REVIEW
An Instructor's Guide to (Some of) the Most Amazing Papers in Neuroscience

Ian A. Harrington[1], William Grisham[2], D. J. Brasier[3], Shawn P. Gallagher[4], Samantha S. Gizerian[5], Rupa G. Gordon[1], Megan H. Hagenauer[6], Monica L. Linden[7], Barbara Lom[8], Richard Olivo[9], Noah J. Sandstrom[10], Shara Stough[1], Ilya Vilinsky[11], Michael C. Wiest[12]

[1]Augustana College, Rock Island, IL 61201; [2]University of California, Los Angeles, Los Angeles CA 90095; [3]Carnegie Mellon University, Pittsburgh, PA 15213; [4]Millersville University, Millersville, PA 17551; [5]Washington State University, Pullman, WA 99164; [6]University of Michigan, Ann Arbor, MI 48106; [7]Brown University, Providence, RI 02912; [8]Davidson College, Davidson, NC 28035; [9]Smith College, Northampton, MA 01063; [10]Williams College, Williamstown, MA 01267; [11]University of Cincinnati, Cincinnati, OH 45221; [12]Wellesley College, Wellesley, MA 02481.

Although textbooks are still assigned in many undergraduate science courses, it is now not uncommon, even in some of the earliest courses in the curriculum, to supplement texts with primary source readings from the scientific literature. Not only does reading these articles help students develop an understanding of specific course content, it also helps foster an ability to engage with the discipline the way its practitioners do. One challenge with this approach, however, is that it can be difficult for instructors to select appropriate readings on topics outside of their areas of expertise as would be required in a survey course, for example. Here we present a subset of the papers that were offered in response to a request for the "most amazing papers in neuroscience" that appeared on the listserv of the Faculty for Undergraduate Neuroscience (FUN). Each contributor was subsequently asked to describe briefly the content of their recommended papers, their pedagogical value, and the audiences for which these papers are best suited. Our goal is to provide readers with sufficient information to decide whether such articles might be useful in their own classes. It is not our intention that any article within this collection will provide the final word on an area of investigation, nor that this collection will provide the final word for the discipline as a whole. Rather, this article is a collection of papers that have proven themselves valuable in the hands of these particular educators. Indeed, it is our hope that this collection represents the inaugural offering of what will become a regular feature in this journal, so that we can continue to benefit from the diverse expertise of the FUN community.

Key words: teaching; scientific literature; neuroscience literature; primary sources; classic papers.

Although the textbook has enjoyed a long period of dominance in the science classroom, trends in the direction of more active, methods-based teaching have bolstered the use of the raw material of science: the journal article. The benefits of teaching neuroscience (or any discipline) using its own literature are diverse and numerous. Perhaps the most obvious benefit has to do with the flexibility and accessibility papers afford. Decisions about whether to include one or more papers can be made quickly and these can be added to a course, as circumstances demand, even when the course is already underway. With the ever-rising costs of textbooks and college in general, a related benefit is that such papers do not lead to additional financial burdens for students. Individual papers or collections of them can serve to either supplement textbooks or, under some conditions, substitute for them altogether. Textbooks are very efficient at conveying large quantities of information; however, they tend to achieve that efficiency by sacrificing depth. Papers allow students to gain a clearer understanding of the methods and practices used in research, and provide an opportunity for a more critical assessment of a study's conclusions (e.g., Hoskins, 2008; Willard and Brasier, 2014). This can be valuable in that it helps support the development of information literacy, critical thinking, and a general scientific disposition in students (e.g., Dirks and Cunningham, 2006; Hoskins et al., 2007; Hoskins et al., 2011; Kozeracki et al., 2006).

Late last summer one of us (Grisham) received an interesting request from a group of students as they neared the end of their summer research experience. Having read numerous articles relevant to their specific research projects, these students now wanted to read the most amazing neuroscience article ever. We are not certain they appreciated how tall an order this was. Is there a single most amazing neuroscience article ever? How would such a title be decided? When this request was put to the members of the Faculty for Undergraduate Neuroscience (FUN) by way of the organization's listserv, more than a dozen nominations were made in short order. Although some of these papers could be considered landmarks (e.g., according to Google Scholar, Hodgkin and Huxley (1952d) has been cited more than 16,000 times), others were far more contemporary. Not surprisingly, however, there was little evidence of consensus (although Hubel and Wiesel's 1962 paper on the physiology of the visual cortex, cited some 9,800 times, received multiple nominations). The nominations that were received are undoubtedly just the tip of the iceberg.

Given the nature of our training, it can be difficult to identify key readings on topics outside of our immediate areas of expertise. One of us (Harrington) was reminded of a quote that was prominently displayed in the lab of one of his undergraduate professors, Vincent LoLordo: "I am so

small, and the literature…so vast." In teaching practice, however, and this is especially true for those who teach survey courses, there is an expectation that we can find our way through this vast literature. The purpose of this article is to provide diverse recommendations for pedagogically valuable papers—recommendations made by undergraduate neuroscience educators, for undergraduate neuroscience educators—in order to promote a "collective expansion" of our appreciation of the neuroscientific literature. Each of the contributors has offered what they identified to be among the most amazing papers in a particular corner of the literature. Those who responded to the listserv request were asked to submit short descriptions of their recommended papers. In addition to describing the general content of these papers, they were also asked to describe how these papers have been useful in their teaching (what we have here termed their 'value'). Finally, they were asked to describe the appropriate audience for their recommended papers.

We have organized the fourteen submissions included here by topic to the extent that was possible. The first four submissions address more fundamental issues including neural transmission (Gizerian), electrical excitability and K+ channels (Vilinsky), long-term potentiation (Brasier), and adult neurogenesis (Lom). These papers are followed by two concerning biological rhythms, the first addressing the effects of time-cue deprivation (Hagenauer) and the second related to sensory control of circadian rhythms (Gallagher). From here we turn to a paper about the study of the visual cortex (Olivo), and two papers that address plasticity: sensory plasticity following brain rewiring (Harrington) and cognitive plasticity following brain damage (Gordon). Following this are three papers related to the endocrine system including the effects of steroids (Sandstrom), neural correlates of sexual orientation (Grisham), and sex differences in spatial abilities (Stough). Like the paper reviewed by Stough, the final two submissions also relate to the hippocampus but instead of its role in spatial behavior they focus on memory, specifically on the induction of false memories (Linden) and the transplanting of memories (Wiest) by hippocampal stimulation. We hope that these brief descriptions will be sufficient to guide decisions about whether to include some of these papers in your courses. Moreover, we hope that collections like this one will become a regular feature of *JUNE* in the future.

How neurons conduct messages

Contributor: Samantha Gizerian

Topics: Membrane currents; membrane potential; ionic current; action potential; conduction; *Loligo*

References: Hodgkin, Huxley, and Katz, 1952; Hodgkin and Huxley, 1952a, 1952b, 1952c, 1952d

Description: In a series of five elegant papers, Hodgkin and Huxley (and Katz) describe the movement of current through the squid (*Loligo forbesi*) giant axon as well as the relationship between membrane potentials and currents. These papers together were the first to describe the electrical properties of neurons and neuronal membranes. In addition to their invaluable contribution to science, these papers represent the development of technologies still in use today. At 400-800 μm in diameter, the *Loligo* giant axon was the first nerve structure discovered that was large enough to be penetrated by a microelectrode and, thus, could be investigated using the tools available at the time (1939-1952). In the first paper of this series, Hodgkin and Huxley describe the electrode, amplifier, and signal recorder they created and then demonstrate proof of concept for both the current clamp and voltage clamp techniques. Modern current/voltage clamp experiments are done with equipment based on these early instruments. The next three papers in the series use the techniques set forth in the initial paper to describe the currents that travel through neuronal membranes, the ions whose movement are the basis of those currents, membrane potentials, and the relationship between membrane potentials and the movement of ions through the neuronal membrane. The fifth and final paper in the series summarizes all of the previous results into the mathematical model that serves as the foundation for our understanding of membrane properties and action potential production and propagation today.

Value: This series of papers is invaluable to the history of neuroscience as well as to our understanding of the electrical properties of neurons. Hodgkin and Huxley's findings serve as the foundation of modern neuro-physiology and have broadly influenced scientists in many disciplines. Moreover, studying these papers gives students a unique insight into how data analysis is used to build models. The electrical properties of neurons, as presented in most textbooks, are represented by a series of increasingly complicated mathematical equations. Students, even those with a strong calculus background, often find these equations cumbersome to manipulate and apply because they have little understanding of the physiological processes represented. In reading these papers, students can approach the problem from the other direction. That is, how does the physiology of the neuron serve as the basis for the mathematical model? Students typically know about as much about membrane currents at the beginning of a course as Hodgkin and Huxley did at the beginning of their studies, so it is easy for students to walk alongside these pioneers in their own journey of discovery, learning how neurons work as they build and apply the mathematical model of electrical signaling in neurons and, thus, gain a deeper understanding both of the function of neurons and the basis of many of our investigations of them. Moreover, if the appropriate facilities are available, students can reconstruct Hodgkin and Huxley's experiment as a laboratory exercise, collecting and analyzing data de novo.

Audience: These papers would be suitable for an upper-level course (or an introductory graduate course) on electrophysiology or biophysics, or in a neural physiology unit in an upper-level anatomy/physiology course. It is important that students have a strong background in math and physics, including differential calculus and electricity/magnetism in order to work through the mathematics of the model, so these papers are less suitable for lower division or introductory classes in

neuroscience or physiology.

Discovering the mechanisms of electrical excitability

Contributor: Ilya Vilinsky

Topics: Voltage-gated ion channels; genetics; biochemistry

References: Kamb et al., 1987; Tempel et al., 1987; Wei et al., 1990; Zhou et al., 2001

Description: The first two papers in this series (Kamb et al., 1987; Tempel et al., 1987) are independent accounts of how "forward genetics" was first used to fish out the first voltage-gated K+ channel sequence in Drosophila. In forward genetics, investigators start with an interesting phenotype and use it as a "hook" to find the corresponding gene. Electrophysiology on the mutant line known as "Shaker," where the flies display characteristic leg twitches when anesthetized, reveals defects in potassium currents. The predicted structure of the molecule responsible bore the hallmarks of a transmembrane protein and fit within a framework of how K+ channels were thought to work. For students, it is especially interesting to read these classic papers in light of our current knowledge of K+ channel structure and function. A fun exercise is to see how many of the early predictions from the initial sequence have been proven correct.

Wei et al. (1990) extends the fast-growing field of K+ channel physiology by using sequence homology to find related channels. The K+ channel family is vast. In fact, it is the most abundant member of the voltage-gated ion superfamily. Wei et al. describe four major types of K+ channels—Shaker, Shab, Shal and Shaw—in Drosophila, mouse, and by extension all animals (the naming of these genes, and the naming schemes for Drosophila genes in general, make for interesting stories on their own).

Zhou et al. (2001) exemplifies more recent structural and biochemical work on K+ channels, a field that has expanded greatly since the late 1980's and now includes computational theorists, biochemists, and ecologists. The MacKinnon group described a high-resolution crystal structure of a K+ channel for the first time. This paper, surprisingly readable by undergraduates despite the highly specialized techniques used, is one of the reasons Rod MacKinnon was awarded the 2003 Nobel Prize in Chemistry. Some of the questions addressed by this and similar reports include: 1. How can an ion channel be so selective, especially for ions like K+ and Na+, which have similar physical characteristics? 2. Given this extreme selectivity, how is it that K+ channels have such a high conductance, with the speed of K+ ion transport being similar to that of K+ ion diffusion through water? 3. How does the K+ channel actually change shape in response to electrostatic charge across the membrane? 4 How does the detailed knowledge gained from the high-resolution structure affect the view of channel function inspired by previous experiments?

Value: This series of papers ranges from "classical" to "cutting-edge." Voltage-gated ion channels drive electrical excitability in neurons, and thus determine how information is processed in the brain. This is especially true for voltage-gated K+ channels; these molecules are astoundingly diverse, yet share fundamental functional principles and largely determine the excitation characteristics of neurons. The story of how K+ channel structure was characterized is a great example of interdisciplinary research, incorporating genetics, electrophysiology, evolutionary biology, genomics, and biochemistry. In my courses, I use these papers to drive home the importance of utilizing multiple levels of analysis and diverse model systems.

Audience: I have taught selections from these papers in a neurophysiology lab course, where they served as a great complement to the applied work, and allowed students to put their experimental results into context. These papers would work well in a mid-level to advanced undergraduate neuroscience or neurobiology course, and are perfect for graduate level courses.

Is LTP expressed pre- or post-synaptically?

Contributor: DJ Brasier

Topics: Plasticity; LTP; synapse function; electrophysiology

References: Kauer et al., 1988; Malinow and Tsien, 1990; Stevens and Wang, 1994; Liao et al., 1995

Description: This material is incredibly fun to teach because it is as much a human history as it is a scientific one. Prior to beginning, students should have a background understanding of synaptic release and transmission, including AMPA and NMDA receptors. In the drama that will unfold, the pre-synaptic cells are the CA3 neurons in the hippocampus and the post-synaptic cells are the CA1 neurons. Students get to learn more detail about synaptic physiology (one vs. multiple points of contact and release probability vs. post-synaptic sensitivity) in the context of the debate. Typically, I begin with the Stevens and Wang (1994) and Malinow and Tsien (1990) studies to explore the pre-synaptic side of the debate. These studies, in particular, require students to review basic probability and statistics. Then, I present apparently contradictory results from Kauer et al. (1988). We discuss the assumptions and caveats of each study. Students are frequently asked to evaluate and re-evaluate their positions as the discussion unfolds. Typically, after the Stevens/Wang and Malinow/Tsien papers are discussed, the majority of the class believes LTP is pre-synaptic. Subsequent discussion of the Kauer et al. study usually leaves the class split with many students unsure or believing both changes happen. I often conclude with the discovery of silent synapses (Liao et al., 1995). This is finding especially dramatic because it provides a novel theoretical framework that upends some of the assumptions made by the Stevens/Wang and Malinow/Tsien studies; a postsynaptic change can explain most – but not all – of the results the pre-synaptic camp relied on to support their view. After this, a majority of students tend to believe the post-synaptic theory, but a minority still cites particular unanswered questions. I do not insist that students accept the consensus postsynaptic view, but encourage them to evaluate the data and come to their own conclusions.

Value: Students have the opportunity to follow an historic story in neuroscience. They experience difficulty reconciling two contradictory models each with its own supporting evidence. The personalities of the scientists involved can also be discussed. One central figure, Roberto Malinow, is especially interesting as he provides a rare case of someone experimentally overturning his own opinion. The resolution of the controversy provides a great example of how new data can force a re-evaluation of past assumptions and suddenly allow a single consistent model to explain seemingly contradictory pieces of data. Although the material is difficult for students at all levels, the insight into the scientific process is profound (Willard and Brasier, 2014). Also, a good deal of experimental cellular neuroscience is explored and students are given a chance to apply math to neuroscience. Finally, although students are not required to learn the current consensus view that LTP at this synapse is postsynaptic, at the end I do tell them that that is the consensus; the minority who feel that this consensus is not completely satisfying (there are some results it cannot fully explain) are encouraged to share their views. Students also begin to consider not only the value of data, but the reproducibility of data.

Audience: The sequence as described works for introductory students with no specific background other than synaptic transmission which is discussed leading up to this. The sequence takes three 50-minute class periods on top of the pre-requisite knowledge of how synapses work, AMPA vs. NMDA receptors, and a basic introduction to LTP. For introductory students, a good deal of class time is spent on the mathematical and theoretical foundations of the work as well as some superficial explanations of the methods of data collection and analysis. The key to success with this difficult material is targeted homework assignments before each class period to prepare the students for thinking about the data. More advanced students with a stronger statistics background can go further and explore other synapses (Weisskopf et al., 1995) or continuing challenges to the post-synaptic model (Enoki et al., 2009).

Neurogenesis in the adult human brain

Contributor: Barbara Lom

Topics: Postnatal neurogenesis; neuronal differentiation; staining, tracing, and imaging techniques

Reference: Eriksson et al., 1998

Description: This paper is a simple and powerful clinical study that asked the question, “Is the adult human brain capable of making new neurons?” in response to the longstanding view that neuron loss was irreversible in the primate brain. (Adult neurogenesis in many other vertebrates had long been known and its absence in primates had been hypothesized as a potential evolutionary trade-off.) In the 1990s new evidence of adult neurogenesis in non-human primates began to emerge, acknowledging earlier evidence of neurogenesis in the adult primate brain that had gone largely ignored. To answer this important question Eriksson et al. were fortunate to have access to rare postmortem brain tissue of cancer patients who had consented to receive injections of BrdU, a marker of dividing cells, to assess tumor proliferation near the end of their lives. BrdU is a widely used synthetic nucleoside analog of thymidine (T) that can incorporate into the DNA of S-phase cells undergoing DNA synthesis. Due to its short half-life as a monomer, but long stability when incorporated into a new DNA strand, BrdU offers a unique opportunity for scientists to obtain a snapshot of cells preparing to divide at the time of BrdU administration. Given BrdU’s ability to integrate into the genome, it is a potential mutagen, thus, not appropriate for most human studies, yet widely used in animal studies of neurogenesis. Examining the brains of five consenting cancer patients after their natural deaths (roughly two weeks to two years after BrdU administration), this team of scientists in Sweden and California report a singular and striking result: hippocampal cells in the subventricular zone (SVZ), hilus, and granule cell layer (GCL) had incorporated BrdU. Thus, these images provided the first direct evidence that the adult human hippocampus is capable of generating new neurons, many decades into its life. The research team also combined BrdU staining with immunostaining for specific and widely used neuronal markers (NeuN, NSE, Calbindin) to confirm that BrdU-stained cells also stained for these markers of differentiated neurons, suggesting neuronal differentiation had occurred.

Value: This paper firmly put out of business the popular conception that humans are born with all the neurons they will ever have. Even though the age of this paper is now approaching the age of college students, in my recent experiences many undergraduates have still heard from at least one source that adult neurogenesis is impossible in humans. Consequently, introducing this paper as a paradigm-shattering example motivates considerable student engagement. This paper can also be paired nicely with other papers examining neurogenesis in rodents and non-human primates, opening up lively conversations on the utility of animal models and species differences. In addition, this paper is particularly valuable as an example of a clinical research study which thereby stimulates natural and engaging discussions of critical research issues such informed consent, human subjects institutional review boards (HSIRBs), institutional animal care and use committees (IACUCs), appropriate sample sizes, and other important considerations for responsible conduct and scientific rigor in contemporary research.

Audience: Students in my 200-level seminar (Neuroscience of Exercise) and 300-level lab courses (Cellular and Molecular Neuroscience) have read this paper with ease and enthusiasm. The paper is accessible in part because it is short and simple; using just two related staining techniques (BrdU labeling of mitotic cells and immuno-staining of neuronal markers). I expect this paper could be similarly interesting, accessible, and relevant in just about any undergraduate neuroscience course as well as in cell biology and developmental biology courses.

Living without time: Internal timekeeping in students isolated in a WWII bunker

Contributor: Megan Hagenauer

Topics: Circadian rhythms; sleep; chronobiology
Reference: Aschoff, 1965
Description: Like many classic papers, this one is not only a forceful scientific argument, but also a personal account of an adventure exploring the unknown. It describes the rationale, methods, and results for a series of studies in which German students volunteered to live in complete timeless isolation in an underground WWII bunker for 3-4 weeks to discover whether the human body was capable of independently tracking time by means of a biological clock. The paper introduces all of the major concepts of modern chronobiology, including free-running period, entrainment, zeitgebers, and desynchrony. It is also full of fascinating details regarding what the experiment felt like to the subjects—from their initial optimism regarding how much studying they would accomplish while living in total isolation, to the system of double doors for the delivery of goods and messages from the outside world, and the inclusion of beer as part of their daily provisions. The author, Jurgen Aschoff, is considered a father of chronobiology, and one of my favorite parts of this paper is his description of his own experiences in the bunker, trying out the experimental set-up. He describes his disorientation in response to waking up in isolation and having no idea how long he had slept, as well as his complete surprise when he emerged from the bunker on the "last morning" of the experiment and discovered that it was actually 3 p.m. Through the figures, including a beautiful chart of the daily fluctuations in metabolites in Aschoff's own urine, we can clearly see evidence of the human body generating its own daily physiological schedule in isolation, and how it slowly drifts later relative to the outside world due to the complete absence of environmental time cues. We are also introduced to the evolutionary adaptiveness of a self-sustained timekeeping system, as well as the importance of biological clocks for human health. To make this last point, Aschoff presents evidence from an individual who had his sleep/wake cycle spontaneously desynchronize from his other physiological rhythms while in the bunker. On the days when his rhythms were properly re-synchronized, his diary notes that he felt "especially well and fit." Using these data, Aschoff correctly predicts that forced internal desynchronization may explain the malaise felt by shift-workers, astronauts, and jet-lagged international travelers. In the end, it is impossible to read this paper without wondering whether you would be willing to take the challenge, and (in the name of science!) insert a rectal thermometer and enter an underground bunker to experience true timelessness.
Value: I have used Aschoff (1965) as the first paper in a series of class periods aimed at introducing both the fundamental concepts of biological rhythms and skill of active reading. Since this is the first paper in the series, I typically recommend that the students start by reading a two-page popular science article that provides a colorful, illustrated description of the history of circadian biology and the bunker experiments (Globig, 2007). I also provide a brief introduction to the research question and basic rhythm terminology (e.g., oscillator, frequency/period, phase, amplitude), and a few pieces of advice on how to extract the most important information from scientific papers.

The text of Aschoff (1965) is unusual for a scientific paper because it is short (five pages) and relatively unintimidating. In contrast, the figures can be quite challenging, so on the day that we discuss the paper, I have the students initially work through the paper in groups with a particular focus on deciphering and explaining the most important figures (Figs. 1-4 and 7). I structure the lesson this way because over the years I have found that approximately 1/5 of my upper-level science students still have serious difficulties interpreting graphs (even scatterplots or bar charts). Approximately 15 minutes into the class period, we come back together as a class and work our way through the key concepts, methods, results, and conclusions in the paper. My goal for this exercise is to encourage students to treat scientific writing and figures as a puzzle to decipher strategically, and to create an atmosphere where students feel comfortable building their own understanding of the concepts instead of simply hiding their ignorance by parroting the paper's own formal scientific language and figure legends. I also use the theme of self-quantification and exploration in the Aschoff paper to introduce the first project for the semester: tracking personal sleep/wake rhythms using free, downloadable smart-phone applications (e.g., Sleep Cycle, Sleep as Android, SleepBot) or commonly-sold wrist actigraphy (e.g., Jawbone Up, Fitbit, iWatch).
Audience: I have used this paper in a 400-level seminar that I teach on sleep and circadian rhythms using classic primary literature, but I believe that it could be easily adapted for a unit in an introductory neuroscience course.

Circadian rhythms are driven by photosensitive retinal ganglion cells

Contributor: Shawn P. Gallagher
Topics: Sensory and motor systems; vision; retina; photoreceptors; biological rhythms; sleep; SCN anatomy, physiology, neurochemistry
References: Freedman et al., 1999; Berson et al., 2002
Description: These two short papers describe the prediction and subsequent discovery of light-sensitive retinal ganglion cells that project to the suprachiasmatic nucleus (SCN) and influence circadian behavior. In the first report, Freedman et al. (1999) conducted behavioral experiments with blind transgenic mice. Despite having no rods or cones, the mice exhibited normal circadian wheel-running behavior that vanished when the eyes were removed. This study, using a combination of transgenics, behavior, and the crude but effective practice of enucleation, made a compelling case that something in the eye, other than rods or cones, could detect changes in ambient illumination. The second report, by Berson et al. (2002), takes the next step and provides evidence that the circadian clock is set by a subset of retinal ganglion cells that contain the photopigment melanopsin and project directly to the SCN. Using retrograde tracings (hypothalamus to retina) in rats, the authors marked the cells and recorded from them in isolated retina

preparations. The recordings showed that, unlike the unmarked ganglion cells, these cells had unusually slow response times and were photosensitive, even when they were functionally disconnected from rods and cones. These ganglion cells, although inappropriate for image-forming visual pathways, are suitable for providing the SCN with information about slow-changing, ambient levels of illumination.

Value: These studies elucidate the link between the mammalian retina and circadian rhythms. Taken together, the papers also present an excellent example of progressive science. One group conducts behavioral studies and makes a prediction while the next group completes the story with anatomical and electrophysiological evidence. In the classroom, these papers could bridge a description of the retina to discussions of the hypothalamus, circadian rhythms, or parallel processing in the optic nerve. Even novice neuroscience students should be familiar with basic retinal anatomy and be impressed by the discovery of photoreceptive ganglion cells. For psychology students, the results could be used to address the clinical significance of these cells since they may present a key to understanding seasonal affective disorder. Students interested in comparative neuroanatomy could explore the evolutionary history of melanopsin, a pigment that is present in the pineal gland of non-mammalian vertebrates. Darwin, himself, was troubled by his inability to imagine intermediate stages of the eye's evolution; I think he would have liked the story of the ganglion cells that monitor sunrise and sunset.

Audience: These papers are clear and describe experiments that tell a simple story. The significance of the findings, however, can be discussed at many different levels. I recommend these papers for any course that introduces the anatomy of the retina. Students in basic psychology and neuroanatomy courses should understand how some retinal cells serve functions that lie, perhaps exclusively, beneath conscious visual perception. More advanced students, like those in a mid-level neurophysiology class, can compare the electrophysiology of the photosensitive and non-photosensitive ganglion cells to understand how the different response types serve different functions. Finally, students in experimental design classes should appreciate how the many techniques employed in these studies converge on a single, profound discovery.

Structure and function of the mammalian visual cortex

Contributor: Richard Olivo

Topics: Cortical physiology; receptive fields; visual cortex

Reference: Hubel, 1982 [Although David Hubel died in 2013, this paper is still available (2015) on his website at Harvard Medical School:
http://hubel.med.harvard.edu/papers/Hubel1982Nature.pdf]

Description: This paper, David Hubel's 1981 Nobel Prize address, is a clearly written account of his collaboration with Torsten Wiesel to unravel the structure and function of the primary visual cortex (V1) in cats and monkeys. It is written from a personal viewpoint, explaining the decisions that were made and why they made them. It covers the physiology of single unit recordings, including a number of figures from Hubel and Wiesel's early papers (e.g., Hubel and Wiesel, 1962; 1968) showing responses to oriented bars and edges, as well as anatomical figures showing layers in V1, ocular dominance columns, and even cytochrome oxidase blobs. It also includes their original summary figures showing models of synaptic circuits and the famous "ice cube" model of a cortical module. A few aspects have been refined by subsequent research ("hypercomplex" cells are now regarded as an extreme form of complex cells, and the "ice cube" model that shows wide ocular dominance columns perpendicular to narrow orientation columns demonstrates the concept but not the actual microanatomy of V1), but most of the information remains valid. The paper presents a detailed overview of what many consider the most important research program into the mammalian cortex, written by a pioneer in the field.

Value: Although many people would regard Hubel and Wiesel's two massive research papers on primary visual cortex in cat (1962) and monkey (1968) as the true classics of this era, this review of their work is in its own way a classic that serves students very well. While it is not as detailed as the original research papers, it does provide many original figures embedded in the context of the overall research program. The review covers both their physiological experiments to record from and classify single units in primary visual cortex (V1), and also their experimental attempts to determine the functional architecture of V1. The physiological models of how simple and complex cells might be driven by excitatory input from their presynaptic elements are also included, which have remained viable, if simplified, models of V1's neural circuitry. The anatomical experiments have been superseded by newer optical techniques that more clearly reveal the overlap of ocular dominance bands and orientation pinwheels, but the "ice cube" module they proposed is of historical importance and still provides basic insight into the organization of V1. Finally, the paper includes anecdotes of Hubel and Wiesel's personal experience, starting as postdocs with Stephen Kuffler at Johns Hopkins before they moved to Harvard Medical School. The personal accounts are a further reflection of Hubel's clear and unpretentious writing style that makes this a very accessible paper for students.

Audience: I have used this paper as a reading assignment in an upper-level Neurophysiology course, where we spend several weeks on visual processing from retina through extrastriate cortex. The paper provides an appropriately detailed supplement to the relatively brief account of visual cortex in most textbooks; it hits the sweet spot between overly simplified textbook accounts and the original research papers.

Seeing with a rewired auditory cortex

Contributor: Ian Harrington

Topics: Plasticity; cross-modal rewiring; cortical receptive fields; animal behavior

References: Sharma et al., 2000; von Melchner et al., 2000

Description: Although any number of papers by this group could have been considered for inclusion here, I have found that these two papers, published in the same issue of Nature, work particularly well together. The first paper, by Sharma et al. (2000), addressed whether cortical receptive field properties are determined by afferent inputs or reflect characteristics of the fields themselves. Considered another way, does auditory cortex look like auditory cortex regardless of the modality of its inputs? To address this question, neonatal ferrets had the projections from their eyes redirected to the auditory thalamus. This changed the modality of the input to the auditory cortex while maintaining the integrity of the projections from the thalamus to the cortex. The study demonstrated that cells in the rewired auditory cortex were not only visually responsive, but that their tuning for orientation and their local connections were similar to those found in normal visual cortex. The second paper, by von Melchner et al. (2000), addressed a natural follow-up question raised by the previous one: When an animal with a rewired auditory cortex is exposed to visual stimuli, does it have visual or auditory experiences? In this study, ferrets were only rewired unilaterally to allow the animals to serve as their own controls. The animals were trained to make one response to centrally presented sounds, and another response to lights presented contralateral to their intact visual pathway. Once the animals were performing the task well, visual stimuli were presented from the central location and one contralateral to the rewired pathway. The animals were tested again following the destruction of all visual pathways other than the novel one from the auditory thalamus to the auditory cortex. The results showed that when visual stimuli were presented to the rewired auditory cortex alone, they were experienced visually. As was suggested by Sharma et al. (2000), although the rewired auditory cortex is not an exact reproduction of the normal visual cortex (suggesting some intrinsic influences), it shares certain characteristics and is able to support visual experiences.

Value: With only a small risk of hyperbole, these papers have it all: interesting surgical interventions, plasticity, cortical physiology (optical imaging and some single-cell recording), retrograde tracing of cortical connections, complex behavioral testing (with good experimental controls), animal psychophysics, and lesions. Perhaps the greatest value of these papers is to demonstrate the multidisciplinary approaches that are necessary to address complex questions in neuroscience. The methods can be challenging for undergraduate students to follow but these challenges are not insurmountable. The papers, given the format of Nature, are fairly brief, but are well written and include clear graphs and other figures. Because of the format, however, some methodological details are referred to other sources. These papers can also be read at different levels. I have mentioned some of the key findings of these studies in 5-10 minutes of class time (or had students work to understand a single data figure in small groups), but could also imagine spending one or more class periods working through the details of the papers with students.

Audience: I have used these papers in several courses including a 200-level Brain & Behavior and a 300-level Sensation & Perception, but could also imagine them being used in other upper level courses, especially in a senior seminar. As mentioned above, the papers and their findings can be pitched at several levels, as their use demands.

The prefrontal cortex and moral judgments

Contributor: Rupa Gupta Gordon

Topics: Human cognition and behavior; decision making and reasoning; moral judgments; prefrontal cortex; plasticity

References: Koenigs et al., 2007; Taber-Thomas et al., 2014

Description: These two studies address the role of the ventromedial prefrontal cortex (vmPFC) in moral decision-making using the lesion method. The first, by Koenigs et al. (2007), compares the moral judgments of patients with adult-onset vmPFC damage to healthy comparison participants on personal versus impersonal moral dilemmas. These two forms of dilemma differ in that the personal form requires direct action (e.g., pushing a fat man off of a footbridge) rather than indirect action (e.g., pushing a button that diverts a train to a different track) in the interests of saving lives. Patients with vmPFC damage are more likely to endorse utilitarian actions in personal moral dilemmas, due to the lack of emotional response to the personal aspect of the moral dilemma. This finding suggests that the emotionally aversive reaction typically experienced when considering personal moral dilemmas depends upon the vmPFC. The second article, by Taber-Thomas et al. (2014), builds upon this line of research by studying the effect of developmental vmPFC damage on moral judgments. Unlike adult-onset vmPFC patients, those with developmental vmPFC exhibit more self-serving behavior (e.g., pushing an annoying boss off of a building). This demonstrates the importance of the vmPFC for learning social and moral norms during development. However, once learned, the ability to use knowledge of these norms can occur in adults independent of the vmPFC, as adult-onset vmPFC patients do not endorse self-serving situations, but the vmPFC must be intact during development for the acquisition of intact moral knowledge.

Value: Not only are these excellent examples of lesion studies using groups rather than single cases, but they also address a topic that evokes a flurry of debate in class. Furthermore, it leads nicely to a discussion of the role of free will in moral responsibility and the influence of neuroscience on other disciplines like law. It is beneficial for teaching about the research process, as it demonstrates the progression of a systematic line of research across time. Beyond the topic, there are valuable teaching opportunities in these articles to demonstrate basic research concepts. For example, in Koenigs et al. (2007), students can discuss how “personal” vs. “impersonal” moral judgments were operationally defined

based on the content of the story, while "high" and "low" conflict moral judgments were operationally defined based on the consistency of participants' responses.
Audience: I have used these articles in an upper level seminar course on Cognitive Neuropsychology, where students read and analyze primary literature. However, the content is also appropriate for an introductory course in human neuroscience.

Steroids as a rejuvenating or anti-aging agent

Contributor: Noah Sandstrom
Topics: Testosterone; steroids; aging; human behavior; history of neuroscience
Reference: Brown-Séquard, 1889
Description: The world of professional sports is fraught with cases of athletes seeking to gain a competitive edge through the use of performance enhancing drugs. In many instances, the drugs of choice are anabolic steroids (e.g., testosterone). In recent years, steroid allegations have been made about Barry Bonds, Jose Canseco, Lance Armstrong, and countless others. At the same time, a legitimate scientific literature has explored the potential clinical utility of steroid replacement/supplementation for a variety of conditions (e.g., Alzheimer's disease, hypogonadism) as well an intervention against naturally occurring declines in androgen production associated with aging. This report by Brown-Séquard is an absolute classic in which the author engages in self-experimentation to explore whether administration of extracts from the testicles of animals (guinea pigs and dogs) might positively impact some of the abilities and faculties that he notes have been waning with age. Brown-Séquard, noting these deficiencies (e.g., a developing inability to concentrate, constipation, fatigue, forgetfulness) uses a certain logic, misguided as we may now understand it to be, to design a study in which he grinds up testicles from animals, filters them (no sense in injecting anything gross!), and injects the extract into his bloodstream. He soon reports remarkable changes in his intellect, his stamina, and his powers of defecation and urination.
Value: This is a wonderfully engaging paper that has value in several important regards. First, it speaks to the long history of interest and research in the effects of gonadal steroids on human behaviour. These ideas are at the foundation of the steroid scandals that plague so much of professional sports – an area of interest to many students. Second, it provides a rich case with which to begin discussing issues of experimental design and clinical trials. The "study" had no controls. The researcher wasn't blind; the subject wasn't blind. In fact, they were the same person and we can quite confidently conclude that much of the effect that was reported was placebo in nature. But the paper can be a wonderful tool to start students on the assignment of trying to design an appropriate clinical trial to explore the fundamental questions of interest to Brown-Séquard. The paper is a not a state-of-the-art paper – rather, the complete opposite. It is a classic. Don't use it to educate as to the current state of knowledge regarding hormone replacement therapy. Instead, use it to introduce the topic and get people to appreciate that some of the same questions we find fascinating today are the same ones that researchers were intrigued by over 100 years ago.
Audience: I have used this paper in an upper-level seminar on Hormones & Behavior. It's on the reading list for day 1 alongside a couple of news reports or sports magazine articles on steroid abuse. I use it primarily to introduce the concept of hormones influencing behaviour but we revisit the topic later in the term when we talk specifically about hormones and cognition (and talk about current research in that area). I could also imagine it being used in a research methods class when talking about clinical trials.

Neural correlates of human sexual orientation

Contributor: William Grisham
Topics: Homeostatic and neuroendocrine systems; anatomy; sexual orientation
References: LeVay, 1991; Byne et al., 2001
Description: These papers were selected because they both investigate differences in a hypothalamic nucleus that is related/correlated with differences in sexual orientation. The second is an attempt at a replication of the first, which we almost never see in neuroscience. In the original paper, LeVay (1991) extends the work of Allen et al. (1989) who found marked sex difference in two cell groups in the anterior hypothalamus of humans. The interstitial nuclei of the anterior hypothalamus (INAH 2 and INAH 3) were larger in males than females. LeVay extended their investigation by examining this nucleus in homosexual men as well as heterosexual men and women. LeVay did not replicate the sex difference in INAH 2 but did replicate the sex difference in INAH 3. More importantly, LeVay found that INAH 3 was much smaller in homosexual men than heterosexual men. Indeed, the difference in INAH 3 was about the same as the one between heterosexual men and women. A decade later, Byne et al. (2001) confirmed the sex difference in INAH 3—men again were found to have a larger INAH 3 than women have. However, they failed to find a difference in INAH 3 between heterosexual men and homosexual men in either the volume of the nucleus, the neural number, or the neural density (LeVay only measured volumes).
Value: Despite a beautifully written and well-reasoned discussion in which LeVay clearly defines the limitations of the conclusions, this article is still severely criticized in both academic and non-academic circles. Indeed, although it was published nearly 25 years ago, critiques can still be found on the web with ill-founded allegations about what the data actually mean and what the article actually says. These critiques and allegations, however, provide good starting points for discussions. I don't lead the students to the refutations, but rather asked them to figure out if the critiques or allegations are valid or not. These critiques and allegations are listed below. 1) The study shows that homosexual men are "born that way"—sexual orientation is either genetic and/or congenital. Refutation: LeVay makes it clear that the finding is a correlate and that the difference could either be a cause or a consequence of engaging in homosexual sex. 2) All of the homosexual men in LeVay's

study had died of AIDS, so sexual orientation and HIV+ status are confounded. Refutation: A sub-group of the heterosexual men in LeVay's study had also died of AIDS, and the difference between this subgroup of heterosexual men with AIDS vs. homosexual men was still present. Also, LeVay found there was no correlation between the volume of INAH 3 and the length of survival from the time of HIV+ diagnosis. 3) Promiscuity could actually be responsible for the decrease of INAH 3 size in homosexual men rather than sexual orientation. Refutation: LeVay admits that it could be a possible explanation. 4) LeVay is openly homosexual, so his results cannot be trusted. Refutation: The study was done blind. 5) INAH 3 is much too small to be measured reliably. Refutation: My students and I measure much smaller objects (neuron soma sizes) with great reliability (Grisham et al., 2003)—it just takes the right lens on a microscope. 6) The heterosexual HIV+ men in LeVay's study were actually "in the closet" and should have been assigned to the homosexual group. Reassigning all of the allegedly heterosexual HIV+ men would make the difference in INAH size between homosexual and heterosexual men disappear. Refutation: Combining the data across these groups would indeed markedly reduce the difference between homosexual and heterosexual men. Nonetheless, the question would then be why there is a difference between HIV+ men who were identified as homosexual on their medical records versus those who were not. 7) The final two arguments revolve around statistical considerations. The first is that there is some overlap between the groups in INAH 3 size, therefore the differences aren't real because every last individual wasn't different. Refutation: Notably, we perform statistics on differences between group means, so this is possible. LeVay discusses these outliers and suggests that sexual orientation may not be the only variable that determines the size of this nucleus. 8) Byne et al. did not replicate LeVay's finding. Refutation: I have my students take the values from Table 3 of Byne et al. and run a simple t-test on INAH 3 volume between the homosexual vs. heterosexual. (Students will have to figure out the standard deviation, but they have the standard error of the mean and the sample size, so they can.) When doing this, students will find that the t-test actually does show a significant difference. Byne et al. used a post-hoc Tukey–Kramer HSD test, which did not reveal the difference. This can generate discussions about statistical power, whether or not stringent criteria are appropriate in statistical testing, and how sacred the 0.05 criterion should be. As a footnote, Garcia-Falgueras and Swaab (2008) found similar results with male-to-female transsexuals: they had a smaller INAH 3 volume than did controls.

Audience: Clearly these papers will be of interest to students, especially in light of current legal decisions, and could be used in a variety of curricular contexts. Conceivably, they could be used in a Neuroscience and Society course. I have used this pair of papers as a part of a focused course on sex differences and sexual differentiation of the nervous system in vertebrates. I have also used the LeVay paper in my behavioral neuroscience lab class as a supplementary reading when examining sex differences in the spinal cord (cf. Grisham et al., 2003), and https://mdcune.psych.ucla.edu/modules/ratscia).

Investigating sex differences in spatial ability using multiple approaches

Contributor: Shara Stough

Topics: Sex differences; neuroethology; animal behavior and cognition; spatial learning; hippocampus

References: Gaulin and FitzGerald, 1986; Jacobs, Gaulin, Sherry, and Hoffman, 1990

Description: On average, males demonstrate superior spatial navigation skills compared to females. These sex differences are demonstrated across species. The papers I chose for this collection attempt to answer the question of why these differences exist and point to a possible neurobiological basis for this sexually dimorphic behavior. The first paper, by Gaulin and FitzGerald (1986), makes use of two closely related species, meadow voles and pine voles, with distinct mating systems to test the evolutionary hypothesis that differences in spatial ability arise due to the larger home ranges of males in polygynous species. In a field study, the authors first measure the home ranges of male and female voles of each species using implanted radio transmitters. They find that in the polygynous meadow voles, males range much farther than females, but in the monogamous pine voles, males and females have similar home ranges. The researchers then re-capture the monitored voles to test their spatial ability in a maze in the lab. As expected, the male meadow voles demonstrate better maze performance than female meadow voles, while male and female pine voles perform similarly in the maze. The second paper, by Jacobs et al. (1990), provides evidence suggesting that differences in hippocampal volume may play a role in the sexual-dimorphism observed in spatial ability in meadow voles. In this study, the researchers measured the relative hippocampal volume (hippocampal volume/brain volume) of wild-caught male and female meadow voles and pine voles. As predicted from previous behavioral results, male meadow voles had larger hippocampal volumes than female meadow voles and there was no difference between hippocampal volumes in male and female pine voles, providing a possible neurobiological basis for the observed differences in behavior.

Value: I think the greatest value of this set of papers is that they demonstrate the utility of investigating a question from multiple perspectives. The papers use both field and laboratory studies, and move from an investigation of behavior to the neurobiology underlying behavior. The papers are fairly straightforward, so students have a relatively easy time understanding the experiments and following the logic connecting each approach. This gives us the opportunity to move beyond simple understanding to discuss the strengths and weaknesses of each approach and to appreciate how evidence can be strengthened with the combination of multiple approaches. The papers also present fairly low-hanging fruit for students to identify follow-up experiments that would provide stronger support for the authors' hypotheses. The papers are selected from a time point early enough in this line of research and leave

enough unanswered questions for students to engage with the results and process as actual researchers would.

Audience: I use these papers in a senior seminar course. The course is focused more on skill development than content memorization. Students learn to read primary articles, evaluate information within articles, and synthesize information across articles to form their own hypotheses and follow-up experiments. Although the first article is a little long, neither article is particularly difficult. Both articles can easily be discussed together in a single 75-minute class period.

Creating false memories

Contributor: Monica Linden

Topics: Learning and memory; hippocampus; amygdala; fear; optogenetics; associative learning

References: Reijmers et al., 2007; Liu et al., 2012; Ramirez et al., 2013

Description: There are multiple papers by this group that could be considered including review articles, however the Ramirez et al. article is a tractable primary source article and is a slightly more exciting finding than the Liu et al. article. The Ramirez paper focuses on how the researchers can create a false memory of fear in a "safe" box by activating the neurons representing the "safe" box while the animal is learning to fear a "scary" box. This is accomplished using c-fos-tTA mice in combination with an AAV-TRE-ChR2-mChery virus to express channelrhodopsin with temporal specificity in the hippocampus. There are several versions of the experiment, but in general, channelrhodopsin is expressed in neurons active in a "safe" context. These neurons are then reactivated using light while the animal is fear conditioned in a separate context. The animal's response is then tested in the safe context, where we now see a fear response. The researchers compare the results of the experiment when the virus is injected into the dentate gyrus versus the CA1 region of the hippocampus, showing that these results are observed for dentate gyrus but not for CA1. They also use fluorescent imaging to compare expression patterns of the channelrhodopsin-expressing neurons and cFos. In an additional experiment, the researchers show that conditioned place avoidance can be induced using a similar protocol wherein the animal is fear-conditioned in a separate context, but will express a fear memory for the context reactivated during the fear conditioning. These results produce the remarkable conclusion that neurons reactivated during the delivery of an unconditioned stimulus can create a false associative fear memory to a conditioned stimulus that was not present during the delivery of the unconditioned stimulus.

Value: This paper excites the students as it exposes them to cutting-edge technology coupled with clear experimental design and easy-to-understand behavioral experiments. Students are drawn in by the idea of the "Marilyn Monroe Experiment" (i.e., can you artificially give the memory of one night with Marilyn Monroe?), as they see a real implementation of mice fearing a location where they have never received a shock. They also enjoy learning about optogenetics. While the technique itself is complicated, using Reijmers et al. (2007) and Liu et al. (2012) as background material allows students to appreciate the need for both temporal and anatomical specificity in gene expression. Furthermore, reviewing the results of Liu et al. helps the students understand the basic setup of the experiments in Ramirez et al. With guidance, the students can understand how each type of specificity is accomplished and why it is necessary. The paper also uses clear figures to illustrate the behavioral paradigms, so it is quite easy to follow what is happening during each iteration of the experiment. Furthermore, this paper can serve as a nice capstone in a learning and memory class because it brings together the functioning of the hippocampus with fear conditioning in an exciting, new way. Because the paper is in *Science*, it is a condensed format that is not overwhelming to the students. At the same time, it is useful to direct the students to some of the supplementary figures. (Alternatively, interpretation of the supplementary figures can make for good exam questions!)

Audience: I have used this paper in a junior/senior level Neurobiology of Learning and Memory course. I could imagine this paper being used in a variety of upper level courses including senior seminars. The methods could also be used in a techniques-focused course. Additionally, the findings could be discussed in a lower-level course or a non-majors course as a way to get students excited about the future of neuroscience research.

Knowledge transplant

Contributor: Michael C. Wiest

Topics: Learning and memory; rodent; hippocampus; micro stimulation; electrical stimulation; memory-transfer; ensemble; neuro-prosthetic

Reference: Deadwyler et al., 2013

Description: Deadwyler et al. (2013) demonstrates a transfer of task-relevant knowledge from a well-trained donor rat to a relatively naïve recipient rat in the form of neural activity patterns induced by multi-site electrical micro-stimulation in the recipient hippocampus. The task is a well-studied delayed non-match to sample (DNMS) task that involves remembering the position of a sample lever over the course of a 1 to 60 second delay. Distributed spiking activity patterns were measured using multi-site recordings in the donor rat, and these formed the basis for a computational model of the hippocampal "ensemble codes" or spatial activity patterns corresponding to successful and unsuccessful memory encoding during the sample phase of the task. "Successful" activity patterns were then induced in the donor hippocampus by multi-site electrical stimulation, resulting in dramatic performance improvements compared to un-stimulated trials or stimulation with unfavorable activity patterns. This suggests the exciting possibility of transferring memories from one brain to another in order to enhance memory performance or recover lost memory functions — as distinct from transferring immediate sensory information or motor commands as in a related "brain-to-brain interface" paper (Pais-Vierra et al., 2013). Another paper from the Deadwyler and Hampson group (Hampson et al., 2013)

shows that neuro-prosthetic memory enhancement is feasible in primates; however that paper does not show transfer between animals as in the rat paper above (Deadwyler et al., 2013).

Value: The idea of directly inducing specific experiences and knowledge by brain stimulation is naturally exciting. It evokes images from popular science fiction movies like The Matrix and Inception and can lead one to fascinating philosophical issues. But for more practical-minded students, it is not that difficult to imagine huge medical and societal benefits if we become able to implant skills and knowledge as needed in people — people with memory loss or people with important and difficult jobs. Given these motivations for studying the paper, there is also a substantial pedagogical payoff in terms of understanding the experimental design, the multi-channel recording and stimulation methods, distinct functional roles for hippocampal areas CA1 and CA3, and the concept of an ensemble code that undergoes transformations over time that predict success or failure in the task. The "non-linear multiple-input multiple-output" model in the paper may be taken as an example of the importance of mathematical and computational modeling approaches in systems neuroscience.

Audience: I have had a small group of senior undergraduate neuroscience majors present Deadwyler et al. (2013) for discussion in our senior capstone seminar course. I consider it a challenging paper even for that relatively advanced group of students. However, I think the gist of the paper is accessible and valuable even if some technical details are skimmed over. For example, students can get some appreciation of how computational modeling can be useful from Deadwyler et al. (2013), even if they are not immediately motivated to master those methods themselves. Thus, I think this paper could be discussed in lower-level classes, but in that case I would probably not expect students to read the whole paper and I would present some of the core ideas myself rather than expecting students to lead the discussion. For non-majors, I would probably present a digested version of the results rather than assigning sections of the paper.

REFERENCES

Allen LS, Hines M, Shryne JE, Gorski RA (1989) Two sexually dimorphic cell groups in the human brain. J Neurosci 9:497-506.

Aschoff J (1965) Circadian rhythms in man. Science 148:1427-1432.

Berson DM, Dunn FA, Takao M (2002) Phototransduction by retinal ganglion cells that set the circadian clock. Science 295:1070-1073.

Brown-Séquard CE (1889) Note on the effects produced on man by subcutaneous injections of a liquid obtained from the testicles of animals. Lancet 2:105-107.

Byne W, Tobet S, Mattiace LA, Lasco MS, Kemether E, Edgar MA, Morgello S, Buchsbaum MS, Jones LB (2001) The interstitial nuclei of the human anterior hypothalamus: an investigation of variation with sex, sexual orientation, and HIV status. Horm Behav 40:86-92.

Deadwyler SA, Berger TW, Sweatt AJ, Song D, Chan RHM, Opris I, Gerhardt GA, Marmarelis VZ, Hampson RE (2013) Donor/recipient enhancement of memory in rat hippocampus. Front Syst Neurosci 7:1-11.

Dirks C, Cunningham M (2006) Enhancing diversity in science: Is teaching science process skills the answer? CBE Life Sci Educ 5:218-226.

Enoki R, Hu YL, Hamilton D, Fine A (2009) Expression of long-term plasticity at individual synapses in hippocampus is graded, bidirectional, and mainly presynaptic: optical quantal analysis. Neuron 62:242-253.

Eriksson PS, Perfileva E, Björk-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH (1998) Neurogenesis in the adult human hippocampus. Nat Med 4:1313-1317.

Freedman MS, Lucas RJ, Soni B, von Schantz M, Muñoz M, David-Gray Z, Foster R (1999) Regulation of mammalian circadian behavior by non-rod, non-cone, ocular photoreceptors. Science 284:502-504.

Garcia-Falgueras A, Swaab DF (2008) A sex difference in the hypothalamic uncinate nucleus: relationship to gender identity. Brain 131:3132-3146.

Gaulin SJC, FitzGerald RW (1986) Sex differences in spatial ability: an evolutionary hypothesis and test. Am Nat 127:74-88.

Globig M (2007) A world without day or night. Max Planck Res 2:60-61. www.mpg.de/943613/S003_Flashback_060_061.pdf.

Grisham W, Jones HB, Park SH (2003) Sex differences and organizational effects of androgen in spinal cord motor nuclei. J Undergrad Neurosci Educ 2:A29-A35.

Hampson RE, Song D, Opris I, Santos LM, Shin DC, Gerhardt GA, Marmarelis VZ, Berger TW, Deadwyler SA (2013) Facilitation of memory encoding in primate hippocampus by a neuroprosthesis that promotes task-specific neural firing. J Neural Eng 10:066013.

Hodgkin AL, Huxley AF (1952a) A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol 117:500-544.

Hodgkin AL, Huxley AF (1952b) Currents carried by sodium and potassium ions through the membrane of the giant axon of *Loligo*. J Physiol 116:449-472.

Hodgkin AL, Huxley AF (1952c) The components of membrane conductance in the giant axon of *Loligo*. J Physiol 116:473-496.

Hodgkin AL, Huxley AF (1952d) The dual effect of membrane potential on sodium conductance in the giant axon of *Loligo*. J Physiol 116:497-506.

Hodgkin AL, Huxley AF, Katz B (1952) Measurement of current-voltage relations in the giant axon of *Loligo*. J Physiol 116:424-448.

Hoskins SG (2008) Using a paradigm shift to teach neurobiology and the nature of science—a C.R.E.A.T.E.-based approach. J Undergrad Neurosci Educ 6:A40-A52.

Hoskins SG, Stevens LM, Nehm RH (2007) Selective use of the primary literature transforms the classroom into a virtual laboratory. Genetics 176:1381-1389.

Hoskins SG, Lopatto D, Stevens LM (2011) The C.R.E.A.T.E. approach to primary literature shifts undergraduates' self-assessed ability to read and analyze journal articles, attitudes about science, and epistemological beliefs. CBE Life Sci Educ 10:368-378.

Hubel DH (1982) Exploration of the primary visual cortex, 1955-1978. Nature 299:515-524.

Hubel DH, Wiesel TN (1962) Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. J Physiol 160:106-154.

Hubel DH, Wiesel TN (1968) Receptive fields and functional architecture of monkey striate cortex. J Physiol 195:215-243.

Jacobs LF, Gaulin SJC, Sherry DF, Hoffman GE (1990) Evolution of spatial cognition: sex-specific patterns of spatial behavior predict hippocampal size. Proc Natl Acad Sci U S A 87:6349-6352.

Kamb A, Iverson LE, Tanouye MA (1987) Molecular

characterization of Shaker, a Drosophila gene that encodes a potassium channel. Cell 50:405-413.
Kauer JA, Malenka RC, Nicoll RA (1988) A persistent postsynaptic modification mediates long-term potentiation in the hippocampus. Neuron 1:911-917.
Koenigs M, Young L, Adolphs R, Tranel D, Cushman F, Hauser M, Damasio A (2007) Damage to the prefrontal cortex increases utilitarian moral judgements. Nature 446:908-911.
Kozeracki CA, Carey MF, Colicelli J, Levis-Fitzgerald M, Grossel M (2006) An intensive primary literature-based teaching program directly benefits undergraduate science majors and facilitates their transition to doctoral programs. CBE Life Sci Educ 5:340–347.
LeVay S (1991) A difference in hypothalamic structure between heterosexual and homosexual men. Science 253:1034-1037.
Liao D, Hessler NA, Malinow R (1995) Activation of postsynaptically silent synapses during pairing-induced LTP in CA1 region of hippocampal slice. Nature 375:400-404.
Liu X, Ramirez S, Pang PT, Puryear CB, Govindarajan A, Deisseroth K, Tonegawa S (2012) Optogenetic stimulation of a hippocampal engram activates fear memory recall. Nature 484:381-385.
Malinow R, Tsien RW (1990) Presynaptic enhancement shown by whole-cell recordings of long-term potentiation in hippocampal slices. Nature 346:177-180.
von Melchner L, Pallas SL, Sur M (2000) Visual behaviour mediated by retinal projections directed to the auditory pathway. Nature 404:871-876.
Pais-Vierra M, Lebedev M, Kunicki C, Wang J, Nicolelis MAL (2013) A brain-to-brain interface for sharing real-time sensorimotor information. Sci Rep 3:1319.
Ramirez S, Liu X, Lin P-A, Suh J, Pignatelli M, Redondo RL, Ryan TJ, Tonegawa S (2013) Creating a false memory in the hippocampus. Science 341:387-391.
Reijmers LJ, Perkins BL, Matsuo N, Mayford M (2007) Localization of a stable neural correlate of associative memory. Science 317:1230-1233.
Sharma J, Angelucci A, Sur M (2000) Induction of visual orientation modules in auditory cortex. Nature 404:841-847.
Stevens CF, Wang Y (1994) Changes in reliability of synaptic function as a mechanism for plasticity. Nature 371:704-707.
Taber-Thomas BC, Asp EW, Koenigs M, Sutterer M, Anderson SW, Tranel D (2014) Arrested development: early prefrontal lesions impair the maturation of moral judgement. Brain 137:1254-1261.
Tempel BL, Papazian DM, Schwarz TL, Jan YN, Jan LY (1987) Sequence of a probable potassium channel component encoded at Shaker locus of Drosophila. Science 237:770-775.
Wei A, Covarrubias M, Butler A, Baker K, Pak M, Salkoff L (1990) K+ current diversity is produced by an extended gene family conserved in Drosophila and mouse. Science 248:599-603.
Weisskopf MG, Nicoll RA (1995) Presynaptic changes during mossy fibre LTP revealed by NMDA receptor-mediated synaptic responses. Nature 376:256-259.
Willard AM, Brasier DJ (2014) Controversies in neuroscience: a literature-based course for first year undergraduates that improves scientific confidence while teaching concepts. J Undergrad Neurosci Educ 12:A159-A166.
Zhou Y, Morais-Cabral JH, Kaufman A, MacKinnon R (2001) Chemistry of ion coordination and hydration revealed by a K+ channel-Fab complex at 2.0 A resolution. Nature 414:43-48.

Received August 13, 2015; accepted August 22, 2015.

The authors thank the membership of the Faculty for Undergraduate Neuroscience whose open discussions make this kind of collaboration possible.

Address general correspondence to: Dr. Ian A. Harrington, Department of Psychology and Program in Neuroscience, 639 38th St., Augustana College, Rock Island, IL 61201. Email: ianharrington@augustana.edu

Specific correspondence can be sent to individual contributors: D. J. Brasier, dbrasier@cmu.edu; Shawn P. Gallagher, Shawn.Gallagher@millersville.edu; Samantha S. Gizerian, sgizerian@vetmed.wsu.edu; Rupa Gordon, rupagordon@augustana.edu; William Grisham, grisham@lifesci.ucla.edu; Megan Hagenauer, hagenaue@umich.edu; Monica Linden, monica_linden@brown.edu; Barbara Lom, balom@davidson.edu; Richard Olivo, rolivo@smith.edu; Noah J. Sandstrom, nsandstr@williams.edu; Shara Stough, sharastough@augustana.edu; Ilya Vilinsky, vilinsia@ucmail.uc.edu; Michael Wiest, mwiest@wellesley.edu.