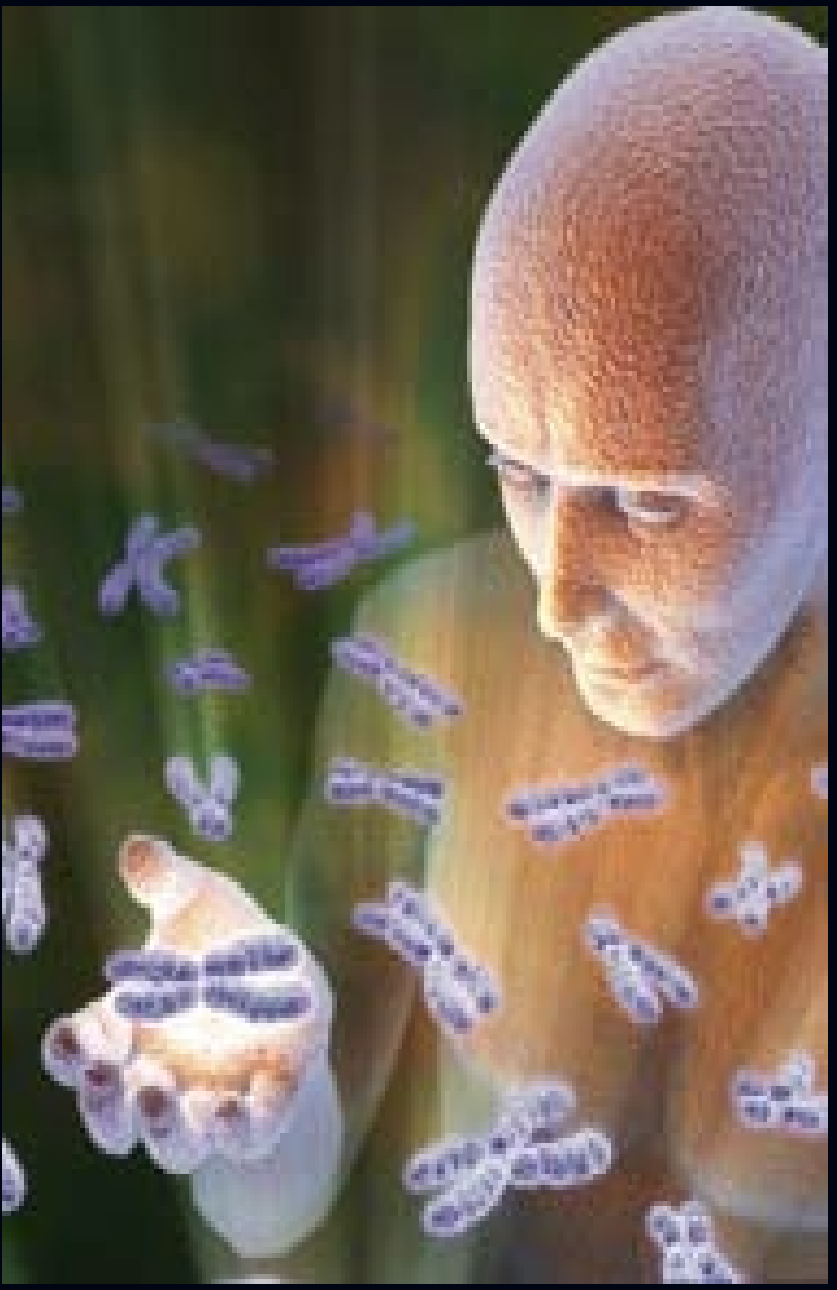


Cognitive assessment in mouse models of disease

Jared W. Young, Ph.D.

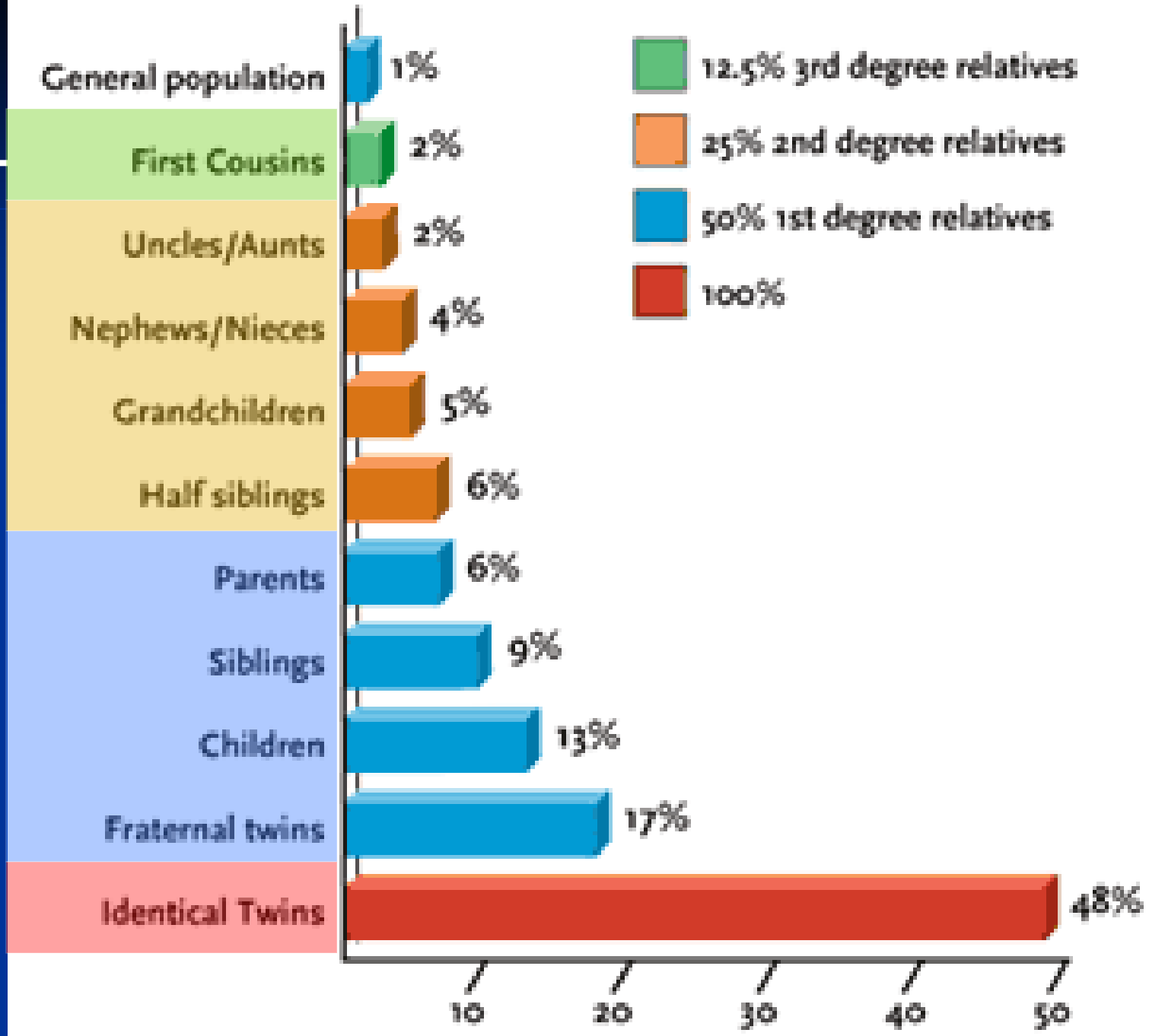
Department of Psychiatry,
University of California, San Diego
jaredyoung@ucsd.edu

JWY

Schizophrenia: Genetic contribution

- Horrobin postulated that the genes that separates us from chimpanzees, contain those that lead to schizophrenia
- True that schizophrenia has a genetic basis:

JWY


General population
First Cousins
Uncles/Aunts
Nephews/Nieces
Grandchildren
Half siblings
Parents
Siblings
Children
Fraternal twins
Identical Twins
1%
2%
2%
4%
5%
6%
6%
9%
13%
17%
48%
12.5% 3rd degree relatives
25% 2nd degree relatives
50% 1st degree relatives
100%
10
20
30
40
50

Szgene – Top 20 (see Arguello & Gogos, 2010)

UCSD

RANKING BASED ON HUGENET INTERIM GUIDELINES FOR THE ASSESSMENT OF GENETIC ASSOCIATION STUDIES							
#	Gene	Ethnicity	Polymorphism	N minor (Grade)	I^2 (Grade)	Bias Reason (Grade)	Overall Grade
1	PGBD1	All	rs13211507	5075 (A)	0 (A)	(A)	A
2	NRGN	All	rs12807809	12620 (A)	0 (A)	(A)	A
3	NOTCH4	All	rs3131296	7829 (A)	19 (A)	(A)	A
4	PDE4B	All	rs910694	2393 (A)	2 (A)	(A)	A
5	TCF4	All	rs9960767	4143 (A)	20 (A)	(A)	A
6	DAOA	Asian	rs778293	3609 (A)	18 (A)	(A)	A
7	TPH1	All	rs1800532	6039 (A)	20 (A)	(A)	A
8	HTR2A	Caucasian	rs6311	4665 (A)	22 (A)	(A)	A
9	RELN	Caucasian	rs7341475	3170 (A)	0 (A)	(A)	A
10	MDGA1	All	rs11759115	1347 (A)	15 (A)	(A)	A
11	CCKAR	All	rs1800857	1326 (A)	0 (A)	(A)	A
12	DRD4	Asian	rs1800955	2881 (A)	0	(A)	A
13	DRD1	All	rs4532	1089 (A)	0 (A)	(A)	A
14	APOE	Caucasian	APOE_e2/3/4	1118 (A)	0 (A)	(A)	A
15	SNAP-11p14.1	Caucasian	rs1602565	3973 (A)	46 (B)	(A)	B
16	DISC1	Caucasian	rs3737597	102 (B)	0 (A)	(A)	B
17	PLXNA2	Caucasian	rs841865	506 (B)	24 (A)	(A)	B
18	GABRB2	Caucasian	rs6556547	182 (B)	0 (A)	(A)	B
19	AKT1	Caucasian	rs3803300	506 (B)	40 (B)	(A)	B
20	DRD2	All	rs1801028	901 (B)	19 (A)	(A)	B

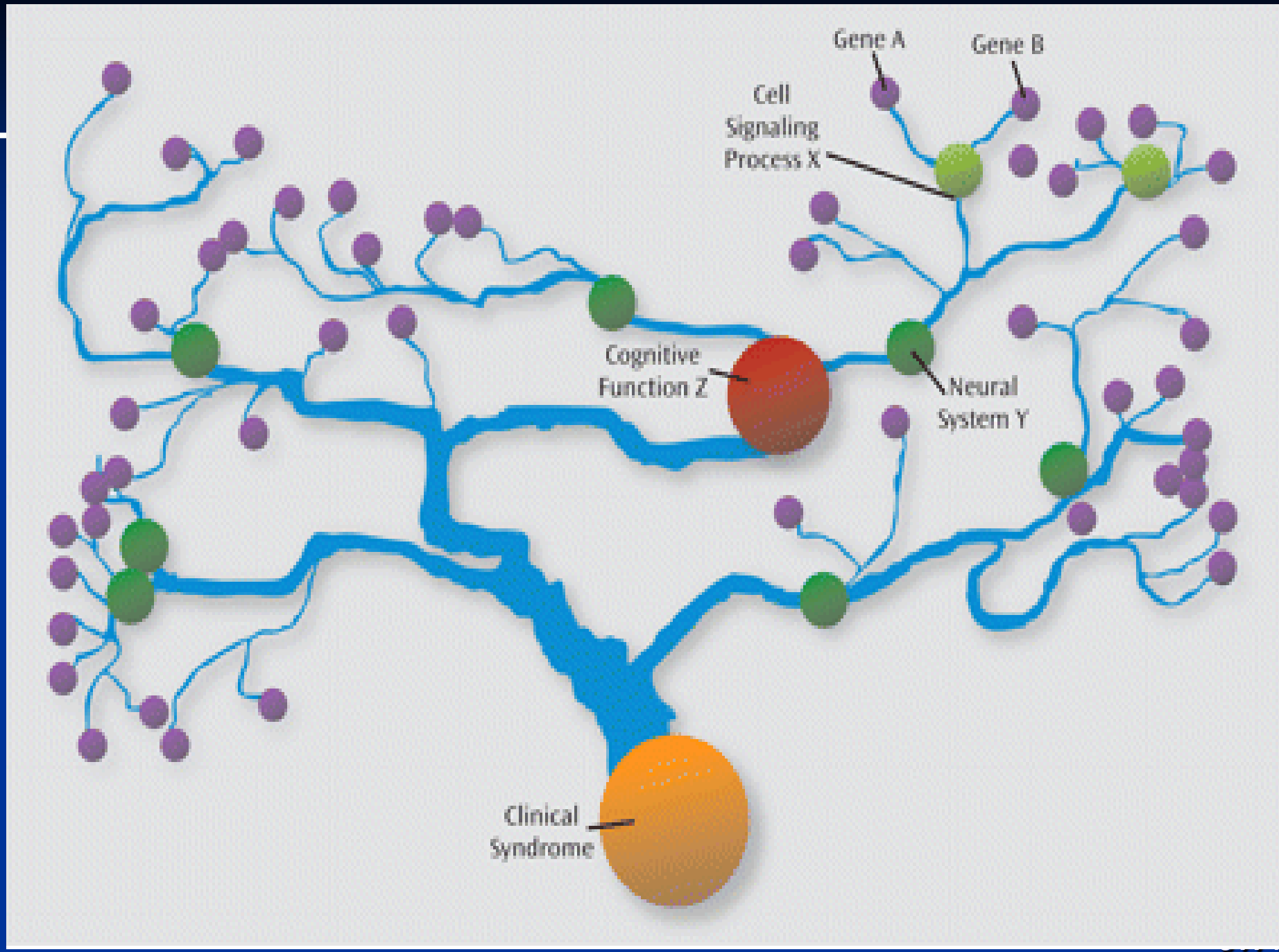
JWY

Realistic genetic influence

- Heterogeneity of schizophrenia means individual gene effects on the clinical syndrome are small
- Genes are more likely to influence intermediate phenotypes which are theoretically closer to the gene action
- Thus, a single genetic model should not be expected to reproduce the entire clinical syndrome
- Each model may prove fruitful for specific aspects of the disease

(Cannon & Keller, 2006, the water shed model)

JWY


Gene A
Gene B
Cell
Signaling
Process X
Cognitive
Function Z
Neural
System Y
Clinical
Syndrome

NIMH drive for mice with human alleles

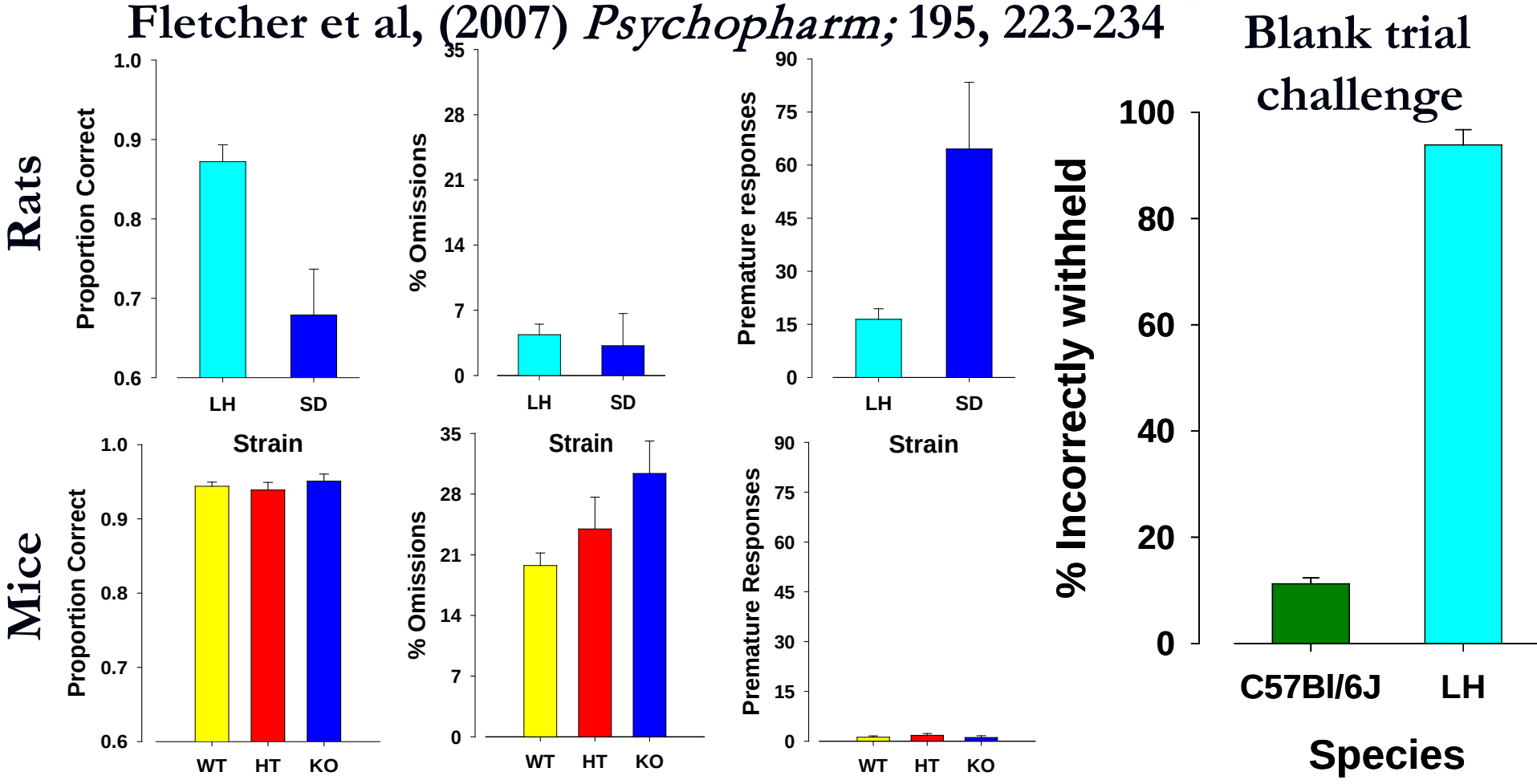
- NIMH issued a RFA in 2007 RFA-MH-08-050 "Mouse Models Containing Human Alleles" a R21/R33
- Since reissued in 2008 as PAR-08-158
- Funded 5 of 11 with links to schizophrenia:
  - GAD67-ERB4
  - COMT VARIANTS IN SENSORIMOTOR GATING
  - G72/G30 TRANSGENIC MICE
  - DISC1-BOYMAW FUSION TRANSCRIPTS
  - DRD2 SER311CYS POLYMORPHISM

JWY

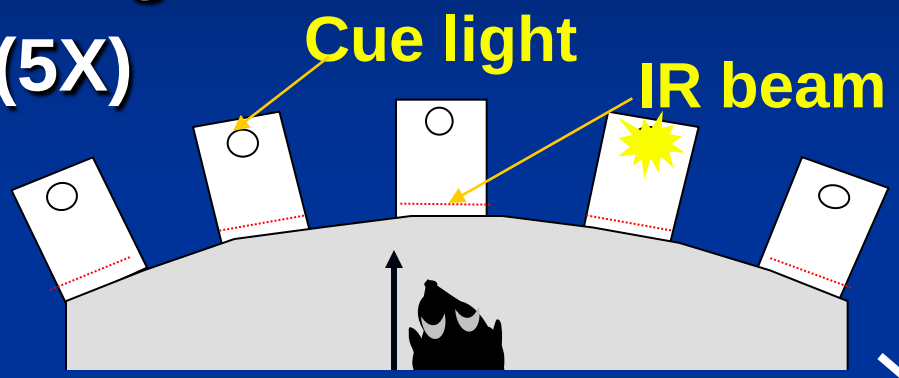
Testing cognition in mice? Comparing rats e.g. 5CSR task

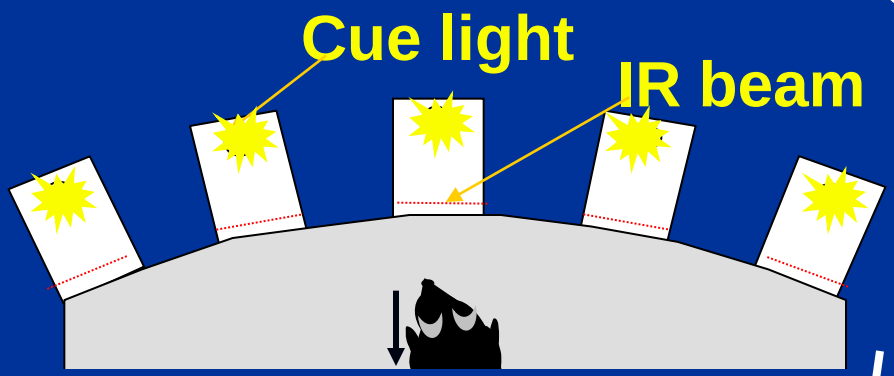
- Better performers? – depends on the measure:
  - Accuracy = mice, % omissions = rats, premature responses = mice…

Fletcher et al, (2007) *Psychopharm;* 195, 223-234



Evolution of the 5-CSRTT





Non-target Trial (1X)

Hit

Misses

False Alarm

Correct Rejections

Signal Detection Theory

	Response	Inhibited
Signal	Hit	Miss
Non-Signal	False Alarm	Correct Rejection

d′ + Bias

(Vigilance) + (Responsivity)

Importantly distinct mechanisms of inhibition to nontarget vs response to target, consistent with humans

(Young et al, 2009; *PLoS ONE*)

JWY

5choice-continuous performance test (5C-CPT)

- Top-down control of attention requiring both response to target and inhibition to non-target stimuli
- If stimulus type is not observed, guessing and responding is a less viable strategy compared to the 5-CSR task
- Utilize a variable ITI (3-7 s), ↓ predictability of the stimulus onset, increasing the 'attentional-load'
- Non-target responses dissociable from premature responses
  - e.g. D4 HT mice & Vitamin D deficient rats ↑ false alarms, no effect on premature (Young et al, 2011; Burne et al, 2011)
- Rats need to be trained on a 2:1 stimulus ratio initially, but can perform a 5:1 once trained – mice train on the 5:1
- Rats are more responsive to their environment, mice are less responsive and more cautious

JWY

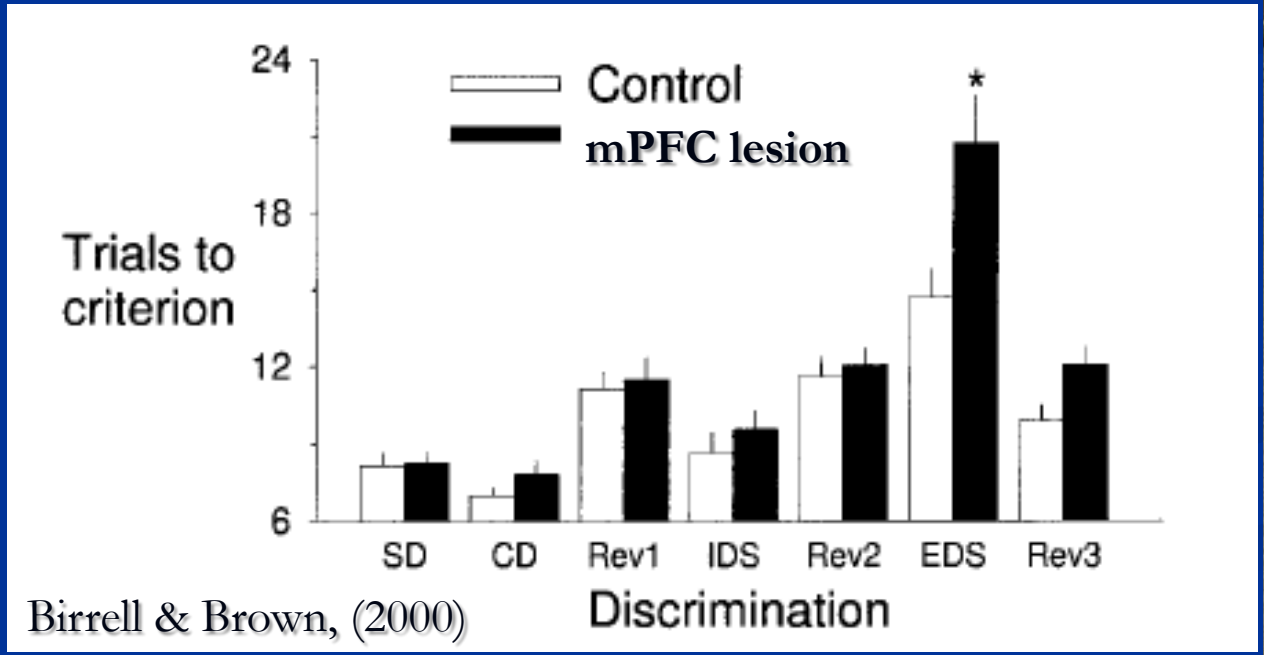
Reactive Rats

- Rats compared to mice: Olfactometers
- Challenge performance by increasing scent similarity:
  - mixing 60% of scent A to 40% of scent B
- When challenged, mice and rats respond differently:
  - Mice slow their reaction, remain accurate (Abraham et al, 2004; Rinberg et al 2006)
  - Rats react as fast as before but become less accurate (Uchida & Mainen, 2003), if forced to sample longer, accuracy increases
- Rats are very reactive to stimuli
- Of course rats can be trained to inhibit e.g. SSRT

JWY

Attentional set-shifting task (ASST) in rats

- Developed for rats to assess set-shifting (Birrell & Brown, 2000)
- Using trial and error search, rat uses stimuli to guide choice of digging in one of two presented bowls:
  - Odors, digging medium, bowl texture
- Originally 7 stages:

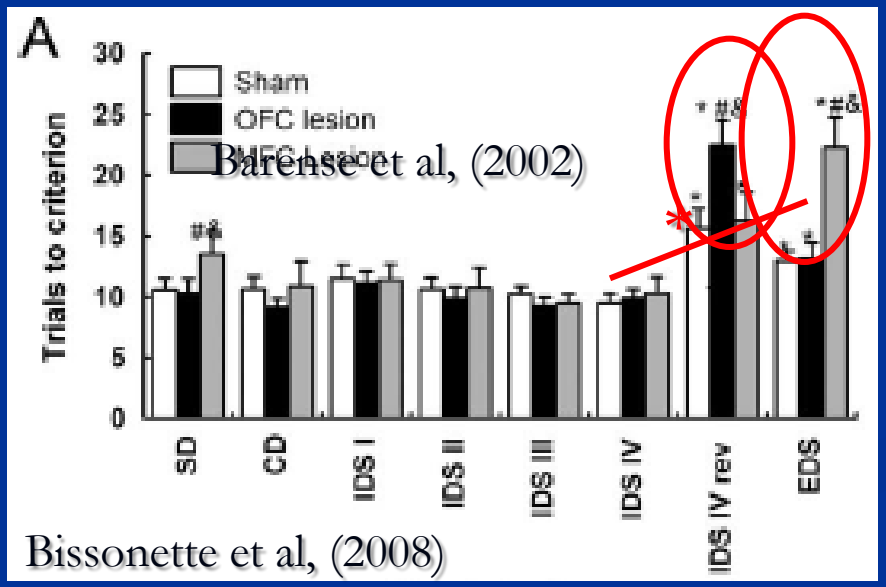


Birrell & Brown, (2000)

From V. Brown

ASST in mice

- Testing mice in the ASST –difficult to identify a mouse sampling the digging medium vs. digging for the bait!
- We found mice were reticent to dig in a variety of media
- Used different textured platforms leading up to bowls - the latter were scented with different odors (Young et al, 2010)
- Similar to cross-maze set-shifting floor covers (Floresco et al)



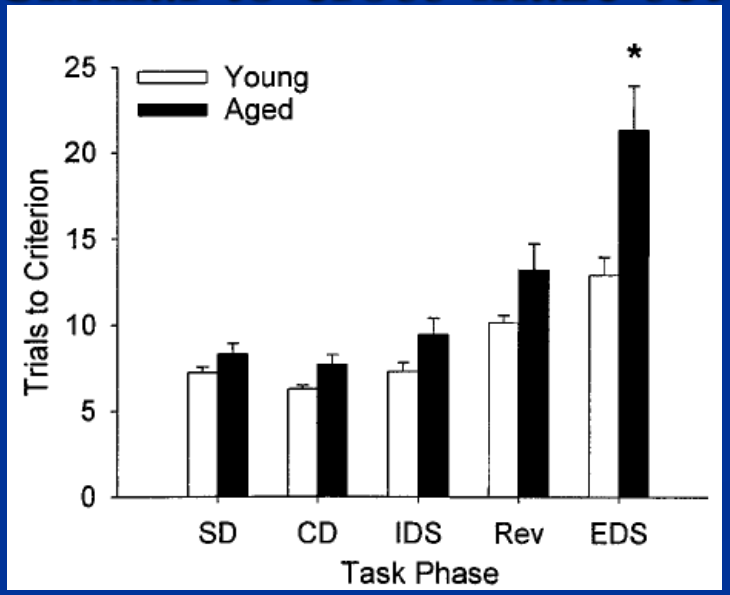
Barense et al, (2002)

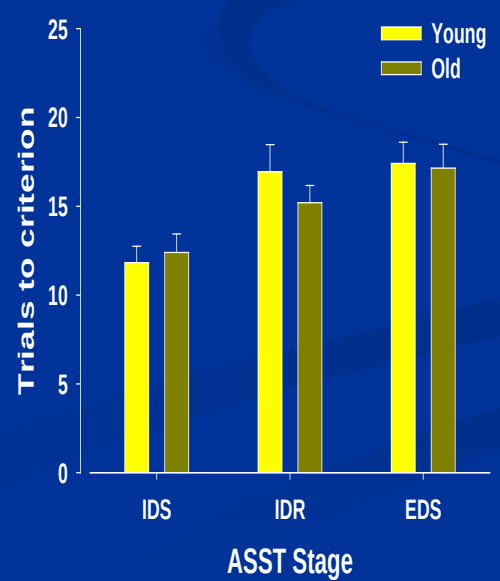
Bissonette et al, (2008)

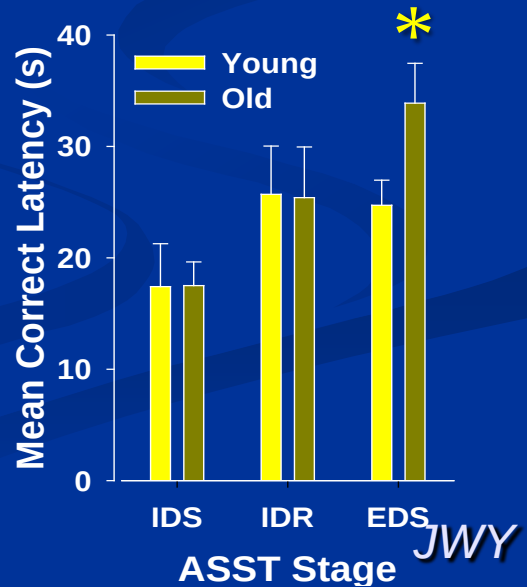
JWY

ASST in mice

- Testing mice in the ASST –difficult to identify a mouse sampling the digging medium vs. digging for the bait!
- We found mice were reticent to dig in a variety of media
- Used different textured platforms leading up to bowls - the latter were scented with different odors (Young et al, 2010)
- Similar to cross-maze set-shifting floor covers (Floresco et al)



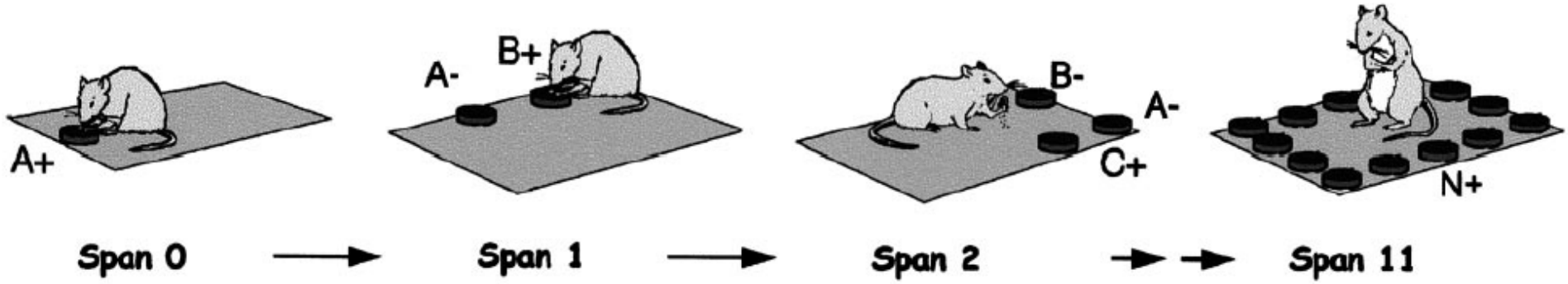




JWY

Odor Span Task (OST)

- Developed for rats to assess the effects of hippocampal/nBM lesions on non-spatial memory (Dudchenko et al, 2000; Turchi & Sarter, 2000)
- Simple task utilizing ethologically relevant stimuli
  - Odors are presented in sequential order
  - Required to remember previously sampled odors and only dig in the novel presented odor
  - Used sand in pots for the digging medium



Taken from Dudchenko et al, 2000: J Neurosci: **20**(8):2964-2967

JWY

Odor Span Task (OST)

- The OST for mice required some adjustment:
  - E.g. using bedding instead of sand for ease of digging
  - No lip to the table because the mice liked to jump…
  - Used velcro to keep bowls in place
- OST was useful in identifying effects of genetic mutations:
  - Caspase3 over-expression produced an age-independent deficit (Young et al, 2007)
  - APPswe TG2576 mouse model of Alzheimer's disease exhibited an age-dependent deficit in performance, coinciding with cholinergic abnormalities (Young et al, 2008)
  - α7 nAChR KO mice exhibited poorer performance – attentive in nature? (Young et al, 2007)
  - Plans to test mice with reduced NR1 expression
- Being used again in rats, some pharmacology being worked out
  - Nicotinic agonist induced improvement (Rushforth et al, 2010)

JWY

Questions for testing in genetic models

- What situations require a genetic model & which don't?
- Assume task performance recruits the same circuits (or biological processes) as rats or re-validate in mice?
  - E.g. ASST – Birrell & Brown, 2000; McAlonan & Brown, 2003; Bissonnette et al 2008
- Proper controls for mouse genetic models?
  - E.g. littermate WT from HT breeding pairs
- What effect size do we expect in these/any model?
- Designing experiments to see meaningful drug effects?
  - Main effect of drug? If so then why bother with the disease model?
  - Or a genotype [disease]-dependent effect of drug

JWY

Conclusion for Genetic Models

- Positives:
  - ↑ in number & sophistication for the human allele
  - Are developmental in nature
  - Allow for:
    - Genetic + environmental models
    - Drug X gene interaction studies
- Negatives:
  - Cognitive tasks not as well developed cf. rats
    - Most tasks developed in rats first, then implemented in mice
    - Lesion and pharmacological validation required

JWY

Thank you for listening

JWY