BIOGRAPHICAL SKETCH

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NAME: Boettiger, Charlotte A.

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

POSITION TITLE: 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.	05/1993	Integrative Biology
University of California, San Francisco	Ph.D.	12/2000	Neuroscience
University of California, San Francisco	Postdoctoral	06/2001	Psychiatry
University of California, Berkeley	Postdoctoral	08/2003	Neuroscience

A. Personal Statement

I have a broad background in neuroscience, with specific training and expertise in the use of neuroimaging and neuropharmacology to probe executive function, particularly in the setting of alcohol and other substance use disorders (SUDs). My lab uses cognitive testing, neuroimaging, behavioral pharmacology, non-invasive brain stimulation, EEG, genetic, epigenetic, and biochemical analysis methods in human subjects and samples. The goal of the proposed research is to test how adolescent binge alcohol exposure effects on learned, automatic responses to stimuli in adulthood can be ameliorated by adult choline supplementation. Clarifying the neurobiology of making and overcoming such automaticity, and how this circuitry can be modulated in adulthood may significantly advance our ability to identify new targets and strategies for preventing and treating disorders characterized by behavioral inflexibility. My expertise is well suited to contribute to the proposed work. As a postdoctoral fellow at UC Berkeley, I carried out fMRI studies in healthy control subjects to investigate the neurobiological underpinnings of stimulus-response (S-R) learning, which is the basic process underlying habitual responding. As an Associate Investigator at the Ernest Gallo Clinic and Research Center at UCSF, I expanded my research to include behavioral pharmacology and fMRI studies of impulsive decision-making in people with a personal or family history of alcohol use disorder. Since establishing my own lab at UNC Chapel Hill, the majority of our work has focused on AUDs, and on neuroimaging, pharmacological, and genetic investigations of executive function. Dr. Robinson and I have successfully worked together since 2011, producing numerous joint publications to date. We are currently conducting a translational investigation of the role of adolescent alcohol exposure on brain connectivity and automatic, learned behaviors. The proposed experiments build logically on our emerging data, as well as my and Dr. Robinson's complementary expertise. Our collaborator (Dr. Mooney) provides additional expertise in the use of choline supplements. We have worked closely and shared data in the preparation of this proposal, and recently collaborated on a submitted review article. We will continue to communicate in regular joint lab meetings.

1. Crews FT, **Boettiger CA** (2009) Impulsivity, Frontal Lobes and Risk for Addiction. *Pharmacol Biochem Behav* **93**:237-247. PMCID: PMC2730661
2. McKim TH, Shnitko TA, Robinson DL, **Boettiger CA** (2016) Translational Research on Habit and Alcohol. *Curr Addict Rep*. 3:37-49. PMCID: PMC4767272.
3. McKim TH, Bauer DJ, **Boettiger CA** (2016) A history of addiction is associated with a propensity to form habits. *J Cognitive Neurosci* 28:1024-1038. PMCID: PMC5046041.
4. Elton A, Dove S, Spencer C, Robinson DL **Boettiger CA**. (2019) Naltrexone acutely enhances functional connectivity between the ventromedial prefrontal cortex and a left frontoparietal network. *Alcoholism Clin Exp Res* 43:965-978. PMCID: PMC6528472.

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 (UCSF), 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., UCSF
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 Neuroscience, UNC-CH
2008-	Faculty Member, Bowles Center for Alcohol Studies, UNC-CH
2015-2020	Associate Professor, Psychology and Neuroscience Dept. & BRIC, UNC-CH
2021-	Professor, Psychology and Neuroscience Dept. & BRIC, UNC-CH

Other Experience and Professional Memberships

1996-present	Member, Society for Neuroscience (SfN)
2001-present	Member, Cognitive Neuroscience Society
2005-2007	Founding President & Representative, San Francisco Bay Area Chapter of SfN
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-present	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
2014-2015	Councilor, Triangle Chapter of the Society for Neuroscience
2015	Italian Ministry of Health, ad hoc grant reviewer
2015-present	Associate Editor, *Frontiers in Human Neuroscience*
2015-present	Editorial Board Member (Neuroscience section), *Wiley Encyclopedia of Life Sciences* (*eLS*)
2015-2018	Member, Government and Public Affairs Committee of the Society for Neuroscience
2015-2017	Consultant, BlackThorn Therapeutics, Inc.
2016	King Baudouin Foundation - Fund For Research in Psychiatry (Belgium), ad hoc grant reviewer
2016	NIAAA Special Emphasis Panel, NIAAA Member conflict applications - Epidemiology and prevention research (ZAA1 DD-03), ad hoc grant reviewer
2017	NIAAA Special Emphasis Panel, Review of the Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) - (ZAA1 CC-05), ad hoc grant reviewer
2018	Agence Nationale de la Recherche (France), ad hoc grant reviewer
2019	European Research Council (ERC), SH4 panel *"The Human Mind and Its Complexity"*, ad hoc grant reviewer
2019	NIH Study Section, *Cognition and Perception* (CP), ad hoc reviewer
2020	NIH Study Section, *Neurobiology of Motivated Behavior* (NMB), ad hoc reviewer

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
2014	UNC Psychology Dept. Award for Outstanding Undergraduate Research Mentor
2015	Kavli Frontiers of Science Fellow – U.S. National Academy of Sciences

C. Contributions to Science

1. My graduate work in systems neuroscience used neurophysiological techniques to study learning mechanisms in a cortico-striato-thalamic loop dedicated to a motivated behavior: birdsong. Using an *in vitro* slice preparation of the zebra finch anterior forebrain, I identified physiological characteristics in the principal neurons of the forebrain nucleus, LMAN, specific to the sensory critical period for song learning, including intrinsic properties, synaptic properties, and forms of long-term synaptic plasticity. Closure of the sensory critical period was associated with shortening of membrane time constants and a decline in spike adaptation, which could underlie the *in vivo* increase in auditory selectivity and sustained firing of LMAN neurons. Synaptic changes included decreased paired-pulse depression of thalamic inputs, and shorter responses to excitatory recurrent collateral inputs. Such changes are expected to reduce non-specific amplification of thalamic input by the recurrent circuitry of LMAN, resulting in higher fidelity transmission of thalamic input, potentially increasing auditory selectivity. Thalamic and recurrent synapses each expressed long-term activity-dependent plasticity restricted to the sensory critical period: a Hebbian, NMDA receptor-dependent LTP at recurrent synapses, and a heterosynaptic LTD of thalamic inputs, each of which may play a role in sensory learning.
    a. **Boettiger CA**, Doupe AJ (1998) Intrinsic and thalamic excitatory inputs onto songbird LMAN neurons differ in their pharmacological and temporal properties. *J. Neurophysiol.* **79**: 2615–2628.
    b. **Boettiger CA**, Doupe AJ (2001) Developmentally restricted synaptic plasticity in a songbird nucleus required for song learning. *Neuron,* **31**:809-818.
    c. Doupe AJ, Solis, MM, Kimpo R, **Boettiger CA** (2004). Cellular, Circuit, and Synaptic Mechanisms in Song Learning. *Annals NY Acad Sci* **1016**:495-523.
    d. Solis MM, Hessler NA, **Boettiger CA**, Doupe AJ (2008) Song selectivity, singing and synaptic plasticity in songbirds. In: Topics in Integrative Neuroscience: From Cells to Cognition. JR Pomerantz, ed. pp 363-384. Cambridge University Press.

2. An increasingly established intermediate phenotype for SUDs 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 an 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 an alcohol use disorder (AUD) history show elevated *Now* bias compared to controls. Based on evidence implying that endogenous opioids modulate *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.
    a. **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.
    b. 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.
    c. Elton A, Smith CT, Parrish MH, **Boettiger CA**. (2017) Neural systems underlying individual differences in intertemporal decision making. *J Cognitive Neurosci.* PMCID: PMC5285502.
    d. Elton A, Dove S, Spencer C, Robinson DL **Boettiger CA**. (2019) Naltrexone acutely enhances functional connectivity between the ventromedial prefrontal cortex and a left frontoparietal network. *Alcoholism Clin Exp Res* **43**:965-978. PMCID: PMC6528472.

3. The model I proposed to explain 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 frontal dopamine changes on *Now* bias should interact with trait-based tonic frontal dopamine levels. Evidence supporting this model has come from several studies. First, in a much larger sample, we confirmed 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. 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. In addition, we have recently identified an independent role for putamen dopamine level (measured via PET) in *Now* bias.

a. 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.
b. 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.
c. Smith CT, Wallace DL, Dang LC, Aarts E, Jagust WJ, D'Esposito M, **Boettiger CA** Modulation of Impulsivity and Reward Sensitivity in Intertemporal Choice by Striatal and Midbrain Dopamine Synthesis in Healthy Adults (2016). *J Neurophysiol.* 115:1146-1156. PMCID: PMC4808128.
d. Elton A, Smith CT, Parrish MH, **Boettiger CA** (2017) COMT Val(158)Met Polymorphism Exerts Sex-Dependent Effects on fMRI Measures of Brain Function. Front Hum Neurosci 11:578. doi: 10.3389/fnhum.2017.00578. PMCID: PMC5723646.

4. 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). When I arrived at UNC, I thus established 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 EL, **Boettiger CA**, Howard MO. (2011) Targeting cognitive-affective risk mechanisms in stress-precipitated alcohol dependence: an integrated, biopsychosocial model of automaticity, allostasis, and addiction. *Med Hypotheses*. **76**:745-54. PMCID: PMC3076531.
    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.
    d. Elton A, Chanon VW, **Boettiger CA** (2019) Multivariate Pattern Analysis of the Neural Correlates of Smoking Cue Attentional Bias. *Pharmacol Biochem Behav* 180:1-10. PMCID: PMC6529249.

5. 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. Data from animal models indicate that chronic use of drugs of abuse (particularly alcohol, or 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. We used this task to show that people with an SUD history transition from a goal-directed to a habit-based response strategy more quickly than people with no SUD history do, and that transcranial brain stimulation can modulate this behavior.

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, Shnitko TA, Robinson DL, **Boettiger CA**. (2016) Translational Research on Habit and Alcohol. *Curr Addict Rep*. 3:37-49. PMCID: PMC4767272.
c. McKim TH, Bauer DJ, **Boettiger CA** (2016) A history of addiction is associated with a propensity to form habits. *J Cognitive Neurosci* 28:1024-1038. PMCID: PMC5046041.
d. McKim TH, Dove S, Robinson DL, Fröhlich F, **Boettiger CA**. (2021) Addiction History Moderates the Effect of Alpha Frequency Transcranial Alternating Current Stimulation (α-tACS) of the Dorsolateral Prefrontal Cortex on Habitual Action Selection in Humans. *J Neurophysiol* 125:768-780. PMCID: in progress.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/charlotte.boettiger.1/bibliography/public/

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

F31 AA028427 Robertson (PI) 8/1/20 – 7/31/23
Excitatory/Inhibitory Balance and Behavioral Flexibility in Adults with a History of Adolescent Binge Drinking
Goal: To investigate the relationship between variations in frontolimbic circuitry, behavioral flexibility, and adolescent alcohol history using EEG and transcranial alternating current stimulation (tACS).
Role: Sponsor (Mentor)

K01 AA026334 Elton (PI) 9/1/18 – 8/31/23
The neural mechanisms of risk for alcohol use disorder among college students
Goal: To examine the neural and behavioral mediators between risk factors (genetic and environmental) and the development of pathological alcohol use.
Role: Sponsor (Mentor)

K01 AA025383 Broadwater (PI)
Effects of adolescent alcohol exposure on functional brain connectivity 9/1/18 – 8/31/23
Goal: To characterize the development of frontal brain connectivity in rats and investigate how brain connectivity is changed after adolescent alcohol exposure.
Role: Co-Sponsor (Mentor)

5P60AA011605 Crews (PI) 12/1/17 – 11/30/22
Comprehensive Alcohol Research Center Research Component: Component 3 - *Frontolimbic circuitry, behavioral flexibility, and adolescent alcohol history.*
Goal: To characterize neural mediators of the relationship between adolescent binge alcohol exposure and inflexible behavior in adulthood.
Role: Component PI

Selected Completed Research Support (past 3 years)

5R01NR017221 Boettiger (Sub-Contract PI; PI:Swift-Scanlan, VCU) 8/10/18 – 8/31/19
Genetic and Epigenetic Regulation of COMT, a Key Moderator of Cognitive Decline
Goal: To identify compounds that can selectively suppress expression of the catechol-O-methyl-transferase (COMT) enzyme isoform predominantly expressed in the brain.
Role: Sub-Contract PI

F31 DA043329 Yi (PI) 8/1/17-7/31/19
Working Memory Network Connectivity and Inhibitory Control in Cocaine Use
Goal: to test the mediating effect of connectivity within the working memory network and impaired inhibitory control among cocaine abusers.
Role: Co-Sponsor (Mentor)