BIOGRAPHICAL SKETCH

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NAME: Boettiger, Charlotte A.

eRA COMMONS USER NAME (credential, e.g., agency login): cboettiger

POSITION TITLE: Associate Professor of Psychology and Neuroscience

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of California, Berkeley	A.B.	05/93	Integrative Biology
University of California, San Francisco	Ph.D.	12/00	Neuroscience
University of California, San Francisco	Postdoctoral	06/01	Psychiatry
University of California, Berkeley	Postdoctoral	08/03	Neuroscience

A. Personal Statement

The goal of the proposed research is to provide mechanistic insight into how habits can come to control human behavior. Clarifying the neurobiology of making and breaking habits, and how this circuitry is disturbed among people with substance use disorders (SUDs) will significantly advance our ability to identify new targets and strategies for preventing and treating disorders in which habitual actions come to dominate more desirable goal-directed actions. My expertise is well suited to carry out the proposed work. I have a broad background in neuroscience, with specific training and expertise in neuroimaging, psychopharmacology, and SUDs. As a postdoctoral fellow at UC Berkeley, I carried out functional neuroimaging (fMRI) in healthy control subjects to investigate the neurobiological underpinnings of stimulus-response (S-R) learning, which is the basic process underlying habitual responding. At the Ernest Gallo Clinic and Research Center at UC San Francisco, I expanded my research to include human behavioral pharmacology and studies in alcoholic populations. Since establishing my own lab at UNC Chapel Hill, my lab has focused on investigating the neurobiological bases of intermediate phenotypes for SUDs, with the majority of our work focused on alcohol use disorders, and pharmacological and genetic investigations of executive functions. As a result of these previous experiences, I am aware of the importance of meticulous logistical planning, which is required for successful neuroimaging studies with humans, and for conducting work with special populations. The current application builds logically on my expertise in alcohol use disorders and our existing behavioral data and I have chosen collaborators (Drs. Frohlich, Grewen, and Cooney) who provide additional expertise in human brain stimulation techniques, stress physiology, and medicine. Funding of this project will lay the foundation for a cutting edge research program in an under-investigated area of mental health research. In summary, I have demonstrated my capacity for successful and productive research in an area of high relevance to SUDs, and my expertise and experience, coupled with the additional expertise available in my local research environment, will enable me to successfully carry out the proposed project. During 2009 and 2011 my career was disrupted due to family obligations; however, since that time, I have reestablished full research momentum.

1. Mitchell JM, Fields HL, D'Esposito M, **Boettiger CA**. (2005) Impulsive Responding in Alcoholics. *Alcohol: Clin Exp Res* **29**:2158-2169.
2. Crews FT, **Boettiger CA.** (2009) Impulsivity, Frontal Lobes and Risk for Addiction. *Pharmacol Biochem Behav* **93**:237-247. PMCID: PMC2730661
3. Leeman RF, Bogart D, Fucito LM., **Boettiger CA** (2014) "Killing two birds with one stone": Alcohol use reduction interventions with potential efficacy in enhancing self-control. *Curr Addict Rep* **1**:41-52. PMCID: PMC4048018.

4. McKim TH, **Boettiger CA** (2015) Addiction as Maladaptive Learning, with a Focus on Habit Learning. In: The Wiley Handbook on the Cognitive Neuroscience of Addiction (Wilson SJ, ed), pp 3-28: John Wiley & Sons.

B. Positions and Honors

Positions and Employment

1992-1994	Research Asst., University of California, Berkeley, Molecular and Cell Biology Dept.
2001	Postdoctoral Fellow, University of California, San Francisco, Psychiatry Dept.
2001-2003	Postdoctoral Fellow, University of California, Berkeley, H. Wills Neuroscience Institute
2003-2005	Assistant Research Scientist, Ernest Gallo Clinic & Research Center (EGCRC)
2005-2007	Associate Investigator, EGCRC
2005-2007	Adjunct Assistant Professor, Neurology Dept., University of California, San Francisco
2007-2015	Assistant Professor, Psychology Dept. & Biomedical Research Imaging Center (BRIC), University of North Carolina, Chapel Hill (UNC-CH)
2007-	Graduate Faculty Member, Curriculum in Neurobiology, UNC-CH
2008-	Faculty Member, Bowles Center for Alcohol Studies, UNC-CH
2010-	Member, UNC Nutrition Obesity Research Center, UNC-CH
2013-	Member, UNC Neuroscience Center, UNC-CH
2015-	Associate Professor, Psychology and Neuroscience Dept. & BRIC, UNC-CH

Other Experience and Professional Memberships

1994-	Member, American Association for the Advancement of Science
1996-	Member, Society for Neuroscience
2001-	Member, Cognitive Neuroscience Society
2005-2007	Founding President & Representative, San Francisco Bay Area Chapter of the Society for Neuroscience
2007	Medical Research Council (London), ad hoc grant reviewer
2008	NIAAA Special Emphasis Panel: Behavioral Mechanisms in the Transition to Habitual Alcohol Seeking and Drinking, ad hoc reviewer
2009	NIAAA Scientific Review Group: Neuroscience Research Review Subcommittee (AA-4), ad hoc reviewer
2009-	Member, Research Society on Alcoholism
2010	Behavioral and Social Advisory Council, Alcoholic Beverage Medical Research Foundation, ad hoc grant reviewer
2010	The Netherlands National Initiative Brain and Cognition, ad hoc grant reviewer
2011-	International Society for Biomedical Research on Alcoholism
2014-2015	Councilor, Triangle Chapter of the Society for Neuroscience

Selected Honors and Awards

1992	University of California President's Undergraduate Fellowship
1993	HHMI U.C. Berkeley Undergraduate Biology Fellowship
1995	National Science Foundation Graduate Fellowship Honorable Mention
1995	UCSF Graduate Opportunity Fellowship
1997	Pre-doctoral National Research Service Award (NIH/NIMH; F31 MH011896)
1998	UCSF Graduate Dean's/Anthony Fellowship in Neuroscience
2001	McDonnell Summer Institute in Cognitive Neuroscience Fellowship
2002	Wheeler Center for the Neurobiology of Addiction Hugh O'Connor Memorial Fellowship
2009	IBM Junior Faculty Development Award, UNC-CH
2011	Mason and Linda Stephenson Faculty Award, Dept. Psychology, UNC-CH
2012	Lindquist Faculty Award, Dept. Psychology, UNC-CH
2014	UNC Psychology Dept. Award for Outstanding Undergraduate Research Mentor

C. Contribution to Science

1. A promising intermediate phenotype for SUDs that has emerged in recent years is the tendency to select smaller, immediate rewards ("*Now*") over larger, delayed rewards ("*Later*"), or "*Now* bias". The

neurobiological bases of *Now* bias remain incompletely understood, but my research program has contributed to advances in this area. One of my early goals in this area was to develop a functional magnetic resonance imaging (fMRI)-compatible behavioral task quantifying *Now* bias that would robustly differentiate the behavior of control subjects from those with SUDs. In a series of experiments, I demonstrated that, even after long-term abstinence, people with a history of alcohol use disorders (AUDs) show markedly elevated *Now* bias compared to controls. Based on evidence implying a role for endogenous opioids in modulating *Now* bias, I tested the impact of acute naltrexone, an opioid receptor antagonist used to treat alcoholism, on *Now*/*Later* decision-making. An underlying motivation for that study is our incomplete understanding of how naltrexone reduces drinking. This study broke new ground in evaluating cognitive effects of naltrexone and produced two novel findings. First, that naltrexone shifts *Now* bias depending on a personality measure linked to frontal dopamine function: Rotter's Internal-External Locus of Control Scale; this relationship was particularly strong among those with an AUD history. We replicated this finding in a second naltrexone study, finding that the relationship was limited to those with a family history of AUDs. I proposed a model accounting for this finding whereby naltrexone effects on *Now* bias reflect an interaction between trait-based tonic frontal dopamine and acute changes in frontal dopamine mediated via kappa opioid receptor actions. In the past few years, I have conducted several studies that further support this model, which I detail in the next section.

   a. Mitchell JM, Fields HL, D'Esposito M, **Boettiger CA**. (2005) Impulsive Responding in Alcoholics. *Alcohol: Clin Exp Res* **29**:2158-2169.
   b. Mitchell JM, Tavares VC, Fields HL, D'Esposito M, **Boettiger CA**. (2007) Regulation of Impulsivity by Endogenous Opioids in Alcoholics and Healthy Controls. *Neuropsychopharmacol*, **32**:439-449
   c. **Boettiger CA**, Mitchell JM, Tavares VC, D'Esposito M, Fields HL. (2007) Immediate reward bias in humans: fronto-parietal networks and a role for the catechol-*O*-methyltransferase 158(Val/Val) genotype. *J Neurosci* **27**:14383-14391.
   d. Altamirano LJ, Fields HL, D'Esposito M, **Boettiger CA** (2011) Interaction Between Family History of Alcoholism and Locus of Control in the Opioid Regulation of Impulsive Responding under the Influence of Alcohol. *Alcoholism Clin Exp Res.* **35**:1905-1914. PMCID: PMC3158828.

2. The model I proposed to account for naltrexone effects on *Now* bias predicts that *Now* bias varies with frontal dopamine according to a U-shaped function. According to this model, the effect of acute changes in frontal dopamine on *Now* bias should interact with trait-based tonic frontal dopamine levels. I have gathered evidence supporting this model in several studies. First, in a much larger sample, we confirmed my previous finding that *COMT* genotype predicts *Now* bias in adults Notably, we also found a novel interaction between age and *COMT* genotype that reconciles my previous findings with conflicting data in adolescent boys. A variety of factors may account for this interaction, but developmental changes in *COMT* gene expression is one possibility. Gene expression is regulated in part by DNA methylation, and the *COMT* gene is extraordinarily rich in methylation sites; therefore, my research program recently began investigating differential methylation of *COMT* between individuals. Prior studies had investigated differential methylation at a small number of sites in the *COMT* promoter region, but we conducted the first comprehensive analysis of differential methylation across the entire gene. We found differential methylation at loci throughout the *COMT* gene, as well as evidence for associations between methylation at specific sites in the *COMT* gene and possible upstream mediators, including ethnicity, socioeconomic status, and level of alcohol use. We also observed associations between locus specific *COMT* methylation and differential *COMT* expression in human cell lines. I have also shown that acute manipulations of dopamine can shift individual *Now* bias. First, we tested the effect of acute dopamine depletion on *Now* bias. In adult males, we found that dopamine depletion effects on *Now* bias depend on *COMT* genotype: it increases *Now* bias among Val/Val individuals, but not among Met carriers. The second approach was to measure *Now* bias in naturally cycling women at points in their ovarian cycle corresponding to peak and trough estrogen levels. Based on evidence that estrogen levels vary directly with frontal dopamine function, I predicted reduced *Now* bias at mid-cycle (peak estrogen). We found that *Now* bias indeed decreases from early- to mid-cycle, and that the magnitude of the decrease is proportional to the estrogen rise. Consistent with my model, cycle effects on *Now* bias depend on *COMT* genotype.

   a. Smith CS, **Boettiger CA** (2012) Age modulates the effect of COMT genotype on delay discounting behavior**.** Psychopharmacology 222:609-617. PMCID:PMC3401276.

b. Swift-Scanlan T, Smith CT, Bardowell SA, **Boettiger CA**. (2014) Comprehensive interrogation of CpG islands in the gene encoding COMT, a key estrogen and catecholamine regulator. *BMC Med Genom* 7:5. PMCID: PMC3910242.
c. Kelm MK, **Boettiger CA** (2013) Effects of Acute Dopamine Precusor Depletion on Immediate Reward Selection Bias and Working Memory Depend on Catechol-*O*-methyltransferase Genotype. *J Cognit Neurosci* **25**:2061-2071. PMCID: PMC3816120.
d. Smith CT, Sierra Y, Oppler HS, **Boettiger CA** (2014) Ovarian Cycle Effects on Immediate Reward Selection Bias in humans: a role for estradiol. *J Neurosci* **34**:5468-5476. PMCID: PMC3988406.

3. When my first naltrexone study found that the drug appeared to reduce response conflict in control subjects, I hypothesized an underlying reduction in attentional bias toward attractive cues (Mitchell et al., 2007). In light of this, an early goal when I arrived at UNC was to establish paradigms amenable to fMRI and behavioral pharmacology studies to directly investigate attentional bias. This research direction was further motivated by many behavioral studies reporting attentional bias to addiction cues in SUDs. Specifically, in laboratory-based measures of attention, people with SUDs preferentially attend to stimuli associated with their SUD; this phenomenon is reported in a wide variety of addictions. Although widely investigated, it wasn't clear whether SUD attentional bias reflects addiction cues preferentially capturing or holding attention, or both. We addressed this question by testing participants in two different attentional bias tasks. The first task is a spatial cuing task, in which participants respond to targets that appear in the location formerly occupied by either a drug-related stimulus or a neutral stimulus. Using a short (150 ms) interval between the stimulus and target yields a measure of biased attentional *capture*. The second task is an attentional blink paradigm, in which a stream of visual stimuli with two embedded targets is rapidly presented. The ability of the first target to block detection of the second target indexes sustained attentional *hold*. By administering both tasks to active smokers and non-smoking controls, we found that smoking cues preferentially *capture* smokers' attention, but do not selectively *hold* attention. This distinction is an important one as differing neural circuits are likely involved, and each may call for different therapeutic interventions. We next adapted these attention paradigms for use in AUD studies.
    a. Chanon VW, Sours CR, **Boettiger CA** (2010) Attentional bias toward cigarette cues in active smokers. *Psychopharmacol*, **212**:309-320. PMCID: PMC2967198.
    b. Garland E, Gaylord, SA, **Boettiger CA**, Howard MO (2010) Mindfulness training modifies cognitive, affective, and physiological mechanisms implicated in alcohol dependence: Results from a randomized controlled pilot trial. J Psychoactive Drugs 42:177-192.
    c. Garland E, **Boettiger CA**, Gaylord S, Chanon VW Howard M (2012) Mindfulness is Inversely Associated with Alcohol Attentional Bias *Among* Recovering Alcohol-Dependent Adults. *Cognitive Ther Res* 36:441-450. PMCID: PMC3532517.

4. Learning to replace habitual responses to drug-related stimuli with more adaptive responses is a crucial task in recovery from addiction. However, little is understood about how such learning is implemented or regulated in the human brain. Moreover, it is unknown whether a general impairment in this type of learning occurs in those with SUDs, which could hinder their capacity to achieve abstinence. To address this issue, I have undertaken studies focused on understanding the neurobiology of learning new stimulus-response (S-R) associations and replacing learned S-R associations; processes fundamental to forming and replacing habits, and known to involve the frontal lobe. Non-human primate data indicate that chronic use of drugs of abuse (particularly stimulants) impairs S-R *unlearning*, but this area has not been well investigated in humans. As a first step in this area, I established a paradigm to study S-R learning in humans and then identified fronto-striatal circuits in the human brain associated with the ability to learn S-R associations.
    a. **Boettiger CA**, D'Esposito M. (2005) Frontal Networks for Learning and Executing Arbitrary Stimulus-Response Associations. Journal of Neuroscience, 25:2723-2732.
    b. McKim TH, **Boettiger CA** (2015) Addiction as Maladaptive Learning, with a Focus on Habit Learning. In: The Wiley Handbook on the Cognitive Neuroscience of Addiction (Wilson SJ, ed), pp 3-28: John Wiley & Sons.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/charlotte.boettiger.1/bibliography/40345946/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

N/A Boettiger (PI) 7/1/13 – 6/30/15
ABMRF Research Grant*:* Neural circuit bases of impulsive choice in emerging adults and heavy drinking adults
Goal: to identify and compare the neural circuit-bases of impulsive choice in emerging adults and heavy-drinking adults.
Role: PI

5P60AA011605 Crews (PI) 12/6/12 – 11/30/17
Comprehensive Alcohol Research Center Research Component: Component 3 - Frontolimbic circuits, dopamine and attentional bias to alcohol cues.
Goal: to test whether acute manipulation of dopamine signaling reduces conditioned responses to alcohol cues in both rats and binge-drinking humans.
Role: Component Co-PI (PI: Robinson)

R03 DA037405 Sheridan (PI) 2/1/15-1/31/16
Development of control over rewarding stimuli: A cognitive neuroscience approach
Goal: to investigate the neural correlates of the developmental progression of inhibition of reward in the context of reward during adolescence using a new task, the Habitual Appetitive Behavior Inhibition Task.
Role: Consultant

Pending Research Support

R21 AA024197 Boettiger (PI) 7/1/15 – 6/30/17
Differential Methylation of the COMT gene: upstream and downstream associations
Goal: to identify the functional units of DNA methylation in the COMT gene and identify associations between site-specific methylation and downstream factors, including COMT-genotype dependent impulsive choice, as well as upstream factors, including alcohol use and childhood adversity.

U01 #*TBD* Dichter/Daniels (PI/Co-PI) 10/1/15-9/30/20
NIH U01 Consortium: Adolescent Brain and Cognitive Development Study-US (ABCD-US)-Research Project
Goal: to inform the development of tools for the prediction, prevention, and treatment of problematic substance use, and to identify substance use-related neurobehavioral trajectories for follow-up investigations.
Role: Co-Investigator

Selected Completed Research Support (past 3 years)

F31 AA020132 Smith (PI) 8/01/11 – 7/31/14
Now versus Later decision-making: effects of frontal development and alcohol use
Goal: to identify functional brain changes from early (18-23) to later (25-40) adulthood that correlate with age-dependent changes in immediate reward bias in humans.
Role: Sponsor (Mentor)

UL1 RR025747 Runge (PI) 11/1/12 – 10/31/13
UNC-CH Clinical Translational Science Award - NC TraC$2K Pilot Grant: Addiction history and COMT genotype are independently associated with impairments in learning and replacing arbitrary stimulus-response associations
Goal: to determine whether a common polymorphisms in the COMT gene and substance use history individually predict individual differences in stimulus-response learning and re-learning.
Role: Pilot Project Mentor (McKim, PI)

N/A Boettiger (PI) 12/1/12 – 5/31/13
Lindquist Faculty Award: Ovarian Cycle Effects on Immediate Reward Selection Bias
The goal of this study is to determine the relationship between changes in circulating estradiol and ovarian cycle effects on immediate reward bias in humans.
Role: PI

F32 DA025442 Chanon (PI) 8/1/10 – 7/31/13
Neurobiological Correlates of Attentional Bias in Addiction
Goal: to identify the neurobiological basis of attentional bias towards smoking cues in active smokers.
Role: Sponsor (Mentor)