DukeMedicine

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Dr. Sheinberg:

Please find enclosed my application for the faculty position in the Department of Neuroscience at Brown. I am currently a postdoctoral researcher in the labs of Michael Platt and Dennis Turner in the Center for Cognitive Neuroscience and Departments of Neurobiology and Surgery at Duke University. It contains a copy of my cv, along with a brief description of my current and proposed research, a statement of my teaching philosophy, and three recent publications.

My research focuses on mechanisms of motivation and decision-making, particularly the problem of impulse control. I investigate these questions using a combination of computational modeling and single-neuron recording in non-human primates and humans undergoing surgery to implant deep brain stimulators (DBS). My interests combine behavioral modeling with analysis of neuronal firing, computational theories of learning and control with signal processing. My work lies at the interface of systems biology and cognitive neuroscience, and my graduate training in physics imbues this work with a strong quantitative bias. Just as importantly, my experience in experimental design and data collection shapes and grounds my more computational work.

I am applying to the Brown Institute for Brain Science because its expertise spans a wide range of domains and approaches, from cellular signaling to systems neuroscience to devices. I am especially excited about the institute's strong record of collaboration between theorists and experimentalists and across methods and models. I hope you will agree that my own work stands to complement this rich body of research.

Again, I have enclosed my application materials below. Please do not hesitate to contact me with any questions. Thank you for your time, and I look forward to hearing from you in the future.

Sincerely,

John Pearson

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Education and Training

Duke University Medical Center **May 2011 — Present**

Postdoctoral Associate in the Turner lab, investigating impulse control in patients with Parkinson's Disease.

Duke University Medical Center **January 2008 — Present**

Postdoctoral Associate in the Platt Lab, investigating the neural bases of decision making in primates.

Duke University Medical Center **November 2005 — December 2007**

Postdoctoral Associate in the Raghavachari Lab, investigating the neural bases of numerical cognition via theoretical and computational modeling.

Princeton University **Fall 1999 — Spring 2004**

PhD in Physics: String theory and quantum gravity. Thesis: *Gravitons, Inflatons, Twisted Bits: A Noncommutative Bestiary.* National Science Foundation Graduate Research Fellow

University of Kentucky **Fall 1996 — Spring 1999**

BSc. in Physics and Mathematics. Summa Cum Laude. Finalist for the American Physical Society's Leroy Apker Undergraduate Research Award. Led both the Society of Physics Students and Math Club. Recruited speakers, organized and publicized meetings.

Peer-Reviewed Publications

Benjamin Y. Hayden, **John M. Pearson**, Michael L. Platt
Neuronal basis of sequential foraging decisions in a patchy environment
Nature Neuroscience (2011) vol. 14, pp 933-939

John M. Pearson, Sarah R. Heilbronner, David L. Barack, Benjamin Y. Hayden, Michael L. Platt
Posterior cingulate cortex: adapting behavior to a changing world
Trends in Cognitive Sciences (2011) vol. 15(4), pp 143-151

Benjamin Y. Hayden, Sarah R. Heilbronner, **John M. Pearson**, Michael L. Platt
Surprise signals in anterior cingulate cortex: neuronal encoding of unsigned reward prediction errors driving adjustment in behavior
The Journal of Neuroscience (2011) vol. 31 (11), pp 4178-4187

John M. Pearson, Benjamin Y. Hayden, Michael L. Platt
Explicit information reduces discounting behavior in monkeys
Frontiers in Psychology (2010) vol. 1, article 237

John M. Pearson, Jamie D. Roitman, Elizabeth M. Brannon, Michael L. Platt, Sridhar Raghavachari
A physiologically-inspired model of numerical classification based on graded stimulus coding
Frontiers in Behavioral Neuroscience (2010) vol. 4 (0), 12pp

John M. Pearson, Benjamin Y. Hayden, Sridhar Raghavachari, Michael L. Platt
Neurons in posterior cingulate cortex signal exploratory decisions in a dynamic multi-option choice task

Current Biology (2009) vol. 19 (18), pp 1-6

Benjamin Y. Hayden, **John M. Pearson**, and Michael L. Platt
Fictive learning signals in anterior cingulate cortex
Science (2009) vol. 324 (5929) p. 948-950. PMID 19443783.
New York Times: "In that tucked tail, real pangs of regret?" http://www.benhayden.com/pub/nytimes.pdf

John M. Pearson
Gravitons, Inflatons, Twisted Bits: A Noncommutative Bestiary
PhD Thesis (accepted, May 2004)

In the following, authors are listed in alphabetical order, as is conventional in physics:

John Pearson, Marcus Spradlin, Diana Vaman, Anastasia Volovich, Herman Verlinde
Tracing the String: BMN correspondence at Finite J^2/N
hep-th/0210102; JHEP **0305** (2003) 022

Shamit Kachru, **John Pearson**, Herman Verlinde
Brane/Flux Annihilation and the String Dual of a Non-Supersymmetric Field Theory
hep-th/0112197; JHEP **0206** (2002) 021

Eric Braaten, **John Pearson**
Semiclassical Corrections to the Oscillation Frequencies of a Trapped Bose-Enstein Condensate
cond-mat/9808088; Phys. Rev. Lett. **82**, 255-258 (1999)

Chapters and Previews

Geoffrey K. Adams, Karli K. Watson, **John M. Pearson,** and Michael L. Platt
Neuroethology of Decision-making
Dahlem Conference discussion paper (forthcoming)

John M. Pearson and Michael L. Platt
Dynamic decision making in the brain
Nature Neuroscience (2012) vol. 15(3), pp 341-342

John M. Pearson, Benjamin Y. Hayden, Michael L. Platt
A role for posterior cingulate cortex in policy switching and cognitive control
in *Neural Basis of Motivational and Cognitive Control*
Attention and Performance XXIV, Sallett and Rushworth, eds.

John M. Pearson and Michael L. Platt
Confidence and corrections: how we make and un-make up our minds
Neuron (2009) vol. 63 (6), pp 724-726

Invited and Conference Talks

Impulse Control Disorders in Parkinson's Disease
Duke University Brain Awareness Week Public Lecture
Durham, North Carolina, March 2012

The Cingulate Cortex in Foraging Control

Winter Conference on Brain Research
Snowbird, Utah, February 2012

Tracking Dynamic Environments in Cingulate Cortex
Cold Spring Harbor Laboratory, May 2009

Single neurons in CGp predict explore/exploit decisions in a dynamic foraging task
Society for Neuroeconomics Annual Meeting, Park City, Utah, September 2008

Popular Press

John Pearson
Coaxing Order From Chaos
Duke Magazine (Sep-Oct 2009) vol. 95 (5)

John Pearson
Let It Ride: The Neuroscience of Risk
Duke Magazine (Nov-Dec 2008) vol. 94 (6)

John Pearson and Michael Platt
Decision Making in the Brain: Eavesdropping on Neurons
Mind Matters (Scientific American mind and brain blog) (Aug 5, 2008)
http://www.scientificamerican.com/article.cfm?id=decision-making-in-brain

Teaching and Mentoring

Duke University **Spring 2009 — Present**

- Developed and taught (Summer 2011 and Fall 2011) a 12-session introduction to Matlab course for Duke graduate students and postdocs across the brain sciences.
- Mentored nine undergraduates and three graduate students in four separate research projects. Taught data collection and analysis techniques, assigned and led discussions of published research relevant to the projects, guided preparation of scientific posters and presentations.
- Jointly supervised one senior thesis in the Economics department. Worked with student to develop a research question, build mathematical models of data, and translate scientific findings to a non-neuroscience audience.
- Guest-lectured to students in graduate Theoretical Neuroscience course and Neuroscience 132 (Decision Neuroscience). Delivered a series of summer lectures to graduate students and postdocs on computational models of reinforcement learning.

Princeton University **2002 — 2004**

- PHY 111: Contemporary Physics (“Physics for Poets”): 4 semesters. Led weekly laboratory and homework review sessions; conducted supplementary help sessions; graded tests and homework.
- PHY 529: General Relativity: 1 semester. Graded graduate student homework and produced formatted solutions to problem sets.

Honors and Awards

National Science Foundation Graduate Research Fellowship (1999-2002)

First Year Graduate Science Fellowship (1999-2000)
Princeton University

Finalist, Leroy Apker Award (1999)
American Physical Society

Special Award for Research by an Undergraduate (1999; inaugural recipient)
Physics Department, University of Kentucky

Research Statement **John Pearson**

Overview

The problem of *akrasia*—the conflict between what we want and what we believe is best for us—forms one of the oldest conundrums of human behavior. In the public health arena, this becomes most apparent in our often destructive tastes for calorie-dense foods, sexual imagery, and drugs of abuse. As a result, failures of decision-making take center stage in many neurological disorders, including substance abuse, obsessive-compulsive disorder (OCD), and Parkinson's Disease (PD). From a neurobiological perspective, decision-making serves as the primary nexus of all other mental phenomena, integrating what an organism knows (sensation), what it wants (motivation), what it can do to obtain this (action), and what it can expect in consequence (reinforcement and belief).

My work focuses on the computational principles underlying judgment and decision-making. I focus on computation because the techniques and concepts available in physics, engineering, and computer science provide a rich toolbox for the analysis of complex systems like the brain, and because design principles discovered in this way are likely to be applicable across decision problems and brain regions. In this framework, decision-making is of primary importance because it links the sensation and motor systems and encompasses the higher-level mental representations responsible for generating complex behaviors. More importantly, elucidating the mechanisms responsible for choice is our best hope for refining and discovering treatments like deep brain stimulation (DBS) that operate at the circuit level.

To pursue these goals, I focus on two complementary techniques: recordings of single neurons in humans undergoing brain surgery and modeling of choice behavior and underlying neuronal firing rates. In addition, I collaborate on modeling and analysis projects with investigators using a host of other methods including ERP, fMRI, and eye tracking. My graduate training in physics provides a uniquely powerful background that allows me to apply computational theories of learning, Bayesian inference, control theory, and foraging theory to problems of choice, efforts grounded in the single unit electrophysiology I have practiced for the last four years, most recently in the intraoperative context. From early work focusing on models of number encoding based on the firing rates of actual number-sensitive cells (Pearson, Roitman, Brannon, Platt, and Raghavachari, *Frontiers in Behavioral Neuroscience*, 2010) to my more recent work on failures of impulse control in PD patients, my goal is to provide a set of simple yet powerful computational principles underlying choice, models strongly constrained by the data and realities of experimental neuroscience.

Change Detection and Exploration

While most choice experiments involve the repeated presentation of a few options, most of our decisions take place in dynamic environments in which outcomes are subject to sudden change. However, we are only beginning to discover the mechanisms by which the brain adapts to produce flexible behavior in the face of environmental change. A key competency for this adaption is the so-called "explore-exploit" tradeoff, the balance agents must strike between exploiting the current best course of action and exploring uncertain alternatives. This tradeoff is captured by the k-armed bandit task, in which agents make choices from among k options whose values vary gradually in time. Because these changes are unsignaled, agents aiming to maximize reward must balance choices of the current best option against sampling of alternatives that may have improved. Building on human imaging work that showed activation in striatal and frontal structures, I previously showed that single neurons in the posterior cingulate cortex (CGp) of monkeys, an area known to encode both reward and propensity to switch between choice options, signaled the probability of an upcoming exploratory strategy switch in a four-armed bandit task, suggesting a more general role in exploratory behavior for this region (Pearson, Hayden, Raghavachari, and Platt, *Current Biology*, 2009).

In related work, I also demonstrated that the anterior cingulate cortex (ACC) plays a key role in choices following two important types of outcomes: unexpected or surprising outcomes, and fictive outcomes, potential rewards that are signaled but never experienced. Computational theories of learning suggest that in the former case, the rate of learning should increase following surprise, since this may be an indication of environmental change. In the latter case, use of fictive outcomes is expected to speed learning, since it allows agents to learn about unchosen as well as chosen actions. And indeed, ACC neurons encode surprise in the case of unexpected but received and likely but omitted rewards, a signal that drives subsequent changes in behavior (Hayden, Heilbronner, Pearson, and Platt, *Journal of Neuroscience*, 2011). Similarly, fictive outcomes are likewise encoded in ACC neurons, in a manner completely analogous to received rewards, and these signals, too drive subsequent behavioral adjustment, even when fictive outcomes are not informative for future decisions (Hayden, Pearson, and Platt, *Science*, 2009). That is, monkeys' choices are affected by rewards they might have received, even when this information does not result in greater reward. In both of these studies, formal computational models allowed me to place observed patterns of behavior and neuronal firing within a broader information processing context.

More recently, returning to the explore-exploit tradeoff, I found that in monkeys solving a ubiquitous foraging dilemma, the patch leaving problem, ACC neurons also tracked progress toward a strategy change. In patch leaving, animals are confronted with a simple decision: continue to harvest diminishing returns in a current spatial food patch, or sacrifice time and energy to search out a new (presumably richer) one. In a laboratory version of this task, ACC neurons increased their firing with time in the current patch, with leaving decisions triggered when this firing rate reached a fixed threshold (Hayden, Pearson, and Platt, *Nature Neuroscience*, 2011). Here again, formal models allowed us to posit a control systems view of the relevant decision circuit and place the findings in a broader algorithmic context.

Taken together, these results suggest that cingulate cortex plays a key role in both tracking behavioral outcomes and signaling upcoming changes in behavioral strategy. Recently, I proposed a formal model of cingulate cortex in change detection and behavioral adjustment that incorporates these findings along with previous work on CGp (Pearson, Heilbronner, Barack, Hayden, and Platt, 2011). This model predicts that ACC takes the responsibility for adjustments within the current behavioral policy and CGp plays the role of signaling upcoming changes between policies. Moreover, the features of the model can naturally be expressed in the language of optimal control (Pearson and Platt, in prep). Currently, I am working to test the predictions of this model utilizing the patch leaving task in CGp. In the future, I plan to construct a computational model of this change detection process applicable to choice behavior as observed in monkeys adapting to unsignaled switches between task sets.

Impulsivity and self-control

While much careful work has studied the cellular changes responsible for impulsive choice, and much imaging work has focused on large-scale correlates of impulsive choice in humans, little opportunity exists to study *both* the fundamental units of neural computation *and* a model species that shares our qualitative experience of the struggle for self-control. In monkeys, I showed that typical paradigms used to measure impulsivity may instead measure quirks of the cuing paradigm, and that small modifications in the task can lead to large changes in "impulsivity" (Pearson, Hayden, and Platt, 2010). In general, we would like to distinguish between impulsivity as a trait and discounting of future rewards, but this has proven difficult to do in animal models.

Recently, I have begun to investigate these questions via single unit recordings in humans undergoing surgery to implant deep brain stimulators (DBS) for the treatment of Parkinson 's disease (PD). PD patients often exhibit compulsive gambling, hypersexuality, and other forms of impulsive behavior, offering a tantalizing opportunity to study computations at the single neuron level in people. Through studies of choice behavior in these patients, I aim to shed light on the little-understood involvement of motivational circuitry in the pathology of PD, discovering systems-level mechanisms with implications for OCD, substance abuse, and other disorders of choice.

The primary target of my study is the subthalamic nucleus (STN), the site of DBS implantation and a key node in the basal ganglia network. Aside from the striatum, STN receives the only other cortical input to the basal ganglia (the so-called "hyperdirect" pathway), and influential computational theories propose that STN sets a threshold for inhibiting prepotent responses, allowing relevant information to accumulate before a decision is made. However, it remains unclear how top-down cortical effects modulate this threshold and what link it may have to self-control more broadly. Based on the well-known anatomy of cortico-basal ganglia loops, in which motor, associative, and motivational information travel through parallel and overlapping pathways, I hypothesize that hyperdirect cortical inputs likewise gate motivational states, suppressing prepotent approach and avoidance drives as well as motor responses. Such a role for the hyperdirect pathway and STN would explain why PD patients on DBS, which "lifts" the response inhibition bias for movement, are likewise susceptible to impulsive side effects such as compulsive gambling, binge eating, and hypersexuality.

To test this hypothesis, I have begun collecting data in patients performing two standard response inhibition tasks, a Go/No-Go paradigm (GNG) and the balloon analogue risk task (BART). Because impulsivity may not be a unitary construct, I employ each of these tasks to test a specific aspect of response control. Previous work in rats and monkeys has shown that STN contributes to behavioral inhbition in GNG, where higher firing rates correlate with suppressing prepotent movements in response to no-go cues. I will use this task both to provide a measure of motor impulsivity and to investigate information carried across multiple simultaneously recorded neurons that may differentiate false positive, true positive, false negative and true negative responses. In the BART, participants must decide how much to inflate a computer-simulated balloon before stopping. The larger the balloon, the more points the participant earns by stopping, but the risk of a sudden pop grows with the balloon, and a popped balloon earns 0 points. Here, participants must inhibit their drive toward higher point totals in response to varying levels of balloon risk, a function also thought to correspond to higher firing in STN. As a result, the BART provides a second converging measure of impulsivity from a distinct domain. In addition, I have also begun collecting behavioral data in these same tasks from patients with previously implanted DBS and PD controls. Here, I plan to test the hypothesis that DBS supplied to more ventral areas of STN, which correspond anatomically to more motivational circuits, more strongly affect impulsivity in the BART as compared to DBS in more dorsal, motor-related areas of STN. I likewise hypothesize that this pattern of impairment should be reverse for GNG.

Finally, to more directly test the hypothesis that higher STN activity results in a reduction in impulsivity, I am proposing to use real-time feedback from patients' own neurons in an attempt to train them to control STN firing rates. If STN firing is indeed causally related to suppressing impulsive responses, patients who successfully learn to modulate their STN firing in a feedback control task should show significant differences on pre- and post-training impulsivity measures in the GNG and BART. Such an approach, combined with the outpatient DBS study, has clear implications for treating the side effects of PD, since selective behavioral training with feedback may serve to reduce impulsive choice in PD patients while preserving the motor benefits of DBS.

To accomplish these goals in the unpredictable and time-constrained surgical setting, I have developed a system for increasing both the rate and quality of data collection, one that leverages my computational skills outside the OR. Rather than detect and classify individual neurons online, as is typical, I have modified our recording system to save whole signals for offline analysis. For this, I use a combination of sophisticated, publicly available classification tools from the human recording community and my own custom scripts for analysis and artifact removal. In addition, I have worked with outside vendors to procure hardware that will allow us to simultaneously capture up to 17 of 32 active data channels where most intraoperative experiments are limited to 1. These simultaneous recordings will allow us to examine not only single-unit firing rates and field potentials, but synchrony between units, spike-field coherency, and other circuit level properties of the system. In addition, I have developed software that allows for online spike detection and calculation of multi-unit neural activity capable of controlling a display stimulus. This process will allow me to provide nearly real-time feedback to patients attempting to modulate their own STN firing. Such an approach allows for intervention in the local circuit dynamics in a situation where more invasive manipulations would be impractical and potentially unethical.

Lastly, the intraoperative setting allows for recording in a handful of other areas, including the substantia nigra pars reticulata (SNr) and the ventral intermediate (VIM) nucleus of the thalamus in patients undergoing DBS implantation for essential tremor. Recordings in these areas will allow me to examine dynamics at multiple nodes in the relevant circuits and extend the lessons learned in STN through the chain of behavioral output. Most intriguingly, even in PD patients, the SNr is known to contain small numbers of dopaminergic neurons, offering a rare opportunity to characterize the involvement of these cells in uniquely human phenomena like imagination, prospection, and moral judgment.

Currently, I am collecting data in the BART in both surgical patients and patients with implanted DBS. In the future, I propose to expand both the number of tasks and the number of recorded areas, pursuing the relevant motivational signals through the output circuits of the basal ganglia. Most importantly, I plan to incorporate task-related feedback as described above in an attempt to alter neural firing rates and through them, behavioral assays of self-control. These studies stand to elucidate the role of basic subcortical structures in conveying and multiplexing motivational information, as well as suggest novel treatments to meliorate the side-effects of deep brain stimulation.

Teaching Statement **John Pearson**

An ability to combine theory with experiment, quantitation with measurement, is becoming increasingly vital in the biological sciences, but most students in traditional biology backgrounds receive little or no training in this area. Watching as bright, motivated students in biology or psychology are stymied by a lack of quantitative skills, I have become increasingly passionate about statistical and computing education in the biological sciences.

As a result, my contributions to teaching in the brain sciences at Duke have focused primarily on data analysis, software, and statistical literacy. Given my background in physics, I am often asked to participate in informal consultations with co-workers and researchers from other labs regarding appropriate statistical methods and models. As an extension of this work, in the summer of 2011, Duke's Center for Cognitive Neuroscience commissioned me to develop a course to introduce graduate students and postdocs across departments to Matlab, our primary data analysis package. I taught the resulting twelve-session course, complete with homework, twice, in both summer and fall of 2011, with demand filling a waiting list larger than the class size.

In my next appointment, I am eager to build on this by developing an integrated course combining principles of experimental design, data analysis, and modeling with extensive programming practice. The key, I believe, is problem-based learning, in which students must grapple with the complexities of real data in real analysis situations. In fact, my Matlab course makes extensive use of experimental data from my and my colleagues' own experiments across research questions and methods.

In addition, my own research has provided numerous opportunities for one-on-one mentorship. In the past four years, I have mentored nine undergraduates, including one who shares authorship on a forthcoming publication and one high honors senior thesis. During the 2009-2010 academic year, I conducted a separate lab meeting for these students, in which we read and discussed papers relevant to our project in behavioral genotyping. In 2011, I mentored one of the lab's incoming graduate students, including weekly and unscheduled meetings to supervise experimental design and data analysis. More recently, I organized a journal club for two graduate students I mentored as part of a human intraoperative recording project. These students and I met weekly with physicians involved in the project to read and discuss papers as well as plan and organize our own work.

More generally, I am confident teaching decision-making, learning, and systems neuroscience at the graduate level. I would especially enjoy teaching theoretical neuroscience, data analysis, or statistics, and am capable of teaching signal processing or machine learning at the undergraduate level. In addition, I can still teach most of the undergraduate physics curriculum.