Genome-wide association study of cocaine use in Heterogeneous Stock rats

Montana Kay Lara

Palmer Lab

NIDA Center of Excellence for
Genetics, Genomics, and Epigenetics
of Substance Use Disorders in Outbred Rats

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Behavioral Genetics of Mice, Rats and Men

How do we explore the genetic underpinnings of behavior related to addiction?

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Phenotyping

Genotyping

Genetic Analysis

RATTACA

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Behavioral Genetics of Mice, Rats and Men

Phenotyping — Genotyping — Genetic Analysis — RATTACA

Can we identify genetic factors mediating susceptibility or resilience to substance use disorder (SUD)?

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Behavioral Genetics of Mice, Rats and Men

Phenotyping — Genotyping — Genetic Analysis — RATTACA

Can we identify genetic factors mediating susceptibility or resilience to substance use disorder (SUD)?
Specifically, ***cocaine use disorder (CUD)***

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Heterogeneous Stock (HS) Rats

Leah Solberg Woods,
Wake Forest University
School of Medicine

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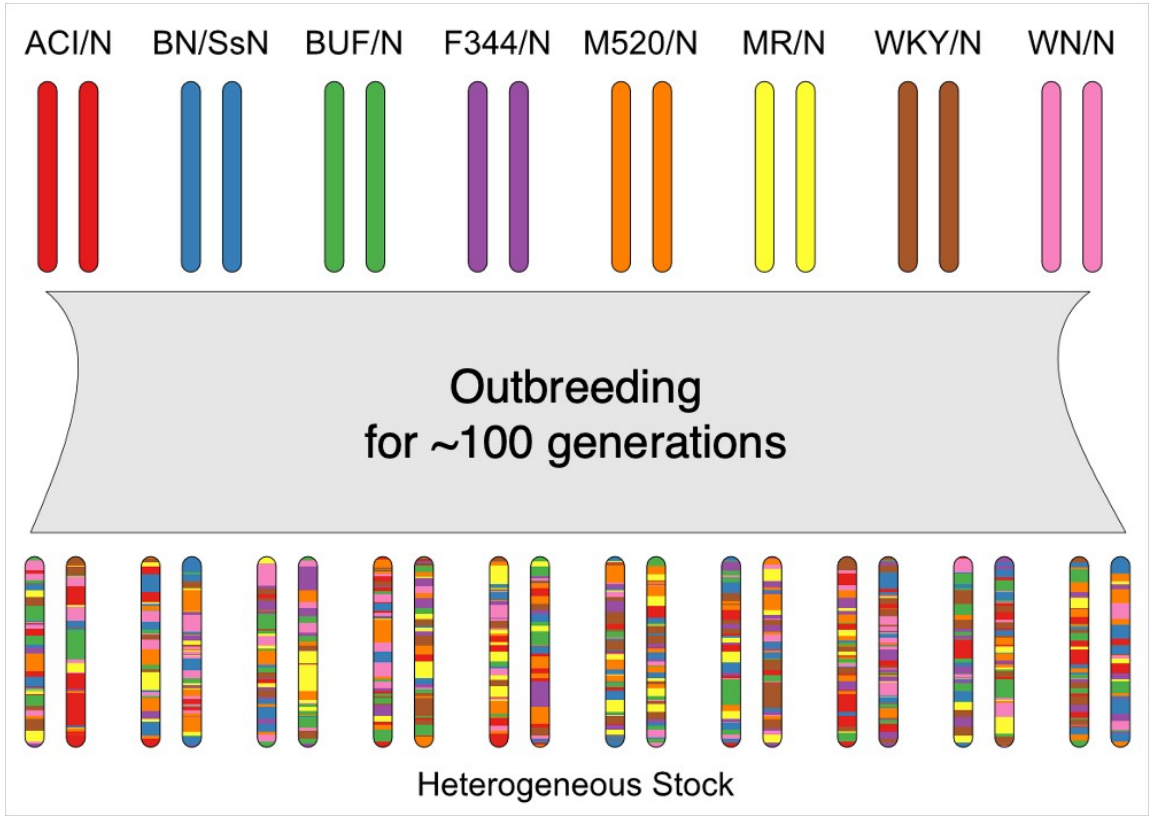
HS West



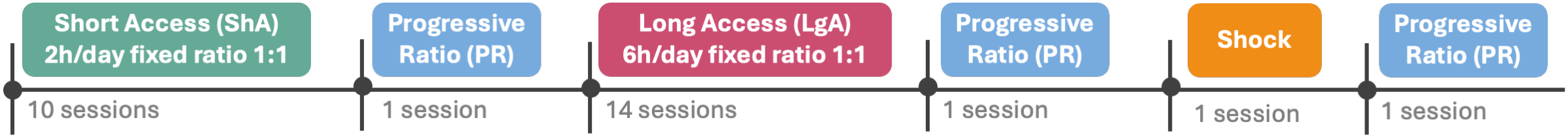
High degree of **genetic and phenotypic diversity** for high-resolution genetic mapping of complex traits

Behavioral phenotyping

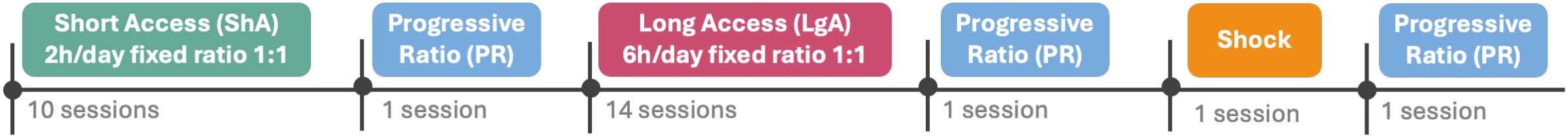
Olivier George and co.

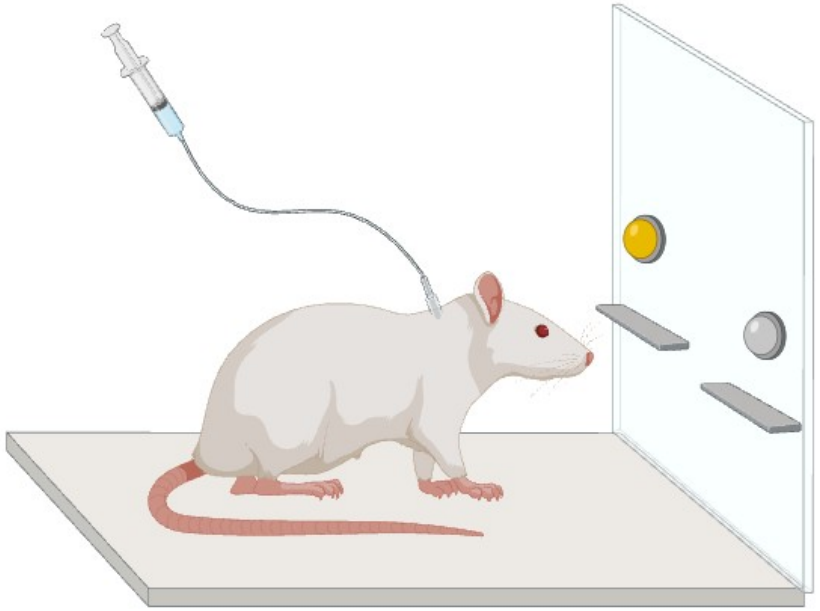
Olivier George
Lieselot L. G. Carrette
Giordano de Guglielmo
Marsida Kallupi
Molly Brennan
Alex Morgan
Dyar Othman
Benjamin Sichel
Selene Bonnet-Zahedi
Brent Boomhower
Dana Elizabeth Conlisk
McKenzie Fannon
Adam Jacob Kimbrough
Angelica Renee Martinez
Lisa Maturin
Jarryd Ramborger
Paul Schweitzer
Kokila Shankar
Sierra Simpson
Lauren Cassandra Smith
Elizabeth A. Sneddon

Cocaine self-administration

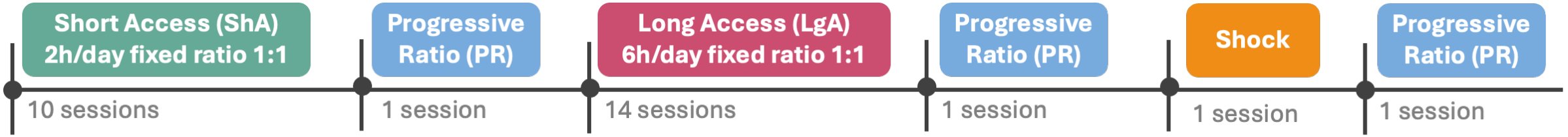


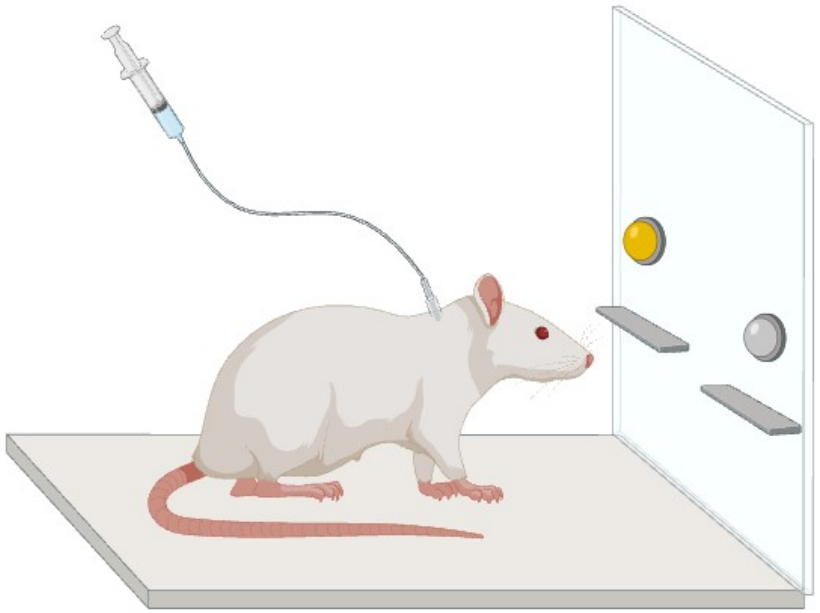
Cocaine self-administration





Cocaine self-administration





- **Escalation** of intake - increased cocaine use over time
- **Motivation** – continued responding despite exponential increase in cost
- **Compulsivity** – continued responding despite adverse consequences

Behavioral phenotyping

Short Access (ShA)
2h/day fixed ratio 1:1
10 sessions

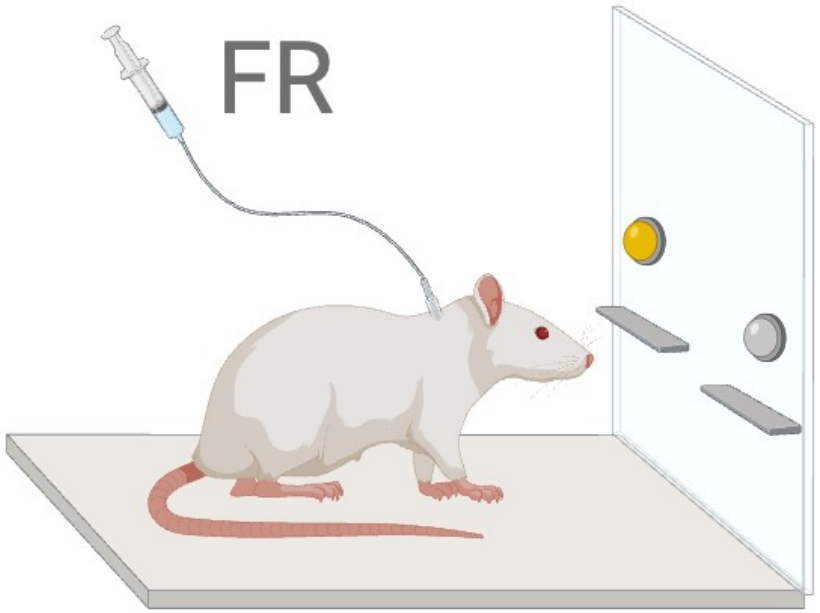
Progressive Ratio (PR)
1 session

Long Access (LgA)
6h/day fixed ratio 1:1
14 sessions

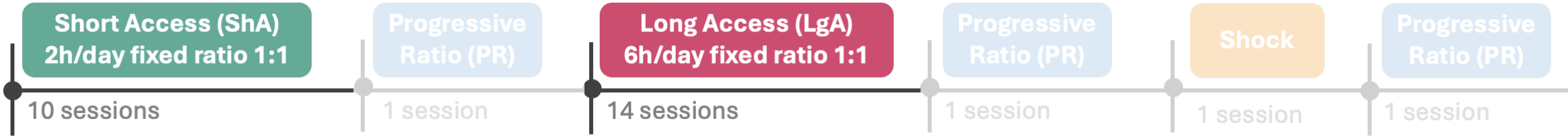
Progressive Ratio (PR)
1 session

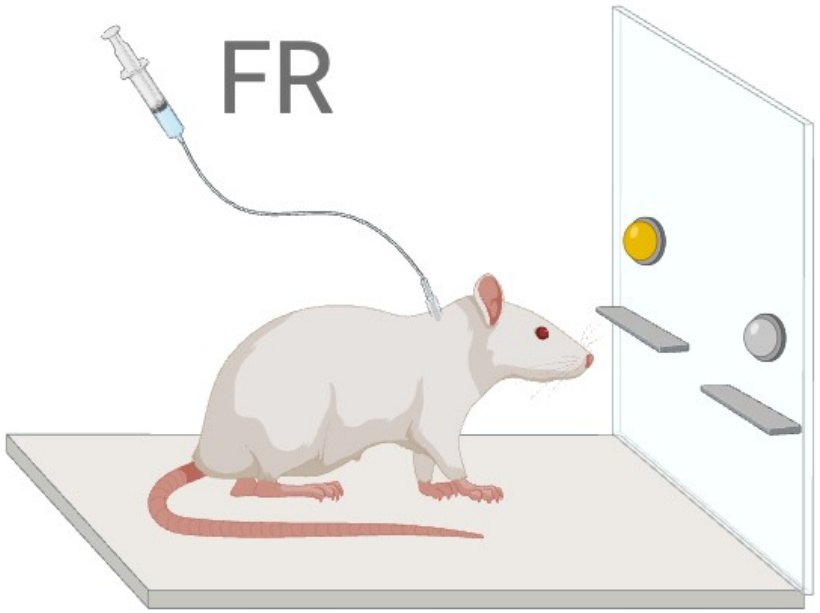
Shock
1 session

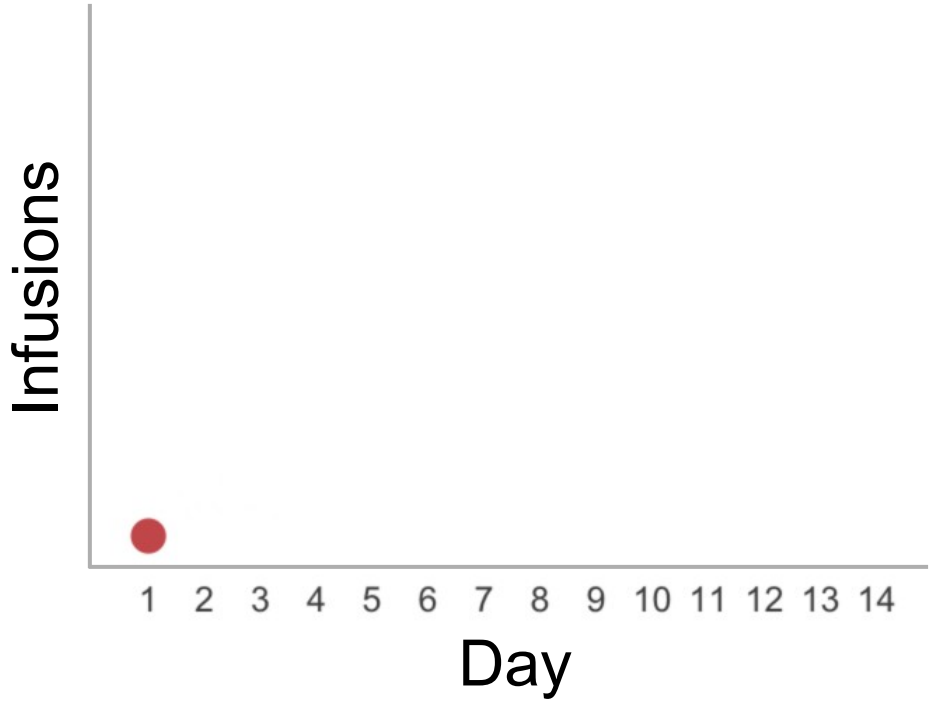
Progressive Ratio (PR)
1 session



Behavioral phenotyping

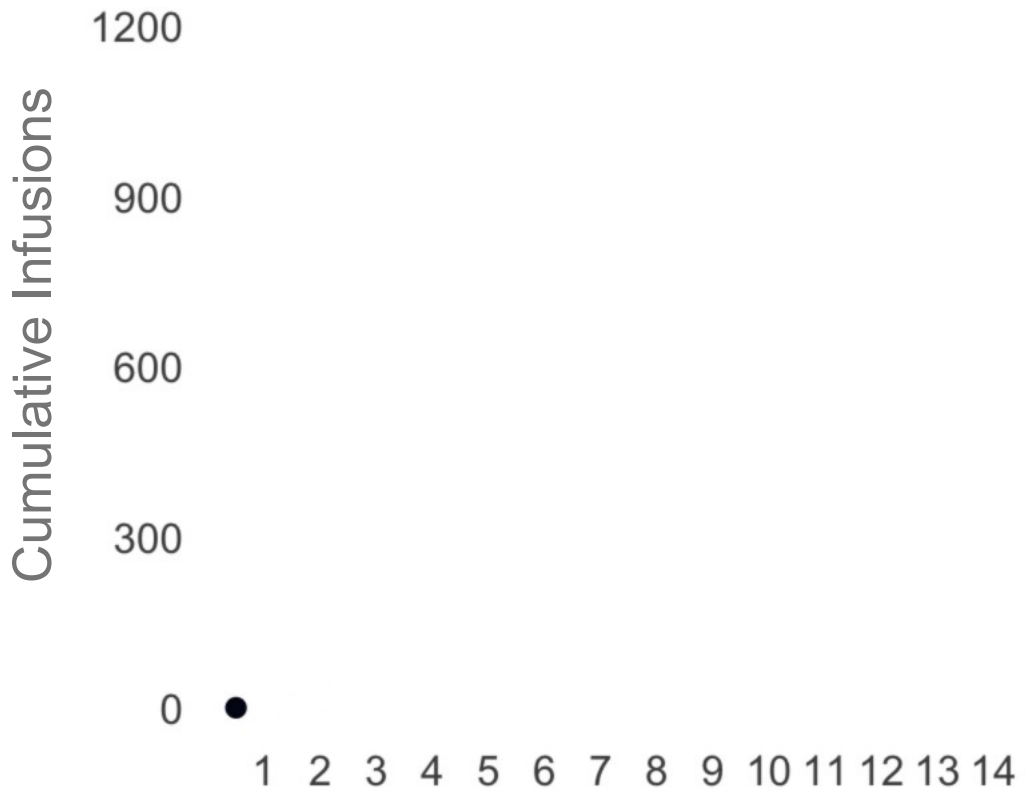






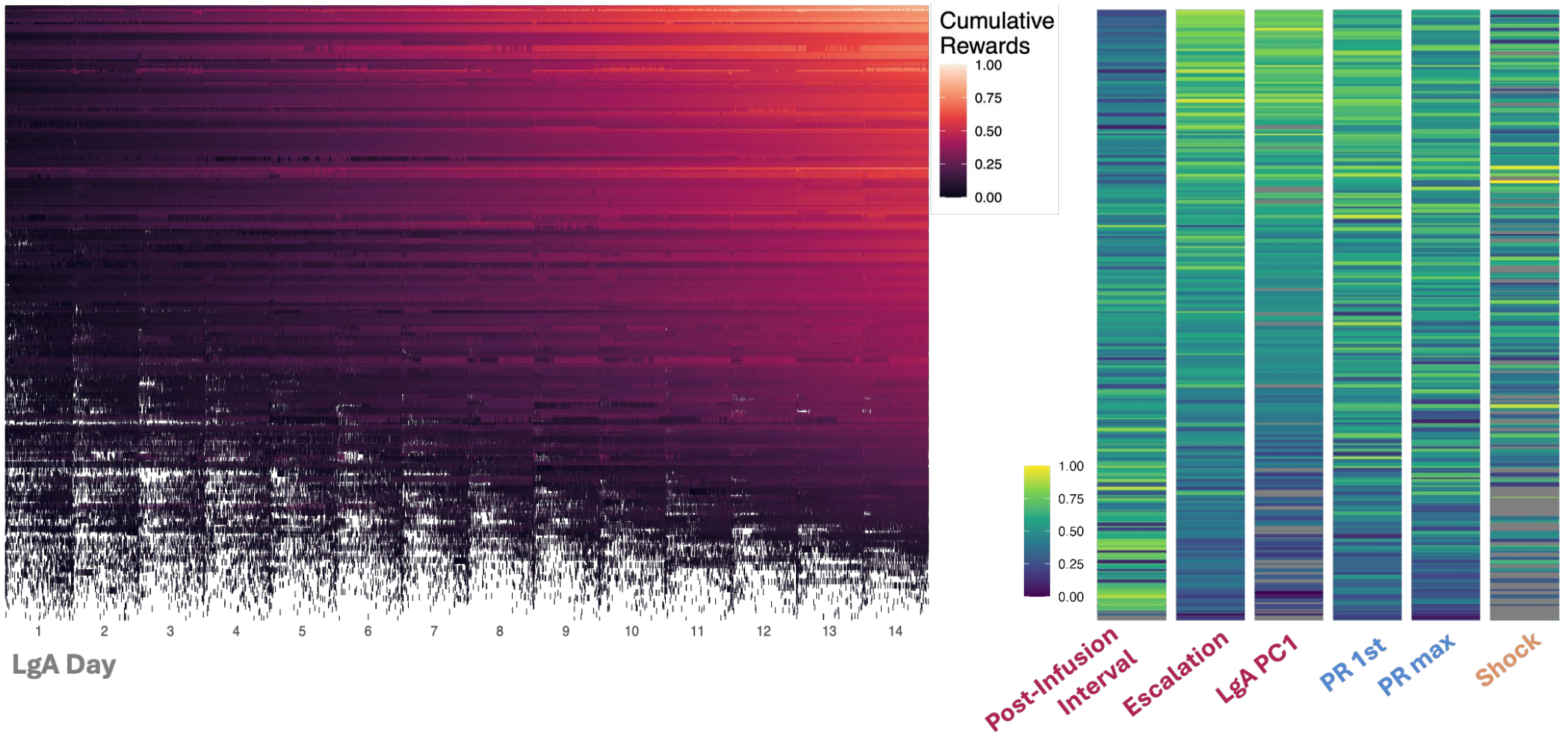
Behavioral phenotyping

Infusions received

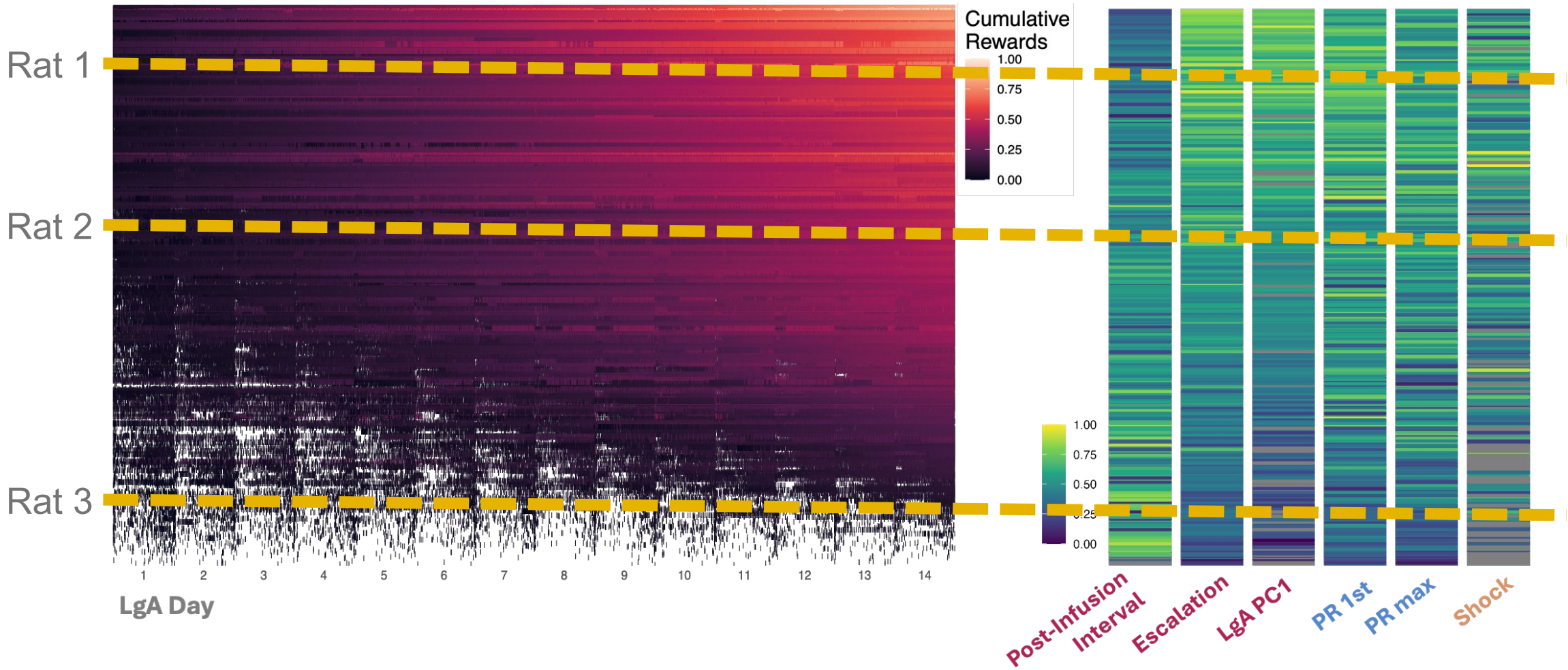


Behavioral phenotyping

Behavioral phenotyping



Behavioral phenotyping



Behavioral phenotyping

Duration of time between presses (post infusion interval)

Behavioral phenotyping conclusion

~900 rats deeply phenotyped and included in this study

Phenotyping

Genotyping

Genetic Analysis

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KHAI-MINH H. NGUYEN, BS

YIZHI WANG, BS

NINA SUZUKI, BS

RUDY AVILA, BS

Phenotyping

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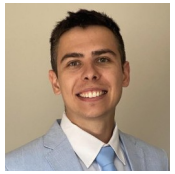
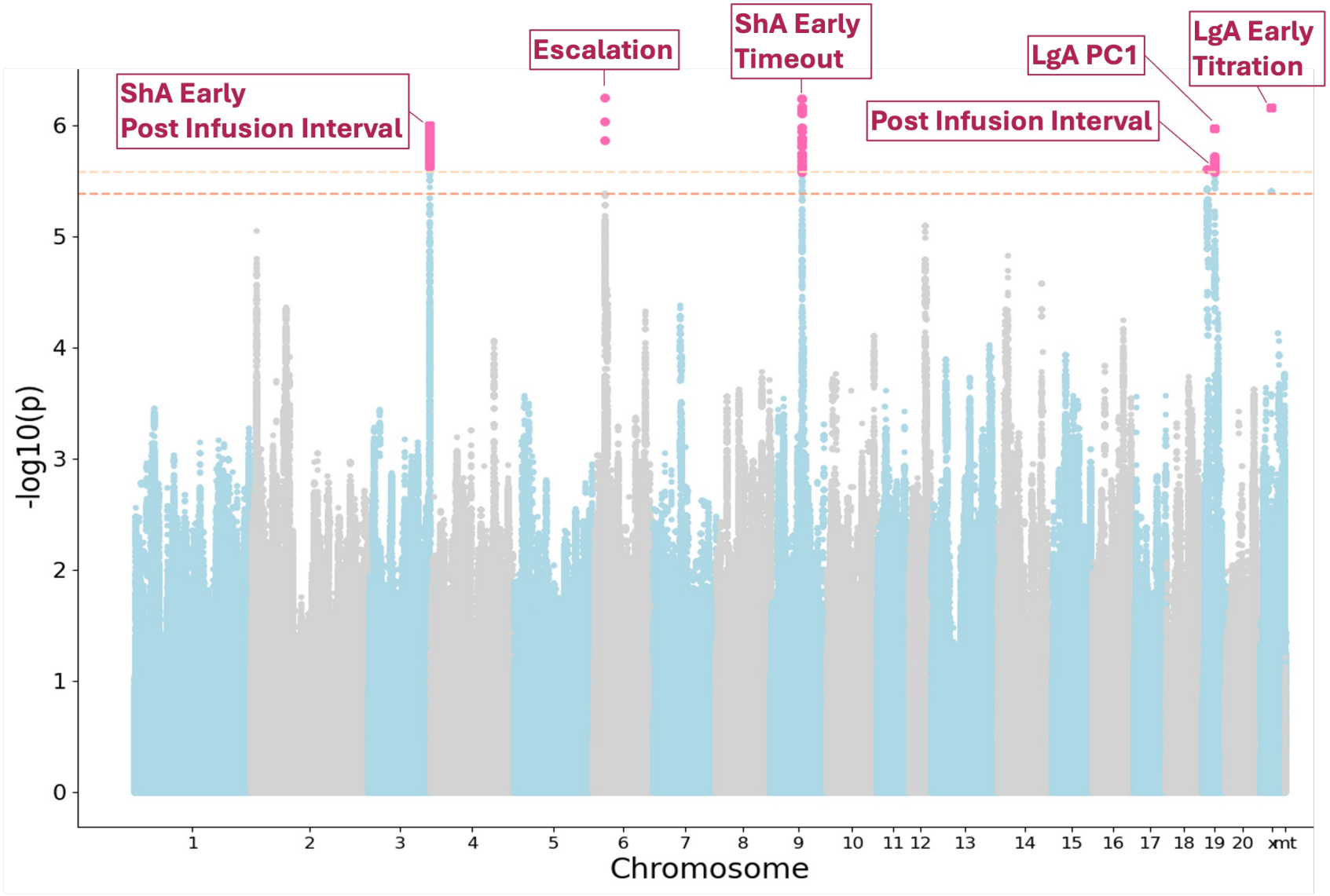


Genome-wide association study



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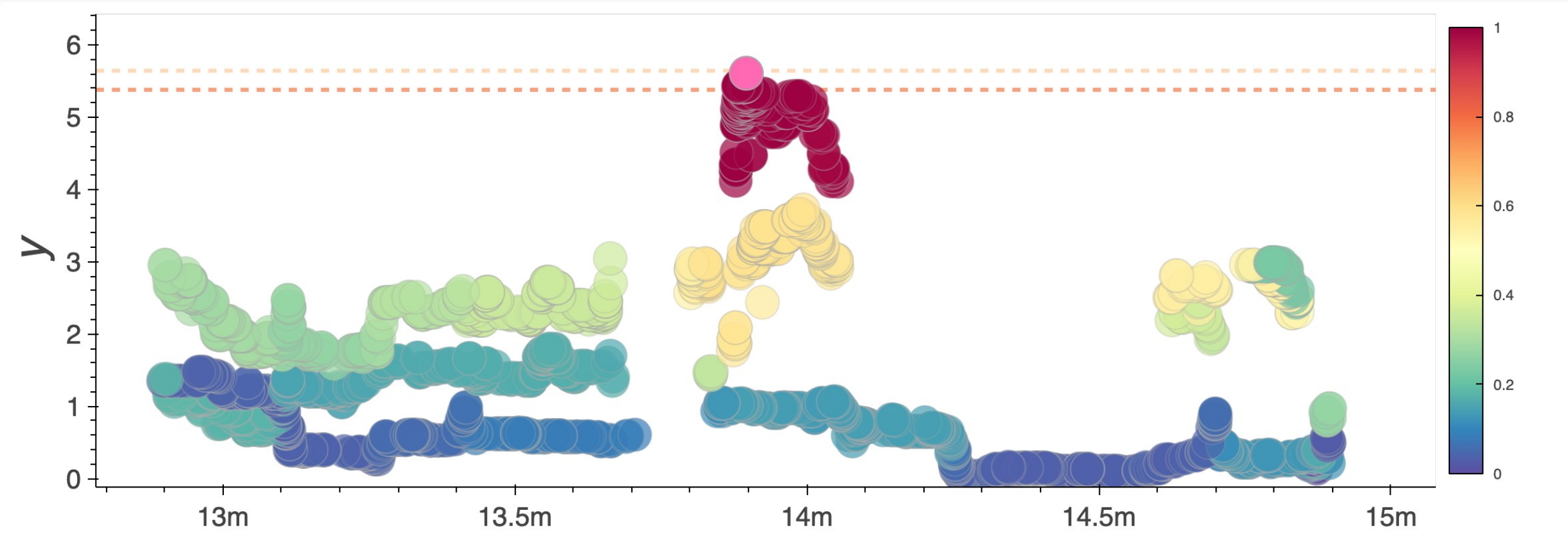
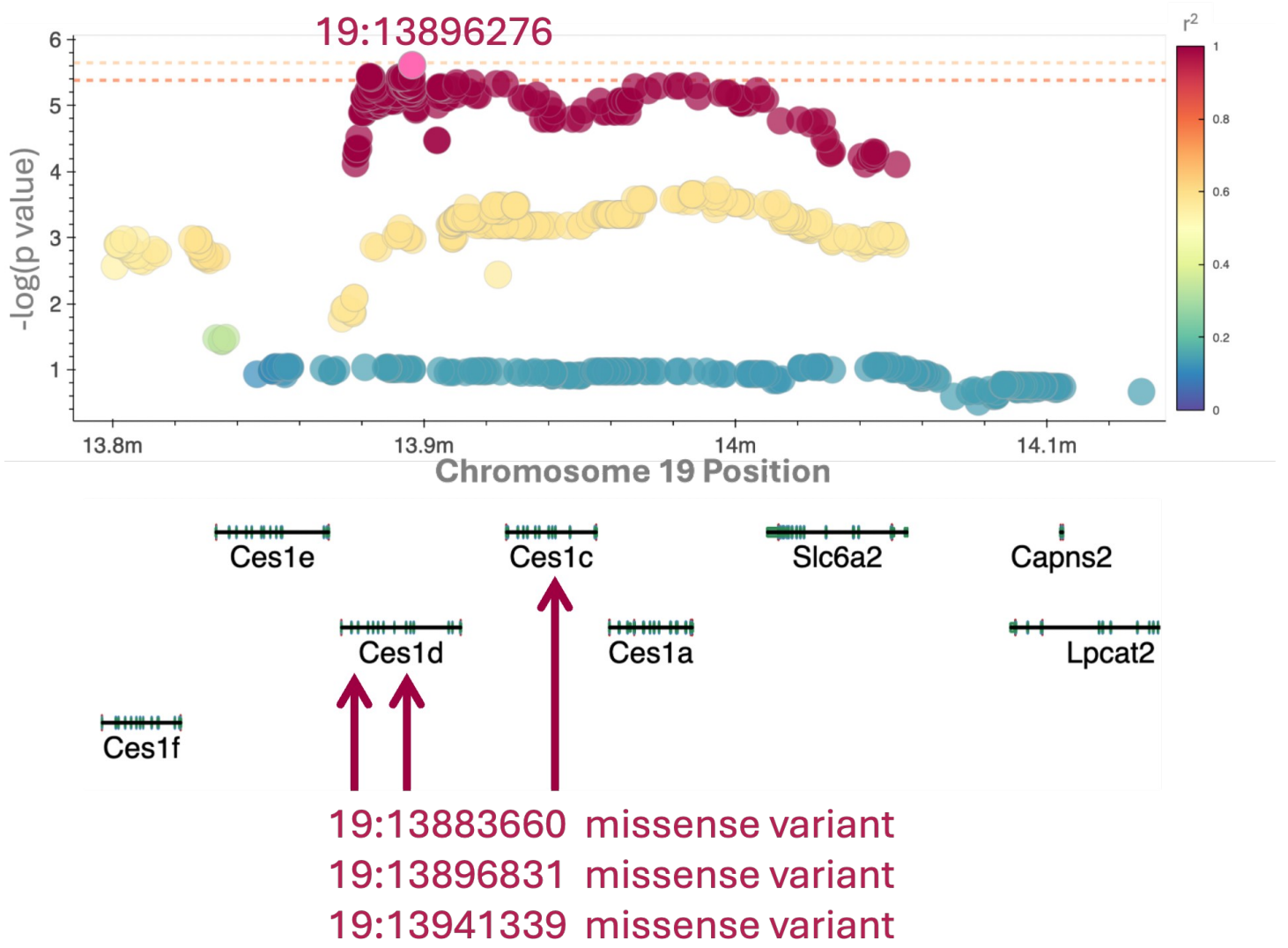


Genome-wide association study



Ces1

CodingVariants_lga_iti_median_11_1419_138

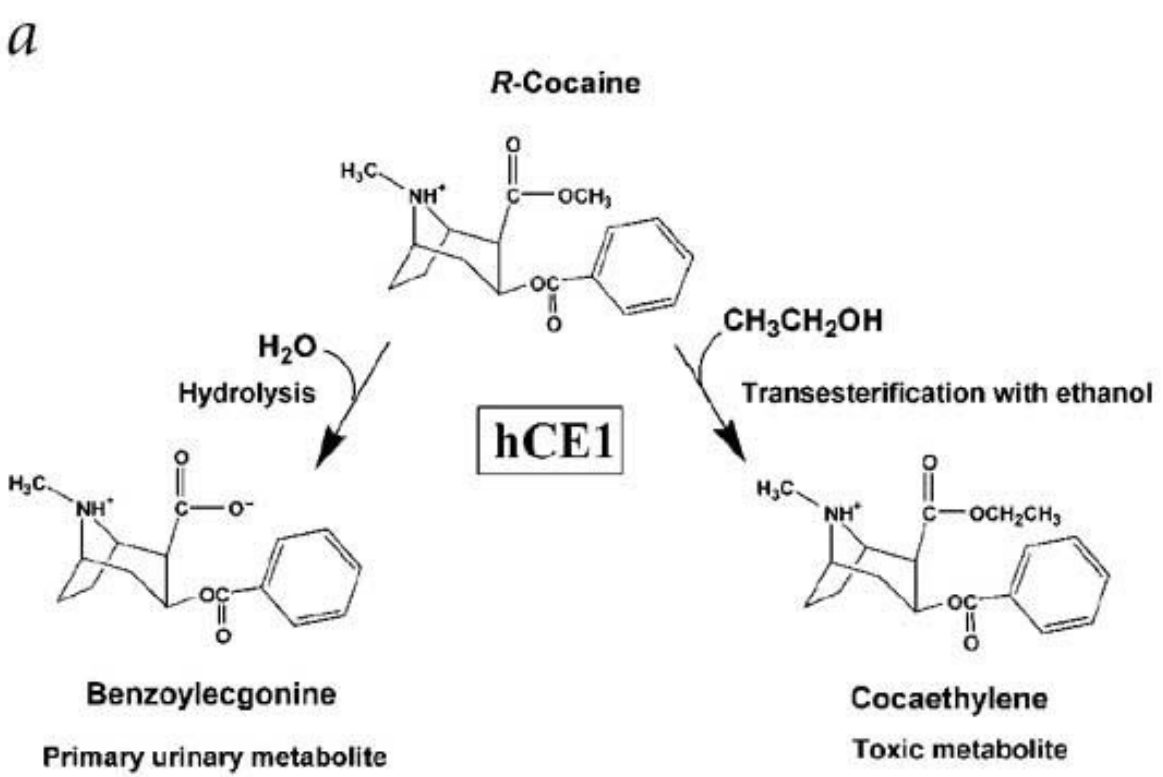
index	SNP	Freq	b	-Log10(p)	R2	DP	annotation	putative_impact	gene	HGVS.c	HGVS.p
	Similarity	Enter	Ent	Enter minir	Ent	Ent	Similarity	Similarity	Simila	Similarity	Similarity
0	19:13883660	0.487	-0.238	5.138	1.0	1.0	missense_variant	MODERATE	Cesl1	c.557A>G	p.Gln186Arg
2	19:13941339	0.488	-0.225	4.794	0.998	1.0	missense_variant	MODERATE	Ces1c	c.1226C>T	p.Pro409Leu
1	19:13896831	0.485	-0.235	5.119	1.0	1.0	missense_variant	MODERATE	Cesl1	c.1269G>A	p.Met423Ile

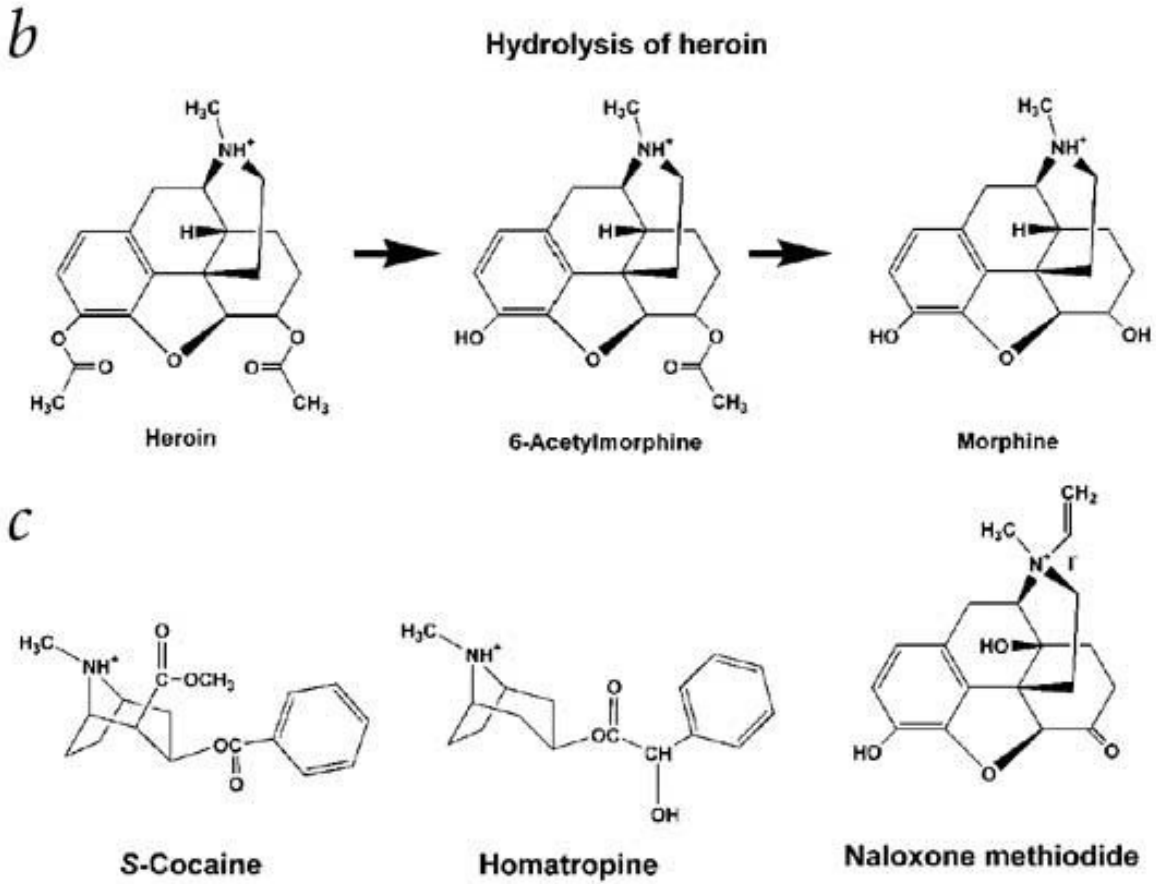
Ces1

phewas_lga_iti_median_11_1419_13896276.(

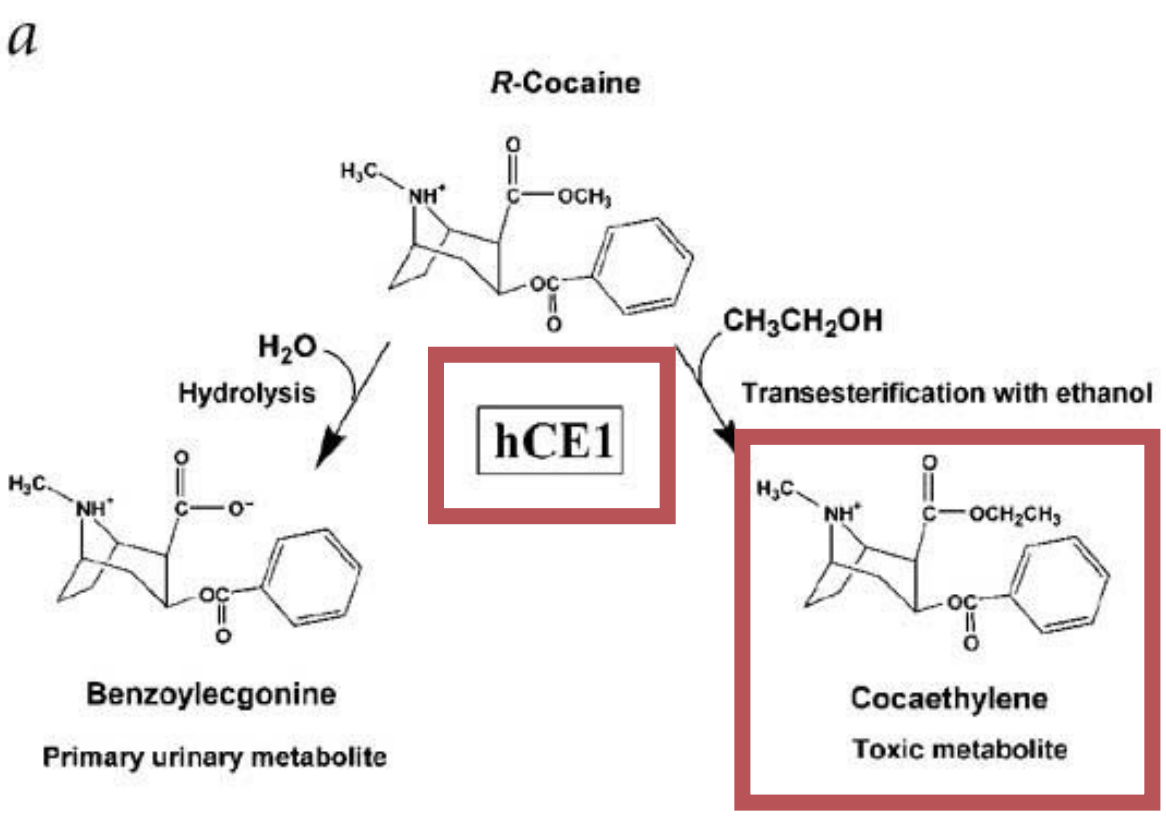
index	SNP_PheDb	-Log10(p)PheDb	R2	DP	trait_PheDb	project
	Similarity	Enter minimum	Ent	Ent	Similarity	Similarity
6	19:13897534	4.364	1.0	1.0	lga_titration_intake_11_14	u01_olivier_george_cocaine
5	19:13879213	4.587	0.997	1.0	sha_inf_d10	p50_paul_meyer_2020_nopilot_noratsbelow57
4	19:13879213	4.639	0.997	1.0	sha_inf_d10	p50_paul_meyer_2020
0	19:14031192	4.572	0.576	0.996	nicsa_day8_activelick	p50_hao_chen_nicsa
2	19:13913939	5.362	0.588	1.0	nicsa_total_activelick_10days	p50_hao_chen_nicsa
3	19:13917793	5.864	0.588	1.0	nicsa_total_infusion_10days	p50_hao_chen_nicsa
1	19:14031192	5.354	0.576	0.996	nicsa_day8_infusion	p50_hao_chen_nicsa

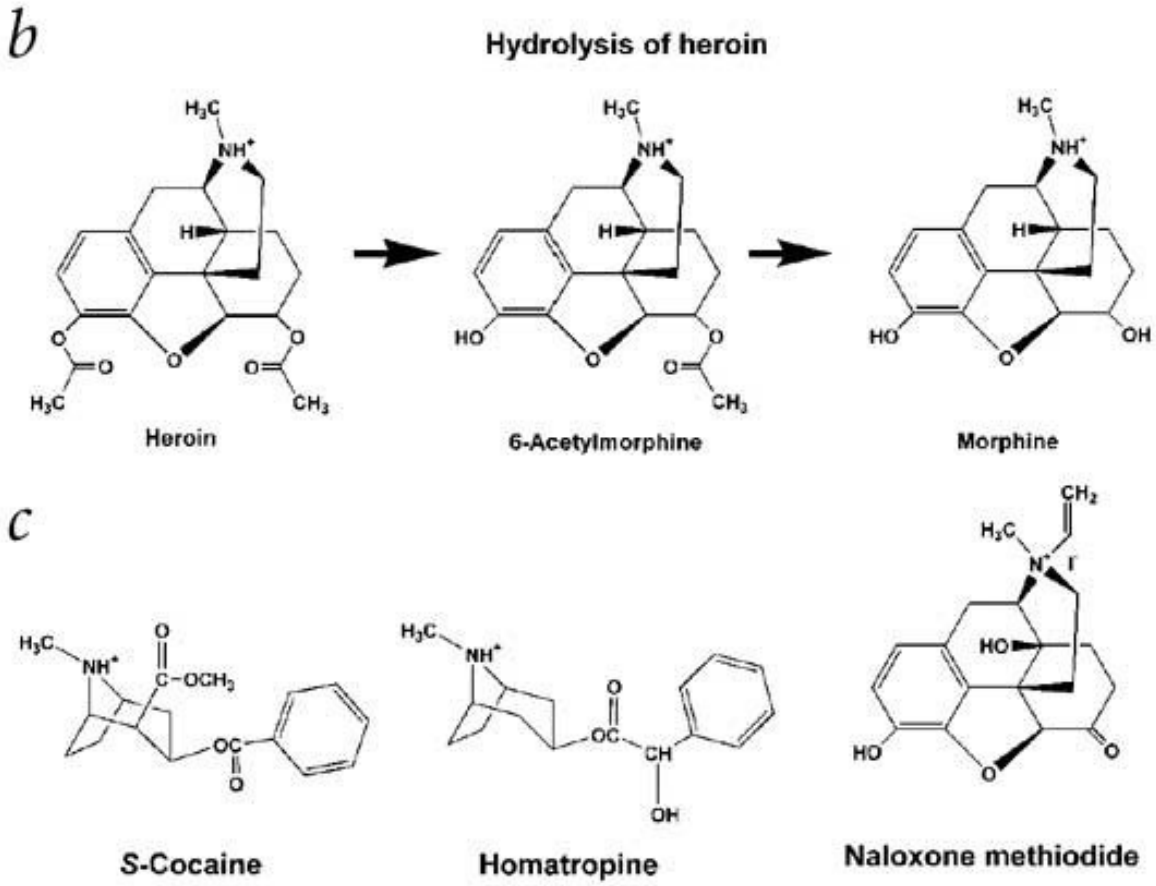
Ces1


a
R-Cocaine
H2O
Hydrolysis
hCE1
CH3CH2OH
Transesterification with ethanol
Benzoylecgonine
Primary urinary metabolite
Cocaethylene
Toxic metabolite


b
Hydrolysis of heroin
Heroin
6-Acetylmorphine
Morphine
c
S-Cocaine
Homatropine
Naloxone methiodide

Ces1


a
R-Cocaine
H2O
Hydrolysis
CH3CH2OH
Transesterification with ethanol
hCE1
Benzoylecgonine
Primary urinary metabolite
Cocaethylene
Toxic metabolite


b
Hydrolysis of heroin
Heroin
6-Acetylmorphine
Morphine
c
S-Cocaine
Homatropine
Naloxone methiodide

Acknowledgements

RatGenes.org

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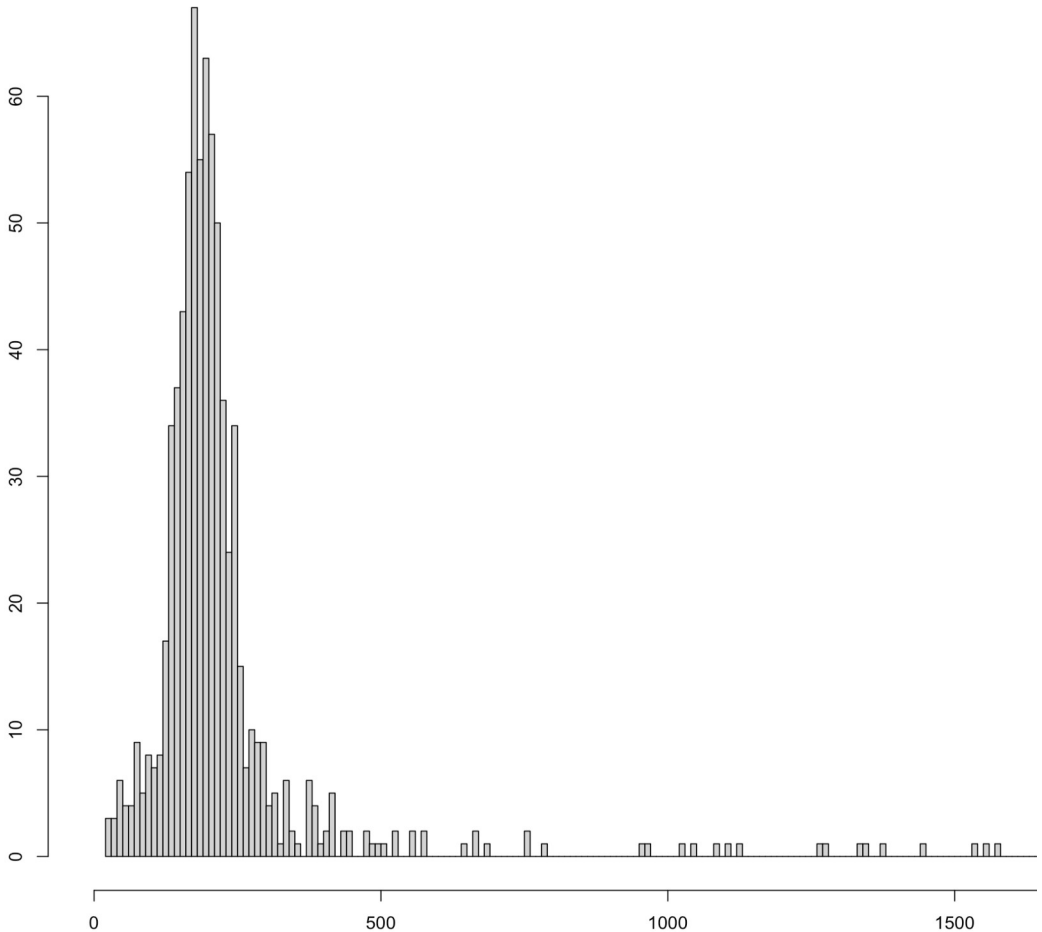
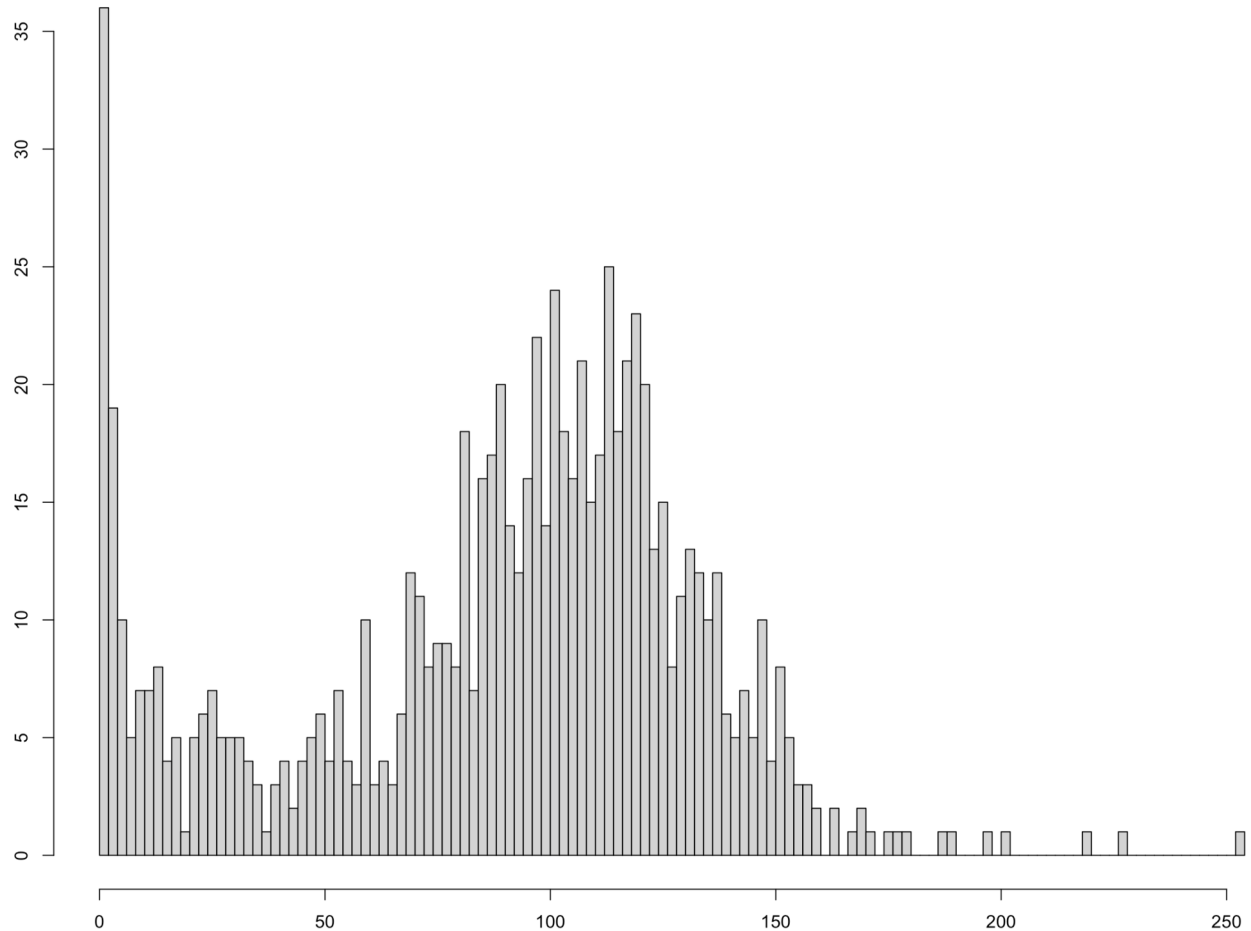
Paul Schweitzer
Kokila Shankar
Lauren Cassandra Smith
Elizabeth A. Sneddon
Dana Elizabeth Conlisk
Sierra Simpson

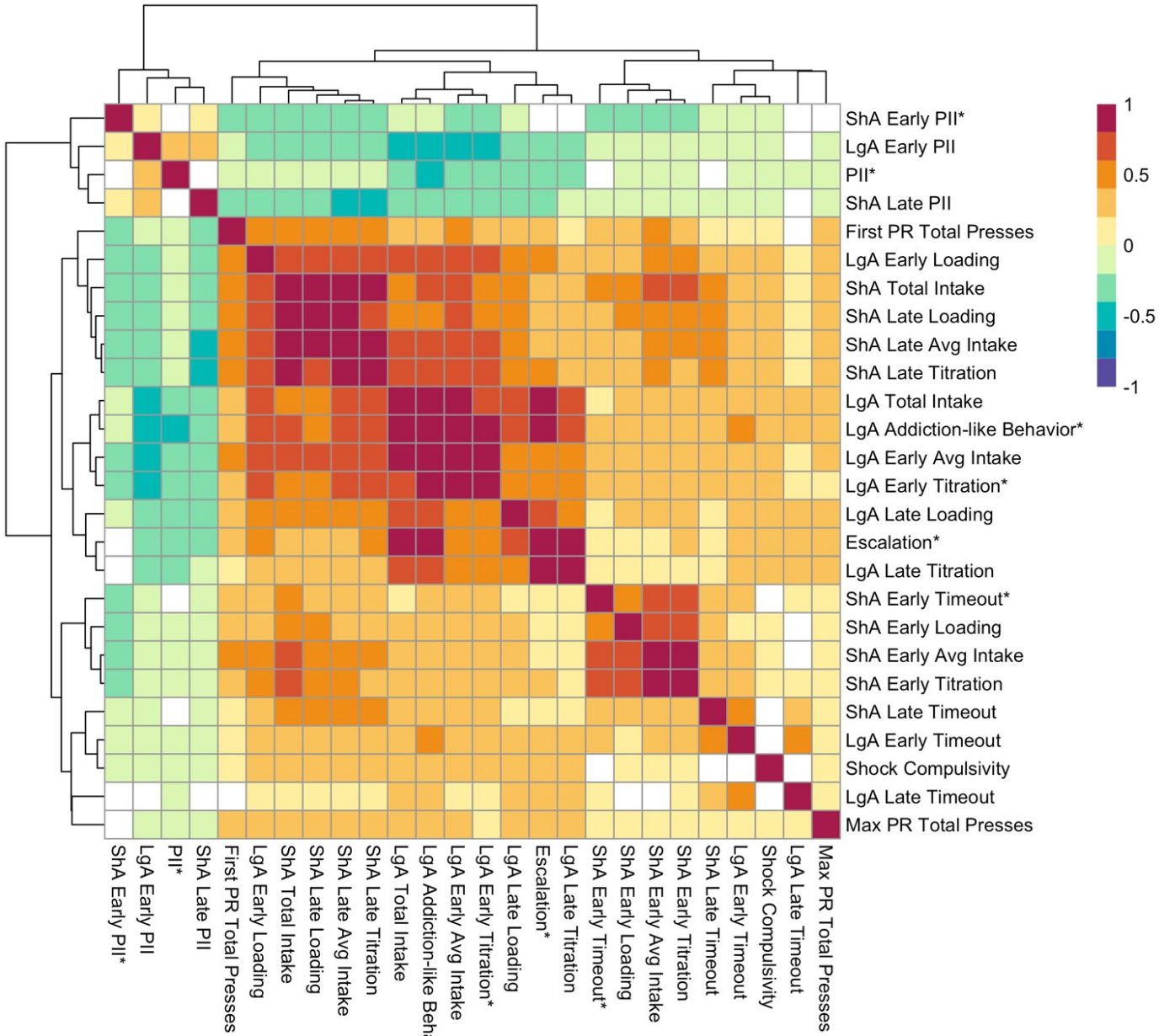
TopSNP	Freq	beta	betase	-Log10(p)	significance_level	trait	ACI	BN	BUF	F344	M520	MR	WKY	WN
Similarity	Simil	Simil	Similarit	Similarity	Similarity	Similarity	Sim	Sim	Simil	Simila	Similar	Sim	Simila	Simi
19:13896276	0.481	-0.249	0.053	5.609	5%	lga_iti_median_11_14	G G	C C	G G	G G	G G	G G	C C	C C

ITI



escalation




ShA Early PII*
LgA Early PII
PII*
ShA Late PII
First PR Total Presses
LgA Early Loading
ShA Total Intake
ShA Late Loading
ShA Late Avg Intake
ShA Late Titration
LgA Total Intake
LgA Addiction-like Behavior*
LgA Early Avg Intake
LgA Early Titration*
LgA Late Loading
Escalation*
LgA Late Titration
ShA Early Timeout*
ShA Early Loading
ShA Early Avg Intake
ShA Early Titration
ShA Late Timeout
LgA Early Timeout
Shock Compulsivity
LgA Late Timeout
Max PR Total Presses
1
0.5
0
-0.5
-1