Genes, Brain, and Behavior

Tenth Annual Meeting of the
International Behavioural and Neural Genetics Society

May 5-9, 2008

University Place Hotel and Conference Center
310 SW Lincoln Street at SW 3rd Avenue, Tel. 503.221.0140
Portland, Oregon USA

Sponsored by

National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, USA
National Institute of Child Health and Human Development, National Institutes of Health, USA
National Institute of Mental Health, National Institutes of Health, USA

Exhibitors: Noldus

Program Committee: Kari Buck (Chair), John Crabbe, Daniel Goldowitz, Andrew Holmes, Helen Kamens, Charalambos Kyriacou, Richard Nowakowski, Inga Poletaeva, Oliver Stork
Local Organizers: Kari Buck, John Crabbe, Tamara Phillips, Mark Rutledge-Gorman

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May 5-9, 2008

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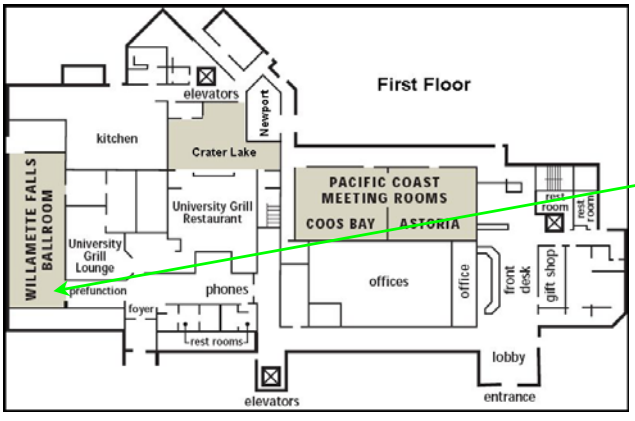
Conference Program Schedule at-a-Glance

	Mon, May 5, 2008	Tues, May 6, 2008	Weds, May 7, 2008	Thurs, May 8, 2008	Fri, May 9, 2008
07:00 -17:00	Breakfast 7:00 - 8:00 **Satellite sympoisum** 8:00 - 17:00 Novelty- and Impulsivity-related Trait Predictors of Genetic Risk for Alcohol and Drug Abuse Organizers: John Crabbe Tamara Phillips				
7:00-8:30		**breakfast** (included) and meeting registration	**breakfast** (included) and meeting registration	**breakfast** (included) and meeting registration	**breakfast** (included) and meeting registration
8:30-8:45		**Opening remarks**			
8:45-9:45		**Presidential plenary lecture: Alcino Silva**			
8:30-9:30			**Program committee plenary lecture: Ulrike Heberlein**	**Distinguished scientist award & lecture John Belknap John Crabbe**	**Young scientist award & lecture Justin Rhodes**
9:30-10:00		coffee (included)	coffee (included)	coffee (included)	coffee (included)
9:45-10:15		coffee (included)			
10:00-12:00			**Symposium III** Methodological Considerations in the Genetical Genomics of Complex Traits Chair: Igor Ponomarev Ch: Robert Hitzemann	**Symposium V** Role of Oxidative Stress in Behavior Chair: Abraham Palmer	**Symposium VI** Learning and Memory: from Causes to Consequences Chair: Matthew Lattal
10:15-12:15		**Symposium I** Thalamus in Physiology and Disease Disease, from Genes to Behavior Chair: Hee-Sup Shin			
12:00-13:30			**lunch** (included)	12:00 **Free Time** **Remainder of the Day** lunch (on your own)	**lunch** (included)
12:15-14:00		**lunch** (included)			
13:30-15:30			**Symposium IV** Approaching the Genetics of Alcoholism across Different Model Organisma Chair: Helen Kamens Ch: Chris Kliethermes		**Paper Session** Talks to be selected from submitted meeting abstracts
14:00-16:00		**Symposium II** Substance Abuse Genetics: Initiation of Drug Use, and Transition to Dependence Chair: John Crabbe		**Wineries Tour** Depart hotel: 13:00 Return hotel: 18:00 Pre-payment required Transportation fee: $35, includes box lunch Tasting Fees: $5 - $15 at each winery We will visit 2 wineries: Anne Amie Vineyards Yamhill County Vineyards	
15:30-16:00			break (included)		break (included)
16:00-16:30		break (included)			
16:00-18:00			**Poster Session** **(Cash Bar)**		
16:00-17:00					**IBANGS business meeting**
16:30-18:30		**Outstanding Young Investigator Award Talks** to be selected from travel award applicants			
17:00-18:30					**Free Time**
18:00 -20:00	**Meeting Registration 18:00-20:00** **Reception** with food & drink (included) **18:00-20:00**				
18:00					
18:30		dinner (on your own)	dinner (on your own)	dinner (on your own)	**Cash Bar opens in the banquet hall**
19:00-22:00					**Closing banquet** (included)

Conference Meeting and Event Hotel Locations



Opening Reception

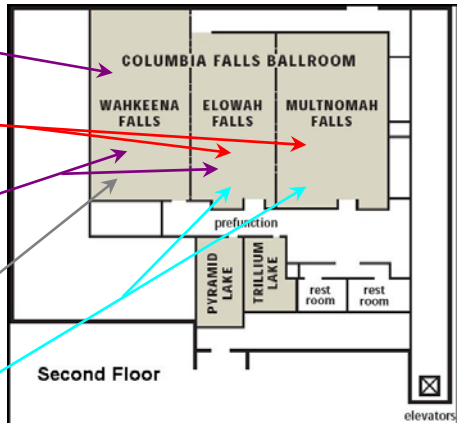
Conference Room for Talks, Symposia, Business Meeting

Poster Session

Closing Banquet

Continental Breakfasts and Lunches

Satellite Symposium (Monday)



Portland, Oregon, downtown map

Northwest Nob Hill restaurants, shops along 23rd, 22nd, 21st

Pearl District restaurants, shops

Powell's City of Books NW Burnside and NW 10th Ave

Portland Airport (PDX) to University Place Hotel
- via MAX Lightrail Red Line and streetcar
$2.05
70-80 min
- via Taxi
$45.00
30 min

Saturday Market under Burnside Bridge

Riverplace Marina restaurants, shops, kayak rental, river walk to downtown

Portland Streetcar Line orange line in legend

Meeting Site: University Place Hotel, 310 SW Lincoln at SW 3rd Ave
Streetcar Station: SW Harrison at SW 1st Ave

Oregon Health & Science University and VA Medical Center

General Information

Accommodation and Emergency Contact
For assistance 24 hours a day contact the University Place Hotel Front Desk at 503.221.0140

Banking and Currency Exchange
A 24-hour automated teller machine (ATM) is available in the main hotel lobby (withdrawal only)

We recommend that any currency exchange is done at the Portland International Airport upon your arrival. *Travelex*, located in the airport ticket lobby near the United Airlines counter, offers currency exchange daily 5:30 – 16:30 (4:30 p.m.); its phone number is 503.281.3045.

Bank of America is located at 1001 SW 5TH Avenue at SW Salmon Street, telephone 503.279.3445, open Monday-Friday 9:00 – 17:00 (5:00PM), and closed Saturday and Sunday. This bank usually offers a less advantageous exchange rate than currency brokers plus a 3% surcharge on the amount exchanged. Other banks downtown will do currency exchanges, often at higher cost. Please inquire for rates and fees, and if you need to be a customer of the bank.

Cultural, Recreation and Athletic Activities
Please consult the hotel front desk for the most current information

E-mail and internet access
Guest rooms have complimentary wired high-speed internet access. Look for an ethernet cable near the guest room's desk. The main meeting room will have wireless internet service.

Emergency Telephone Numbers
Police 911 Ambulance 911 Fire 911

Medical and Dental Treatment
Non-emergency medical treatment is available at Oregon Health & Science University. Please call the 24-hour appointment line at 503.418.3748 and request an appointment with South Waterfront Family Medicine Clinic, 3303 SW Bond Ave at SW Gibbs Street. The clinic is a short 10-minute ride by streetcar from the hotel, and is at the same location as the aerial tram to the OHSU main hospital. See directions to *Tram* below.
Dental treatment is available at Emergency Dental: Telephone 503.234.9911

Medical insurance, and any other insurance, are the responsibility of each individual attending the meeting. The United States does not have a public health plan that covers visitors.

Name Badge
Admission to all conference activities is by name badge, so please be sure to wear your badge at all times.

Parking
Parking is available at University Place Hotel at the rate of:
$ 2.00 / hour
$ 9.00 / day
$12.00 / day and overnight for guests

Posters
There is one poster session, scheduled on Wednesday, May 7th, 16:00 - 18:00, in the Willamette Falls Room, 1st floor of the hotel. Poster size may be a maximum of 120cm tall and 120cm wide (48"x48"). Posters may be put up on Wednesday during the lunch break and must be removed by 12:00 noon Friday, May 9th.

Responsibility

The Organizing Committee and the International Behavioural and Neural Genetics Society assume no responsibility for accident, losses, damage, delays, or any modifications to the program arising from unforeseeable circumstances. They accept no responsibility for travel or accommodation arrangements. Participants acknowledge that they have no right to lodge damage claims against the Organizing Committee or the International Behavioural and Neural Genetics Society should the conference proceedings be hindered or prevented by unexpected political or economic events or generally by acts of weather, or should the non-appearance of speakers or other reasons necessitate program changes.

Smoking

All buildings and indoor spaces at the University Place Hotel are designated non-smoking.
Smoking is permitted outdoors at least 10 meters (30 feet) away from entrances.

Taxes

There is no sales tax in the State of Oregon. Lodging tax in Portland is 12.5%.

Transportation in the Portland Area

From Portland International Airport (PDX) to University Place Hotel

Taxi	30-40 minutes	$45.00 USD
MAX Lightrail, transfer to streetcar	70-80 minutes	$ 2.05 USD

1. At the PDX Airport, Board Lightrail MAX Red Line to City Center & Beaverton Transit Center (Terminal Map: http://www.flypdx.com/PDX_Terminal_Map.aspx)
2. Get off at the Galleria SW 10th Avenue/SW Morrison stop in downtown Portland (see Downtown Portland Map on page 4 above)
3. Walk one block west along SW Morrison to SW 11th Ave, turn right and walk one block north to the SW 11th & SW Alder streetcar stop
4. Board the streetcar to South Waterfront
5. Get off at SW Harrison & SW 1st Ave
6. Turn right on 1st Ave and walk south one block; turn right on SW Lincoln Street and walk one block, University Place is on your left-hand side

MAX Lightrail trains run about every 15 minutes, 4:30-midnight, everyday
Streetcars run about every 15 minutes, 5:30-midnight M-F and 7:30-midnight Sat-Sun

Transportation: Streetcars, Buses, Taxis

Please ask the knowledgeable front desk staff, or visit the full Tri-Met display in the main lobby.
Additional public transportation information is available at http://www.trimet.org/

Tram (Aerial) to Oregon Health & Science University

1. From the hotel front door, turn right and walk one block to SW 1st Ave
2. Turn left and walk one block to SW Harrison
3. Board the streetcar to South Waterfront (buy ticket before boarding, fare $2.05)
4. Get off at SW Gibbs Street stop
5. Aerial tram is across the street (Roundtrip is $4.00 . Your tram ticket is also good for your return streetcar fare.)

IBANGS 2008 Award Winners

Distinguished Scientist Award 2008 DR. JOHN BELKNAP and DR. JOHN CRABBE

Thursday, May 8th, 8:30-9:30, Award Presentation and Lecture

Young Scientist Award 2008 DR. JUSTIN RHODES

Friday, May 9th, 8:30-9:30, Award Presentation and Lecture

Travel Award Recipients 2008:

Tuesday, May 6th, 16:30-18:30

*****Talks presented by **outstanding young investigator travel award winners**

	Affiliation	**Country**
Graduate Students		
Rose Auerbach	State University of New York at Albany	USA
Zoe Brett	University of Sydney	Australia
Deaunne Denmark	Oregon Health & Science University	USA
*** Roman Gersner**	Weizmann Institute of Science	Israel
Sarah Holstein	Oregon Health & Science University	USA
Conny Lin	University of British Columbia	Canada
*** Lauren Milner**	Oregon Health & Science University	USA
Angela Ozburn	University of Texas at Austin	USA
Clarissa Parker	University of Colorado at Boulder	USA
Angela Scibelli	Oregon Health & Science University	USA
Aimee Wong	Dalhousie University	Canada
Postdocs		
*** Camron Bryant**	University of Chicago	USA
Gang Chen	Oregon Health & Science University	USA
David Evans	University of South Florida, Tampa	USA
Helen Kamens	Yale University	USA
Chris Kliethermes	Ernest Gallo Clinic & Res Ctr	USA
Brooke Miller	The Scripps Research Institute Florida	USA
Megan Mulligan	University of Texas at Austin	USA
Scott Philibin	Oregon Health & Science University	USA
Eric Vallender	Harvard University	USA
Jeanna Wheeler	Oregon Health & Science University	USA
Junior Faculty		
Cathy Fernandes	King's College, London	UK
Iiris Hovatta	University of Helsinki	Finland
Raúl Pastor	Universitat Jaume I in Castellón	Spain
*** Andrzej Pietrzykowski**	University of Massachusetts	USA

Genes, Brain, and Behavior

Conference Program

Tenth Annual Meeting of the
International Behavioural and Neural Genetics Society

May 5-9, 2008
Portland, Oregon USA

Monday, May 5th

18:00-20:00	Registration	*Wahkeena Falls – 2nd floor*
18:00-20:00	Reception – hors d'oeuvres and cash bar	*Wahkeena Falls – 2nd floor*

Tuesday, May 6th

7:00-8:15	Tuesday Speakers' Presentation Preparation *(please bring your PPT presentation to be loaded on the meeting computer)*	*Elowah / Multnomah Falls – 2nd floor*
7:00-8:30	Continental Breakfast Meeting Registration available at this time	*Wahkeena Falls – 2nd floor*
8:30-8:45	Opening Remarks	*Elowah / Multnomah Falls – 2nd floor*
8:45-9:45	**Presidential Plenary Address** *Introduced by Daniel Goldowitz, President, IBANGS*	*Elowah / Multnomah Falls – 2nd floor*

Molecular and cellular cognition: from memory mechanisms to treatments

Alcino Silva
Departments of Neurobiology and Psychology, and the Brain Research Institute, University of California at Los Angeles, USA

9:45-10:15	Coffee Break	*Wahkeena Falls – 2nd floor*

10:15-12:15 **Symposium Session I** *Elowah / Multnomah Falls – 2nd floor*

Thalamus in physiology and diseases, from genes to behavior

Hee-Sup Shin, Chair

Sensory signal integration mediated by netrin-G/NGL signaling
Shigeyoshi Itohara, Brain Science Institute, RIKEN, Japan

Tuning thalamic firing modes via simultaneous modulation of T- and L-type Ca^{2+} channels controls sensory gating
Eunji Cheong, Center for Neural Science, Korea Institute of Science & Technology, Korea

Thalamic gating mechanism in the generalization of focal seizures is modulated by T-type calcium channels
Daesoo Kim, Dept of Biological Sciences, KAIST, Korea

T-type calcium channels in the mediodorsal thalamus and fear extinction
Hee-Sup Shin, Center for Neural Science, Korea Institute of Science & Technology, Korea

12:15 -14:00 Lunch *Wahkeena Falls – 2nd floor*

14:00-16:00 **Symposium Session II** *Elowah / Multnomah Falls – 2nd floor*

Substance abuse genetics: initiation of drug use, and transition to dependence

John Crabbe, Chair

Drinking: what's impulsivity got to do with it?
Suzanne Mitchell, Dept of Behavioral Neuroscience, Oregon Health & Science University, USA

Novelty preference predicts amphetamine use in rats
Michael Bardo, Dept of Psychology, University of Kentucky, USA

A mouse line selectively bred for High Drinking in the Dark (HDID) - when does drinking escape their control?
John Crabbe, Dept of Behavioral Neuroscience, Oregon Health & Science University, and Portland VA Medical Center, USA

Impulsivity, conduct problems, and early age of onset of drug use: a genome scan and candidate gene study
Cindy Ehlers, Dept of Molecular and Integrative Neurosciences, The Scripps Research Institute, USA

16:00-16:30 Coffee Break *Wahkeena Falls – 2nd floor*

16:30-18:30 **Invited Talks** *Elowah / Multnomah Falls – 2nd floor*

Outstanding Young Investigator Travel Awardees

Tamara Phillips, Chair

A novel model for depressive and motivated behavior based on selective breeding
Roman Gersner, Dept of Neurobiology, Weizmann Institute of Science, Rehovot, Israel

Kir3.3 (GIRK3) null mutation attenuates alcohol and pentobarbital withdrawal convulsion severity in mice
Lauren Milner, Dept of Behavioral Neuroscience, Oregon Health & Science University, and Portland VA Medical Center, USA

Confirmation of quantitative trait loci influencing methamphetamine- and opioid-induced locomotor stimulation using B6.D2 congenic strains
Camron Bryant, Dept of Human Genetics, University of Chicago, USA

miRNA regulation of gene expression underlies tolerance to alcohol
Andrzej Pietrzykowski, Dept of Psychiatry, University of Massachusetts, USA

_____

18:30- Tuesday evening dinner is on your own

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Wednesday, May 7th

7:00-8:15 Wednesday Speakers' Presentation Preparation *Elowah / Multnomah Falls – 2nd floor*
(please bring your PPT presentation to be loaded on the meeting computer)

7:00-8:30 Continental Breakfast *Wahkeena Falls – 2nd floor*
Meeting Registration available at this time

8:30-9:30 **Program Committee Plenary Address** *Elowah / Multnomah Falls – 2nd floor*
Introduced by Kari Buck, Chair, Program Committee

Of flies and mice: what have flies taught us about drug addiction?

Ulrike Heberlein
Ernest Gallo Clinic and Research Center, Program in Neuroscience, & Department of Anatomy University of California at San Francisco, USA

9:30-10:00 Coffee Break *Wahkeena Falls – 2nd floor*

10:00-12:00 **Symposium Session III** *Elowah / Multnomah Falls – 2nd floor*

Methodological considerations in the genetical genomics of complex traits

Igor Ponomarev and Robert Hitzemann, Chairs

Genetic dissection of genetic control of brain gene expression on a genome-wide scale: QTL analysis of mouse microarray data in two BXDF2 populations.
John Belknap, Dept of Behavioral Neuroscience, Oregon Health & Science University, and Portland VA Medical Center, USA

Mouse brain gene expression analysis: cross platform comparisons
Robert Hitzemann, Dept of Behavioral Neuroscience, Oregon Health & Science University, and Portland VA Medical Center, USA

Integrative genetic and genomic strategies to study mechanisms of excessive ethanol consumption in mice
Igor Ponomarev, Waggoner Center for Alcohol and Addiction Research, The University of Texas at Austin, USA

ARIdb - Alcohol Research Integrator Database: genetical genomic dissection of alcohol drinking
Susan Bergeson, Dept of Pharmacology and Neuroscience, Texas Tech University, USA

12:00 -13:30 Lunch *Wahkeena Falls – 2nd floor*

***Please arrange your posters on the boards provided in the Willamette Falls Room, 1st floor, in preparation for the Poster Session this afternoon*

13:30-15:30 **Symposium Session IV** *Elowah / Multnomah Falls – 2nd floor*

Approaching the genetics of alcoholism across different model organisms

Helen Kamens and Chris Kliethermes, Chairs

A genetic analysis of ethanol sensitivity and tolerance in *C. elegans*
Steve McIntire, Ernest Gallo Clinic & Research Center, University of California at San Francisco, USA

Definition of a dopaminergic neural circuit that controls behavioral responses to drugs of abuse in *Drosophila*
Fred Wolf, Ernest Gallo Clinic & Research Center, University of California at San Francisco, USA

The chromosome 9 quantitative trait locus for ethanol consumption: evidence for polygenic influence within this region
Helen Kamens, Dept of Psychiatry, Yale University, USA

Human studies of neuronal nicotinic receptor genes and their role in the co-morbidity of alcohol and nicotine dependence
Marissa Ehringer, Dept of Integrative Physiology, University of Colorado at Boulder, USA

15:30 -16:00 Break before poster session

16:00-18:00 Poster Session – cash bar *Willamette Falls – 1st floor*

18:00- Wednesday evening dinner is on your own

Thursday, May 8th

7:00-8:15 Thursday Speakers' Presentation Preparation *Elowah / Multnomah Falls – 2nd floor*
(please bring your PPT presentation to be loaded on the meeting computer)

7:00-8:30 Continental Breakfast *Wahkeena Falls – 2nd floor*

8:30-9:30 **Distinguished Scientist Award and Lecture** *Elowah / Multnomah Falls – 2nd floor*
Introduced by Douglas Wahlsten

John Belknap (co-recipient)
Dept of Behavioral Neuroscience, Oregon Health & Science University, and Portland VA Medical Center, USA

John Crabbe (co-recipient)
Dept of Behavioral Neuroscience, Oregon Health & Science University, and Portland VA Medical Center, USA

9:30-10:00 Coffee Break *Wahkeena Falls – 2nd floor*

10:00-12:00 **Symposium Session V** *Elowah / Multnomah Falls – 2nd floor*
Role of oxidative stress in behavior
Abraham Palmer, Chair

Expression differences in Glo1 among mice are due to a common copy number polymorphism
Abraham Palmer, Dept of Human Genetics and Psychiatry, University of Chicago, USA

Studies of glyoxalase 1 and glutathione reductase 1 in mice and humans
Iiris Hovatta, Research Program of Molecular Neurology, Biomedicum, Finland

Identification of promising candidate genes for ethanol dependence and associated withdrawal: a potential role for mitochondira and oxidative stress
Deaunne Denmark, Dept Behavioral Neuroscience, Oregon Health & Science University, USA

Glyoxalase 1 in HAB/LAB mice: from genetic polymorphisms to anxiety-related behavior
Rainer Landgraf, Max Planck Institute of Psychiatry, Germany

Beginning at 12:00, Thursday, May 8th, free time for the remainder of the day

Lunch and dinner are on your own

Please see the list beginning on page 15 of this Conference Program schedule for local cultural, recreational and other opportunities

Friday, May 8th

7:00-8:15 Friday Speakers' Presentation Preparation *Elowah / Multnomah Falls – 2nd floor*
(please bring your PPT presentation to be loaded on the meeting computer)

7:00-8:30 Continental Breakfast *Wahkeena Falls – 2nd floor*

8:30-9:30 **Young Scientist Award and Lecture** *Elowah / Multnomah Falls – 2nd floor*
Introduced by John Crabbe

Mouse genetic differences in exercise-induced adult hippocampal neurogenesis & learning
Justin Rhodes
Dept of Psychology, Beckman Institute, University of Illinois, Urbana, Illinois, USA

9:30-10:00 Coffee Break *Wahkeena Falls – 2nd floor*
***Please take down your posters from the boards in the Willamette Falls Room, 1st floor*

10:00-12:00 **Symposium Session VI** *Elowah / Multnomah Falls – 2nd floor*
Learning and memory: from causes to consequences
K. Matthew Lattal, Chair

Predicting danger: the circumstances that produce fear learning
Gavin McNally, School of Psychology, University of New South Wales, Australia

The contribution of striatal subregions to stimulus-modulation of reward-seeking behaviors
Laura Corbit, Ernest Gallo Clinic & Research Center, Univ of California at San Francisco, USA

Ablation of adult hippocampal neurogenesis both impairs and enhances hippocampusdependent behaviors
Michael Drew, Depts of Psychiatry and Neuroscience, Columbia University, USA

Memory expression, extinction, and the problem of mouse behavior
K. Matthew Lattal, Dept of Behavioral Neuroscience, Oregon Health & Science Univ, USA

12:00 -13:30 Lunch *Wahkeena Falls – 2nd floor*

13:30-15:30 **Paper Session** *Elowah / Multnomah Falls – 2nd floor*

Invited Talks from selected meeting abstracts

Helen Kamens, Chair

Differential effects of voluntary alcohol drinking on brain endocannabinoid levels in female and male rats of the alcohol-preferring AA line
Petri Hyytia, Dept of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland

An evolutionarily conserved sexual signature in the primate brain
Elena Jazin, Dept of Development and Genetics, Uppsala University, Uppsala Sweden

Characterisation of *spiegel*, a novel aggressive zebrafish mutant
William Norton, Zebrafish Neurogenetics, IDG, HelmholtzZentrum muenchen, Neuherberg, Germany

Evaluating the role of $GABA_B$ receptors in ethanol sensitivity
Sarah Holstein, Dept of Behavioral Neuroscience, Portland Alcohol Research Center, Oregon Health & Science University, Department of Veterans Affairs Medical Center, Portland, Oregon USA

LMO4 in nucleus accumbens regulates cocaine-induced behavioral plasticity
Amy Lasek, The Ernest Gallo Clinic and Research Center, University of California at San Francisco, Emeryville, California USA

Organismal and genetic networks in anxiety and depression
Lisa Tarantino, Genomics Institute of the Novartis Research Foundation, San Diego, California and University of North Carolina at Chapel Hill, Chapel Hill, North Carolina USA

15:30-16:00 Coffee Break *Wahkeena Falls – 2nd floor*

16:00-17:00 IBANGS Business Meeting *Elowah / Multnomah Falls – 2nd floor*

18:30 Cash bar opens in the banquet hall *Wahkeena/ Elowah Falls – 2nd floor*

19:00-22:00 Closing Banquet *Wahkeena/ Elowah Falls – 2nd floor*

Conference Social Event, Thursday afternoon, May 8th
Wineries Tour – Yamhill County, Oregon

Meeting participants sign up at meeting registration table and pay transportation fee by Tuesday, May 6th

We will visit two wineries, about 50 minutes by motor coach from Portland, and have tastings:

Anne Amie Vineyards, located in Carlton, Oregon, is known especially for its Pinot Noir, Pinot Gris, and Pinot Blanc. To preview wines please go to www.anneamie.com and click on "Our Wines". To read reviews click on "Blog".

Yamhill Valley Vineyards, in McMinnville, Oregon, is also known for its Pinot Noir, Pinot Gris, and Pinot Blanc. To preview wines and read reviews, please go to www.yamhill.com and click on "Recent Events" and on "Our Wines"

Transportation fee: $35.00 USD for transportation, includes box lunch and beverage
Wineries tasting fees: $5.00 - $15.00 USD at each winery, depending on wines selected

Motor coach departs from the hotel main lobby entrance at 12:45 and returns to the hotel by 18:00 (6:00PM).

Local Cultural, Recreational and Other Opportunities

Biking - Waterfront Bicycle Company
bicycle rentals, just south of the Burnside Bridge
10 SW Ash Street # 100 at SW Naito Parkway
Portland, OR 97204
503.227.1719
Website: http://www.waterfrontbikes.net/

Brewery Guide to Portland and Beyond
Website: http://www.oregonbeer.org/links.html

Columbia River Gorge & Mount Hood
car rental required – complete scenic loop 169 miles/272 kilometers
http://www.fs.fed.us/r6/columbia/forest/documents/GorgeVistas05low-res.pdf
http://www.fs.fed.us/r6/mthood/
http://www.timberlinelodge.com/index.php 6000' (1828m) – Check on road and ski conditions

Downtown Portland - Self-Guided Tours
via walking and/or public transportation
Websites:
http://www.travelportland.com/arts_culture/cultural_tours/culture_district/culture_dis_tour.html
http://www.powells.com/pdf/portland_walking_map.pdf (downtown walking map)
http://www.portlandonline.com/TRANSPORTATION/index.cfm?c=39402

Kayaking - Portland River Company
kayaking rentals on the Willamette River
on the pedestrian way, RiverPlace Marina
503.459.4050
Website: http://www.portlandrivercompany.com/index.html

Maps of the Portland area
detailed for walking, biking, and public transportation
Website: http://www.portlandonline.com/TRANSPORTATION/index.cfm?c=34783

Mt St. Helens National Volcanic Monument
car rental required – Roundtrip travel time only: 6 hours
Coldwater Ridge Visitor Center, may open in May, check on road conditions
Website: http://www.fs.fed.us/gpnf/mshnvm/

Oregon Historical Society
history of Oregon, Oregon Trail
1200 S.W. Park Ave.
Portland, OR 97205
503.222.1741
Website: www.ohs.org

Oregon Maritime Museum
located on Sternwheeler on the Willamette River
at the foot of SW Pine St.
Portland, OR 97204
Phone: 503.224.7724
Website: www.oregonmaritimemuseum.org

Portland Art Museum
1219 SW Park Avenue
Portland, OR 97205
503.226.2811
special exhibit: now through May 11th
The Dancer: Degas, Forain, and Toulouse-Lautrec
Website: http://www.portlandartmuseum.org/

Portland Center for the Performing Arts
twenty-one resident companies
including ballet, opera, symphony, theater
check for current events and tickets

Website: http://www.pcpa.com/index.php

Portland Classical Chinese Garden
located at NW 3rd Ave and NW Everett in Old Town/Chinatown
Portland, OR
503.228.8131
Website: http://www.portlandchinesegarden.org/

Portland Japanese Garden
located in Washington Park
611 SW Kingston Avenue
Portland, Oregon 97205
503.223.1321
Website: http://www.japanesegarden.com/visiting/

Portland Saturday Market
local artisans – open Sunday too
located under the Burnside Bridge
108 W Burnside St
Portland, OR 97209
503. 222.6072
Website: http://www.portlandsaturdaymarket.com/

Powell's City of Books
a Portland landmark
1005 W Burnside at NW 10th Ave
Portland, OR 97209
503.28.4651
Website: http://www.powells.com/

Wineries within about one hour drive time from Portland
Website: http://www.winesnw.com/nwillmap.html

Restaurants

Downtown: by walking, streetcar, or bus				
Abou Karim	Good Lebanese	Moderate	221 SW Pine St	503-223-5058
Al-Amir	Good Middle Eastern (Bishop's House)	Moderate	223 SW Stark St	503-274-0010
Bijou Café	Great Breakfast & Lunch (no dinner)	Moderate	132 SW 3rd Ave	503-222-3187
Cheerful Tortoise	Student Pub (near Portland State Univ and Univ Place Hotel)	Inexpensive	1939 SW6th	503-224-3377
Dragonfish	Sushi, Fusion Japanese Bar / Restaurant	Mod-Expen	909 SW Park Avenue	503-243-5991
Full Sail Brewing	Pub/Brewery	Inexpensive	307 SW Montgomery	503-220-1865
Harborside Restaurant & Pilsner Room	Restaurant: Good fish, great view Pilsner Rm: local microbrews	Moderate	0309 SW Montgomery	503-220-1865
Heathman Hotel	Excellent Restaurant & Wines	Expensive	SW Broadway & Salmon	503-790-7752
Higgins	Northwest; one of the best in Portland; also good vegetarian menu	Expensive	1239 SW Broadway	503-222-9070
Huber's	Old Northwest Saloon, Dining Room	Moderate	411 SW Third Ave	503-228-5686
India House	Indian	Inexpensive	1038 SW Morrison St	503-274-1017

Downtown: by walking, streetcar, or bus				
Jake's	Portland Classic Outstanding Seafood; Extensive Fresh List	Expensive	401 SW 12th Ave	503-226-1419
Jake's Grill	Portland Classic Open Late	Moderate - Expensive	611 SW 10th Ave	503-220-1850
Kell's	Good Irish Pub and Restaurant	Inexpensive - Moderate	112 SW 2nd Ave	503-227-4057
London Grill	International; steaks; fine wine cellar	Expensive	309 SW Broadway Ave (Benson Hotel)	503-295-4110
Lotus Card Room & Café	American; smokey card room; dance hall	Inexpensive - Moderate	932 SW 3rd & Salmon	503-227-6185
Mandarin Cove	Very good Chinese	Inexpensive - Moderate	111 SW Columbia	503-222-0006
Maya's Taqueria	Very good traditional Mexican fast food	Inexpensive	1000 SW Morrison	503-226-1946
McCormick & Schmick's	Same fish & owners as Jake's; steaks; saloon; single malts	Moderate - Expensive	235 SW 1st Ave	503-224-7522
Mother's Bistro & Bar	Comfort, Northwest	Moderate	409 SW 2nd Ave	503-464-1122
La Terrazza	Very good pasta	Inexpensive	1022 SW Morrison	503-916-4388
Pazzo's	Excellent Italian; bread; oil; reds	Expensive	422 SW Broadway	503-228-1515
Pioneer Place Food Court	Many choices; good food; central seating area	Inexpensive	700 SW 5th Bottom floor of mall	NA
Pizzicato Gourmet Pizza	Pizza	Moderate	705 SW Alder St	503-226-1007

Downtown: by walking, streetcar, or bus				
Portland City Grill	Northwest; great view of mountains & city; great wine list, ok food	Expensive	Unico US Bank Tower, 30th fl 111 SW 5th Ave	503-450-0030
Red Star Tavern & Roast House	American, Steakhouse	Moderate	503 SW Alder St	503-222-0005
Rock Bottom Brewery	Chain Brewpub (non-local)	Moderate	210 SW Morrison	503-796-2739
Sungari	Fancy Szechuan; excellent	Moderate	735 SW 1st Ave	503-224-0800
Saucebox	Trendy Bar with Fusion	Moderate	214 SW Broadway	503-241-3393
Southpark	Extensive fresh fish list; great wine list	Expensive	901 SW Salmon	503-326-1300
Todai Restaurant	Japanese, Sushi, Seafood	Moderate	340 SW Morrison St (Pioneer Place)	503-294-0007
Typhoon!	Thai	Moderate	410 SW Broadway	503.224-8285
Veritable Quandary	Northwest (near DoubleTree Hotel)	Moderate	1220 SW 1st Ave	503-227-7342
Voodoo Doughnut Mon-Sat 10pm-10 am Cash only	Walk-up take-out window, hole in the wall. Doubles as Wedding Chapel - a legal commitment is $175 and includes coffee and doughnuts for 10.	Inexpensive	22 SW Third Ave (Near Berbati's Pan)	no phone

NW 23rd Avenue District: by streetcar or bus				
Bamboo	Fancy Chinese	Expensive	103 NW 21st Ave	503-241-8122

NW 23rd Avenue District: by streetcar or bus				
Basta's Trattoria	Very good pasta	Moderate	410 NW 21st Ave	503-274-1572
Beau Thai	Thai/Vietnamese	Expensive	730 NW 21st Ave	503-223-2182
Blue Moon Tavern	Pub; local beer	Inexpensive	432 NW 21st Ave	503-223-3184
The Bull Ring	Very good Mexican; longer bus ride	Inexpensive	1900 NW 27th & Vaughn	503-274-4096
Caffe Mingo	Italian bistro	Expensive	807 NW 21st Ave	503-226-4646
Kornblatt's	Jewish Deli	Inexpensive - Moderate	628 NW 23rd Ave	503-242-0055
Lucy's Table	Northwest, excellent	Moderate - Expensive	706 NW 21st Ave	503-226-6126
Marrakesh	Authentic Moroccan	Moderate - Expensive	1201 NW 21st Ave	503-248-9442
Paley's Place	Northwest;one of Portland's best; great desserts	Expensive	1204 NW 21st Ave	503-243-2403
Papa Hayden	Bistro; great deserts	Moderate - Expensive	701 NW 23rd Ave	503-228-7317
The Ring Side	Classic and excellent Steak & Onions baby	Moderate - Expensive	2165 W Burnside St	503-223-1513
Swagat	Very good Indian cuisine	Moderate	2074 NW Lovejoy Street	503-227-4300
Tara Thai	Very good Thai	Moderate - Expensive	1310 NW 23rd Ave	503-222-7840

NW 23rd Avenue District: by streetcar or bus				
Wildwood	Northwest; one of the best in Portland; wood oven grill	Expensive	1221 NW 21st Avenue	503-248-9663

The Pearl District: by streetcar or bus				
Alexis Greek	Best Greek	Moderate	215 W. Burnside St.	503-24-8577
Bluehour	Excellent, trendy	Expensive	250 NW 13th Ave	503-226-3394
Bridgeport Brew Pub	Local Pub	Moderate	1313 NW Marshall	503-241-3612
Crystal Ballroom	Bars/Pubs; restored dance hall with adjustable floor	Moderate	1332 W Burnside St	503-225-0047
Fratelli's	Excellent Italian, great atmosphere	Moderate - Expensive	1230 NW Hoyt	503-241-8800
Giorgio's	Excellent formal Italian	Expensive	1131 NW Hoyt St	503-221-1888
Le Bouchon	French Bistro	Expensive	517 NW 14th Ave	503-248-2193
Oba!	Latin, trendy	Moderate - Expensive	555 NW 12th	503-228-6161
Obi	Japanese Sushi Bar	Inexpensive	101 NW 2nd Ave	503-226-3826
Park Kitchen	Northwest cuisine	Expensive	422 NW 8th Ave	503- 223-7275
Pearl Bakery	Breakfast/Lunch (Espresso), Cafes/Bagels	Moderate	102 NW Ninth Ave	503-827-0910
Sungari Pearl	Interesting building; excellent Chinese	Mod-Expen	1105 NW Lovejoy	971-222-7327

Additional Restaurants of Note				
Café Castagna	Italian - very creative	Expensive	1758 SE Hawthorne Blvd (cab ride)	503-231-9959
Chart House	Northwest Cuisine; great view of Mt. Hood; food is okay	Expensive	5700 SW Terwilliger Blvd (cab ride)	503-246-6963
Genoa	Italian 7-course pris fixe; One of the US's best restaurants	Expensive	2832 SE Belmont (cab ride)	503-238-1464
Lauro Kitchen	Mediterranean neighborhood restaurant	Moderate	3377 SE Division St (cab ride)	503-239-7000
Wild Abandon	Eclectic northwest neighborhood restaurant	Moderate - Expensive	2411 Se Belmont St (cab ride)	503-232-4458

Genes, Brain, and Behavior

Conference Abstracts

Tenth Annual Meeting of the
International Behavioural and Neural Genetics Society

May 5-9, 2008
Portland, Oregon USA

Tuesday, May 6th

8:45-9:45 **Presidential Plenary Address**

Molecular and cellular cognition: from memory mechanisms to treatments

Alcino Silva
Departments of Neurobiology and Psychology, and the Brain Research Institute, University of California at Los Angeles, USA

Our laboratory is studying molecular and cellular mechanisms of learning and memory, including those associated with learning disabilities. This poorly understood class of disorders affects more than one in 20 people world wide, but unfortunately there are no treatments. Because of the difficulties of unraveling the causes for these disorders in humans, we have used mouse models. For example, mutations in the Neurofibromatosis Type 1 (NF1) gene, encoding Neurofibromin, a p21Ras GTPase Activating Protein (GAP), cause learning disabilities and attention deficits. Our studies have shown that the learning and memory deficits of a mouse model of NF1 ($nf1^{+/-}$) are caused by excessive p21Ras/MAPK signaling leading to hyperphosphorylation of synapsin I, and subsequent enhanced GABA release, which in turn result in impairments in long-term potentiation (LTP), a cellular mechanism of learning and memory. Consistent with increased GABA-mediated inhibition, we (collaboration with Katie Karlsgodt and Ty Cannon) found evidence for brain hypoactivation in fMRI studies of NF1 patients. Recently, we discovered that statins, at concentrations ineffective in controls, can reverse the enhanced p21Ras activity in the brain of $nf1^{+/-}$ mice, rescue their LTP deficits, and reverse their spatial learning and attention impairments. Strikingly, recently completed pilot clinical trials (collaboration with Elgersma *et al*, U. Roterdam) demonstrated that statins can also reverse cognitive deficits in children with NF1. Similarly, we have also been studied another complex disorder that affects a molecular pathway related to p21Ras/MAPK signaling: tuberous sclerosis. This is a single-gene disorder caused by heterozygous mutations in either the *TSC1 or TSC2* gene, and is frequently associated with learning disabilities, mental retardation, and other neurological symptoms. Even TSC patients with a normal IQ (approximately 50%) are commonly affected with specific neuropsychological problems, including long-term and working memory deficits. We found that mice with a heterozygous, inactivating mutation in the *Tsc2* gene ($Tsc2^{+/-}$ mice) show deficits in learning and memory. Cognitive deficits in $Tsc2^{+/-}$ mice emerge in the absence of neuropathology and seizures, demonstrating that other disease mechanims are involved. We show that hyperactive hippocampal mTOR signaling (downstream of p21Ras/MAPK signaling) leads to abnormal hippocampal CA1 LTP and consequently to deficits in hippocampal-dependent learning. These deficits include impairments in spatial learning, and in contextual discrimination. Remarkably, we demonstrate that a brief treatment with the mTOR inhibitor rapamycin in adult mice can rescue not only the synaptic plasticity, but also the behavioral deficits in this animal model of TSC. These results reveal a biological basis for some of the cognitive deficits associated with TSC and they show that treatment with mTOR antagonists may ameliorate cognitive dysfunction in a mouse model of this disorder. Current studies are testing this hypothesis in clinical trials. Altogether the results described above outline a research program designed to unravel mechanisms of learning disorders in mice and bridge these findings with related human studies. This effort not only will elucidate mechanisms and cures for cognitive disorders, such as learning disabilities, it will narrow the current divide between behavioral and cognitive neuroscience.

Tuesday, May 6th

10:15-12:15 **Symposium Session I**

Thalamus in physiology and diseases, from genes to behavior

Hee-Sup Shin, Chair

Genetic dissection of somatosensory circuit maturation in mice

S Itohara, T Iwasato

Lab. Behavioral Genetics, RIKEN Brain Science Institute, Wako, Saitama, Japan

Barrel pattern formation in the somatosensory cortex in rodents provides an excellent model system for studying activity-dependent maturation of neuronal circuits. To unravel the molecular and cellular mechanisms underlying circuit maturation in the somatosensory cortex, we previously developed a cortex-specific conditional mutagenesis system in mice, and revealed essential roles of cortical NMDA receptors (NMDAR) in the patterning and dendritic maturation of layer IV cells and in the development of the full complementation of thalamocortical (TC) patterns. Here, we extended our analyses to type 1 adenylate cyclase (AC1) as a candidate downstream molecule of NMDAR signaling. AC1, which catalyzes the formation of cAMP, is stimulated by increases in intracellular Ca^{2+} levels in an activity-dependent manner. It is well established that the AC1 mutant mouse *barrelless* (*brl*) lacks the typical barrel cytoarchitecture and displays pre- and postsynaptic functional defects at TC synapses. Because AC1 is expressed throughout the trigeminal pathway, however, the barrel cortex phenotype of *brl* mice may be a consequence of AC1 disruption in cortical or subcortical regions. To examine the role of cortical AC1 in the development of anatomic barrels and TC synapses, we generated cortex-specific AC1 knockout (CxAC1KO) mice. Neurons in layer IV formed grossly normal barrels and TC axons filled barrel hollows in CxAC1KO mice. Further, whisker lesion-induced critical period plasticity was not impaired in these mice. There were, however, quantitative reductions in the quality of the cortical barrel cytoarchitecture and in the dendritic asymmetry of layer IV barrel neurons in CxAC1KO mice. Electrophysiologically, CxAC1KO mice have deficits in postsynaptic, but not presynaptic, maturation of TC synapses. These results suggest that activity-dependent postsynaptic AC1-cAMP signaling is required for the functional maturation of TC synapses and the development of normal barrel cortex cytoarchitecture. These findings also suggest that formation of the gross morphologic features of barrels is independent of postnatal AC1 in the barrel cortex.

Tuning thalamic firing modes via simultaneous modulation of T- and L-type Ca^{2+} channels controls sensory gating

E Cheong, S Lee, BJ Choi, M Sun, CJ Lee, H-S Shin

Center for Neural Science, Korea Institute of Science & Technology, Korea

The firing modes of thalamocortical (TC) neurons are thought to reflect the status of signal transmission from thalamus to cortex. However, the behavioral consequences of changes in the thalamic firing have not been well demonstrated. Moreover, although the firing modes of TC neurons are known to be affected by corticothalamic inputs via the mGluR1 pathway, its molecular mechanisms have not been well elucidated. We addressed these questions using phospholipaseCb4 (PLCb4)-deficient mice, which show decreased visceral pain responses. We demonstrate that burst and tonic firing of TC neurons are concomitantly regulated by metabotropic glutamate receptor1 (mGluR1)-PLCb4 pathway. Blocking of this pathway by the mutation simultaneously increases bursting and decreases tonic firing of TC neurons through concurrent up-regulation of T- and L-type calcium currents. The mice with increased bursting and decreased tonic firing of TC neurons showed reduced visceral pain responses. Furthermore, we show that modulation of the calcium channels or protein kinase C (PKC), a downstream molecule of PLCb4, altered the firing modes of TC neurons and pain responses in the predicted ways. Our data demonstrate the molecular mechanism and behavioral consequences of altered firing modes of TC neurons in relaying the visceral pain signals. Our study also highlights the thalamic mGluR1-PLCb4-PKC pathway as a “molecular switch” for the firing modes of TC neurons, and thus for pain sensory gating.

Cortico-thalamo-cortical relay of information modulated by thalamic T-type calcium channels

D Kim

Dept of Biological Sciences, KAIST, Daejeon, Korea

The cortico-thalamo-cortical pathway, a connection between two different cortical regions via the thalamus, has been implicated in higher cognitive functions and in the pathological mechanism of epilepsy in the brain. Here, we established a focal seizure model in mice where focal seizure activities induced by cobalt wire in the frontal cortex were eventually propagated to other cortical regions. Multi-electrode recordings showed that as the focal seizure activities were emerging in the frontal cortex after cobalt-wire implantation the mediodorsal (MD) thalamus showed coherent bursting activities. Ipsilateral ablation of the MD region by electrolytic lesion significantly decreased the incidence of focal seizure in the frontal cortex while contralateral lesion of MD caused no effects. To address the role of burst firing of MD, we tried to examine the effect of cobalt-wire in mice lacking a1G T-type calcium channels which are known to lack burst firings in the thalamus. The cobalt-wire implanted a1G-/- mice showed significantly reduced focal seizure activities induced by cobalt-wire when compared with wildtype mice. Unexpectedly, however, behavioral convulsions were highly increased in the cobalt-wire implanted a1G-/- mice. EEG analysis showed that a1G-/- mice were prone to secondary generalization of seizure activities from the cobalt-wire implanted frontal cortex to other cortical regions. The present results suggest that thalamic T-type calcium channels (a1G) contribute to increase thalamocortical resonance and play an inhibitory role in the cortico-thalamo-cortical relay of information by increasing burst spikes.

Role of the mediodorsal thalamus in fear extinction.

H-S Shin[1], I Hong[2], H Kim[1], S Choi,[2] S Lee[1]

[1]Center for Neural Science, Korea Institute of Science and Technology, Seoul, and [2]School of Biological Sciences, College of Natural Sciences, Seoul National University, Seoul, Korea

The Mediodorsal thalamus (MD) is a part of the limbic system and connects reciprocally with the prefrontal cortex, the amygdala and the hippocampus, which comprise a network of structures involved in emotion. However, the contribution of the MD to behavior is poorly understood. Phospholipase C (PLC) β4 is expressed intensely in the MD but very lightly in the prefrontal cortex and the amygdala, the two key regions known to regulate fear extinction. Hear we examined a role of the MD using the PLCβ4$^{-/-}$ mice in the formation and extinction of auditory-conditioned fear. The PLCβ4$^{-/-}$ mice showed normal acquisition and comparable long-term memory of auditory-conditioned fear. However, the mutant was severely impaired in the fear extinction. An injection of U73122 (a PLC blocker) into the MD of the wild type mice produced suppression of extinction, mimicking the phenotype of the mutant. An infusion of mibefradil (a T-type blocker) into the MD ameliorated the impaired extinction phenotype in PLCβ4$^{-/-}$, and facilitated the extinction in wild type mice. These results suggest that the mediodorsal thalamus is involved in the control of fear extinction and T-type Ca^{2+} channels may play a role in this control.

Tuesday, May 6th

14:00-16:00 **Symposium Session II**

Substance abuse genetics: initiation of drug use, and transition to dependence

John Crabbe, Chair

Drinking: what's impulsivity got to do with it?

S Mitchell

Dept of Behavioral Neuroscience, Oregon Health & Science University, Portland, Oregon USA

Impulsivity can be measured by examining response inhibition and delay aversion. We have used both techniques to examine the relationship between impulsivity and alcohol consumption using rodent models. Two studies will be described in which we have examined the heritability of both measures in 15 standard inbred strains of mice, as well as the strain correlations between impulsivity measures and other measures associated with alcohol consumption (alcohol preference, behavioral sensitization to ethanol). Positive relationships suggest that there are some common genetic substrates between impulsivity and alcohol consumption. However, a study examining impulsivity in strains of mice selected for high or low levels of alcohol consumption found differences between the strains, indicating that the genetic link between impulsivity and alcohol drinking is not straightforward.

Novelty preference predicts amphetamine use in rats

M Bardo

Dept of Psychology, University of Kentucky, USA. *Supported by USPHS grant DA 05312*

Individual differences in response to novelty are known to predict vulnerability to stimulant self-administration in rodent models. Among outbred rats, activity in an inescapable novel environment and preference for novel stimuli have been used as predictor variables for amphetamine reward using either conditioned place preference or intravenous self-administration. Both of these predictor variables have been found to be associated with amphetamine reward and these differences are related to differential activity of the dopamine transporter (DAT) in the prefrontal cortex. To assess the influence of genetics, we have also examined response to novelty and acquisition of amphetamine self-administration in 12 inbred strains of rats: ACI; BDIX (BD9); Brown Norway (BN); Buffalo (Buf); Dahl salt sensitive (DSS); Fawn Hooded (FH); Fischer (F344); Lewis (LEW); Spontaneous hypertensive rat (SHR); Wistar Albino Glaxo (WAG); Wistar Furth (WF); and Wistar Kyoto (WKY). Significant differences in activity in an inescapable novel environment, preference for novel stimuli and acquisition of amphetamine self-administration were obtained across strains, indicating a genetic influence for each of these behaviors. Strain-dependent differences in the dose effect function for amphetamine self-administration were also obtained. More important, among inbred strains, there was a relation between novelty preference and amphetamine self-administration, suggesting a genetic link between novelty seeking and stimulant abuse vulnerability.

A mouse line selectively bred for High Drinking in the Dark (HDID) - when does drinking escape their control?

JC Crabbe

Portland Alcohol Research Center, Dept of Behavioral Neuroscience, Oregon Health & Science University, and Portland VA Medical Center, Portland, Oregon USA, *Supported by the Integrative Neuroscience Initiative on Alcoholism (AA13519), the NIAAA (AA010760), and the Department of Veterans Affairs*

Many animal models have targeted alcohol abuse and dependence, often by studying voluntary alcohol drinking. While some behavioral or genetic manipulations will induce mice or rats to self-administer alcohol to intoxication, these typically require significant food or water restriction and/or a long time to develop. Susceptible (i.e., relatively high-intake) genotypes do not appear to be preferentially susceptible to these effective behavioral manipulations. Some human alcoholics repeatedly drink to intoxication, even in the face of substantial physical and social feedback opposing this behavior. It would be useful to have a mouse genetic animal model that self-administers sufficient alcohol to become intoxicated. This talk will review progress toward that goal. We are selectively breeding High Drinking in the Dark mice to ingest 20% alcohol until they reach blood alcohol levels (BALs) exceeding 100 mg%. After 10 generations of selection, more than 40% of the population exceeds these BALs. These mice should be useful for neurobiological and genetic studies, and for pharmacological experiments designed to limit alcohol self-administration.

Impulsivity, conduct problems, and early age of onset of drug use: a genome scan and candidate gene study

[1]CL Ehlers, [1]DA Gilder, [2]W Slutske, [3]P Lind, [4]K Wilhelmsen

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Native Americans have the highest alcohol-related death rates of all ethnic groups. Explanations for increased drinking in some Native American communities have often focused on the hypothesis that disruption of their traditional cultures was associated with psychological states of anomie and depression which in turn led to increased use of alcohol, a theory that has found little empirical support. In Mission Indians, early age of onset of first intoxication was found to be significantly associated with alcohol dependence. Additionally, a high conditional probability of the development of dependence, given use, an earlier age of onset of dependence and a significant association of alcohol dependence with externalizing disorders were all found in this group of Indians. Analyses of the heritability of externalizing phenotypes, a genome scan and evaluation of candidate genes were accomplished in this population. Antisocial personality disorder (ASPD) and the combined phenotype of participants with ASPD or conduct disorder (CD) were both found to have significant heritability, whereas no significant evidence was found for CD alone. Genotypes were determined for a panel of 791 micro-satellite polymorphisms in 251 of the participants. Analyses of multipoint variance component LOD scores, for the heritable phenotypes of ASPD and ASPD/CD, revealed six locations that had a LOD score of 2.0 or above: on chromosome 13 for ASPD and on chromosomes 1,3,4,14,17 and 20 for ASPD/CD. Since impulsivity is one aspect of externalizing disorder that may be an important intermediate phenotypes we determined if a significant association could be detected between the (AAT)n triplet repeat polymorphism as well as 5 single nucleotide polymorphisms (SNPs) in or near in the *CNR1* receptor gene and impulsivity in this population. Impulsivity was assessed using a scale derived from the Maudsley personality inventory. The estimated heritability for the impulsivity phenotype was 0.20+ 0.12 ($p<0.004$). Impulsivity was significantly associated with the 6-repeat allele of the triplet repeat polymorphism as well as four SNPs in or near the *CNR1* receptor gene. Taken together, these results corroborate the importance of several chromosomal regions highlighted in prior segregation studies and identify new regions of the genome for externalizing diagnoses, and additionally provide data to suggest that the *CNR1* receptor gene may be significantly associated with impulsivity in Mission Indians.

Tuesday, May 6th

16:30-18:30 **Invited Talks – Outstanding Young Investigator Travel Awardees**

A novel model for depressive and motivated behavior based on selective breeding

R Gersner, A Zangen

Dept of Neurobiology, Weizmann Institute of Science, Rehovot, Israel

Depression is a multifactorial illness that is caused by interactions between genetic predisposition and environmental factors. Despite the extensive biomedical research conducted in the field for more than half a century, we still lack basic information about the etiology and pathophysiology of depression. The diagnostic criteria for depression include several symptoms and it has also become clear that the risk for depression is partially genetic. We were therefore encouraged to investigate genetic factors of depressive behavior by establishing a novel animal model for depression based on selective breeding for a depressive phenotype. The selective breeding is based on tests that cover the core symptoms: loss of interest (using an exploration test in automatic locomotion boxes), lack of motivation (using a modified swimming test), anhedonia (using the sucrose preference test) and reduced energy/fatigue by chronically screening locomotor activity (using home-cage-based locomotion system). We are currently testing the tenth generation of our genetic model of depressive and motivated behavior. So far we found significant differences between the rat lines in swimming test, sucrose preference test, in the basal locomotor activity at young ages and in some aspects of exploration. In addition, we found significant difference in BDNF expression in reward-related brain areas between the depressive, normal and motivated rat lines. Electroconvulsive therapy, but not desipramine treatment, was shown to recover some of the behavioral and molecular changes in depressive rats. Therefore some of the features related to depressive or motivated behavior are hereditary in our model, which resembles drug-resistant depression and seems likely to have a genetic basis that we continue to explore.

Kir3.3 (GIRK3) null mutation attenuates alcohol and pentobarbital withdrawal convulsion severity in mice

LC Milner[1], LB Kozell[1], K Wickman[2], KJ Buck[1]

[1]Department of Behavioral Neuroscience & Portland Alcohol Research Center, VA Medical Center and Oregon Health & Science University, Portland, Oregon USA, and [2]Department of Pharmacology, University of Minnesota, Minneapolis, Minnesota USA. *Supported by AA10760, DA05228, AA011114 and a VA Merit grant*

Severity of withdrawal from sedative-hypnotic drugs, including barbiturates and alcohol (ethanol), is a hallmark of drug physiological dependence and may influence drug seeking and relapse behavior in dependent individuals. Although no animal model can exactly duplicate drug dependence, models for specific traits, such as the withdrawal syndrome, are useful for identifying genetic determinants of liability in humans. Previously, we identified quantitative trait loci (QTLs) on chromosome 1 that influence predisposition to barbiturate (pentobarbital) and ethanol withdrawal in mice. We recently narrowed the barbiturate withdrawal QTL to a 0.4 Mb interval containing 11 genes with validated transcript expression and/or non-synonymous coding sequence variation that may underlie the QTL's influence on sedative-hypnotic withdrawal. Here, we report the development of a null mutant for one of these genes, *Kcnj9,* which encodes a G-protein coupled inwardly rectifying potassium channel subunit (Kir3.3/GIRK3). Kir3.3 null mutants showed less severe pentobarbital ($H_{(2,280)}$= 14.5, p< 0.001) and ethanol ($F_{(1,80)}$=13.5, p<0.001) withdrawal convulsions than wildtype littermates (DBA/2J background). This work represents a substantial advancement toward identification of gene(s) underlying the phenotypic effects of this QTL, and identifies a role for *Kcnj9* in barbiturate and ethanol dependence and associated withdrawal.

Confirmation of quantitative trait loci influencing methamphetamine- and opioid-induced locomotor stimulation using B6.D2 congenic strains

CD Bryant, G Sokoloff, AA Palmer

Department of Human Genetics, The University of Chicago, Illinois USA. *Funding support: 5R01DA021336, 2T32DA007255*

We have previously identified quantitative trait loci (QTL) contributing to methamphetamine-induced locomotor stimulation on chromosomes 5, 9, 11, 12, and 15. Accordingly, we selected mice from a set of genome-wide congenic strains with C57BL/6J ("B6") as the recipient strain and DBA/2J ("D2") as the donor strain and confirmed QTLs on 11, 12 and 15. B6.D2 mice that were congenic for either the proximal or distal portion of chromosome 11 each contained QTLs for methamphetamine- and fentanyl-induced locomotor stimulation. We also surveyed a panel of B6.AJ chromosome substitution strains ("CSS") for methamphetamine sensitivity. QTLs were again identified on chromosomes 11 and 12, providing converging evidence for possibly the same loci as those confirmed with B6.D2 mice. The use of CSS mice also revealed novel QTLs on chromosomes 16 and 17 and sex-interacting QTLs on chromosomes 5 and 8. F2 crosses between B6.D2 congenic and B6.AJ CSS mice are currently being generated to narrow the QTLs. The identification of novel genes that contribute to sensitivity to drugs of abuse will be followed up by translational studies in humans in collaboration with Dr. Harriet de Wit's laboratory.

miRNA regulation of gene expression underlies tolerance to alcohol

AZ Pietrzykowski, RM Friesen, C Nowak, GE Martin, SI Puig, PM Wynne, SN Treistman

Brudnick Neuropsychiatric Research Institute, Department of Psychiatry, University of Massachusetts Medical School, Worcester, Massachusetts USA. *Funding support: ABMRF to AZP, NIAAA to SNT*

Susceptibility to alcoholism is influenced by multiple genes. Identification of these genes and mechanisms regulating their expression is a great challenge. Members of the recently discovered group of endogenous RNA species (microRNA) function as powerful "master-switches" of gene expression, with each microRNA modulating expression of multiple genes. Therefore, microRNAs are perfectly suited to work as central integrators of alcohol actions. We present the first example of the regulatory role of microRNA (miR-9) in the development of alcohol tolerance in neurons. Alcohol rapidly increased miR-9 expression in neurons and concomitantly changed expression of several, alcohol-relevant, CNS-specific, miR-9 target genes (BK, DRD2, GABRB2, CACNB1, HDAC5, SYNJ1, PPARA, CLOCK). Using BK channel we have determined a detailed molecular mechanism of that novel regulation. Upregulation of miR-9 causes a subtractive destruction of pre-existing BK mRNA variants, shifting BK mRNA profile towards mRNAs encoding alcohol-insensitive BK channels, via miR-9's binding to selected 3'UTRs associated with alcohol-sensitive channels. Remarkably, two out of three miR-9 genes are located in the chromosomal susceptibility loci for alcohol dependence. These results create a new level of understanding of alcohol actions in the CNS, can help to establish early diagnostics of alcohol susceptibility, and indicate novel therapeutic targets in alcoholism.

Wednesday, May 7th

8:30-9:30 **Program Committee Plenary Address**

Of flies and mice: what have flies taught us about drug addiction?

Ulrike Heberlein

Ernest Gallo Clinic and Research Center, Program in Neuroscience, & Department of Anatomy University of California at San Francisco, USA

To expand our knowledge of the genetic components underlying the behavioral effects of ethanol, we conducted a genetic screen in Drosophila and identified a mutant, *happyhour* (*hppy*), due to its resistance to the sedative effects of ethanol. Reduced hppy function resulted in resistance to ethanol-induced sedation, while neuronal overexpression of *hppy* caused increased sensitivity. Although *hppy* shows strong homology to mammalian Ste20 family kinases involved in JNK signaling, we found that neither activation nor inhibition of the JNK pathway affected ethanol sedation. However, perturbations of the EGF receptor (EGFR)/ERK pathway in specific neuronal subsets in the fly brain strongly affected sensitivity to ethanol-induced sedation. Genetic interaction experiments between *hppy* and components of the EGFR/ERK pathway suggest a role for *hppy* as an inhibitor of the pathway, functioning downstream of the EGFR but upstream of ERK. Finally, acute pharmacological inhibition of the EGFR in adult animals resulted in altered ethanol behaviors in both flies and rats. Our data thus identifies *hppy* as a novel modulator of EGFR/ERK signaling and uncovers a previously uncharacterized role for this pathway in mediating the behavioral response to ethanol in both Drosophila and mammals.

10:00-12:00 **Symposium Session III**

Methodological considerations in the genetical genomics of complex traits

Igor Ponomarev and Robert Hitzemann, Chairs

Genetic dissection of genetic control of brain gene expression on a genome-wide scale: QTL analysis of mouse microarray data in two BXDF2 populations

[1,3]JK Belknap, [1,3]P Darakjian, [1,3]NAR Walter, [1,3]KJ Buck, [1,2]SK McWeeney, [1,3]ML Helms, [1,3]LA O'Toole, [1,3]B Malmanger, [4]L Lu, [4]RW Williams, [1,3]RJ Hitzemann

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Two F_2 populations were subjected to Affymetrix MOE430 microarray analysis based on either whole brain (WB, *N*=56) or corpus striatum (STR, *N*=58) samples using one array per mouse. For WB, about 3,000 significant eQTLs (LOD >4.0) emerged from QTL analysis using *R/qtl*. Based on directional LOD scores, Spearman's rho correlation coefficient was 0.86 between the WB and STR data sets, showing very good agreement. For WB, about 1,600 of the eQTLs showed apparent cis regulation, where the eQTL mapped to the gene location, and about 1,200 showed trans regulation, where the eQTL mapped elsewhere in the genome from the gene whose expression it modulates. The apparent cis eQTLs showed mostly additive inheritance; on average, the magnitude of *d*, the dominance effect, was one-fourth the magnitude of *a*, the additive effect (avg effect of an allele substitution), resulting in a mean *d/a* ratio of 0.26. In marked contrast, the typical trans eQTL showed marked overdominance. The mean *d/a* ratio was 1.8, indicating that the heterozygotes scored well outside the range of the two homozygote classes for most trans eQTLs, and that *d* contributed much more to the genetic variance than did *a*. Overdominance, when compared to mostly additive inheritance, is predominantly associated with traits related to fitness. A genetic correlation matrix was subjected to K-Means cluster analysis followed by vetting of the more weakly correlated cluster members. Most clusters were either predominantly (>70%) cis eQTLs, or predominantly (>70%) trans eQTLs, with fewer clusters comprised of both in intermediate numbers. Most eQTLs within a cluster mapped to the same chromosomal region, showing a strong effect of linkage on clustering, but this effect was much strong for cis-dominated clusters compared to trans-dominated ones. The cluster members of predominantly trans eQTL clusters, but not cis eQTL clusters, showed strikingly similar degrees and direction of *d/a* ratios for eQTLs within a cluster, but very different values between clusters. This suggests that a single (or few) trans eQTL within a cluster drives many of the other trans cluster members; therefore, the number of distinct trans eQTLs is likely much smaller than the number of trans eQTL cluster members.

Mouse brain gene expression analysis: cross platform comparisons

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The past decade has witnessed some remarkable advances in mouse microarray-based gene expression analysis. These improvements resulted in part from completion of the mouse genome, the development of multi-strain SNP maps, new microarray technologies, and advances in data analysis (both low and high level). Data to be presented will examine the performance of three array platforms (Illumina Mouse 6.1, Affymetrix 430 2.0 and the Affymetrix Exon array) a) to detect differences in gene expression between the C57BL/6J(B6) and DBA/2J (D2) inbred strains, b) to detect cis and trans eQTLs in both a B6xD2 F_2 intercross and in heterogeneous stock (HS) animals and c) to detect gene networks. The latter will focus on the networks co-expressed with *Drd2* and *Calb2*. For all platforms, the data analysis will emphasize the role of SNPs in generating false positive differences in gene expression. Overall, the results illustrate that there are some marked differences among platforms in the detection of strain specific differences. In contrast, gene network integrity remains largely intact.

Integrative genetic and genomic strategies to study mechanisms of excessive ethanol consumption in mice

I Ponomarev

Waggoner Center for Alcohol and Addiction Research, The University of Texas at Austin, Austin, Texas, USA

Funding Support: NIAAA INIA grant (AA013517 Pilot Project component)

A growing number of microarray studies have used genetic rodent models to identify gene expression differences related to ethanol drinking. Because individual studies lack statistical power to identify candidate genes with small or moderate effect sizes, strategies that combine results from several studies and also integrate genomic and behavioral data with genetic mapping can be used to approach candidate gene selection with a greater confidence. Microarray data from 6 studies that used mouse genetic models of ethanol consumption (3 pairs of selected lines and 3 sets of inbred strains) were, first, combined into a meta-analysis. This analysis identified a subset of genes that consistently differentiated high-drinking from low-drinking genotypes (251 genes at FDR=5% and 4,124 genes at FDR=30%). Genetic mapping of transcript abundance for these genes using a set of BXD (C57BL/6J X DBA/2J) recombinant inbred strains revealed statistically overrepresented clusters of cis-regulated expression QTLs (eQTLs) that overlapped with 4 major behavioral QTLs (bQTLs) for ethanol consumption (see Belknap and Atkins, 2001 for bQTL info). Many genes regulated by cis-eQTLs were located within the same 1-3 Mb chromosomal intervals, suggesting the presence of “master” eQTLs that regulate the expression of several closely localized genes. Potential mechanisms for a “master” eQTL include SNPs in regulatory regions (such as enhancers and genomic insulators) that influence expression of multiple genes. In a separate analysis, genes with mis-sense mutations within bQTL confidence intervals were identified. Comparing genes with at least one mis-sense mutation and those regulated by cis-eQTLs identified a subset of overlapping genes. The number of these genes within a bQTL on chromosome 4 was significantly greater than expected by chance, suggesting that the two primary mechanisms for a bQTL have some common regulatory elements. Thus, cis-regulated genes with functional polymorphisms, which are located within bQTL confidence intervals can be selected as primary candidates for regulation of ethanol consumption.

ARIdb - Alcohol Research Integrator Database: genetical genomic dissection of alcohol drinking

SE Bergeson,[1] AE Berman[2]

[1]South Plains Alcohol and Addiction Research Consortia, Texas Tech University Health Science Center, Lubbock, Texas, USA, and [2]NCIRE Neurology Service, University of California at San Francisco, VA Medical Center, San Francisco, California, USA. *Supported by NIAAA INIA grant U01AA013475.*

Alcohol consumption and alcoholism continue to be a considerable problem in the United States. Numerous studies over the last half century have cemented that alcoholism and many alcohol-related traits display heritability in the range of 40-60 percent. Confounding the identification of the genes underlying the disease susceptibility and specific endophenotypes in particular is the magnitude of the polygenic contribution; numerous genes of small effect size are likely involved. Over the past five years, the Bergeson lab has completed cDNA microarray analyses of brain for several genetic mouse models commonly used in the alcohol field. An Alcohol Research Integrator database (ARIdb) was developed to publically distribute the results of large datasets in a searchable manner and comply with NIH resource sharing requirements. ARIdb has been licensed under the Gnu Public License (freely available from http://www.sourceforge.net) as an open source, MySQL-based interactive database system that utilizes a web-based Perl program capable of combining results that allows a researcher to ask detailed biological questions about the data it contains. Additionally, a suite of open source Perl command-line driven microarray analysis tools that utilize the R statistical platform and assorted packages accompanies the ARIdb. ARIdb allows facile microarray normalization, standardization, statistical, and mathematical analyses and web end user search and download capabilities. Details of how to acquire the database for use and how to gain access to the alcohol-related microarray data will be presented along with some genetical genomic results from the Bergeson lab studies.

Wednesday, May 7th

13:30-15:30 **Symposium Session IV**

Approaching the genetics of alcoholism across different model organisms

Helen Kamens and Chris Kliethermes, Chairs

A genetic analysis of ethanol sensitivity and tolerance in *C. elegans*

AG Davies, JT Pierce-Shimomura, JC Bettinger, H Kim, C Jee, J Lee, SL McIntire

Ernest Gallo Clinic & Research Center, Program in Neuroscience, Dept. of Neurology University of California at San Francisco, USA

We have pursued genetic studies in *C. elegans* to understand the molecular mechanisms of action of ethanol. Through forward genetic screens, we identified mutants exhibiting altered sensitivity to ethanol. Mapping and molecular characterization of the corresponding genes has revealed targets or biochemical pathways mediating behavioral responses to ethanol. To identify the mechanisms responsible for acute intoxication, we screened for mutants that exhibited resistance to the depressive effects of ethanol. We identified 28 mutants belonging to nine complementation groups. Numerous loss-of-function mutations in *slo-1* emerged from two different resistance screens, suggesting that *slo-1* has an important role in ethanol responses. *slo-1* encodes a large conductance BK channel. *slo-1* mutants show uniquely strong resistance to ethanol. Electrophysiological analysis demonstrated that ethanol activates the SLO-1 channel in vivo, which would inhibit the activity of wild-type neurons but not *slo-1* mutant neurons. Ethanol similarly activates mammalian BK channels in vitro. In a second approach, we explored the genetic basis for natural variation in the behavioral responses to ethanol of different natural isolates of *C. elegans*. Prolonged administration of ethanol to *C. elegans* results in acute tolerance, resulting in adaptation or decreased intoxication over time. We observed that different wild isolates of *C. elegans* exhibit differences in their rate of adaptation to ethanol. We then mapped the difference in acute tolerance between two strains to a single gene, *npr-1*. *npr-1* encodes an NPY-like receptor protein. The difference in the rate of tolerance is due to a single amino acid substitution in the *npr-1* gene.

Definition of a dopaminergic neural circuit that controls behavioral responses to drugs of abuse in *Drosophila*

F Wolf[1], K Woo[2], H Li[4], E Kong[1], N Mayer[3], MR Andres[2], R Bainton[3], J Hirsh[4], U Heberlein[1,2]
[1]Ernest Gallo Clinic and Research Center, Emeryville, California; [2]Dept of Anatomy, [3]Dept of Anesthesiology, University of California at San Francisco, USA; [4]Dept of Biology, University of Virginia, USA

Dopaminergic neurons and their synaptic targets in the mesolimbic region of the mammalian brain are centrally important mediators of the rewarding actions of drugs of abuse, including cocaine, ethanol, and other drugs. In Drosophila, behavioral responses to drug exposure are also regulated by dopamine. We found that evoked neurotransmission from a bilateral pair of dopaminergic neurons in the fly brain correlates with promotion of locomotor activity by ethanol exposure. These dopamine neurons send projections to brain regions that harbor the dendritic processes for the ellipsoid body of the central complex, whose function is required for ethanol-induced locomotor activity. The ellipsoid body expresses the D1-like dopamine receptor DopR, and we found that DopR is required for behavioral responses to ethanol as well as to cocaine. Expression of DopR solely in the ellipsoid body is sufficient for promoting ethanol-induced locomotor activity. DopR mutant flies also exhibit a spectrum of behavioral abnormalities that closely parallel those observed in D1 receptor knockout mice. These data establish a dopaminergic neural circuit in the fly brain that mediates the behavioral responses to drugs of abuse.

The chromosome 9 quantitative trait locus for ethanol consumption: evidence for polygenic influence within this region

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Supported by the Department of Veterans Affairs, NIAAA P60 AA010760 and F31 AA015822

Many studies have revealed that voluntary ethanol consumption is a complex behavior that is influenced by multiple genes, but to date no quantitative trait genes for this trait have been identified. In the mouse, the quantitative trait locus (QTL) with the largest genetic effect size for this behavior resides on chromosome 9. Our laboratory has confirmed the presence of this locus using a congenic strain. In an attempt to more finely map the location of this gene, we created a panel of interval specific congenic strains (ISCS), but these strains provided no additional mapping resolution. In an additional attempt to resolve the location of this gene, we used selective breeding to create lines of mice that exhibited high and low ethanol consumption. These lines were derived from the F2 cross of the high ethanol consuming C57BL/6J strain with one of the chromosome 9 ISCS that captured the QTL. Data from this novel approach suggest that there are at least two genes within a 16.1 Mb region of proximal chromosome 9 that influence this trait. Furthermore, since other non-overlapping ISCS also provide evidence of a QTL, there are likely multiple genes on chromosome 9 that influence this complex trait.

Human studies of neuronal nicotinic receptor genes and their role in the co-morbidity of alcohol and nicotine dependence

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The co-addiction of alcohol and nicotine is well documented and there is strong evidence that shared genetic factors contribute to this co-morbidity. We hypothesize that the neuronal nicotinic receptors (nAChRs) are a likely common site of action for these two substances. The nAChRs are ligand-gated ion channels that act as the primary targets for the endogenous agonist acetylcholine and for nicotine. Several lines of evidence from model systems suggest that alcohol may modulate the pharmacological properties of nicotine binding at nAChRs, usually by enhancing receptor function. Several groups have reported evidence for association between a number of polymorphisms (SNPs) in the nAChR subunit genes and alcohol and tobacco phenotypes in humans, including age-of-initiation, early subjective response, and dependence symptoms. Preliminary functional studies using luciferase reporter assays suggest that some of the associated SNPs may lead to differential levels of mRNA expression for different alleles. These studies will provide insight into the molecular mechanisms of human nAChR function, and how these genes may contribute to the co-morbidity of alcohol and nicotine addictions.

Wednesday, May 7th

16:00-18:00 **Poster Session**

1.

"Halfgate" and "Den" artifices support the notion that one mechanism is the basis of potentiation, learning and seizure

S Adkins

The neuron has elemental functionalities such as voltage-gated pores and allosterically-gated enzymes. Such functionalities are cascaded resulting in complex functionalities. Such a functionality is potentiation. Potentiation is characterized by an excitation frequency/ excitatory-postsynaptic-potential slope relationship. The basis of potentiation is thought to be the same as that of brain seizure and learning. I have reduced these gated elemental functionalities to collections of "Halfgates". The "Den" which I use to simulate this putative potentiation functionality is composed of 17 Halfgates modeling 6 aqueous chambers interfaced via gated pores. The Den model exhibits frequency/ slope behavior like that seen experimentally. In learning simulations, employing a monolayer of Den-based neurons, challenge-induced misfiring was scored. Long-term memory was demonstrated: misfiring decreased regarding each successive session-start. Short-term memory was demonstrated: within a session misfiring was reduced. First session misfiring at start 50%, end <1%; second session start 3.2%, end <0.1%, third session start 1.8%, end <0.01%. Simulating recruitment in seizure initiation, specific high frequency patterns of excitation caused >0.1% of neurons to fire continuously. Models of experience-modified potentiation, environmentally and electrically-modified seizure induction are detailed. Physical model animals, controlled by randomly interconnected Den-based neurons (microcontrollers), spontaneously adapt demonstrating selective response, short-term and long-term memory.

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2.

Role of the dual-specificity tyrosine(Y)-phosphorylation regulated kinase 1A (Dyrk1A) in neuromotor development: implications in Down syndrome

G Arqué[1,2], A Casanovas[3], M Dierssen[1,2]

Individuals with Down syndrome (DS) present important motor deficits in the dynamic production of movement and in postural control, but it is not know to what extent these abnormalities arise from developmental delays. DYRK1A is a candidate gene for DS abnormalities that maps in DS critical region of human chromosome 21. In these work, we performed an exhaustive analysis of its expression pattern in motor nuclei in brainstem and spinal cord during the postnatal period. Dyrk1A was expressed in GABAergic populations of the reticular formation at postnatal day (PND) 7, whereas its expression in motoneurons (MNs) forming the facial motor nucleus at PND14 or the anterior spinal cord started only at PND10, before the appearance of the cholinergic phenotype took place. In transgenic mice overexpressing Dyrk1A (TgDyrk1A), this expression was delayed in facial MNs together with delayed expression of choline acetyltransferase (CHAT) and mild to severe motor dysfunction, at the same postnatal developmental stages. Moreover, morphometric analyses of the facial nucleus showed increased cellularity along with increased cell soma size in TgDyrk1A. The results reveal new regulatory roles for the protein and may have important consequences for the understanding of the neuropathological alteration underlying motor deficits in DS patients.

[1]Genes and Disease Program, Center for Genomic Regulation-CRG, Universitat Pompeu Fabra, Barcelona, Spain. [2]CIBER on Rare Diseases (CIBERER), Valencia, Spain. [3]Unitat de Neurobiologia Cellular, Departament de Medicina Experimental, Universitat de Lleida and IRBLLEIDA, Lleida, Catalonia, Spain. Funding Support: Jerôme Lejeune Foundation and CIBER on Rare Disease (CIBERER)

3.

Relating social interaction to neuropathology in a mouse model of autism

RC Auerbach[1,2], VJ Bolivar[1,2]

Autism spectrum disorders (ASD) vary in their presentation and severity of symptoms; however, they are all characterized by abnormal social interaction. Currently there is no defining neuropathology for these disorders, but studies have implicated the corpus callosum and cerebellum. Our laboratory studies the BTBR *T+ tf*/J (BTBR) mouse as a model of ASD. We measure the interactive behavior of mice through a social approach assay that confines the initiation of social interaction to one mouse of a pair, thereby determining the level of sociability in a single mouse. We generated mice that exhibited a range of social behavior by crossing the minimally social BTBR strain with the highly social FVB/NJ strain, and analyzed the F2 generation. Behavioral tests revealed that sociability levels of the F2 mice were grouped around the average score of the two parental strains. These results deviated from a Mendelian pattern, which suggests that the behavior is controlled by more than one gene. Additionally, midline area of the corpus callosum correlated with social interaction levels. Currently we are analyzing cerebellar and other brain abnormalities and their relationship to social interaction in BTBR mice.

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4.

Reciprocal strain analysis of QTLs for ethanol sensitivity in Long- and Short-Sleep mice

B Bennett[1], P Carosone-Link[1], TE Johnson[1,2]

Interval specific congenic strains (ISCS) allow fine-mapping of a quantitative trait locus (QTL). In earlier work, we mapped four QTLs specifying differential ethanol sensitivity, assessed by Loss of Righting reflex due to Ethanol (Lore), in the Inbred Long Sleep (ILS) and Inbred Short Sleep (ISS) strains, accounting for approximately 50% of the genetic variance for this trait. Subsequently, we generated reciprocal congenic strains in which each full QTL interval from ILS was bred onto the ISS background and vice versa. An earlier paper reported construction and results of the ISCS on the ISS background; here we describe this process and report results on the ILS background. We developed multiple ISCS for each Lore QTL, in which the QTL interval was broken into a number of smaller intervals. For each of four QTL regions (chr 1,2,11,15), at least one strain with a reduced interval and phenotype supporting the introgressed QTL region, was identified. For each QTL on the ILS background these positive strains were overlapped to generate a single, reduced interval. Subsequently, this reduced region was overlaid on previous reductions from the ISS background congenics, resulting in substantial reductions in all QTL regions, by approximately 75% from the initial mapping study. Genes with sequence or expression polymorphisms in the reduced intervals are potential candidates; evidence for these is presented. Genetic background effects can be important in detection of single QTLs; we discuss this problem and how to turn it into an advantage.

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5.

Using chromosome substitution strains to examine the role of genetics in behavioral and neuroanatomical traits

VJ Bolivar[1,2], JP Phoenix,[1], AF Dorman[1,2], T Creten[1,2] , A Smith[1]

Identifying genes that are involved in complex behaviors in mice has proven to be difficult. Recently a new genetic tool has become available to aid in this process – a complete set of chromosome substitution strains developed by crossing C57BL/6J (B6) and A/J inbred strains. As B6 and A/J differ on a variety of behavioral and neuroanatomical characteristics, this set of chromosomes substitution strains can help us to dissect a number of complex traits. Chromosome substitution strains are useful for preliminary mapping studies of quantitative traits, since only 21 of them are necessary to map a trait to a particular chromosome. Gene identification beyond that point requires more traditional genetic procedures. In our laboratory, we have been using chromosome substitution strains to examine the genetics underlying spatial learning and memory, anxiety, motor coordination and mossy fiber structure. Our research indicates that a number of chromosomes (1, 6, 8,10, 15, 16) play roles in one or more of these traits. Our results confirm a number of quantitative trait loci reported in other studies, while other chromosome-trait associations have not been reported before. Taken together, our results highlight the usefulness of these strains for detecting chromosomal contributions to behavioral and neuroanatomical traits.

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Funding Source: NIMH

6.

Genetic analysis of fluid licking in inbred and BXD recombinant inbred mice

JD Boughter Jr.[1], T Bajpai[1], SJ St. John[2], RW Williams[1], L Lu[1], DH Heck[1]

Fluid licking in mice is thought to be under the control of one or more central pattern generators (CPGs) in the medulla. DBA/2J (D2) inbred mice lick water at a faster rate than C57BL/6J (B6) inbred mice (10.6 licks/s vs. 8.5 licks/s), based on the distribution of interlick intervals (ILI) during a 20 minute test. We measured licking in 15 inbred strains in 20 min tests with either water or sucrose following water deprivation to provide a broader characterization of phenotypic variation in lick rate. Lick rates (mean ILI from 50-160 ms) varied among inbred strains in a continuous fashion, and mean strain values ranged from 94.2 ms to 124.2 ms. Mean strain values were unaffected by haplotype variation of the Tas1r3 sweet taste receptor gene. We also measured water and sucrose licking in 56 BXD recombinant inbred (RI) strains during a 20 minute test in order to map quantitative trait loci (QTLs) underlying the phenotypic difference between B6 and D2 mice. There was a continuous distribution of mean ILI scores among BXD strains, supportive of polygenic control of this trait. QTL analysis indicates loci on Chr 1 and 10 reaching genome-wide significance and contributing to variation in lick rate.

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7.

Specific gene expression in the rat periaqueductal grey predicts the animal's preference for proactive, reactive, or shifting coping styles

Z Brett, G Ritchie, KA Keay

Chronic neuropathic pain is characterized by both sensory and affective changes. We have shown that following sciatic nerve constriction injury (CCI), 30% of rats develop a persistent change in their complex behaviors (social interaction, sleep-wake cycle and motivated behaviors) identical to chronic neuropathic pain patients. We have also demonstrated that an animal's intrinsic coping style to physical and/or psychological stressors predicts the development of this pattern of disability following nerve injury. Rats, which fail to adopt a consistent coping style (i.e., either proactive or reactive) are most vulnerable to the development of disabilities after injury. The periaqueductal grey region (PAG) has been shown to be a brain region critical for the expression of emotional coping behaviors, in these experiments we aimed to determine whether rats with proactive, reactive or "shifting" coping styles were characterized also by specific patterns of gene expression in the PAG. Our genes of interest in the first instance were those known to be selectively regulated by CCI: BAX/Bcl2, CAMK2B, CB1, CCK, CD200, GFAP, SYNJ2 and Vimentin. Rats (N=32) were characterized as either, *proactive*, *reactive* or *shifting* using 25 behavioral criteria, in a well characterized behavioral test battery. RT-PCR was used to determine gene expression levels in the PAG following behavioral testing, compared to an un-tested "control" population of age/weight/strain/litter matched rats (N=64). Significantly higher levels of expression of CB1, CCK and GFAP characterized *proactive* rats, and significantly lower levels of BAX:Bcl2 CB1, CCK and Vimentin characterized *reactive* rats. Rats with a shifting coping style did not differ significantly from the control population. Taken together with the earlier observation that it is the "shifter" rats which show high vulnerability to developing disabilities, and which show select regulation of the genes of interest, the degree of gene regulation after CCI is more dramatic than first appreciated.

Anatomy & Histology, School of Biomedical Sciences, The University of Sydney, NSW Australia

8.

Sensory dysfunction versus neurodegeneration as a cause of age-related cognitive impairment in mice

RE Brown

When a mouse or human shows age-related cognitive decline in tests of learning and memory, we infer that this is due to neural degeneration of the brain. In a series of longitudinal studies in which mice were tested from 3 – 20 months of age, we have seen that some cases of cognitive dysfunction are due to sensory dysfunction while others appear to be due to neural degeneration. DBA/2J mice show age-related cognitive impairment in visuo-spatial but not non-visual learning and memory tasks. This is due to the development of blindness due to glaucoma and drugs that treat glaucoma prevent visuo-spatial cognitive dysfunction. Alzheimer model mice develop age-related visuo-spatial cognitive dysfunction and this does not appear to be related to glaucoma. One must, therefore, be able to dissociate sensory from central neurodegeneration as a cause of age-related cognitive dysfunction in mouse models. This presentation examines how a battery of tests using multiple sensory stimuli can be used to dissociate sensory from neural degeneration as a cause of cognitive dysfunction.

Psychology Department & Neuroscience Institute, Dalhousie University, Halifax, Nova Scotia Canada

9.

Neuronal activation in the perirhinal cortex is influenced by a chromosome 1 QTL for acute ethanol withdrawal

G Chen [1,2], L Kozell[1,2], R Hitzemann[1,2], KJ Buck[1,2]

Previously, we identified quantitative trait loci (QTLs) with large effects on predisposition to physical dependence and associated withdrawal following acute and chronic alcohol exposure on distal chromosome 1 in mice (*J Neurosci* 17:3946, 1997; *Psychopharmacology* 160:398, 2002). Because of the near elimination of genetic "noise" from loci elsewhere in the genome, comparisons of the congenic and appropriate background strain animals are invaluable to delineate neural circuitry affected by this chromosome 1 QTL (*Alcw1*). To date, we have assessed c-Fos induction associated with alcohol withdrawal in more than 20 brain regions including limbic forebrain regions and the extended basal ganglia. We report that B6.D2-*Alcw1* congenic mice demonstrate significantly more c-Fos expression (neuronal activation) associated with alcohol withdrawal than C57BL/6J (B6) background strain mice in the perirhinal cortex; and that D2.B6-*Alcw1* congenic mice show significantly less c-Fos induction associated with alcohol withdrawal than DBA/2J (D2) background strain mice in the perirhinal cortex, substantia nigra, ventral pallidum, and lateral globus pallidus. These are the first analyses to implicate the perirhinal cortex in mediating *Alcw1*'s influence on alcohol withdrawal. Our results suggest that the perirhinal cortex may have a critical role in ethanol withdrawal convulsions.

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10.

Different corticosterone response to fear-related stimuli in mice selectively bred for high (HAP) and low (LAP) alcohol preference

GD Barrenha, JA Chester

There is a high rate of co-morbidity between alcohol-related disorders and post-traumatic stress disorder (PTSD). Fear-potentiated startle (FPS) is a procedure used to assess anticipatory fear/anxiety that may be a particularly relevant model for PTSD. We have previously demonstrated greater FPS in mouse lines selectively bred for high alcohol preference (HAP) than low alcohol preference (LAP). In the present study, we sought to determine whether line differences in FPS may be related to differences in corticosterone (CORT) response to fear-related stimuli, in light of many reports that both PTSD and alcohol-related disorders may be associated with dysregulation of the stress axis. Alcohol-naïve, male and female HAP2 and LAP2 mice were randomly assigned to a fear-conditioned or unpaired control group. Blood samples were taken at 0 (immediate), 1 hr, and 2 hr after the end of the FPS test. Both male and female HAP2 mice in the fear-conditioned groups showed greater FPS than LAP2 mice, as previously shown. Overall CORT levels were significantly higher in fear-conditioned LAP2 males compared to LAP2 controls, suggesting greater CORT response to fear-related stimuli. No conditioning group differences in CORT levels were seen in either HAP2 males or females or in LAP2 females. These data suggest that, at least in males, alterations in CORT response to fear-related stimuli may be a biological mechanism related to line difference in FPS. The apparent blunted CORT response in HAP mice is consistent with findings in humans and rodents where lower stress hormone levels following anxiogenic or trauma-related stimuli have been linked with greater susceptibility to develop PTSD and PTSD-like behaviors.

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11.

Habituation to novelty and sensitization to cocaine in urocortin 1 knockout mice

DM Cote, E Spangler, AE Ryabinin

Urocortin 1 (Ucn) is an endogenous peptide related to the corticotropin releasing factor. A growing number of studies show that the perioculomotor urocortin-containing group of neurons (pIIIu) is very sensitive to alcohol and is involved in regulation alcohol intake. Recent studies show that pIIIu is also sensitive to cocaine. Therefore, the present study evaluated whether these neurons could contribute to behavioral actions of cocaine using urocortin 1 knockout (KO) mice. Male Ucn KO and wildtype (WT) littermate mice were habituated to 4 days of saline injections (i.p) followed by locomotor activity testing. The same procedure was performed for the next 6 days except the mice received injections of 10 mg/kg cocaine. On the last day, the mice were injected with saline to test conditioned locomotion. Analysis of locomotor activity revealed that Ucn KO mice habituated to novelty significantly faster than the WT mice. The acquisition of locomotor sensitization to cocaine was not different between Ucn KO and WT mice. However, the conditioned locomotion was significantly lower in Ucn KO versus WT mice. These studies suggest that Ucn is involved in learning and habituation to stress rather than in the actions of cocaine.

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12.

Attentional capture by smoking cues: neural and genetic correlates

DE Evans[1], MN Farag[1,2], JY Park[1,2], DJ Drobes[1,2]

Exposure to smoking-related pictures elicits craving to smoke. That is, smoking-related pictures are appetitive cues among smokers. Research has found that appetitive picture cues enhance N2 (i.e., a component of the event-related brain potential waveform) amplitude. We were therefore interested in examining N2 amplitude as a brain marker of smoking cue reactivity. Studies have also found that possession of the long allele at the dopamine D4 receptor (*DRD4*) gene VNTR polymorphism is associated with greater attention to smoking cues, suggesting deficient dopamine function among smokers who exhibit greater cue reactions. We were interested in integrating these neural and genetic findings by examining this polymorphism as a moderator of N2 reactions to briefly presented smoking cues. We examined N2 amplitude responses to presentation of smoking and neutral pictures among 31 smokers and 22 nonsmokers. Results supported the role of the *DRD4* VNTR polymorphism as a moderator of N2 amplitude responses. Smokers carrying the long allele showed increased N2 amplitude to smoking cues at parietal scalp sites, indicating greater capture of attention among these individuals. Future research may examine these neural and genetic links with smoking cue attentional capture as correlates of abstinence, relapse, and other smoking behavior indices.

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13.

Modelling the environment: the effect of single housing on homecage activity and the stress response in two inbred strains of mouse

C Fernandes[1], F Everts[2], H Oppelaar[2], HA Spierenburg,[2] MJH Kas[2]

Stress is a key environmental factor that influences the development of depression and stressful life events have often been associated with the onset of depression (Nestler et al, 2002). In particular, stressful life events associated with absence or loss of social support have been associated with both the onset and relapse of depression (Paykel, 1994), whereas social support may have a protective effect (deVries et al, 2003). Although adverse life events and the development of behavioral disorders are clearly related, the behavioral and genetic mechanisms underlying this relationship are not fully understood. In this study we have used a mouse model of social support (Westenbroek et al, 2003) to study the effect of manipulating this life event in female mice from two different genetic backgrounds (A/J and C57BL/6J). Continuous telemetric monitoring was carried out in the mouse homecage to assess the effect of housing on locomotion and body temperature. In separate groups of mice, the effect of housing on the corticosterone response to a stressor (forced swim) was measured. A gene by environment interaction was observed for these physiological phenotypes and the results are promising for the mapping of genes underlying these phenotypes in the C57BL/6J-Chr #A/NaJ chromosome substitution panel.

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14.

Effects of nitric oxide synthase inhibition on genomic and proteomic screening of the hippocampus of rats submitted to the forced swimming test

FR Ferreira[1], SR Joca[2], AR Santos[3], Jr WA Silva[3], AM Catalán[4], LJ Greene[4], FS Guimarães[1]

Intra-hippocampal or systemic inhibition of neuronal nitric oxide (NO) decreases immobility time in rodents submitted to the forced swimming test (FST), an animal model predictive of antidepressant activity. The aim of this study was to investigate the effects of chronic treatment with 7-nitroindazole (7NI), a neuronal NO synthase inhibitor, on the profile of protein and gene expression in the hippocampus of male Wistar rats submitted to the FST. The animals were treated daily with 7NI (60 mg/kg), imipramine (15mg/kg) or vehicle for 14 days. FST was performed 1h after the last injection and total hippocampal mRNA/protein was extracted 2h later for serial analysis of gene expression (SAGE) and proteomic analysis. Imipramine and 7NI reduced immobility time compared to vehicle ($F_{2,18}$=15.83, *P*=0.0001). The sequencing of 25,144-61,390 gene tags, and the screening of 45-60 protein spots by 2D gel allows us to identify up to 276 gene differentially expressed in the 7NI-treated group. These genes belong to a variety of functional classes such as basic metabolism, transcription regulation and synaptic plasticity. These results indicate that chronic inhibition of NO formation changes gene expression in the hippocampus, which may be related to the antidepressant effect of this treatment.

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15.

Heritability of a Type II/B cluster construct for cannabis dependence in Southwest California Indians

DA Gilder[1], K Wilhelmsen[2], CL Ehlers[1]

Research has supported a dichotomous construct for cannabis dependence similar to Babor's Types A/B and Cloninger's Types I/ II for alcohol dependence. Little is known about whether subtypes of cannabis dependence are useful across ethnicities or are heritable. Information on demographics, cannabis use and dependence symptoms, and psychiatric symptoms was obtained using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) from a community sample of 202 Southwest California (SWC) Indians with DSM-III-R cannabis dependence. SPSS was used to generate hierarchical average linkage and K means cluster analysis from 2, 3, and 4 cluster solutions using 7 variables hypothesized a priori to differentiate a heritable form of cannabis dependence. The total additive genetic heritability (h^2) and its standard error were estimated using SOLAR. The 3 cluster solution generated the best separation of variables. A Type B/II cluster (N=70, 35%) was characterized by an earlier age of onset of use (mean 11.5 years), higher antisocial behaviors, and more cannabis dependence and withdrawal symptoms. Heritability was only significant for the Type B/II cluster (h^2 =.58, S.E.=0.25, p<0.03). These results suggest that a subtype of cannabis dependence characterized by specific clinical variables may be useful for genotyping for genetic studies.

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16.

Novel anxiolytic effects of cocaine in dopamine transporter knockout mice

FS Hall[1], JD Jones[2], I Sora[3], M Caron[4], DL Murphy[5], KP Lesch[6], AL Riley[2], GR Uhl[1]

Cocaine has both rewarding and aversive effects. Sensitivity to both of these properties may contribute to individual differences in addiction liability. To evaluate the aversive properties of cocaine the anxiogenic effects of cocaine were evaluated in an open field paradigm in mice with gene knockouts of the dopamine transporter (DAT), the serotonin transporter (SERT), and the norepinephrine transporter (NET). Wildtype (+/+) and knockout (-/-) mice were given cocaine (20 mg/kg s.c.) or saline prior to exposure to an open field for 20 minutes. In WT mice cocaine increased locomotor activity, and produced a pronounced anxiogenic effect (reduced center time). After saline administration both NET -/- and SERT -/- mice exhibited reduced center. Cocaine did not produce a further anxiogenic effect in these mice, but floor effects may have prevented the observation of any further reductions. Quite surprisingly, in DAT KO mice cocaine produced anxiolytic effects (increased center time). This occurred despite the fact that the locomotor stimulant effects of cocaine were completely eliminated in DAT -/- mice. These data are consistent with previous data indicative of substantial alterations in response to serotonergic agents in DAT KO mice and indicate that these changes also affect the anxiogenic effects of cocaine.

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[5]Lab of Clinical Science, National Institute on Mental Health, NIH, Bethesda, Maryland USA
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Funding Support: Intramural Research Program, National Institute on Drug Abuse, NIH

17.

Amyloid-β "star", mouse models of Alzheimer's disease, and dementia

C Janus, P Allebon, A Hanna, P Das, T Golde

Alzheimer's disease (AD) is the most common cause of dementia at present. The identification of bio-markers preceding the onset of AD pathogenesis is vital for the development of effective treatment. Recent work using transgenic (Tg) mouse models of AD has implicated extra-cellular soluble oligomeric amyloid-β (Aβ) assemblies, especially a 56 kDa fraction (denoted Aβ*56), as causal factors of memory impairment, rather than amyloid plaques. We demonstrated age-progressing deficits in multiple memory systems in two Tg mouse models of AD. This memory decline is interpreted alongside the corresponding analysis of Aβ*56 levels as a potential bio-marker of the disease. Our findings showed that: (1) levels of oligomeric Aβ*56 species increased with age which contradicts previous findings of consistent Aβ*56 levels throughout pathology. (2) The memory decline was significantly associated with total soluble fractions of Aβ, but not with amyloid plaques, thus supporting the hypothesis the soluble Aβ is neurotoxic. (3) Less-cognitively demanding but procedurally similar tasks were not related to Aβ levels, stressing the selective effect of oligomeric Aβ on mnemonic functions. Also, using novel BRI-Aβ mice we also demonstrated that deposited Aβ plaques were not associated with cognitive performance. In conclusion, results obtained in mouse models indicate that oligomeric soluble fractions of Aβ may provide a diagnostic tool only at the pre-clinical stage of the disease.

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18.

Behavioural analysis of congenic mouse strains confirms stress-responsive loci on Chr 1 and 12

M C Jawahar[1], T C Brodnicki[2], F Quirk[2], Y M Wilson[1],M Murphy[1]

Chronic stress is directly related to anxiety related disorders. To identify genetic factors that influence anxiety, we have studied the stress-responsiveness of inbred mouse strains using a modified form of the open field activity test (OFA), the elevated (e) OFA. Two strains show high (DBA/2J) or low (C57BL/6J) stress-responsiveness in the eOFA. Genetic studies of an F_2 intercross between these two strains identified two regions, on chromosomes (Chr) 1 and 12, linked to anxiety-related behaviour. To confirm these regions, we established separate congenic mouse strains containing the linked Chr1 and Chr12 regions from the DBA/2J strain interval on a C57BL/6J genetic background. Cohorts of parental and congenic mice were analysed for a series of stress-responsive phenotypes using the eOFA test. Both congenic strains had significantly different stress-responsive phenotypes compared to the low-stress C57BL/6J parental strain, but the DBA/2J-derived Chr12 interval had a greater genetic effect than the Chr1 interval for changing the behavioral phenotype of the parental C57BL/6J mouse strain. These results confirmed the presence of stress-responsive loci on Chr1 and Chr12. New stress-related phenotypes were also identified, which aided in comparing and differentiating DBA/2J, C57BL/6J and congenic mice. Fine mapping these loci should help identify the stress-responsive genes.

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19.

Genetic analysis of the highly variable response to an iron deficient diet among the BXD/TyJ recombinant inbred strains

LC Jones, BC Jones

Iron deficiency is highly prevalent worldwide and results in a number of negative effects in the central nervous system and periphery. Little is known about genetic differences in the ability to maintain iron homeostasis in conditions of low dietary iron. To investigate such differences, we used the BXD/TyJ panel of recombinant inbred strains. Mice from 22 strains were fed an iron deficient or control diet from weaning to 120 days, at which time iron was measured in brain tissue and hematological iron status was recorded. Results showed wide genetic-based variability in the magnitude of iron loss in the brain as well as the change in hemoglobin. Moreover, the response to the diet in the brain was independent of that in the periphery. In this report we characterize the varying responses of these strains and report the results of QTL analyses of these data. This work contributes to our understanding of iron deficiency from a genetic perspective and may lead to new insights into iron deficiency treatment and iron deficiency-related syndromes, such as restless legs syndrome.

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20.

PP2A/GSK3β signaling regulates sensorimotor gating in mice

D Kapfhamer[1], K Berger[1], U Heberlein[1,2]

Convergent evidence in multiple systems has implicated components of the WNT (wingless) signaling pathway in aspects of psychiatric disorders, most notably, schizophrenia and mood disorders. Many therapeutic agents act either directly or indirectly on this pathway, providing additional evidence for its role in the pathophysiology of these disorders. To determine if genetic manipulation of WNT signaling can model behavioral aspects of schizophrenia, we have generated mice with a targeted disruption of the *Ppp2r5δ* gene, which encodes a regulatory subunit of the protein phosphatase 2A holoenzyme (PP2A) and tested for sensorimotor gating. *Ppp2r5δ-/-* mice are embryonic lethal, whereas *Ppp2r5δ+/-* mice are viable and normal in appearance. *Ppp2r5δ+/-* mice show reduced prepulse inhibition of the acoustic startle response (PPI), a measure of sensorimotor gating. GSK3β, a downstream target of PP2A, is inhibited by phosphorylation of Ser9. We show that pSer9 levels are increased in brains from *Ppp2r5δ+/-* mice, indicating that PPP2R5δ is a positive regulator of GSK3β activity. *Gsk3β* mice show impaired PPI, which we have pharmacologically phenocopied in wild-type mice by acute treatment with the GSK3 inhibitor SB216763. These data suggest that PP2A/GSK3β signaling may modulate PPI by a developmentally independent mechanism.

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21.

Alcohol consumption in prairie voles

S Kaur[1], J Loftis[2], AE Ryabinin[1]

Alcohol abuse can often lead to social problems. It has been hypothesized that mechanisms regulating alcohol consumption and social behavior overlap. To investigate the correlation between social affiliation and alcohol consumption, we used a novel animal model in alcohol research, the prairie vole. Prairie voles are socially monogamous animals and are sensitive to social isolation. In pilot studies done in our laboratory, prairie voles show a preference for alcohol. In this study, male and female prairie voles were removed from their home cages and divided into three groups: single-housed, single-housed in cages with wire mesh dividers (dividing the cage into two compartments), pair-housed with a sibling in the wire mesh cages. Preliminary data showed that the voles were able to interact through the wire mesh. The voles were each given access to 3% ethanol for the first four days and 6% ethanol thereafter in addition to water. Fluid consumption and preference was measured daily. No significant difference in alcohol consumption or preference was observed between the three groups suggesting lack of overlap between biological mechanisms regulating social behaviors and alcohol intake. Studies in adolescent prairie voles, which might be more sensitive to social manipulations, are planned in the near future.

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22.

The effects of over-expressing insulin-degrading enzyme on ethanol-related behaviors in mice

CL Kliethermes, U Heberlein

Dysregulation of the insulin signaling pathway is the principal feature of diabetes, and aberrant functioning of this pathway has also been implicated in the development of other diseases, including Alzheimer's. Insulin degrading enzyme (IDE) is responsible for the initial degradation of insulin, and appears to be the primary means of regulating insulin levels in the brain. Using WebQTL, we found that hippocampal levels of IDE showed a strong negative genetic correlation with ethanol consumption in mice, suggesting that IDE might be involved in behavioral responses to ethanol. We obtained transgenic mice that over-express IDE in the brain and compared them to the B6D2F1/J background strain on several tests of acute and chronic responses to ethanol. Relative to wild types, IDE transgenic mice showed a slightly reduced latency to initially lose the righting reflex, but the genotypes did not differ for the total sleep time or for ethanol-induced ataxia measured on the accelerating rotarod. No overall genotypic differences were found using the two-bottle ethanol preference assay, although transgenic mice tended to consume more 10% and 20% ethanol. Finally, transgenics and wild types did not differ in the degree of conditioned place preference for ethanol. These results suggest that IDE in the brain might be involved in some behavioral responses to ethanol, but the mechanism for this effect is not known. We are currently producing homozygous IDE transgenic mice to further increase brain levels of IDE and will examine additional ethanol- and drug-related behaviors in these mice.

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23.

Fine genetic mapping of emotionality-related traits on distal end of mouse chromosome 17

A Takahashi[1,3], T Shiroishi[2,3], T Koide[1,3]

Much of the genetic variation that underlies most behavioral traits is complex and is regulated by loci that have a quantitative effect on the phenotype. We aimed to reveal the genetic architecture underlying individual differences in behavior by using consomic strains of mice in which MSM/Ms (*Mus musculus molossinus*) chromosomes have been backcrossed onto a C57BL/6J (*M. m. domesticus*) background. We previously showed that almost all chromosomes were involved in emotionality-related behaviors. To dissect complex traits into fine genetic elements, we focused on chromosome (Chr) 17. B6-17MSM, which carries Chr 17 from MSM/Ms, showed increased risk-assessment in the novel situation, increased fear response in the fear-conditioning paradigm, but no differences in their home-cage activity compared to C57BL/6J. Thus, it is expected that there is a genetic locus or loci associated with emotionality on Chr 17. We then established and analyzed a series of sub-consomic strains of Chr 17 to identify genetic factors related to increased emotionality, and successfully mapped a genetic locus in around a 7Mb segment at the distal end of Chr 17, where about 50 genes are located. Currently, we are trying to characterize both sequence polymorphisms and expression patterns of these genes.

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24.

Genes influencing ethanol metabolism are associated with alcohol use disorders in a Tibetan population

T Li[1,2,3,4], W Guo[1,2], G Lanzi[5], O Luobu[5], X Ma[1,2], Y Wang[1,2], P Zhen[5], G Wei[6], Y Ji[7], Z Wang[1,7], C Yan[1,2], B Zhuoma[5], X Shi[5], X Liu[1], DA Collier[3,4], D Ball[3]

Family, twin and adoption studies have shown that genetic factors are implicated in the etiology of alcohol use disorders. In the present study, we used a sample collected during an epidemiological study of alcohol use disorders in a Tibetan population in China, to perform a case-control study investigating the relationship between the functional polymorphisms of ALDH2*1/*2, ADH2*1/*2 and CYP2E1*c1/c2* and alcohol use disorders, and the potential influence of ALDH2*1/*2, ADH2*1/*2 and CYP2E1*c1/*c2 polymorphisms on the severity and dimensions of alcohol use disorders in this population. 383 individuals (220 males and 163 females) with an AUDIT score ≥10 (the cut-off point for diagnosing alcohol use disorders in our study) and 350 (194 males and 156 females) control subjects with the AUDIT score ≤5 were invited to participate in the genetic study. We confirmed that both ALHD2*2 allele and ADH2*2 are protective alleles for alcohol use disorders in both males and females; while CYP2E1*c2 is a risky allele for alcohol use disorders, especially in males. However, no significant gene-gene interaction was found. We also performed a cumulative association analysis and identified that significant dosage effect of ADH2*2, ALDH2*2 and CYP2E1*c2 allele for protecting individuals from alcohol use disorders. Further studies in independent samples are warranted to replicate our findings.

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[7]Department of Science and Technology, West China Hospital, Sichuan University, Chengdu, PR China
Funding Support: The Department of Science and Technology, Sichuan, China

25.

An epigenetic effect of embryonic ethanol exposure in *C. elegans*

Y Li[1,2], CH Lin[1,3], CH Rankin[1,2,3]

Although there are many studies that investigate the effects of embryonic exposure to ethanol, there are very few that examine later generations to determine whether the initial exposure produces any epigenetic effects that continue to affect these later generations. In this set of experiments we examine the offspring of *C. elegans* who were exposed to ethanol during embryonic development. The original exposure occurred in one of four ways, either 1 hour of exposure at 2 hours or 5 hours or 8 hours after the eggs were laid, or repeated exposure where eggs were exposed for 20 minutes at 2, 5 and 8 hours after they were laid. The results showed that the offspring of exposed worms had altered hatch rates, altered onset of egg laying, and altered longevity compared to controls. These data support the hypothesis that ethanol exposure during development produces epigenetic changes that affect at least the next generation.

[1]Brain Research Centre, [2]Dept of Psychology, [3]Graduate Program in Neuroscience, University of British Columbia, Vancouver, British Columbia Canada. Funding Support: Province of British Columbia, Ministry of Children and Family Health: Human Early Learning Partnership (Canada)

26.

***C. elegans*: A potential high-throughput FASD model for genetic screening and expression profiling for the effect of alcohol at specific stages of development and behaviour**

CH Lin[1,3], Y Li[1,2], CH Rankin[1,2,3]

Fetal alcohol spectrum disorder (FASD) is the leading cause of mental retardation, and affects 1% of live birth in North America. A major challenge for FASD research is that the effect of ethanol during development is age-, dose-, and site, and duration-dependent. To tackle this problem, we are developing an FASD model in *C. elegans* in which the onset, duration and concentration of ethanol exposure can be easily manipulated. *C. elegans* is a powerful genetic model, with a completely mapped nervous system of only 302 neurons. We report differential effects of 1 hour ethanol exposure during gastrulation, elongation, or synaptogenesis on survival rate, reproduction, animal size, and learning in habituation. Decreased survival rate in all groups suggested brief ethanol exposure during embryogenesis affects the general health of the animals. Animals exposed during gastrulation showed opposite effect on reproduction than animals exposed during elongation and synaptogenesis, suggesting that ethanol acts on different underlying mechanisms or influences the same target differently during different stages of development. Analysis for developmental delays (animal size and reproductive onset) showed differential pattern in groups exposed at different times. We are currently investigating expression profile of glutamate receptors involved in our learning circuit, and other behavioural deficits.

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27.

Strain-specific effects of dopaminergic modulation of varieties of impulsivity in mice

M Loos[1], J Staal[1], AB Smit[1], S Spijker[1], T Pattij[2]

The brain dopamine system plays a critical role in varieties of impulsivity relevant to human disorders. Mice of the C57BL6/J and DBA/2J inbred strains are known for profound differences in their dopamine system. We aimed at measuring impulsivity in these strains and investigated whether this was sensitive to dopamine-related drugs. Mice were trained to perform two tasks taxing impulsivity. In the Go-NoGo task, impulsivity was defined as inability to withhold responding during NoGo trials. A second group was trained in the 5-choice serial reaction time task (5-CSRTT), in which impulsivity was defined as anticipatory responses before the onset of a stimulus light. C57BL6/J and DBA/2J did not differ in impulsive responses in the Go-NoGo task, whereas DBA/2J were significantly more impulsive in the 5-CSRTT. Amphetamine did not affect impulsivity in the Go-NoGo task, but dose-dependently increased impulsivity in the 5-CSRTT, to a greater extend in C57BL6/J mice, correlating with their reduced dopamine transmission. This effect was mimicked by the dopamine transporter inhibitor GBR12909. Clearly, the 5-CSRTT detects strain differences in impulsivity and is sensitive to dopamine-enhancing drugs. We conclude that the C57BL6/J and DBA/2J strains may prove useful in the hunt for genes underlying varieties of impulsivity.

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28.

Alcohol relapse induced by the cannabinoid receptor agonist WIN 55,212-2: different regulation of CNR1 and NR1 transcripts in hypothalamus, striatum, cingulated anterior cortex, and amygdala in the rat

F Alen[1], A Santos[2], G Moreno-Sanz[1], G González-Cuevas[1], JA López-Moreno[1]

Treatment with cannabinoid agonists causes an increase in alcohol relapse. It has been shown that activation of CB1 receptors by cannabinoids can reduce glutamatergic transmission. The endocannabinoid system would serve as a feedback mechanism controlling excesses in glutamate liberation. Here, we investigated to what extent the cannabinoid-induced increase in alcohol relapse is associated to CB1 and NR1 subunit receptor transcripts expression in different brain areas involved essentially in drug-addicted behaviors. We found that the cannabinoid receptor agonist WIN during periods of alcohol abstinence can long-lastingly (up to 2 weeks) enhance subsequent alcohol consumption during alcohol relapse. We observed that in the hypothalamus and striatum, which are known to be implicated in individual homeostasis and habit formation respectively, exhibited great levels in CNR1 transcripts after WIN exposure. However, in the anterior cingulated cortex and amygdala, structures highly implicated in motivated and emotional behaviors was found reduced CNR1 transcripts in those subjects treated only with WIN. In conclusion, altered CNR1 transcripst could lead to an abnormal regulatory role of the endocannabinoid system, and in consequence to alter the glutamatergic system, being more likely to relapse in alcohol abuse.

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29.

Mouse Phenome Database (MPD; www.jax.org/phenome)

Maddatu TP, Grubb SC, Bult CJ, Bogue MA

Large-scale phenotyping projects have greatly increased the power of inbred strains for the study of human disease. The phenome approach captures complexities of entire biological pathways that are simply not accessible through conventional approaches. The Mouse Phenome Project, an international collaborative effort, was launched in 2000 to complement the mouse genome sequencing effort. The Project promotes and facilitates phenotyping projects in a strain survey format following a set of recommendations proposed by members of the research community in order to standardize testing across laboratories and over time, and ultimately to maximize data reproducibility and value. Phenotypic and genotypic data on the laboratory mouse collected and curated by the Project is made available through the Mouse Phenome Database (MPD; www.jax.org/phenome). MPD currently contains about 1000 phenotypic measurements contributed by research teams worldwide. These include measurements for phenotypes relevant to human diseases, including cancer susceptibility, aging, obesity, susceptibility to infectious diseases, cardiovascular diseases, and neurosensory disorders. Additionally, MPD provides analysis tools for comparing strains, correlating phenotypes, and linking phenotype and genotype. With electronic access to centralized strain data, investigators can choose appropriate strains for modeling human diseases and many systems-based research applications. This functionality, in turn, accelerates research and leverages existing community resources.

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30.

A common quantitative trait locus for sensitivity to the locomotor stimulant effects of drugs that have multiple initial mechanisms of action

CS McKinnon[1,2], HM Kamens[*1,2], TJ Phillips[1,2,3]

Quantitative trait locus (QTL) mapping previously identified a QTL on mouse chromosome 2 for sensitivity to the locomotor stimulant effects of ethanol and the neuroactive steroid, allopregnanolone. Evidence for the QTL came from several mapping populations including chromosome 2 congenic mice. Because these drugs share the ability to allosterically modulate gamma-aminobutyric acid (GABA)-A receptor function, we speculated that a gene on chromosome 2 has a pleiotropic influence on traits that share a GABA-A receptor mechanism of action. To test the alternative hypothesis that the gene influences sensitivity to all drugs with stimulant effects, we measured the locomotor response of chromosome 2 congenic mice to two drugs that do not have actions at the GABA-A receptor: an *N*-methyl-D-aspartate (NMDA)-receptor antagonist, ketamine, and a dopamine releaser, methamphetamine. For both drugs, congenic mice possessing a DBA/2J chromosome 2 segment exhibited a larger stimulant response compared to the C57BL/6J background strain; the same direction of effect found for the GABA-A-acting compounds. A single gene on mouse chromosome 2 may pleiotropically influence the stimulant response to drugs with multiple initial mechanisms of action. These drugs share the ability to increase mesolimbic dopamine; thus, the QTL may be relevant to this mechanism.

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31.

The genetic basis of behavioral despair in inbred strains of mice

BH Miller, LA Schultz, BC Long, MT Pletcher

Inbred mouse strains exhibit strain-dependent phenotypic differences that mirror the phenotypic range in human populations. Performance in mouse models of behavioral despair such as the Tail Suspension Test (TST) is affected by genes linked to the occurrence of depression in humans, suggesting that identification of regulators of behavioral despair in mice may aid the investigation of depression in humans. We phenotyped 33 inbred strains for TST behavior and used inter-strain phenotypic variation as a quantitative trait for haplotype association mapping (HAM). Six QTL ranging from 3 - 12 kb in size were identified. To provide secondary confirmation of HAM-generated associations, the QTLs were assayed for significance in two separate F2 populations. The F2 results confirmed loci on MMU9, MMU10, and MMU19, each of which contains a small number of genes that are expressed in the brain and are likely to play a role in the propensity for despair. The potential role for two of these genes, *Rab6b* and *Socs2*, is supported by hippocampal gene expression data or SNP variations. These results indicate that HAM can be successfully used to identify narrow genomic loci that regulate the expression of complex behaviors, and identify new candidate genes in the study of depression.

Dept of Molecular Therapeutics, Scripps Florida, Jupiter, Florida USA. Funding support: State of Florida

32.

Binge alcohol consumption differentially remodels the brain transcriptome in juvenile and adult FVB.B6 hybrid mice

MK Mulligan[1], JA Owen[2], O Velasquez[1], PS Levin[1], Y Wang[1], H Krishnan[1], NS Atkinson[1], SE Bergeson[2]

The adolescent brain is especially susceptible to alcohol abuse and the subsequent increased risk of alcoholism in adulthood. Isogenic FVB.B6 (F1) hybrid mice display increased rates of voluntary consumption of high concentrations of alcohol and represent an ideal genetic model for studying the effects of alcohol on brain gene expression. A drinking in the dark (DID) paradigm that promotes high alcohol consumption over a short time period (binge-like) was used to explore the effects of alcohol and age on brain gene expression in male F1 hybrid mice. Juvenile F1 mice consumed more alcohol than adult mice and consumption was correlated with blood alcohol concentration (BAC) with juvenile animals achieving an average BAC of 1.2 mg/ml. Whole brain gene expression analysis revealed significant differences in gene regulation dependent on age and suggested perturbation of different molecular pathways. Epigenetic consequences were also uncovered. Chromatin immunoprecipitation (ChIP) analysis revealed that the expression of *Scn4b*, a sodium channel beta subunit responsible for modulating channel firing kinetics previously associated with high alcohol consumption, was regulated by alcohol exposure through acetylation of histone H4. These findings indicate a clear age-related difference in brain transcriptome plasticity following binge alcohol consumption.

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33.

Chronic voluntary self-administration of ethanol results in tolerance to sedative effects of ethanol in C57Bl/6J x FVB/NJ F1 hybrid mice

AR Ozburn, RA Harris, YA Blednov

C57Bl/6JxFVB/NJ and FVB/NJxC57Bl/6J F1 hybrid mice display a higher intake and preference for ethanol than either parental strain. In order to test the validity of this genetic model of high alcohol consumption, we evaluated the sedative, acute withdrawal and hypothermic response to ethanol after chronic self-administration using a continuous access two-bottle choice paradigm. Ethanol experienced mice stably consumed 16-18 g/kg/day ethanol. After 59 days of drinking, acute withdrawal severity was assessed by scoring handling-induced convulsions after ethanol (3.8 g/kg, i.p.). Withdrawal severity was minimal and did not differ between groups. After 71 days, the rate of ethanol metabolism (4 g/kg, i.p.) was greater for ethanol experienced mice ($p<0.01$). After 78 days, ethanol-induced (3.6 g/kg i.p.) loss of righting reflex (LORR) was tested daily for 5 days. Blood alcohol concentrations (BAC) were measured at gain of righting reflex (GORR) on the 1st and 5th day. Ethanol naïve mice exhibited a steeper rate of tolerance (decrease in sleeptime/days of experiment) than ethanol experienced mice. Though the BAC@GORR was greater on day 5 than on day 1, there was no difference between groups. It is important to note that at GORR, there was no difference between groups for BAC at the corresponding time points from the metabolism experiment. Ethanol experienced mice developed tolerance to ethanol-induced hypothermia when measured after 98 days of drinking. Chronic voluntary ethanol consumption resulted in tolerance to sedative, metabolic, and hypothermic responses to ethanol.

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34.

Methamphetamine-induced behavioral activation in Chromosome 11 and Chromosome 15 congenic mice

CC Parker[1, 2], AA Palmer[3], B Bennett[2]

Quantitative trait loci (QTL) for METH stimulant response on Chromosomes 11 & 15 have been reported in short term selected lines derived from a B6 x D2 F_2 population. We expand on these findings using congenic strains based on the ILS and ISS. Male and female ISS.ILS-*Lore4*^{L} ("4LA", introgressed region from 54.65 Mb to 96.1 Mb), ISS.ILS-*Lore5*^{L} ("5LA", introgressed region from 61.66 Mb to 98.07 Mb), and ILS.ISS-*Lore5*^{S} ("5SA", introgressed region from 30.94 Mb to 95.04 Mb) mice were given 2 mg/kg METH. Locomotor behavior was measured for 60 minutes on 4 days (day 1 and 2 saline, day 3 AND 4 methamphetamine or saline (counterbalanced). A two-way ANOVA found main effects for strain ($F_{1, 101} = 30.8$; $p < 0.0001$), but not sex on distance traveled following METH with 4LA mice traveling the farthest (mean distance = 28520.1 cm), followed by 5SA (mean distance = 24643.1 cm) and 5LA (mean distance = 10679.5 cm). Additionally, a two-way ANOVA found main effects for strain ($F_{1, 101} = 44.7$; $p < 0.0001$), but not sex on stereotypic behaviors following METH with 4LA showing the highest amount of stereotypy (mean stereotypy = 11240.4), followed by 5SA (mean stereotypy = 4456.6) and 5LA (mean stereotypy = 4046.4). These findings support previously identified QTLs for METH-induced locomotor response and suggest the same alleles may segregate in crosses of both B6 x D2 and ILS x ISS, which will aid in our efforts to identify the causative alleles.

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35.

Stress induces a difference in ethanol consumption between mice deficient in corticotropin-releasing factor (CRF) receptors and their wildtype controls

R Pastor[1,3,5], C Reed[1,3], S Burkhart-Kasch[1,3], N Li, AL Sharpe[1,3], SC Coste[2], MP Stenzel-Poore[2], TJ Phillips[1,3,4]

Stressful events have been shown to promote excessive ethanol consumption and enhance drug craving during abstinence, which facilitates relapse. However, initial levels of ethanol consumption can influence the effect on subsequent drinking. Corticotropin releasing factor (CRF) systems are critical in behavioral stress responses. The present experiments investigated the involvement of CRF receptors in stress-induced changes in ethanol consumption. Genetically engineered mice lacking CRF type-1 (CRF-r1), CRF type-2 (CRF-r2) and double knockout (KO) animals for both CRF receptors were tested for ethanol consumption before and after acute or repeated (three consecutive sessions, one per day) swim-stress exposures. Spontaneous ethanol intake was not affected by single or double CRF receptor deletion. Swim-stress produced acute reductions in ethanol consumption that recovered to higher levels of consumption in wild-type (WT) mice than in genotypes lacking CRF-r1. Differences between WT and double KO mice were of longer duration than between WT and CRF-r1 mice. WT and CRF-r2 mice did not differ in the effects of stress on ethanol drinking. Together, our data suggest a prominent role of CRF-r1 with a more subtle involvement of CRF-r2 in mediating stress-induced increases in ethanol consumption.

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36.

The effect of dopamine transporter knockout in an animal model of anhedonia

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Contrary to expectation, gene knockout (KO) of the dopamine transporter (DAT) has greater effects on baseline "antidepressant-like" phenotypes than either gene knockout of the serotonin transporter (SERT) or the norepinephrine transporter (NET), in the forced swim and the tail suspension tests. These pronounced "antidepressant-like" effects of DAT KO might merely reflect locomotor hyperactivity however. Therefore, DAT KO and SERT KO mice were observed in the sucrose model of anhedonia. Mice were placed into fluid consumption chambers daily and allowed to consume sucrose solutions for 30 minutes (0.7%, 7%, 34% sucrose; 3 days/concentration) and water. Greatly increased consumption of sucrose was observed in DAT KO mice compared to WT controls, including the lowest sucrose concentration which WT mice did not consume more than water. This effect was not observed in SERT KO mice, which demonstrated a trend towards reduced overall consumption, perhaps indicative of increased anxiety. This data provides further support for the idea that differences in the expression of DAT may produce greater effects on "antidepressant-like" phenotypes than differences in SERT expression. Furthermore, these differences are unlikely to result from locomotor hyperactivity in DAT KO mice, which would most likely reduce sucrose consumption if behavioral competition were a confounding factor.

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Funding Support: Intramural Research Program, National Institute on Drug Abuse, NIH

37.

The effects of calorie restricted diet on survival rate and locomotive stability in two life-extended strains of *Drosophila*

A Petrosyan

Life extension is a recent and rapidly growing area of research in behavioral genetics. We are examining longevity and locomotive functions in two life-extended lines of Drosophila in a caloric restricted diet paradigm explored independently as well as collectively in temperature and humidity fluctuating conditions. Survival rates and a random-walk activity as a function of age in *methuselah* and in a transgenic strain containing the human SOD1 gene in caloric restricted diet paradigm is being explored. We are investigating two lines of life-extended *Drosophila*: 1) The *methuselah* mutant (*mth*) which has a chromosome 3 mutation leading to 35% average life extension and 2) a transgenic *Drosophila* line (*HS1*) which contains human DNA that codes for a stress-reducing protein in humans, and which live an average of 40% longer than its parental strain that does not contain this human gene. We have collected substantial data on the motor abilities of these lines as a function of their age. A natural motor function that one may examine as a biologically relevant measure is wing-beat frequency (WBF).

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38.

Ethanol withdrawal-induced motor impairment provides a novel withdrawal phenotype in mice

SD Philibin, AJ Cameron, JC Crabbe

Alcoholism is a complex disorder comprised of both genetic and environmental factors. One criterion for an alcohol dependence diagnosis is the presence of withdrawal symptoms. Genetic animal models have been used to quantify various behavioral effects of ethanol withdrawal in rodents. These different withdrawal signs may have distinct genetic etiologies, so elucidating potential neurobiological mechanisms related to separate withdrawal symptoms would facilitate our understanding of this complex phenotype. We report that ethanol-induced motor incoordination may provide a novel phenotype of alcohol withdrawal in mice. The effects of ethanol withdrawal in mice were assessed on acquisition of the accelerating rotarod, a simple motor learning task. Ethanol withdrawal disrupted acquisition in mice. Inbred mouse strain comparisons suggest genetic differences in sensitivity to this withdrawal phenotype. The withdrawal-induced deficits were not correlated with the selection response difference in handling convulsion severity in selectively bred Withdrawal Seizure-Prone and Withdrawal Seizure-Resistant mouse lines. The disruptive effects of withdrawal on accelerating rotarod performance were time dependent and suggest a performance versus a learning deficit. The accelerating rotarod appears to be a simple and novel behavioral measure of ethanol withdrawal that is suitable to compare genotypes.

Portland Alcohol Research Center, Portland VA Medical Center, Dept of Behavioral Neuroscience, Oregon Health & Science University, Portland, Oregon USA. Funding Support: NIH grants AA010760, AA13519, AA07468 and the Department of Veterans Affairs (USA)

39.

Environmental and genetic factors driving exploration in *Drosophila*

G Roman, L Liu

Drosophila melanogaster, when placed into a circular open field arena, displays an initially high level of activity, followed by a stable, lower level of spontaneous activity. Exploration is the foremost component of the elevated initial activity phase since: 1) the initial activity, but not the spontaneous activity is proportional to the circumference of the arena, 2) the increased activity is independent of handling prior to placement within the arena and 3) the decay to spontaneous activity requires both visual and olfactory input. The absence of food in the arena leads to a rapid decay in exploration activity, while hunger increases the initial activity phase. Flies spend a majority of their time at the edge of either a circular or a square open field arena. Interestingly, we have been able to rescue a w^{1118} exploration defect by blackening the edge of the arena. Furthermore, wild type flies prefer external but not internal corners in an open field arena. We propose that flies are attending to the edge and not displaying either centrophobicity or thigmotaxis. By combining the analysis of specific mutant phenotypes with a detailed behavioral dissection, we are furthering our understanding of the neurobiology and environmental stimulation that underlies exploration.

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40.

The effect of acute caffeine administration on behavior in C57BL/6J and DBA/2J mice

J Saputra, KM Hamre, VL Savchenko, JD Boughter Jr.

Caffeine is the most widely used drug in the world, and produces both stimulatory and anxiogenic effects in mice. We sought to characterize the range of effects of caffeine in two strains of mice that have been found to differ in anxiety-related and motor behaviors, C57BL/6J (B6) and DBA/2J (D2). Caffeine was administered (I.P.) to male and female adult B6 and D2 mice 1 h prior to a behavioral screen. Doses used were 15, 33, 66, 100, and 160 mg/kg. In the activity chamber, total distance traveled varied as a function of caffeine dose. Robust strain differences were found: Low doses (15, 33 mg/kg) were far more stimulatory to D2 mice, while high doses (100 and 160 mg/kg) produced greater inhibition in B6 mice. On the rotorod, 100 and 160 mg/kg caffeine significantly decreased the mean time and speed of B6 mice, whereas all concentrations increased the time and speed for D2 mice. For the elevated plus maze, concentration-dependent effects of caffeine were found for the number of beam breaks in both strains. Collectively, these data indicate several differential effects of caffeine on motor behavior, and an opportunity for genetic analysis of caffeine effects on behavior.

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41.

Mice selectively bred for low and high methamphetamine-induced sensitization differ in oral consumption of methamphetamine

AC Scibelli[1,2], CS McKinnon[1,2], S Burkhart-Kasch[1,2], N Li[1,2], C Reed[1,2], TJ Phillips[1,2,3]

Short-term selected lines of mice are being bred for low (MALSEN) and high (MAHSEN) levels of methamphetamine-induced behavioral sensitization using mass selection. Magnitude of sensitization is defined as the difference in locomotor response to the fifth and first injection of 1 mg/kg methamphetamine. The MAHSEN line displayed a significantly greater sensitized response to methamphetamine than did the MALSEN line in the first (S1) and second (S2) selection generations. We plan to continue selective breeding for at least two additional generations. To test the hypothesis that oral consumption of methamphetamine is genetically correlated with methamphetamine sensitization, we are testing mice of each generation and have completed the testing of S1 mice. MALSEN and MAHSEN mice were tested for consumption of 20 and 40 mg/L methamphetamine solutions, and the MAHSEN line consumed significantly more of the 40 mg/L solution than did the MALSEN line. There was no difference between the lines in consumption of the 20 mg/L methamphetamine solution. These results indicate that genes that result in higher levels of methamphetamine sensitization also promote higher levels of oral consumption of methamphetamine.

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42.

Diagnosis of diabetic neuropathy at genetic level

R Singh, A Singh, V Dixit

Objective: This paper tries to find out a genetic marker for diabetic neuropathy patients. Aldose reductase gene has been used as a genetic marker because product of this gene plays important role in pathogenesis of diabetic neuropathy. In Indian peoples we are performing 1st time this analysis and trying to find some relation between polymorphism and diabetic neuropathy. Methods: The present work has used aldose reductase gene as a genetic marker. Aldose reductase enzyme is the product of this gene. Aldose reductase is an enzyme in carbohydrate metabolism that converts glucose to its sugar alcohol form, sorbitol, using NADPH as the reducing agent. Glucose concentrations are often elevated in diabetics and this enzyme has long been believed to be responsible for diabetic complications involving a number of organs. Single strand conformation polymorphism (SSCP) experiment conducted for promoter and exon-3 of aldose reductase gene. Results: The promoter sequences and exon have been analyzed in 3 patients suffering from diabetic neuropathy. After sequencing we observed that two mutations are present in promoter sequences (C-106T) that lead to overproduction of aldose reductase enzyme. No polymorphism has been found in exons. Conclusion: This is a pilot study. By the study of 3 patients and 3 control we can conclude following aspect: Promoter polymorphism cause the overproduction of aldose reductase enzyme that lead to finally neuropathy.

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43.

Urocortin immunoreactivity in Sardinian and Marchigian Sardinian alcohol preferring rats

E Spangler[1], I Fonavera[1], R Ciccocioppo[2], EP Zorrilla[3], AE Ryabinin[1]

The peptide Urocortin (Ucn) has been implicated in the regulation of alcohol consumption. For example, several studies have shown that Ucn immunoreactivity in peri-oculomotor urocortin-containing neurons (pIIIu) and/or pIIIu projections to the lateral septum are positively correlated with alcohol preference in mice (Bachtell et al. 2003). However, the studies in rats have not revealed a consistent relationship between alcohol preference and Ucn immunoreacivity (Turek et al., 2005). Moreover, previous studies did not explore whether the relationship between alcohol intake and Ucn is influenced by gender. Therefore, the present study investigated Ucn immunoreactivity in male and female Sardinian alcohol preferring (sP) and Marchigian Sardinian alcohol preferring (msP) rats. Ucn expression in the pIIIu was analyzed by immunohistochemistry in brains from naïve sP, msP and non-preferring Wistar rats. A positive correlation was found between alcohol preference and Ucn expression in the pIIIu nucleus at peak bregma levels ($p<.05$) in male, but not females of both lines of rats. These data confirm previous studies implicating Ucn in regulation of alcohol consumption. Further studies are being conducted to test the correlation of Ucn fibers in the lateral septum and dorsal with alcohol preference in sP and msP lines of rats.

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44.

Inherited neurological disorders in *Peromyscus*

GJ Szalai, J Crossland, MR Felder

Deer mice are among the most abundant mammals in North America. They range from Alaska to Central America and occur in many natural habitats. They are known to exhibit stereotypic behavior such as jumping, back flips, or pattern running. In addition to stereotypic behavior, there are genetic movement behaviors such as juvenile ataxia, and boggler. Juvenile ataxia is evident in deer mice from about 15 days of age until 35 – 45 days. The boggler deer mice exhibit a pronounced tremor and staggering, awkward gait. The tremor is expressed whenever the animal is awake and at rest. The awkward gait is due to uncoordinated movements of the hind limbs. The trait cannot be recognized until after three months of age, and expression occasionally is delayed until the animal is more than a year old. Another neurological disorder in *Peromyscus* is sensitivity to audiogenic seizures. When subjected to certain stimuli, especially high intensity sound, susceptible animals go into convulsions, whirl rapidly, become stuporous or exhibit other abnormal behaviors. Genetic and phenotypic analysis of these animals will be presented.

Peromyscus Genetic Stock Center, Department of Biological Sciences University of South Carolina, Columbia, South Carolina USA. Funding support: NIH(NCRR): P40-RR14279, NSF: DBI-0444165, NIH: R01GM069601, University of South Carolina ROP 13010-070154

45.

Genetic analysis of inter-male aggression using consomic mouse strains established from C57BL/6J and MSM

A Takahashi[1,3], K Tomihara[2], T Shiroishi[1], T Koide[1]

Aggression is very important emotion for animals and evolutionarily conserved behavior. Genetic contribution for the aggressive behavior has long been known, and recent studies with gene-altered mice have successfully elucidated several genes related to aggressive behavior. However, the attempts to identify naturally occurring genetic variation related to aggressive behavior have not been sufficiently done yet. We here report the forward genetics approach for inter-male aggression by using consomic mouse strains. Consomic strains have the same genetic background as C57BL/6J except for one chromosome from MSM. We found male of one consomic strain B6-15MSM, which have MSM chromosome 15, showed increased aggressive behavior in resident-intruder test. Behavioral analysis showed that the increased aggression of B6-15MSM was mainly caused by the effect of intruder. Several congenic strains of B6-15MSM were established to identify the genetic locus/loci related to the aggressive behavior, and revealed that there are several genetic loci that increased or decreased the aggressive behavior on the chromosome 15.

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46.

Modeling human neurogenetic variation underlying alcoholism, drug abuse, and mental health disorders in non-human primates

EJ Vallender[1], G-L Chen[1], MA Novak[2], CM Priddy[1], H Yang[1], DM Platt[2], GM Miller[1]

Various human genetic variation associated with mental health disorders, including alcoholism and drug abuse diseases, appears to be functionally mimicked by similar, though not identical, variation in non-human primates. Using human association studies as a guide, we have identified similar relevant polymorphisms in the rhesus macaque and assessed their in vitro functional consequences and in vivo behavioral consequences. Specifically, rhesus monkey genetic variation in tryptophan hydroxylase 2 (*TPH2*), serotonin transporter (*SLC6A4*), monoamine oxidase A (*MAOA*), and opioid receptor mu (*OPRM1*) functionally parallels variation seen in humans with regards to effects on gene expression and binding affinity as well as phenotypes including alcoholism. Current preliminary data on four monkeys with defined functional alleles suggests an influence of variation in these genes on time required for acquisition of stable alcohol intake patterns and increased overall alcohol consumption behavior, substantially modeling observed human alcoholism pharmacogenetics. Additionally, we observe a pharmacogenomic-mediated response to naltrexone in alcohol-drinking monkeys similar to that seen in humans. In addition to increasing the tools available to researchers studying the mechanisms of these diseases, genetically-based rhesus macaque models elevate the transitional validity of these studies for understanding and treating human disease.

Division of [1]Neurochemistry and [2]Behavioral Biology, New England Primate Research Center, Harvard Medical School, Southborough, Massachusetts USA. Funding support: AA016194 (GMM), AA016179 (DMP) MH082507 (EJV), DA021180 (GMM), and RR00168

47.

Generality of inbred strain differences in learning ability across different tasks

D Wahlsten[1,2], E Marcotte[2], S Prada[2], E Munn[2]

It has been argued that general learning ability can explain much of the variation in learning by mice as well as humans. When the same mice are given multiple tests, however, it is very difficult to disentangle task correlations because of carryover and test order effects. A clearer perspective on this issue can be obtained by testing independent samples of the same set of inbred strains on multiple tasks. We now report data on learning of air puff inhibitory avoidance, accelerating rotarod, Lashley 3 maze for food reward, and a 4-arm water escape maze by 8 inbred strains from List A of the Mouse Phenome Project. Half of the animals in one experiment received injections of saline or ethanol before training each day. Large and replicable strain differences were seen on all tasks, but there was little consistency across tasks in the best and worst performing strains. Instead, a number of task-specific behavioral adaptations and motivations were clearly important. Strong alcohol effects were seen only for the inhibitory avoidance task.

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48.

Reverse complex trait analysis of transcripts involved in CNS function

XS Wang[1], RT Hori[2], L Lu[1], RW Williams[1]

Large numbers of transcripts in CNS have significant differences in expression. These differences are often generated by polymorphisms near the parent gene. We refer to mRNAs of this type as cis-regulated transcripts (CRTs). CRTs are potentially excellent resources to study effects of variation in gene dosage on higher order phenotypes. We have used multiple large expression data sets in GeneNetwork to extract CRTs. CRTs that we selected had to have high LOD scores in two or more independent crosses (BXD and LXS). Twenty-one transcripts and 19 genes met our criteria, including *Adamts4, Cacna2d1, Camk4, Comt, Cuedc1, Dgat2, Eif4g3, Kcnq5, Lrig1, Map2k5, Nptn, Paip1, Per3, Rora, Rps15a, Slc1a2, Stard4, Trpm3,* and *Ucp2.* We validated expression differences for 15 of these genes using allele-specific amplification (SNaPshot assay) of mRNA and control DNA from reciprocal F1s. We are currently quantifying transcriptional efficiency of *B* and *D* promoters in a subset of these genes by luciferase assay using Neuro2a and NB41 cell lines. Neuroplastin (*Nptn*) is one of these CRTs. It is a postsynaptic transmembrane Ig-type glycoprotein associated with neural plasticity and schizophrenia. We have shown that *B* vs *D* haplotypes of its promoter produce approximately a 1.5-fold difference in expression.

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49.

Methamphetamine metabolism in lines of mice selectively bred for high or low methamphetamine consumption

JM Wheeler[1,2], C Reed[1,2], TJ Phillips[1,2,3]

We are creating selectively bred lines of mice using mass selection for high or low consumption of methamphetamine (MA) in a two-bottle preference drinking procedure. Animals are offered a 20 mg/L MA solution followed by a 40 mg/L solution for four days each. As of the third generation of selection, the high (MAHDR) and low (MALDR) lines differ greatly in their consumption levels. Differences in MA metabolism could contribute to differential levels of MA self-administration. We measured MA levels in both sexes of third generation MAHDR and MALDR lines in blood samples taken at 7.5, 15, 30, 60, 120, and 180 minutes after an acute injection of 1 mg/kg MA. MA levels were determined using an ELISA kit (Neogen; Lexington, KY). Mice were given four additional injections of 1 mg/kg MA at 48 hour intervals, and blood MA levels were determined at the same time points after the final administration. We found a significant difference in blood MA levels following acute versus chronic MA administration, with lower peak blood levels after the final injection (main effect (day); $p=0.0003$). Although MA levels in the lines did not differ following acute injection, we observed a main effect of line ($p=0.001$) after chronic MA administration. MALDR animals showed lower peak blood MA concentrations than MAHDR animals after the final injection. These data show that MA metabolism is altered in response to repeated MA injections, and may become more efficient with chronic exposure. Although these results do not address tissue distribution or brain levels of MA, they do suggest that variation in the ability to metabolize MA could contribute to behavioral differences between these selected lines.

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50.

Assessing spontaneous behavior, behavioral timing and learning of mouse strains in the IntelliCage

V Voikar[1], G Colacicco[1], H-P Lipp[1], DP Wolfer[1,2]

The IntelliCage is a fully automated test system permitting assessment of different aspects of mouse behaviour in a social context, including spontaneous behavior, anxiety, learning and memory. The system has a great potential for behavioral phenotyping of genetically modified mouse strains. However, validation is required for reliable testing of those lines. Therefore, we compared three common strains (C57BL/6, DBA/2 and C57BL/6 x DBA/2 F1) in a set of simple test modules: free adaptation, nosepoke adaptation, drinking session adaptation, place preference learning, and place reversal learning. Two replications of the experiment were performed. After testing in IntelliCage, the animals were also tested individually in three commonly used behavioral tests: fear conditioning with extinction sessions, nesting test and burrowing test. The latter two represent the species-specific behaviors and all three have been shown to depend on intact hippocampus in mice. The replications in the IntelliCage produced almost identical results, confirming the reliability of the system. We found significant strain differences in all tests and discuss these in the light of developing new strategies for behavioral phenotyping of mutant mice.

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51.

Age-related changes in visual ability and cognitive function in the DBA/2J mouse model of glaucoma

AA Wong, RE Brown

The DBA/2J mouse shows age-related increases in intraocular pressure, retinal ganglion cell death and visual impairment (Moon 2005, Cell Tis Res, 320, 51). Visual ability declines from 9 -12 months of age, after which time these mice are functionally blind (Wong & Brown 2007, Neurobiol Aging, 28, 1577). Visual impairment is correlated with poor performance in visuo-spatial tasks but not in non-visually dependent tasks (Brown & Wong 2007, Learn Mem. 13, 134). We treated DBA/2J mice with anti-glaucoma eye drops (Timoptic-XE, 0.0, 0.25 or 0.5%) daily from 2.2 - 12 months of age. At all ages tested (3, 6, 9 and 12 months of age), mice treated with Timolol (0.25 and 0.5%) maintained a high level of performance, while 12 month old control mice (0%) exhibited impaired performance in visually-dependent, but not non-visual tasks. These results demonstrate that when sensory function is preserved, cognitive function is normalized. Thus, any mouse model of cognitive dysfunction must be examined to ensure that behavioral results are not confounded by sensory dysfunction.

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52.

OntologicalDiscovery.org: a web resource for the integration of gene-centered data across species and experimental systems

J Jay[2], Z Li[2], V Philip[3], Y Zhang[2], R Kirova[4], MA Langston[2,4], EJ Baker[1], EJ Chesler[4]

The Ontological Discovery Environment (http://ontologicaldiscovery.org) is a free, public Internet resource for storage, sharing, and analysis of phenotype-centered genomic data sets. The tool is designed to meet a growing demand for data integration and hypothesis discovery across experimental platforms, including technologies, species and phenotype domains. Analyses of similarity, distance and hierarchical relations among neuro-behavioral traits are performed through a suite of tools. These analyses are based on a network of gene-phenotype relations stored in the form of annotated gene sets. Gene sets may be created, stored and curated by individual users, shared among virtual working groups, or made public. Several published genomic data sets are included in the public repository, and users continue to add new results. Examples include alcohol preference and response in mice and rats, traumatic brain injury, human stress response, drug addicts, and literature based candidate gene lists. The modular tools can extract new knowledge on the biological organization of traits and develop converging evidence for gene candidacy. Gene sets can be integrated into PHenome Interdependency and Similarity Hierarchy (PhISH) graphs, which are hierarchical trees of phenotypes based on the genes to which they are associated, providing an empirical derivation of the natural phenotype ontology.

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53.

New candidate genes for susceptibility to addiction from mouse genetics

V Philip[1], L Galloway[1], T Ansah[2], C Blaha[3], M Cook[3], KM Hamre[4], WR Lariviere[5], G Mittleman[3], D Goldowitz[6], EJ Chesler[1]

Identifying novel candidate genes for predictive genetics of drug abuse requires the analysis of susceptibility related phenotypes that predispose individuals to drug seeking and drug taking behaviors. Many of these traits are readily modeled by common mouse behavioral assays which can be measured in genetic mapping populations and correlated with existing gene expression and other molecular characteristics. Members of the Tennessee Mouse Genome Consortium have been measuring 39 primary traits spanning domains of self-administration and response to cocaine, MDMA, morphine and alcohol, novelty seeking, behavioral despair and related neurological phenomena, pain and stress sensitivity, anxiety, hyperactivity and sleep/wake cycles. All traits have been measured in both sexes and the expanded panel of BXD recombinant inbred strains (N=69) for deposit in GeneNetwork.org. Each trait has been subject to QTL analysis and genes residing in the corresponding intervals and multiple tissue expression correlates were identified. Genes were ranked based on the breadth of relationship to predisposing drug abuse phenotypes. All results were integrated with public genomic data sets using the Ontological Discovery Environment. Many of these genes were not previously identified in human studies of drug abuse genomics and will make excellent candidates for SNP association and other genetic analyses.

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Thursday, May 8th

8:30-9:30 **Distinguished Scientist Award and Lecture**

A tale of two johns: common environmental determinants of behavior genetics investigations

John Belknap (co-recipient)
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John Crabbe (co-recipient)
Dept of Behavioral Neuroscience, Oregon Health & Science University, and Portland VA Medical Center, USA

We have elected to dredge the sump of our memories for this jointly delivered talk. We will cover such topics as: where we came from, how on earth we arrived here; what we have learned from one another; and assorted highlights from our unique, and especially our joint, misadventures. We have structured our talk loosely on The First Part of the Delightful History of the Most Ingenious Knight Don Quixote of the Mancha, by Miguel de Cervantes Saavedra. The roles of Don Quixote and Sancho Panza will be inhabited interchangeably by the two Johns.

10:00-12:00 **Symposium Session V**

Role of oxidative stress in behavior

Abraham Palmer, Chair

Expression differences in Glo1 among mice are due to a common copy number polymorphism

AA Palmer
Depts of Human Genetics, Psychiatry and Behavioral Neuroscience, University of Chicago, Illinois, USA. *Supported by MH70933, MH79103, NARSAD, and the Schweppe Foundation*

Glo1 has been previously implicated in anxiety-like behavior in mice and multiple psychiatric diseases in humans; however these results have been inconsistent and even contradictory. We used mouse Affymetrix exon arrays to detect copy number polymorphisms (CNP) among inbred mouse strains, including a ~475 kb tandem duplication on chromosome 17 that includes Glo1. We developed a PCR-based strategy and used it to detect this duplication in 23 out of 71 inbred strains and in outbred and wild caught mice. This duplication contains complete copies of Glo1 and Dnahc8 and partial copies of Glp1r and Btbd9. This duplication is associated with a cis-acting expression QTLs for *Glo1* in many different tissues (LOD>30) in the BXD recombinant inbred strains. However, evidence for an eQTL for Glo1 was not obtained when single SNPs or 3-SNP haplotypes in a panel of 25 inbred strains were analyzed. We show, unexpectedly, that the duplication exists on multiple highly divergent haplotypes making it refractory to mapping with inbred strains. Furthermore, we present evidence of multiple independent reversions to the non-duplicated state among inbred strains, further confounding the relationship between the duplication and flanking SNPs. When we used our PCR-based approach to directly assess duplication status, we identified the expected cis-eQTL in the inbred strain panel. Similar associations were also observed among outbred and wild mice. These observations demonstrate that association-based approaches using panels of inbred strains may fail when variability is due to large CNP. Our findings inform but do not resolve the inconsistent literature about the role of Glo1 in anxiety-like behavior.

Studies of glyoxalase 1 and glutathione reductase 1 in mice and humans

I Hovatta

Research Program of Molecular Neurology, Biomedicum, Finland

Multiple lines of evidence have implicated oxidative stress in diseases including autism, anxiety and Alzheimer's disease. This young field deviates from the traditional focus on neurotransmitters and their receptors and thus has the potential to fundamentally advance out understanding of the molecular basis of health and disease. This talk will be one of four that features different approaches to the problem and examine the role of oxidative stress in both model organisms and human disease. In particular, glyoxalase 1 (Glo1) has been associated with both increased and decreased anxiety-like behavior in mice. Data supporting both positions will be presented in an effort to reconcile these apparently discordant findings. The present talk will discuss studies of glyoxalase 1 and glutathione reductase 1 in mice and humans. Gene expression profiling of inbred strains identified these genes as being strongly correlated with anxiety-like behavior. This correlation was shown to be causal by over-expressing and knocking down expression of both genes using viral vectors, which caused corresponding differences in anxiety-like behaviors. Additional data will be presented regarding the role of these genes in autism and anxiety spectrum disorders in human populations.

Identification of promising candidate genes for ethanol dependence and associated withdrawal: a potential role for mitochondria and oxidative stress

DL Denmark, KJ Buck

Dept of Behavioral Neuroscience, Portland Alcohol Research Center, Oregon Health & Science University, Portland VA Medical Center, Portland, Oregon USA . *Supported by AA011114, P60 AA06243, F30 AA 17342-01, and a VA Merit grant.*

We recently used a panel of interval specific congenic strains derived from C57BL/6J (B6) and DBA/2J (D2) mice to fine-map quantitative trait loci (QTL) with large effects on predisposition to ethanol physical dependence and associated withdrawal severity to a 1.1 Mb interval of mouse chromosome 1 (Kozell *et al*. 2008). Systematic molecular analyses revealed that 17 of the 40 genes in this interval demonstrate validated genotype-dependent brain expression and/or non-synonymous coding sequence variation, and can thus be considered high priority candidates to underlie this region's influence on ethanol dependence/withdrawal (Denmark & Buck, 2008). Four candidates code for proteins involved in oxidative stress pathways, a prominent and well-known pathogenic cellular response to ethanol exposure. Two of these are integral subunits of the mitochondrial respiratory chain, an important mediator and direct target of ethanol-induced oxidative stress. Therefore, we have begun to explore whether differences in brain oxidative stress and mitochondrial function play a role in ethanol withdrawal severity using ELISA quantitation of protein carbonyl content and blue native gel electrophoresis (BN-PAGE) in B6, D2, and congenic strains. Tissue was collected immediately (ethanol-dependent) and 7 hr (ethanol-withdrawn) after discontinuation of 72 hr continuous ethanol vapor (plus alcohol dehydrogenase inhibition), and compared to naïve and air-exposed control animals of each strain. Genotype-dependent oxidative stress levels and/or mitochondrial respiratory chain complex amount or activity between treatment groups may indicate a mechanism by which genetic susceptibility to ethanol withdrawal/dependence is directed by the chromosome 1 QTL, and perhaps suggest specific genes likely to contribute to this phenotype.

Glyoxalase 1 in HAB/LAB mice: from genetic polymorphisms to anxiety-related behavior

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Max Planck Institute of Psychiatry, Munich, Germany. *Funding Support: BMBF QuantPro 0313863*

In an intra-strain approach, CD1 mice are selectively inbred for either high (HAB) or low (LAB) anxiety-related behavior. While keeping the integration of anxiety-related factors and pathways intact, the clear-cut difference in the genetic predisposition to anxiety might help to identify genes and SNPs likely to contribute to the traits. After more than 25 generations, a variety of molecular-genetic, proteomic and behavioral approaches have been used to demonstrate that glyoxalase 1 is consistently expressed to a higher extent in several brain areas and in blood of LABs and to a lower extent in HABs. Phenotype-specific polymorphisms in the promoter of the glyoxalase 1 gene, including T(-2456)G and C(-344)T, might explain the enhanced transcription in LABs compared to HAB and HABxLAB cross-mated F1 animals, the latter always showing intermediate genotypes and phenotypes. The functional impact of the promoter SNPs will be further tested in allele-specific transcription and gene reporter assays, including a freely segregating F2 panel. The putative role of transcription factors, particularly HNF3 and NF1, is discussed as are the effects of the glyoxalase 1 substrates methylglyoxal and glutathione on enzyme activity and expression. In an extension of these studies, the animal model data will be examined in blood samples from psychiatric patients.

Friday, May 8th

8:30-9:30 **Young Scientist Award and Lecture**

Mouse genetic differences in exercise-induced adult hippocampal neurogenesis & learning

Justin Rhodes

Dept of Psychology, Beckman Institute, University of Illinois, Urbana, Illinois, USA

Growing evidence suggests aerobic exercise can improve cognitive performance. Recent data has established that exercise increases the number of new neurons in the hippocampus and enhances spatial learning in C57BL/6J mice, but surprisingly few studies have explored whether this relationship holds for other mouse genotypes. To test the hypothesis that genetic background modulates effects of exercise on neuroplasticity, mice from C57BL/6J (n=34 both males and females) or DBA/2J (n=34 both males and females) were placed with or without running wheels for 40 days. The first 10 days mice received daily injections of BrdU to label dividing cells. The last 10 days mice were tested on 3 cognitive tasks, water maze, rotarod, and contextual fear conditioning, then measured for neurogenesis. C57BL/6J mice ran more, produced more new neurons and displayed enhanced spatial learning on water maze and enhanced performance on rotarod as compared to DBA/2J which showed no gains in performance on rotarod or water maze from exercise. However, exercise slightly increased fear conditioned responses in both genotypes. After multiple genotypes are measured we propose using a systems approach to identify genes and pathways that mediate high and low genetic sensitivity to cognitive effects of exercise.

Friday, May 8th

10:00-12:00 **Symposium Session VI**

Learning and memory: from causes to consequences

K. Matthew Lattal, Chair

Predicting danger: the circumstances that produce fear learning

G McNally

School of Psychology, University of New South Wales, Australia

Funding support: The Australian Research Council, DP0343808 & DP0877430

Associative learning proceeds as a function of the discrepancy (or error) between the outcome that the organism expects in a given environment and the outcome that it actually receives. This error of prediction determines learning and changes how the organism attends to the events it learns about. We have begun to identify some of the neural and cellular systems that underlie such predictive fear learning. This talk will cover our recent work showing important and complementary roles of the periaqueductal gray, nucleus accumbens, and basolateral amygdala in predictive fear learning. This work suggests that opioid receptors in the ventrolateral quadrant of the periaqueductal gray regulate predictive fear learning directly whereas opioid receptors in the nucleus accumbens regulate predictive fear learning indirectly by controlling allocation of attention. In contrast, NMDA receptors in amygdala contribute to fear learning independently of the magnitude and direction of predictive error. These findings suggest that there are dissociable neural mechanisms for different components of predictive fear learning and they highlight the usefulness of associative learning theory for behavioral and neural genetic analyses of learning and memory.

The contribution of striatal subregions to stimulus-modulation of reward-seeking behaviors

LH Corbit,[1] PH Janak[1,2]

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Funding Support: Funds from the state of California for medical research on alcohol and substance abuse through the University of California at San Francisco

In instrumental conditioning animals form associations between their actions and the consequences produced by those actions. Knowledge of this association alone, however, is insufficient for determining instrumental performance. Levels of responding and choices between responses are also affected by the current incentive value of the instrumental outcome and can be modulated by reward-related stimuli. Using the Pavlovian-instrumental transfer paradigm we can examine the effects of reward-related stimuli on instrumental responding. I will describe studies examining the role of stimuli in modulating behaviors reinforced with both alcohol and natural (sucrose) reward. Using reversible inactivation techniques we have identified distinct roles for subregions of the striatum in controlling stimulus-modulation of reward-seeking behaviors. Further, I will describe data that suggest that the associative and neural structures controlling behavior may differ for alcohol versus natural reward.

Ablation of adult hippocampal neurogenesis both impairs and enhances hippocampus dependent behaviors

MR Drew[1], R Hen[1,2]

Depts of [1]Psychiatry, [1]Neuroscience, and [2]Pharmacology, Columbia University, New York, New York; [1]Division of Integrative Neuroscience, New York State Psychiatric Institute, USA

It is now well-established that the adult hippocampus retains the ability to generate neurons. In the rodent, the species for which the best data are available, it is estimated that 9000 cells are generated each day. Many of these cells mature into dentate granule neurons with functional synapses, but prior to reaching maturity they exhibit unique properties such as enhanced excitability and depolarizing responses to GABA. My talk describes research aimed at understanding how adult hippocampal neurogenesis contributes to psychological processing. I have found that ablating adult hippocampal neurogenesis in mice using irradiation or a genetic method fails to alter measures of emotionality but impairs contextual fear conditioning, a hippocampus-dependent form of Pavlovian conditioning. Performance in hippocampus-dependent spatial maze tasks is relatively spared, and some hippocampus-dependent behaviors are enhanced. I will describe this work and provide a theoretical framework explaining how the ablation of neurogenesis might alter psychological processing so as to impair some behaviors and enhance others.

Memory expression, extinction, and the problem of mouse behavior

KM Lattal

Dept of Behavioral Neuroscience, Oregon Health & Science University, Portland, Oregon USA.

Funding support: NIMH R01 MH077111, NIAAA P60 AA010760, NIDA P50 DA018165

A major challenge for behavioral genetic approaches to learning and memory is to determine whether differences in behavior (or performance) reflect differences in learning or differences in expression of learning. This learning-performance distinction is particularly important in the study of extinction, in which organisms learn that previously established environmental relations have been severed. Extinction results in a loss of behavior, even as the original memory remains intact. At a neurobiological level, altering the action of receptors, intra-cellular signaling cascades, and nuclear targets may enhance or impair the development of extinction. Because many inbred and genetically modified mice differ in initial learning, the study of extinction in these mice is particularly challenging. This talk will review some recent studies with inbred and genetically modified mice that demonstrate (1) strategies for studying extinction in mice that have deficits in initial learning, (2) that there are some intriguing similarities and differences in the behavioral, cellular, and molecular mechanisms of initial learning and extinction, and (3) the importance of distinguishing between effects of genetic and pharmacological manipulations on memory storage and memory expression during extinction.

Friday, May 8th

13:30-15:30 **Paper Session**

Invited Talks from selected meeting abstracts

Differential effects of voluntary alcohol drinking on brain endocannabinoid levels in female and male rats of the alcohol-preferring AA line

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The endocannabinoid system has been suggested to regulate alcohol drinking. However, the precise mechanism by which endocannabinoids control alcohol consumption remains to be established. In this study, we examined the role of anandamide (AEA) and 2-arachidonoyl-glycerol (2-AG) in alcohol drinking by male and female rats of the genetic model of high alcohol drinking, the alcohol-preferring AA line. Both male and female rats were trained to drink 10% alcohol during 90-min sessions. Following stable alcohol drinking, half of the alcohol-drinking rats were sacrificed immediately before the drinking session, whereas half of rats were sacrificed immediately after alcohol drinking. The following brain regions were dissected: prefrontal cortex (PFC), nucleus accumbens (NAC), caudate-putamen (CPU), amygdala (AMYG), and hippocampus (HIP). Samples were analyzed with chromatography-tandem mass spectrometry. Generally, changes induced by acute voluntary alcohol in endocannabinoid levels were greater in the female than male rats. In females, 2-AG increased in PFC and NACC, while decreases were seen in AEA in PFC, CPU, AMYG, and HIP. In males, the only changes were increased AEA levels in NAC and CPU. These results show that voluntary ethanol drinking alters endocannabinoid levels in several brain areas, and that these alterations are more pronounced in female than male rats.

An evolutionarily conserved sexual signature in the primate brain

B Reinius[1], P Saetre[3], JA Leonard[2], R Blekhman[5], R Martinez[4], Y Gilad[5], E Jazin[1]

[1]Dept of Development and Genetics and [2]Dept of Evolutionary Biology, Uppsala University, Uppsala Sweden; [3]Dept of Clinical Neuroscience and [4]Dept of Molecular Medicine, Karolinska Institutet and Hospital, Stockholm, Sweden; [5]Dept of Human Genetics, University of Chicago, Chicago, Illinois USA. *Funding Support: by grants from the Börströms Foundation to EJ and JAL, the Swedish Science Foundation to EJ, and NIH (GM077959) to YG*

The question of a potential biological sexual signature in the human brain is a heavily disputed subject. In order to provide further insight into this issue, we used an evolutionary approach to identify genes with sex differences in brain expression level among primates. We reasoned that expression patterns important to uphold key male and female characteristics may be conserved during evolution. We compared gene expression profiles in the occipital cortex of male and female humans (Homo sapiens, a great ape) and cynomolgus macaques (Macaca fascicularis, an old world monkey), two catarrhine species that show abundant morphological sexual dimorphism, as well as in common marmosets (Callithrix Jacchus, a new world monkey) which are relatively sexually monomorphic. We identified hundreds of genes with sex-biased expression patterns in humans and macaques, while fewer than ten were differentially expressed between the sexes in marmosets. In primates, a general rule is that many of the morphological and behavioral sexual dimorphisms in polygamous species, such as macaques, are typically less pronounced in monogamous species such as the marmosets. Our observations suggest that this correlation may also be reflected in the extent of sex-biased gene expression in the brain. We identified 85 genes with common sex-biased expression in both human and macaque ($p=0.05$) and 2 genes; X inactivation-specific transcript (XIST) and Heat shock factor binding protein 1 (HSBP1), that were consistently sex-biased in the female direction in human, macaque and marmoset ($p=0.001$). Further, we found that genes with conserved sexual gene expression dimorphism in the brain also evolve under more evolutionary constraint at the coding region level than other brain-expressed genes. These observations imply a conserved signature of sexual gene expression dimorphism in the brains of primates. Our results suggest that genes with conserved sexually distinct expression profiles in catarrhines may underlie important functional differences between the sexes, with possible importance during primate evolution.

Characterisation of *spiegel*, a novel aggressive zebrafish mutant

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Mood disorders are debilitating diseases that show high prevalence and comorbidity in society. Observations from other species have implicated 5-HT signalling in the control of some mood disorders including aggression, anxiety and addiction, although the pathways involved are not completely understood. In this project, we analyse the neural circuits that mediate aggression in zebrafish, with particular emphasis on 5-HTergic signalling. We first identified a novel aggressive mutant, *spiegel*. *spiegel* mutants show increased attacks on conspecifics, failure to down-regulate aggression following initiation, and increased boldness compared to wild-type siblings. *spiegel* harbours an adult viable, hypomorphic mutation in *fgf receptor 1*. Expression analyses in *spiegel* demonstrate that the Fgf signalling defect is localised to a small nucleus in the inferior hypothalamus, which has been linked to aggression in other teleosts. Furthermore the behavioural phenotype may be caused by a reduction of 5-HT activity in mutants. Future plans aim to modulate 5-HT within *spiegel* in an attempt to rescue the aggressive phenotype. This work uncovers a novel role for Fgf signalling in controlling aggression in the adult brain, possibly via modulation of 5HT activity.

Evaluating the role of $GABA_B$ receptors in ethanol sensitivity

SE Holstein[1,2], HM Kamens[1,2], N Li[1,2], AJ Eshleman[1,2,3], TJ Phillips[1,2,4]*

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Acute sensitivity to alcohol is a heritable trait that is correlated with alcohol consumption history and familial risk of alcoholism. The $GABA_B$ receptor is critically involved in this response, as $GABA_B$ receptor activation blocks the stimulant effects ethanol. To further assess the contribution of $GABA_B$ receptors to ethanol sensitivity, we examined $GABA_B$ receptor expression and function in the FAST and SLOW mouse lines, which were selectively bred for extreme sensitivity and insensitivity, respectively, to the locomotor stimulant effects of ethanol. There was a significant increase in whole brain *Gabbr1* ($GABA_{B1}$ subunit) mRNA expression in SLOW mice, but only in one replicate; there was no line difference in *Gabbr2* ($GABA_{B2}$ subunit) expression. Within the ventral midbrain, a line difference in baclofen-stimulated $GABA_B$ receptor function was found, with greater receptor function in SLOW mice; there was, however, no change in function in other limbic or motor structures. Acute ethanol did not alter $GABA_B$ receptor function in either line. These data provide modest evidence for selection-induced alterations in $GABA_B$ systems. However, it is possible that $GABA_B$ receptor localization, second messenger signaling, or interactions with dopamine are the important factors that mediate the stimulant response difference to ethanol in FAST and SLOW mice.

LMO4 in nucleus accumbens regulates cocaine-induced behavioral plasticity

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An estimated 1.5 million Americans abuse or are dependent on cocaine, resulting in large personal and societal costs. We have focused on using genetic approaches to identify new pathways and genes involved in drug abuse. Previously, mutations in the Drosophila LIM-only (dLmo) gene were identified due to their increased behavioral sensitivity to cocaine. Here we show that the mammalian homolog Lmo4, which is highly expressed in brain regions implicated in drug addiction, plays a similar role in cocaine-induced behaviors. Mice with a global reduction in Lmo4 levels showed enhanced sensitivity to the locomotor stimulatory effects of cocaine after acute and chronic cocaine administration. This effect was reproduced upon down-regulation of Lmo4 in the nucleus accumbens by RNA interference. Since Lmo4 has been demonstrated to be a transcriptional regulator, studies are underway using genomic approaches (microarrays and ChIP) to identify the transcriptional targets of Lmo4. Novel targets of Lmo4 may lead to new strategies for the treatment of cocaine addiction.

Organismal and genetic networks in anxiety and depression

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The identification of susceptibility genes associated with human neuropsychiatric disorders like anxiety and depression has been hampered by the genetic complexity of these diseases. Although it is not possible to develop an animal model that exhibits the entire spectrum of symptoms seen in humans with these disorders, particular behavioral aspects of these diseases can be modeled in rodents. Paradigms for measuring anxiety and depression-related behaviors, including the open field, elevated plus maze and tail suspension tests, have been used effectively in the pharmaceutical industry for screening the efficacy of new and existing anxiolytics and anti-depressants. Recently, our lab and others have utilized an approach called haplotype association mapping to identify genetic loci associated with these behaviors. This strategy takes advantage of the naturally occurring phenotypic variation that exists between inbred strains and the recent development of the mouse haplotype map. We have characterized the behavioral phenotypes of over 35 inbred strains in seven different assays measuring anxiety- and depression-related behaviors. In addition, we have conducted gene expression analysis in eight relevant brain regions across 30 strains. Together, these phenotype, genotype and gene expression data across strains provide a valuable resource for investigating the genetic networks contributing to neuropsychiatric disorders.