CASE STUDY
Using Case Studies to Promote Student Engagement in Primary Literature Data Analysis and Evaluation

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Analyzing and evaluating primary literature data is a common learning objective in undergraduate neuroscience courses. However, students with more clinically focused career goals often dismiss the relevance of evaluating basic neuroscience literature. Here, we describe using case studies to promote student engagement in primary literature in a cellular and molecular neuroscience course. Two example literature-based case studies are provided: Untwisting Pretzel Syndrome, a neurodevelopment case exploring synapse formation in a pretzel syndrome patient, and The Trials of ALS, a neurodegeneration case exploring axon degeneration and repair in an amyotrophic lateral sclerosis patient. These cases were assigned after neurodevelopment and neurodegeneration lectures covering key concepts. Both cases begin by introducing the patient and hypothesizing symptoms and diagnoses, followed by scenes incorporating primary data to illustrate disease pathogenesis and treatments. Students complete questions embedded in these cases as homework, and class time is used to discuss their answers. Discussion emphasizes that there can be multiple "correct" answers, and the best answers are accurate and well-supported. Accordingly, students edit their answers in class, and these annotations are factored into a pass/fail grade on the case. Additional scenes and questions from the same case studies are used on the course’s take-home exams, thereby allowing students to practice primary data analysis and evaluation before a graded assignment. Student evaluations support literature-based case studies as an effective learning tool, with students identifying cases as the most valuable aspect of the course, and reporting increased confidence in understanding cellular and molecular neuroscience.

Key words: case study; primary literature; active learning; neurodevelopment; neurodegeneration; pretzel syndrome; amyotrophic lateral sclerosis

CONTEXT
Core competencies in undergraduate neuroscience curricula prioritize the development of quantitative and critical thinking skills, including reading and analyzing primary literature (Kerchner et al., 2012; Ledbetter, 2012). Indeed, incorporation of primary literature into the classroom is essential for students’ future success as research scientists, evidence-based clinicians, or informed citizens (Alberts, 2009; Greenhalgh, 2014; Hartman et al., 2017). Unfortunately, students focused on clinical health care professions often dismiss the relevance of evaluating basic neuroscience literature. Here, we describe using case studies to promote student learning and engagement with primary literature, building upon substantial evidence supporting cases as effective active learning tools (Handelsman et al., 2004; Herreid et al., 2012; Wiertelak et al., 2016). Previous research has provided a framework for converting a primary article into a case (Prud’homme-Généreux, 2016), and the literature-based case studies described here add to this approach by focusing on data analysis from multiple articles to emphasize quantitative and critical thinking skills.

Case Descriptions
Two interrupted, literature-based case studies are included in this article: Untwisting Pretzel Syndrome, a neurodevelopment case exploring synapse formation in a pretzel syndrome patient, and The Trials of ALS, a neurodegeneration case exploring axon degeneration and repair in an amyotrophic lateral sclerosis patient. Both cases follow a standard biomedical teaching structure, where the case introduces a patient's symptoms and determines the patient’s diagnosis, pathogenesis, and treatment options through primary literature figures. Student materials, answer keys, and teaching notes for these cases are available from the corresponding author or from cases.at.june@gmail.com.

Untwisting Pretzel Syndrome follows pediatric neurologist Dr. Patricia Lopez as she investigates the pathogenesis of pretzel syndrome, also called polyhydramnios, megalencephaly, and symptomatic epilepsy syndrome (PMSE; Puffenberger et al., 2007). PMSE is a neurodevelopmental disorder characterized by a “pretzel-like” posture (loose joints, floppy muscles), developmental delay, and frequent seizures, and is caused by a single loss-of-function mutation in STE20-related kinase adaptor α (STRADα). In the case, Dr. Lopez meets Katelyn, an 18-month-old showing symptoms of PMSE (Harnish, 2010). Students follow Dr. Lopez through the multi-part case study as she learns of Katelyn’s symptoms (Harnish, 2010), describes the diagnosis of PMSE (Orlova et al., 2010), and investigates the role of STRADα in neurodevelopment using data from the primary literature (Shelly et al., 2007; Orlova et al., 2010; Zhang et al., 2016). Although names have been changed in the case, Katelyn’s story describes a real PMSE patient and real pre-clinical investigations of this rare neurodevelopmental disorder.
The Trials of ALS follows Eric and his neurologist, Dr. Samantha Reiter, as they discuss Eric’s diagnosis with amyotrophic lateral sclerosis (ALS), a progressive neurodegenerative disease characterized by muscle weakness and dysfunction due to loss of motor neurons (Bensimon et al., 1994). The case uses multiple parts to discuss Eric’s symptoms (McCain, 2005), diagnosis (Bensimon et al., 1994), and new experimental treatments for ALS using primary literature data (Kagitani-Shimono et al., 2005; Ledeboer, et al., 2007; Son et al., 2011). Eric’s story describes a fictional patient from a previous case study (McCain, 2005), but his disease presentation is consistent with ALS epidemiology (NINDS, 2013).

Course Description
Untwisting Pretzel Syndrome and The Trials of ALS were developed for a one-semester, cellular and molecular neuroscience course for junior and senior neuroscience majors at a small liberal arts college. Enrollment for the course is typically 25-30 students, with greater than 60% of students reporting clinically focused health care career goals. The most common career goals are physician (MD or DO), physician assistant, physical or occupational therapist, and neuropsychologist, consistent with the hypothesis that students believe a neuroscience major will better prepare them for health care careers (Prichard, 2015; Ramos et al., 2016a, 2016b).

Both cases were administered as cumulative activities following a module on neurodevelopment and neurodegeneration covering relevant background material from the course textbook (Kandel et al., 2013). Untwisting Pretzel Syndrome required two 65-minute class periods and The Trials of ALS used one 65-minute class to complete the case and associated discussion. The cases can be edited to contain fewer parts for shorter class periods, or used for other advanced biology, psychology, or neuroscience courses as long as substantial course time is devoted to neurodevelopment and neurodegeneration.

Learning Objectives
Untwisting Pretzel Syndrome: Content Objectives
In this case study, students will apply their knowledge of neurodevelopment to solve biomedically-relevant problems covering:

- Neurogenesis, including radial glial division
- Neuronal migration, specifically within the cortex
- Neuronal polarization, including axon and dendrite differentiation
- Synapse formation, specifically at the neuromuscular junction
- Immunohistochemistry and immunocytochemistry as methods to investigate neurodevelopment

The Trials of ALS: Content Objectives
In this case study, students will apply their knowledge of axon degeneration and repair to solve biomedically-relevant problems covering:

- ALS symptoms and diagnosis
- Established and experimental treatment options for ALS
- Immunohistochemistry and immunocytochemistry as methods to investigate neurodegeneration

Skills Objectives for Both Cases:
Additionally, students will increase their skills in:

- Analysis and evaluation of primary literature
- Science writing
- Teamwork

CLASSROOM MANAGEMENT
Untwisting Pretzel Syndrome and The Trials of ALS both used the following workflow:

1) Classroom lectures cover background material relevant to the case. To gain familiarity with background material, students were expected to complete assigned textbook readings before class (Kandel et al., 2013; the exact chapters and pages are provided in the Teaching Notes of each case). Short, comprehension quizzes on the assigned textbook readings were administered electronically before class to incentivize students to complete the reading. In class, lectures incorporated frequent active learning activities, like group problem solving, to discuss and expand on the textbook’s content, and to improve student understanding (Freeman et al., 2014).

2) An electronic copy of the case is posted on the course website. Untwisting Pretzel Syndrome and The Trials of ALS were both cumulative case studies, posted after three weeks of lectures on neurodevelopment and one week on neurodegeneration, respectively. The cases were given sequentially, with the following schedule: neurodevelopment lectures → Untwisting Pretzel Syndrome → neurodegeneration lectures → The Trials of ALS. Cases were posted approximately one week before their due date, but website analytics suggest that most students downloaded the case 48 hours or less before the due date. These cases were used as part of a paperless class, where all assignments were distributed, collected, and graded electronically, but any method of distribution is appropriate.

3) Students complete short answer questions embedded in the case as homework. Students completed the case’s questions as homework, and their answers were submitted electronically to Turnitin (www.turnitin.com) before class started. Turnitin checks student work for plagiarism and allows incorporation of rubrics for easy grading, but any submission method is appropriate.

4) Students discuss and edit their answers in class. Students were provided 5-10 minutes to discuss their answers for a given part of the case in self-selected groups of 3-4 students. The instructor then asked for volunteers to report their group’s answers, and the instructor recorded these answers on the whiteboard at the front of the class. Class discussion emphasized that there can be multiple “correct” answers, and the best answers are accurate and well-supported by the data. Students were expected to edit their original answers based on class discussion. This provided students with immediate feedback on the instructor’s expectations of “correct” answers, while allowing for student reflection and guided practice on improving their answers. This discussion structure also reinforced
core competencies of independent/self-motivated learning and scientific communication (Kerchner et al., 2012).

5) **Students submit their edited answers for pass/fail grading.** Immediately after class, students re-submitted their edited answers to Turnitin for pass/fail grading. The following rubric was used:
- Are the original and edited answers well-supported by the data?
- Are original answers plus substantial edits included for every question?
- Are original and edited answers turned in immediately after class?

6) **Literature-based case studies are used as take-home exams.** Take-home exams follow the same structure as case studies, where short answer exam questions discuss a patient’s symptoms, diagnosis, pathogenesis, and treatment options through primary literature figures. Exams consist of additional scenes and questions from the same cases discussed in class, and new cases not discussed in class. The goal of these exams was to assess students’ analysis and evaluation skills in applying course content to novel situations. By implementing the workflow outlined here, students practiced these skills before being graded for accurate and well-supported answers on the exams.

**CASE EVALUATION**

**Assessment**

Student learning was primarily assessed with take-home exams composed of new, literature-based case study questions. For example, the exam covering neurodevelopment and neurodegeneration contained three additional figures and short answer questions from Untwisting Pretzel Syndrome, two additional figures and short answer questions from The Trials of ALS, and a new case defining a role for neural progenitor cells after stroke. An example exam question is included in the Teaching Notes of each case.

By design, lectures, cases, and exam questions all covered similar content. For the neurodevelopment and neurodegeneration exam, only 5 of 27 questions covered material discussed in lecture but not in cases. While this content repetition allows students to practice applying their knowledge and analyzing relevant primary data before being graded on a high-stakes exam, it does not allow for assessment of student learning and case study efficacy as previously described (Brielmaier 2016; Lemons, 2017). The majority of questions on the exam are “case-relevant,” leaving few questions as “control” for valid analysis. However, we did compare average exam grades on questions continuing Untwisting Pretzel Syndrome and the Trials of ALS versus the new case on neural progenitors and stroke, and we found no significant difference between student performance on any case (Figure 1). This finding suggests that content knowledge and course skills practiced in the course’s case studies are retained and applied to novel cases. This finding is consistent with previous research suggesting that active learning, including case studies, increases overall student performance on exams (Freeman et al., 2014).

![Figure 1. Student exam performance was similar for all literature-based case study questions. Exam scores were calculated for questions continuing Untwisting Pretzel Syndrome and The Trials of ALS, and for a new case on neural progenitors and stroke. Bar graphs plot the average exam score ± SD (n = 29).](image)

**Student Feedback**

Qualitative and quantitative student evaluations further support literature-based case studies as an effective learning tool. When asked what aspects of the cellular and molecular neuroscience course were most valuable, students often emphasized case studies, as exemplified by the following responses:
- “This class really challenged me and my way of thinking. I have always loved case studies, but in this class they really helped me to apply my learning and grow intellectually more than any other class I’ve done case studies in.”
- “The case studies and relating what we were learning to real life situations was the most beneficial for me.”
- “The case studies were extremely beneficial, especially for those who are going into health-related fields. Incorporating those into the curriculum was a great idea.”

Unexpectedly, a few students’ appreciation for case studies extended into identifying take-home exams as the most valuable aspect of the course. As one student wrote, “I like that we had take-home exams. I felt like it helped me understand the material more, rather than just trying to memorize crunch-time for an exam.”

Quantitative evaluations of the cellular and molecular neuroscience course as a whole also suggest the efficacy of literature-based case studies. Students used a Likert scale before and after the course to assess changes in their confidence in content and skills learning objectives. These evaluations suggest significantly increased student confidence in three content objectives: understanding neurodevelopment, cellular and molecular neuroscience, and diseases and drugs that affect cellular and molecular neuroscience (Figure 2A). Students also significantly increased confidence in skills objectives related to answering application questions and questions focused on health and disease (Figure 2B). Additionally, students reported high levels of overall satisfaction with the course as teaching them what they wanted to know, and challenging them to think critically (Figure 3). Considering students’ emphasis on case studies as the most valuable aspect of the course, these data suggest that cases
positively contributed to achieving course learning objectives and student satisfaction.

Interestingly, students did not increase their confidence in reading and analyzing scientific articles after the course (Figure 2B). This may be due to high self-reported student confidence before the course started, or may suggest that literature-based case studies are not effective for teaching students to analyze primary literature. More investigation is needed to determine the utility of literature-based case studies in primary literature reading and analysis.

**SUMMARY AND FUTURE DIRECTIONS**

Overall, we believe that the two interrupted, literature-based case studies provided here serve to humanize the primary literature, increasing student engagement and interest by relating basic neuroscience data to a patient case (Hartman et al., 2017). Although direct and indirect assessment of Untwisting Pretzel Syndrome and The Trials of ALS are needed to provide more definitive data on their efficacy (Muir, 2015), student exam scores suggest that content and skills practiced through cases are retained and correctly applied to future scenarios (Figure 1). Moreover, student evaluations of the course as a whole suggest that literature-based case studies are effective learning tools for achieving course learning objectives and student satisfaction (Figures 2, 3). At minimum, the structure of these cases is highly recommended for other instructors seeking to improve student engagement with and performance on analyzing and evaluating primary literature. This structure makes the literature relevant and approachable to students, while still challenging them to think critically about course content.

Importantly, both cases have only been used in a small, upper-level course for neuroscience majors at a small liberal arts college. A substantial body of research supports incorporating case studies and primary literature into a wide variety of classes, including small and large introductory courses for science and non-science majors (Gottesman and Hoskins, 2013; Willard and Brasier, 2014; Bodnar et al, 2016; Roesch and Frenzel, 2016; Hartman et al., 2017; Nagel and Nicholas, 2017).

In the future, Untwisting Pretzel Syndrome and The Trials of ALS could be adapted for introductory courses, larger courses, or non-majors courses by incorporating them into the existing models of case study and/or primary literature education. For example, clicker case studies, in which cases are converted into PowerPoint slides with embedded multiple-choice questions, could be an effective use of these cases in a large course (Herreid, 2006).

One particularly promising future direction is incorporation of case studies into the C.R.E.A.T.E. method for primary literature analysis, which has demonstrated efficacy in a variety of courses (Hoskins et al., 2007; Hoskins et al., 2011; Gottesman and Hoskins, 2013; Bodnar et al, 2016). The C.R.E.A.T.E. method takes a highly scaffolded approach to teaching primary literature, using an array of active learning techniques to dissect each part of a research article. Adding case studies into the C.R.E.A.T.E. method could make the primary literature even more relevant and approachable to students.
Students could be introduced to the patient and their symptoms before or concurrent with the Consider step, the first step in the C.R.E.A.T.E. method. Questions focused on applying diagnosis-, pathogenesis- and treatment-relevant data back to the patient could be incorporated into the Analyze and Think of the Next Experiment steps, the last two steps in the C.R.E.A.T.E. method. Indeed, a recently published case study incorporates the C.R.E.A.T.E. method into a larger, interrupted, patient narrative case on Retinitis pigmentosa (Ogilvia and Ribbens, 2016). Overall, these future directions aim to implement literature-based case studies in a wider variety of courses and primary literature teaching methods, extending their reach as effective tools for engaging students in the primary literature.

REFERENCES


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