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 am a Professor of Psychology and Neuroscience, and my research is focused on neurocognitive abnormalities associated with alcohol and other substance use disorders (AODs). I have a broad background in neuroscience, with specific training and expertise in the use of neuroimaging and interventions to probe executive function. As PI or co-PI on several foundation- and NIH-funded grants, I built a foundation for the proposed research by demonstrating success in measuring habitual action-selection, in measuring functional connectivity in fMRI data, in the use of transcranial alternating current stimulation (tACS), EEG, magnetic resonance spectroscopy (MRS), and conducting mediation analyses. Moreover, I have demonstrated success in recruiting the population to be studied in this proposal, including successfully completing multi-session studies with this group. Moreover, I have been successfully collaborating on translational projects with the Co-PI, Dr. Robinson, for a decade. Together these facts ensure that we will be able to recruit and retain participants over time as documented in the following publications. In addition, I successfully administered the projects (e.g. staffing, research protections, budget), collaborated with other researchers, and produced peer-reviewed publications from them. As a result of these previous experiences, I am aware of the importance of frequent communication among project members and of constructing a realistic research plan, timeline, and budget. The current application builds logically on my prior collaborative work with Dr. Robinson. In summary, I have the expertise, leadership, training, expertise and motivation necessary to successfully carry out the proposed research project.

Ongoing projects that I would like to highlight include:

P60 AA011605
Kash (Center PI), Role: Research Component PI
12/1/17 – 11/30/22
Comprehensive Alcohol Research Center Research Component: Component 3 - *Frontolimbic circuitry, behavioral flexibility, and adolescent alcohol history.*

F31 AA028427
Robertson (PI), Role: Sponsor
8/1/20 – 7/31/23
Excitatory/Inhibitory Balance and Behavioral Flexibility in Adults with a History of Adolescent Binge Drinking

P60 AA011605 Administrative Supplement
Kash (Center PI), Role: Co-Investigator
7/1/2021 – 6/30/22
Dietary choline mitigation of adolescent alcohol-induced deficits in adult cognitive flexibility

Citations:

1. Robertson MM, Furlong S, Voytek B, Donoghue T, **Boettiger CA**, Sheridan MA. (2019) EEG Power Spectral Slope differs by ADHD status and stimulant medication exposure in early childhood. *J Neurophysiol* 122: 2427-2437. PMCID: PMC6966317.
2. Elton A, Faulkner ML, Robinson DL, **Boettiger CA**. (2021) Acute Depletion of Dopamine Precursors in the Human Brain: Effects on Functional Connectivity and Alcohol Attentional Bias. *Neuropsychopharmacol* 46:1421-1431. PMCID: PMC8209208.
3. 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: PMC7988748.
4. Dannenhoffer CA, *Robertson MM, Macht VA, Mooney SM, **Boettiger CA**, Robinson DL. (2021) Chronic Alcohol Exposure during Critical Developmental Periods Differentially Impacts Persistence of Deficits in Cognitive Flexibility and Related Circuitry. *Internat Rev Neurobiol* **161**: *in press*.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021	NIAAA Scientific Review Group: *Neuroscience Research Review Subcommittee* (AA-4), ad hoc reviewer
2021	NIH Study Section, *NIH Special Emphasis Panel, Member conflict: - Cognition, Perception, and Motor Function (ZRG1 BBBP-J-02)*, reviewer
2021-	Professor, Psychology and Neuroscience Dept. & Biomedical Research Imaging Center (BRIC), University of North Carolina, Chapel Hill (UNC-CH)
2020	NIH Study Section, *Neurobiology of Motivated Behavior* (NMB), ad hoc reviewer
2019	NIH Study Section, *Cognition and Perception* (CP), ad hoc reviewer
2019	European Research Council (ERC), SH4 panel *"The Human Mind and Its Complexity"*, ad hoc grant reviewer
2018	Agence Nationale de la Recherche (France), 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
2016	NIAAA Special Emphasis Panel, *NIAAA Member conflict applications - Epidemiology and prevention research* (ZAA1 DD-03), ad hoc grant reviewer
2016	King Baudouin Foundation - Fund For Research in Psychiatry (Belgium), ad hoc grant reviewer
2015-2020	Associate Professor, Psychology and Neuroscience Dept. & BRIC, UNC-CH
2015	Italian Ministry of Health, ad hoc grant reviewer
2015-present	Editorial Board Member (Neuroscience section), *Wiley Encyclopedia of Life Sciences* (*eLS*)
2015-present	Associate Editor, *Frontiers in Human Neuroscience*
2015-2018	Member, Government and Public Affairs Committee of the Society for Neuroscience
2015-2017	Consultant, BlackThorn Therapeutics, Inc.
2014-2015	Councilor, Triangle Chapter of the Society for Neuroscience
2010	The Netherlands National Initiative Brain and Cognition, ad hoc grant reviewer
2010	Behavioral and Social Advisory Council, Foundation for Alcohol Research, ad hoc grant reviewer
2009-present	Member, Research Society on Alcoholism
2009	NIAAA Scientific Review Group: *Neuroscience Research Review Subcommittee* (AA-4), ad hoc reviewer
2008-	Faculty Member, Bowles Center for Alcohol Studies, UNC-CH
2008	NIAAA Special Emphasis Panel: *Behavioral Mechanisms in the Transition to Habitual Alcohol Seeking and Drinking*, ad hoc reviewer
2007-	Graduate Faculty Member, Curriculum in Neuroscience, UNC-CH
2007-2015	Assistant Professor, Psychology Dept. & BRIC, UNC-CH

2007 Medical Research Council (London), ad hoc grant reviewer
2005-2007 Adjunct Assistant Professor, Neurology Dept., University of California, San Francisco (UCSF)
2005-2007 Associate Investigator, Ernest Gallo Clinic & Research Center (EGCRC)
2005-2007 Founding President & Representative, San Francisco Bay Area Chapter of SfN
2003-2005 Assistant Research Scientist, EGCRC
2001-2003 Postdoctoral Fellow, University of California, Berkeley, H. Wills Neuroscience Institute
2001-present Member, Cognitive Neuroscience Society
2001 Postdoctoral Fellow, UCSF, Psychiatry Dept.
1996-present Member, Society for Neuroscience (SfN)
1992-1994 Research Asst., University of California, Berkeley, Molecular and Cell Biology Dept.

Selected Honors
2015 Kavli Frontiers of Science Fellow – U.S. National Academy of Sciences
2014 UNC Psychology Dept. Award for Outstanding Undergraduate Research Mentor
2002 Wheeler Center for the Neurobiology of Addiction, Hugh O'Connor Memorial Fellowship
2001 McDonnell Summer Institute in Cognitive Neuroscience Fellowship
1998 UCSF Graduate Dean's/Anthony Fellowship in Neuroscience
1997 Pre-doctoral National Research Service Award (NIH/NIMH; F31 MH011896)
1995 National Science Foundation Graduate Fellowship Honorable Mention
1993 HHMI U.C. Berkeley Undergraduate Biology Scholars Fellowship
1992 University of California President's Undergraduate Fellowship

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, recently demonstrating a role for dopamine in mediating attentional bias to both alcohol and reward-conditioned cues.

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, **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.
c. 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.
d. Elton A, Faulkner ML, Robinson DL, **Boettiger CA**. (2021) Acute Depletion of Dopamine Precursors in the Human Brain: Effects on Functional Connectivity and Alcohol Attentional Bias. *Neuropsychopharmacol* (in press) PMCID: in progress.

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: PMC7988748.

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