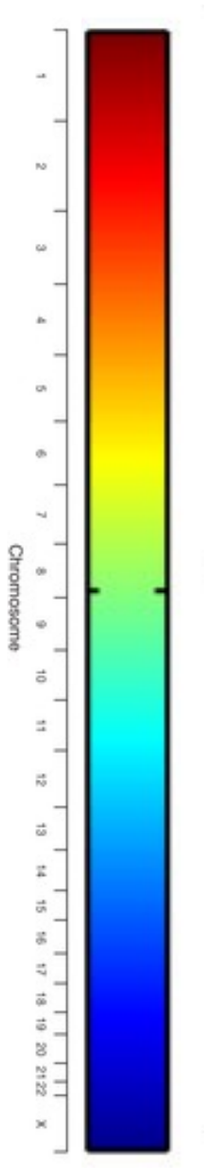
GENOTYPIC PATTERNS

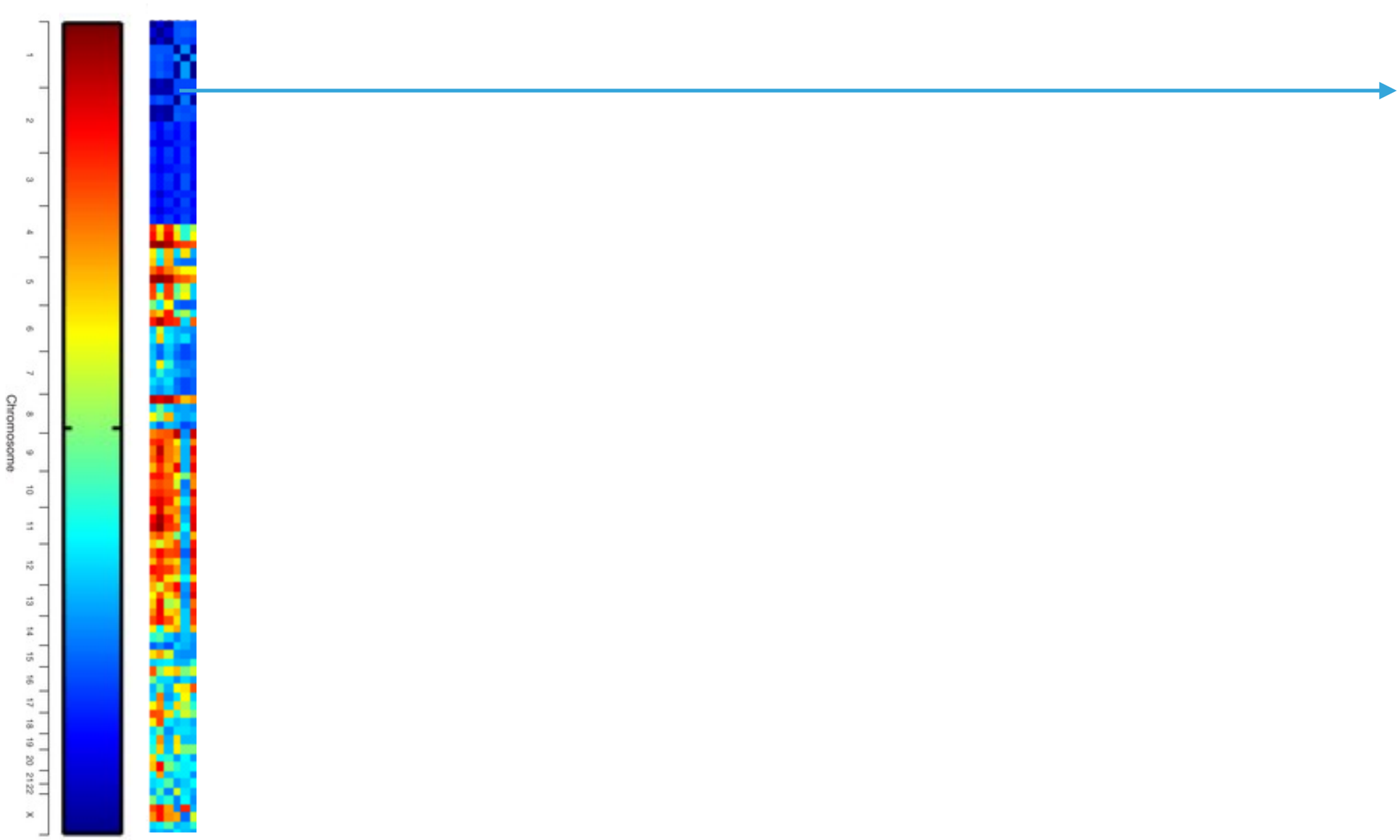
GENES ▸ proteins ▸ cells ▸ circuits ▸ networks ▸ BEHAVIOR

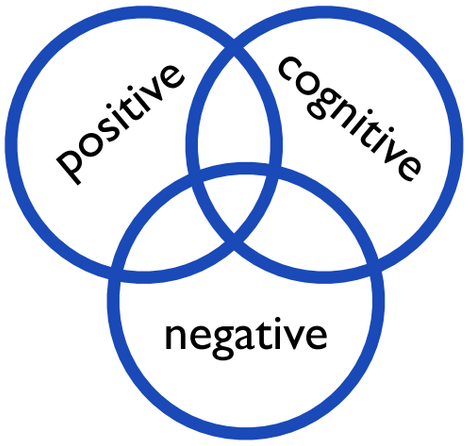
GENOTYPIC PATTERNS



GENES ▸ proteins ▸ cells ▸ circuits ▸ networks ▸ BEHAVIOR

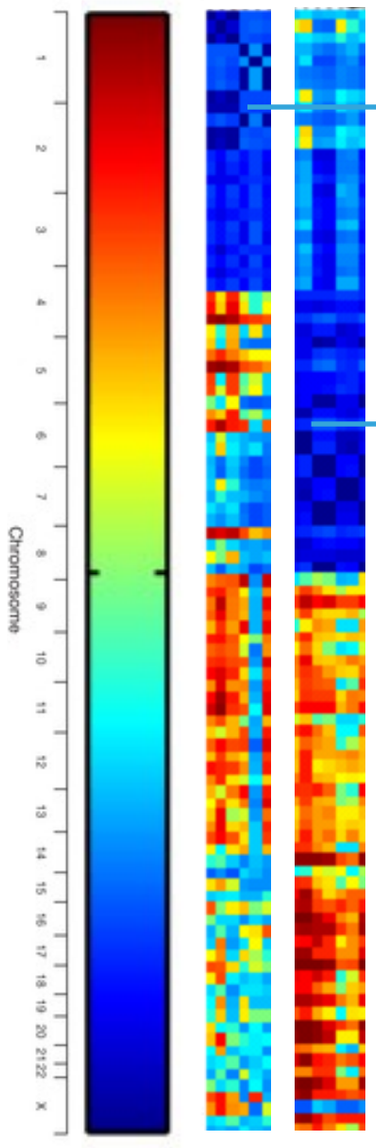
GENOTYPIC PATTERNS

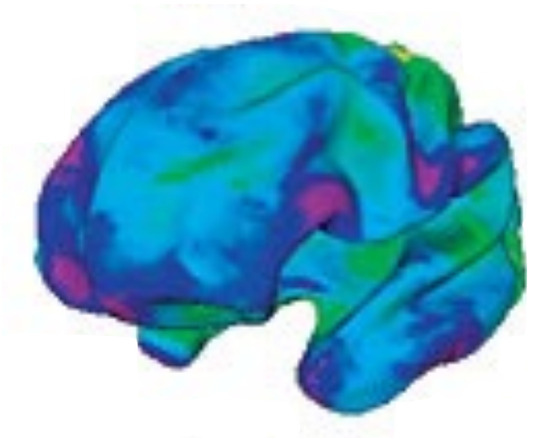


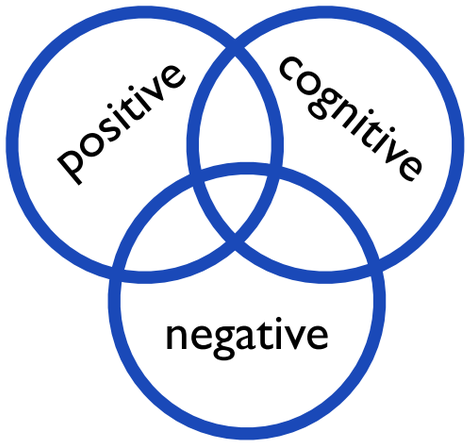


GENES ▸ proteins ▸ cells ▸ circuits ▸ networks ▸ BEHAVIOR

GENOTYPIC PATTERNS







GENES ▸ proteins ▸ cells ▸ circuits ▸ networks ▸ BEHAVIOR

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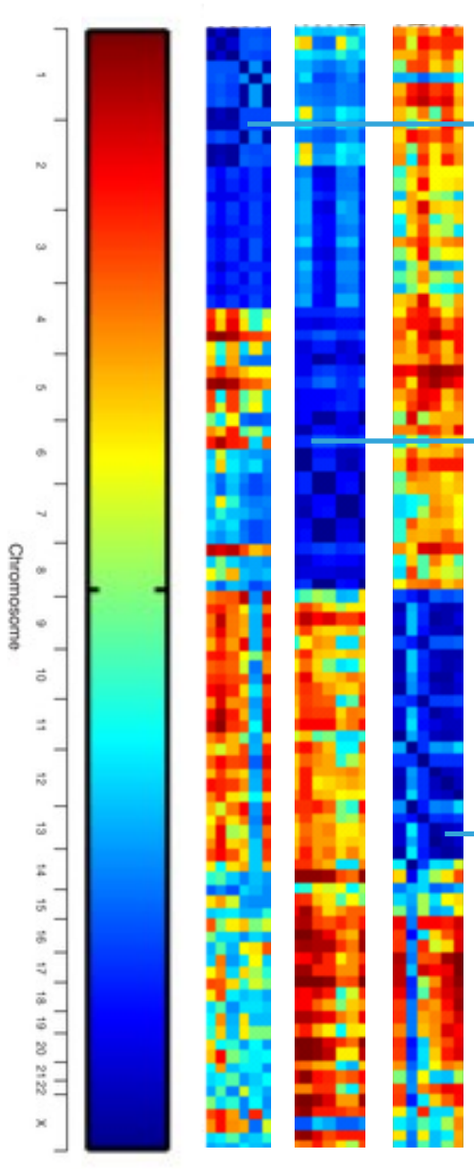

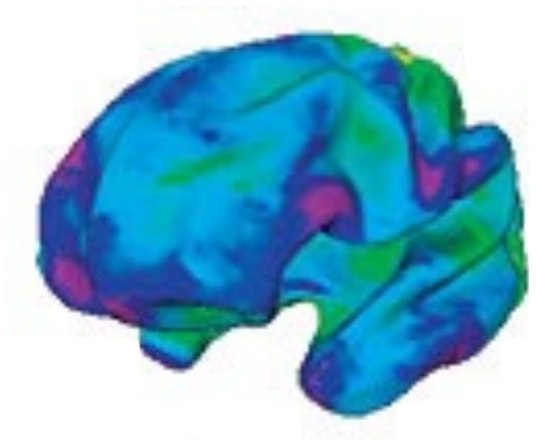

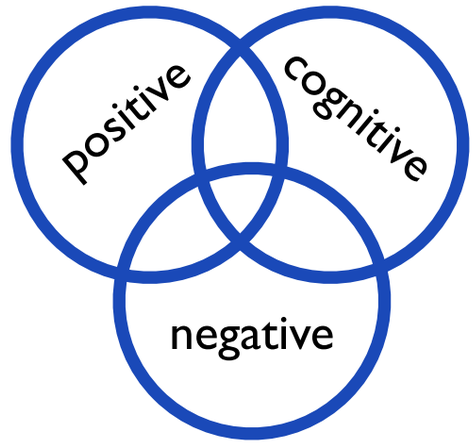

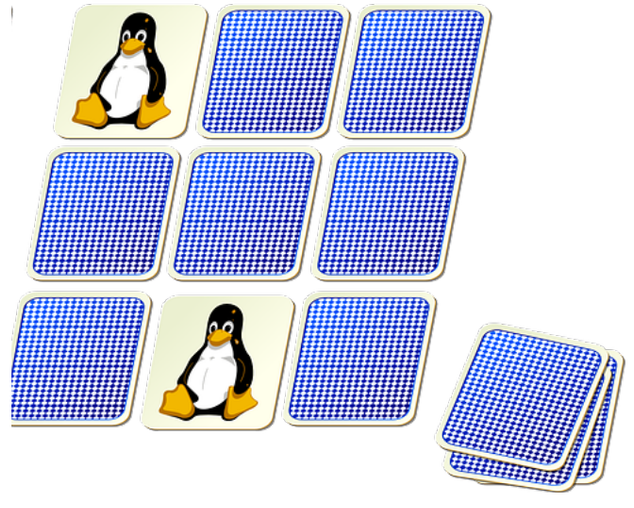

GENES ▸ proteins ▸ cells ▸ circuits ▸ networks ▸ BEHAVIOR

FUNCTIONAL CHARACTERIZATION

Derks et al., 2012, *PLoS One;* Fanous et al., 2012, *AJP;* Martin et al., 2015, *Psych Res;* Lencz et al., 2014, *Mol Psych;* Hatzimanolis et al., 2015, *AJMG B Neuropsych Gen;* Kauppi et al., 2015, *Schizophrenia Bull;* Whalley et al., 2013, *Biol Psych;* van Scheltinga et al., 2013, *Biol Psych;* Heck et al., 2014, *Neuron*

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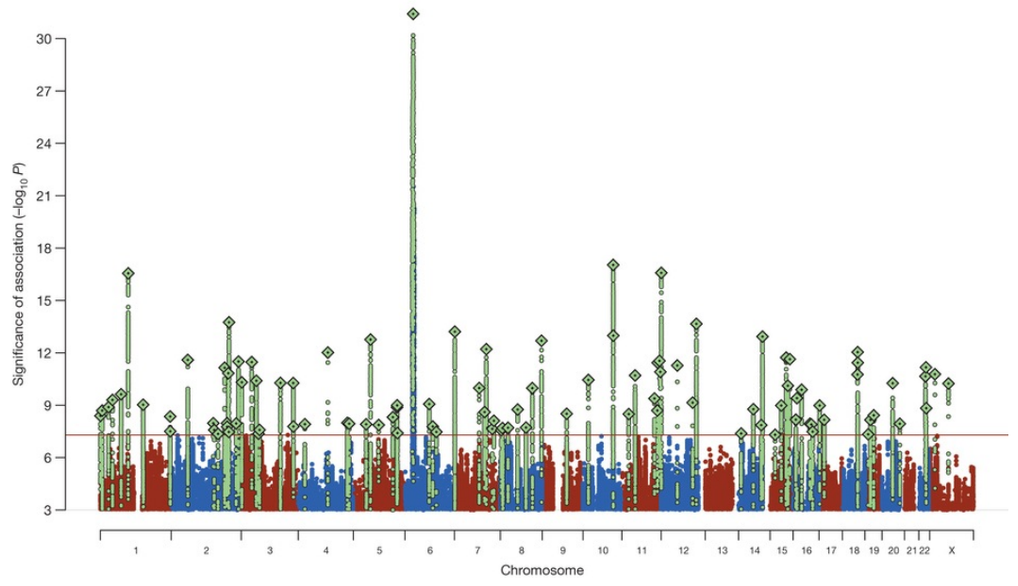

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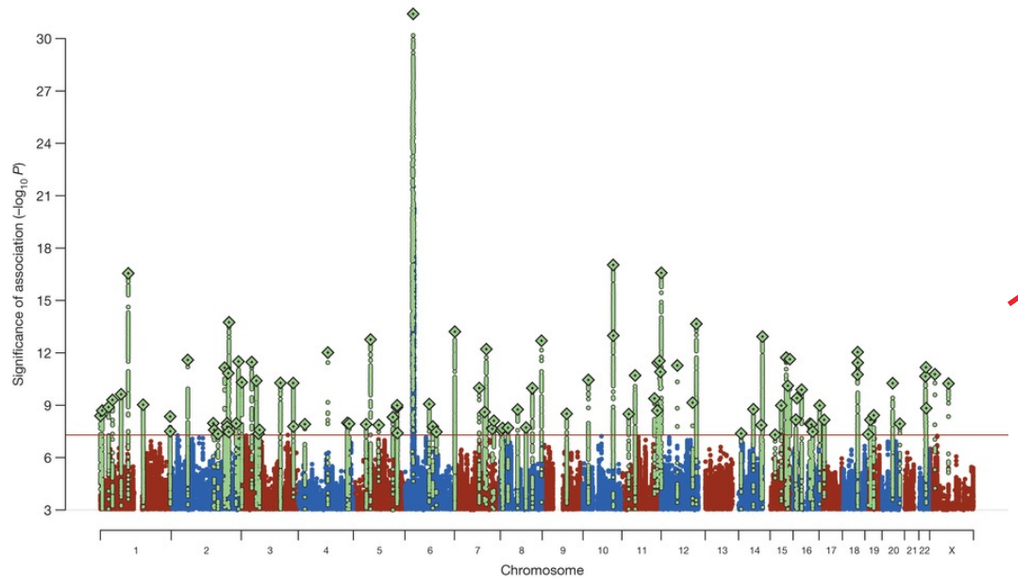

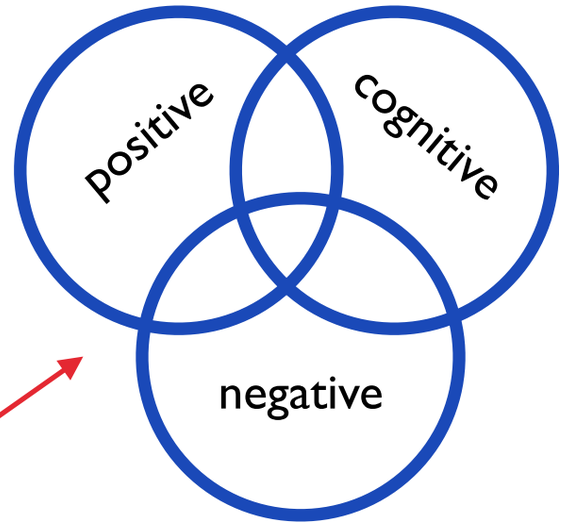

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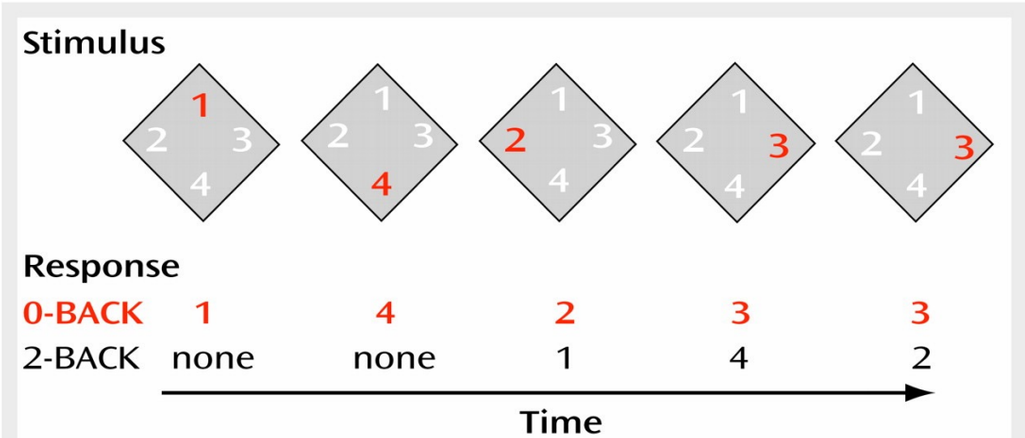

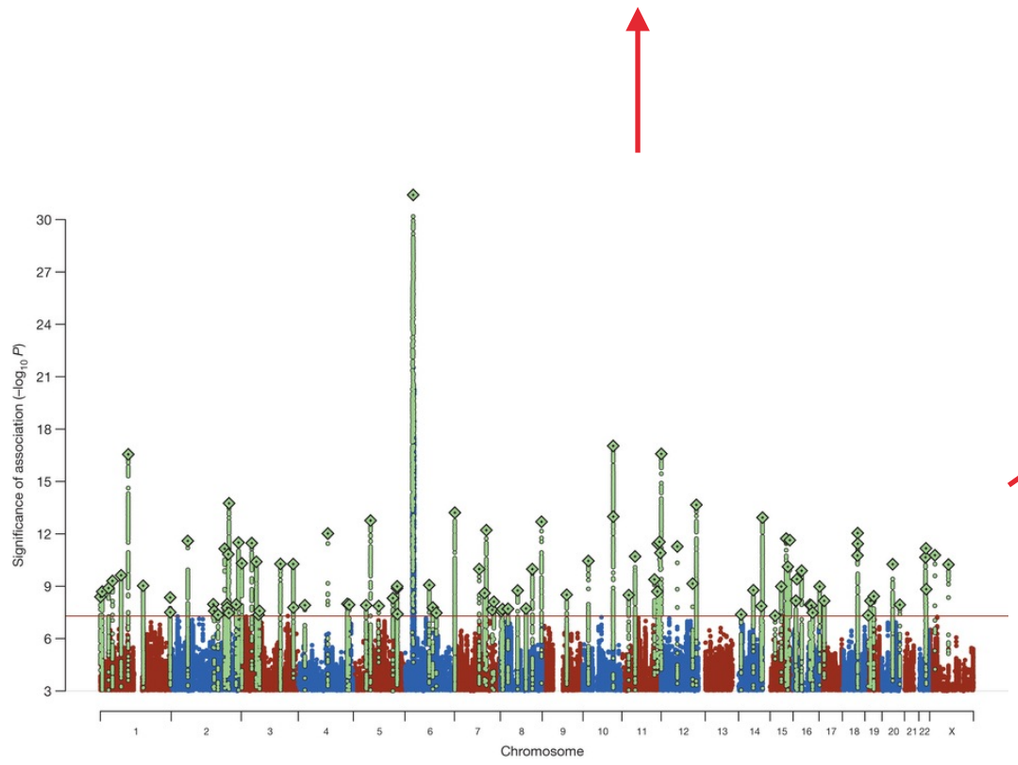

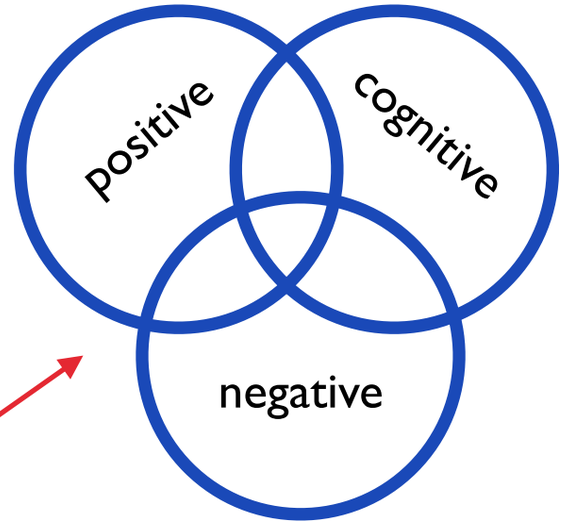

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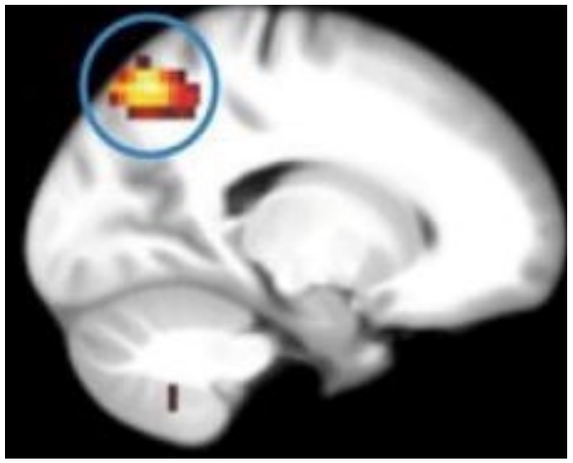

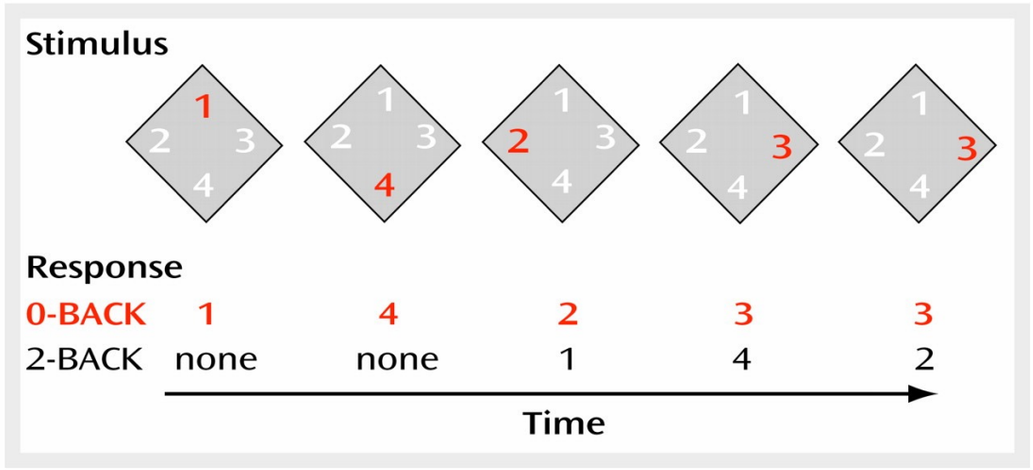

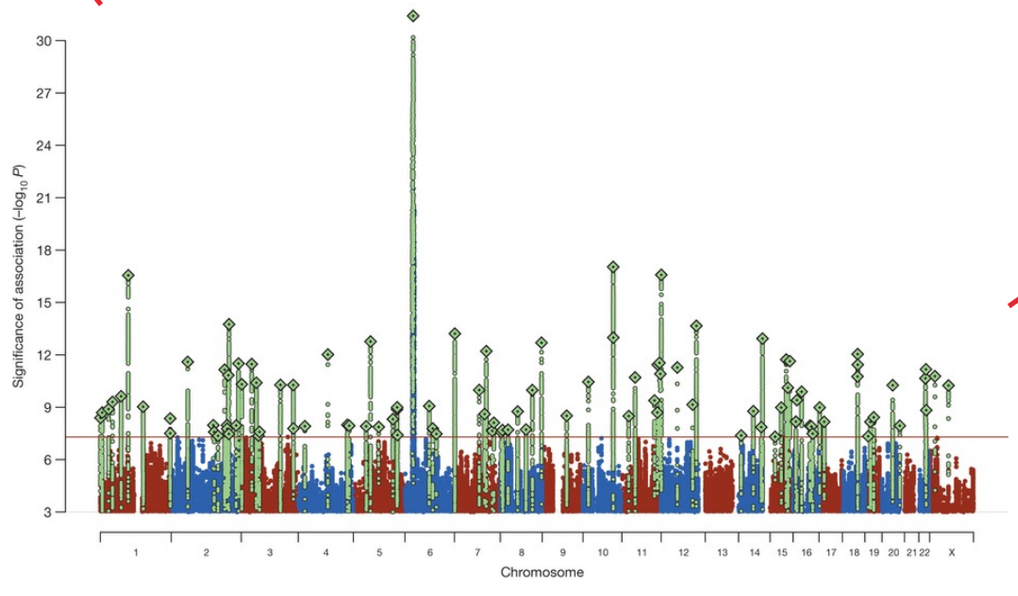

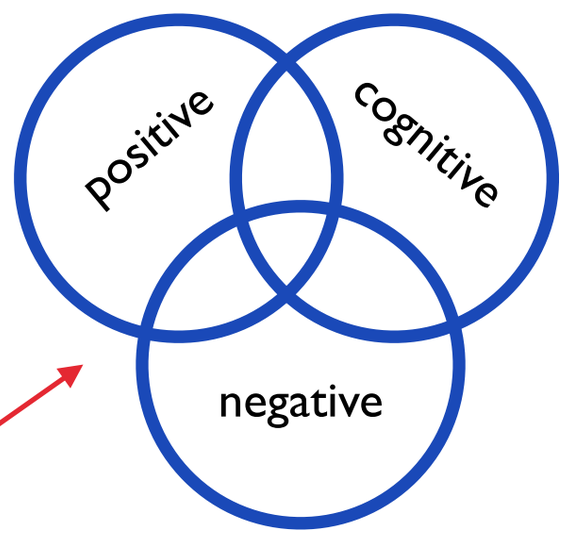

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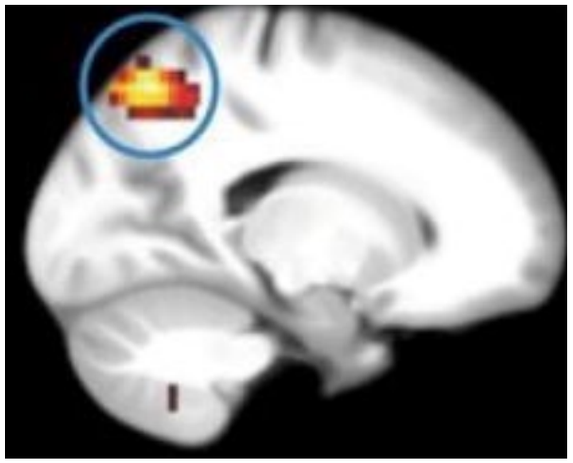

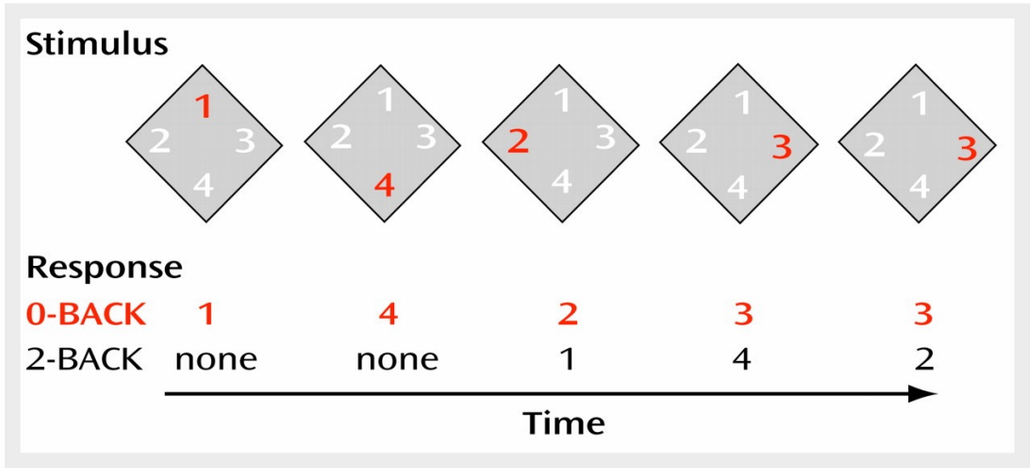

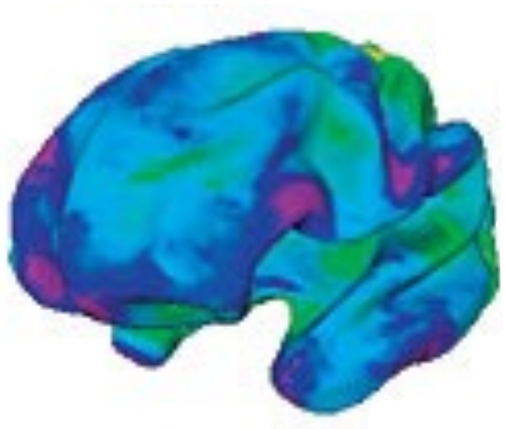

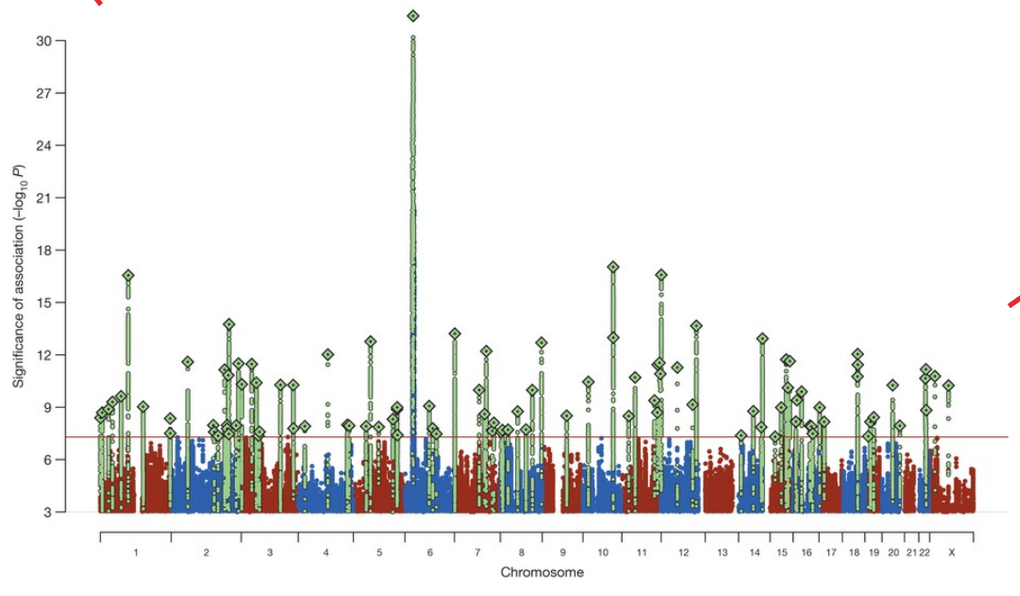

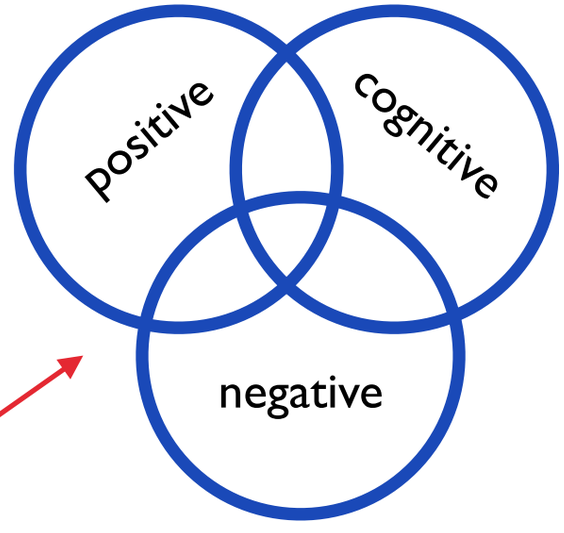

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