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AMAZING PAPERS IN NEUROSCIENCE
Primary Literature In Clinical Neuroscience for In-Person Or Remote Instruction

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Structure and function relationships in the nervous system are a major component of neuroscience education. Readings and/or discussion of lesion studies in animal models are often used to demonstrate how brain injury/damage affects specific behaviors or cognitive processes. In contrast, primary literature in clinical neuroscience is less often used to teach brain structure and function relationships and this literature often describes remarkable stories of preserved brain function despite major brain injury/lesion. Here we describe a series of published articles in clinical neuroscience that we used in an undergraduate neuroscience course that challenge the simplistic views of brain localization of function and demonstrate the dynamic and plastic properties of the brain. Discussion of these primary articles can take place in-person or remote via video conferencing platforms.

Key words: clinical neuroscience, primary literature, programs; neuroscience majors; neuroscience graduates

It is now well-established that reading of primary literature has many benefits in undergraduate neuroscience courses as well as in other science, technology, engineering, and mathematics (STEM) courses (Kozeracki et al., 2006; Hoskins et al., 2011; Round et al., 2013; Willard and Brasier, 2014; Harrington et al., 2015; Carter et al., 2017; O'Keefe and McCarthy, 2017). However, a challenge for neuroscience educators who wish to use primary literature in their courses includes selecting the most appropriate articles that align with the course learning objectives. Thus, primary articles in neuroscience are often selected for novel discoveries that advance our understanding of brain function or articles about groundbreaking methods that open new avenues of inquiry.

Undergraduate neuroscience majors learn about brain structure and function relationships throughout their curriculum (Ramos et al., 2011; Pinard-Welyczko et al., 2017; Rochon et al., 2019) including in lecture or laboratory courses such as neuroanatomy. However, by the end of their coursework, students often have a largely superficial understanding of the function of specific brain areas. Examples of such relationships include: hippocampus=memory, amygdala=emotion, basal ganglia=motor function, and hypothalamus=circadian rhythms/homeostasis. In the present report, we describe a collection of amazing clinical neuroscience articles that are valuable in demonstrating brain plasticity and that challenge simplistic notions of brain structure and function relationships.

Summary of Articles

1] Early bilateral and massive compromise of the frontal lobes. (2018) Ibáñez A, Zimerman M, Sedeño L, Lori N, Rapacioli M, Cardona JF, Suarez DMA, Herrera E, García AM, Manes F. Neuroimage Clin 18:543-552.

This is a case study reporting behavioral and cognitive testing in an 8-year-old girl with bilateral agenesis of the frontal lobes. The extensive magnetic resonance (MR) images (sagittal, coronal, and horizontal planes) of the patient showing massive empty space where cortical tissue would otherwise reside will astound students. The detailed descriptions of the extensive behavioral and cognitive tests performed (speech, language, motor, etc.) will captivate readers. Finally, the 10 supplementary videos of the patient engaged in the behavioral and cognitive tasks will humanize and "bring to life" the paper and stir up many different emotions in students including what it might be like to be the parent of the patient or part the medical team evaluating her.

An instructor interested in using this article will recognize many topics for student discussion. For example, students can discuss those neuroanatomical regions which are altered and preserved in this patient and how those changes correlate with the results from behavioral and cognitive testing. Students could discuss the impressive number of tasks used to evaluate the patient which are described in detail in the Supplementary Material and identify how these tasks help to determine specific brain function and cognition. Students might propose other cognitive or behavioral tasks they would have wanted to perform if they were the clinical investigator evaluating this patient. Another interesting topic of discussion is the description of early childhood signs of neurological deficit and developmental delay. Finally, a discussion of this paper in the context of the well-known cases of Phineas Gage (Damasio et al., 1994) or frontal lobotomy patients (Terrier et al., 2019) could be of interest to students as well as the broader comparisons between developmental lesions versus lesions that come from disease (e.g., tumors, infections, etc.) or brain injury.

Instructors should be prepared to advise students how to approach the highly technical parts of the paper that relate to descriptions of how the MR imaging (MRI) was performed. We recommend that instructors tell students to only skim these parts of the paper. Instructors should make it clear to students that they should look up any word or phrase they are unfamiliar with as there are some clinical/medical terms in the paper.

2] Human Olfaction without Apparent Olfactory Bulbs. (2020) Weiss T, Soroka T, Gorodisky L, Shushan S, Snitz K, Weissgross R, Furman-Haran E, Dhollander T, Sobel N. Neuron. 105(1):35-45.e5. doi: 10.1016/j.neuron.2019.10.006.

As part of the data collection for a larger study using MRI and behavioral testing of olfactory function, the authors of this paper report the remarkable discovery of two left-handed females who lack olfactory bulbs but have intact olfaction. Extensive high-resolution MR images found in the paper provides compelling evidence that these individuals indeed lack olfactory bulbs and comparisons are made with normal controls with intact olfactory bulbs (positive controls) as well as another patient with congenital anosmia and no olfactory bulbs (negative control). Detailed description of results from subjective and objective olfaction testing shows how the two females without olfactory bulbs perform better than many control subjects with intact olfactory bulbs. Using functional MRI (fMRI), the authors show near normal activation of central olfactory centers such as the pirifom cortex in the two subjects lacking olfactory bulbs consistent with behavioral tests. Finally, the authors report their herculean search through the Human Connectome Project MRI and behavior database of 1,113 individuals which revealed 3 additional females (1 left-handed) lacking olfactory bulbs but with intact olfaction providing further evidence that, although a rare finding, there exist individuals lacking olfactory bulbs but with normal olfaction.

An instructor interested in using this article will recognize many topics for student discussion. For example, students can review the anatomy of the peripheral and central olfactory centers in the context of the individuals reported in the paper and how they continue to display normal olfaction. Students could discuss the different tasks used to evaluate olfactory function in the subjects and how olfactory stimuli have unique physical properties that make them different than other sensory stimuli (sound, light, etc.). An interesting topic for discussion revolves around the finding that only women were found to lack olfactory bulbs and that a majority of these individuals were left-handed. Finally, the topic of pheromones and the vomeronasal organ in human olfactory communication (Meredith, 2001) could be of interest to students.

Instructors should be prepared to advise students how to approach the highly technical parts of the paper that relate to description of how the MRI was performed. We recommend that instructors tell students to only skim these parts of the paper.

3] Volumetric MRI Analysis of a Case of Severe Ventriculomegaly. (2018) Alders GL, Minuzzi L, Sarin S, Frey BN, Hall GB, Samaan Z. Front Hum Neurosci. 12:495. doi: 10.3389/fnhum.2018.00495.

This is a case study reporting behavioral and cognitive testing in a 60-year-old male with massive dilation of the cerebral ventricles and increasing severity of psychiatric illness. MR images (sagittal, coronal, and horizontal planes) of the patient show massive empty space where the diencephalon and basal ganglia would normally be present as well as remarkable thinning of the neocortical gray and white matter. In addition to imaging, description of neuropsychiatric testing and life history of the patient paint a surprising picture of preserved and impaired brain function that would not be predicted by the dramatic brain changes. In particular, neurological testing which includes cranial nerve function and sensory-motor function are reported to be near normal in this patient.

An instructor interested in using this short case report (which is only 5 pages) will recognize several interesting points for student discussion. Like the other articles described above, students can compare the preserved and affected brain functions observed in this patient. The anatomy of the ventricular system as well as different types of hydrocephaly would be valuable topics of discussion that relate to the anatomical changes found in this patient. Students can discuss the different kinds of psychiatric drugs that the patient had taken throughout his life and describe the mechanism of action of the drugs. Finally, students can compare this article with another case report of ventriculomegaly (Feuillet et al. 2007) with largely preserved cognitive function in a 44-year-old married father of two.

4] Life without a brain: Neuroradiological and behavioral evidence of neuroplasticity necessary to sustain brain function in the face of severe hydrocephalus. (2019) Ferris CF, Cai X, Qiao J, Switzer B, Baun J, Morrison T, Iriah S, Madularu D, Sinkevicius KW, Kulkarni P. Sci Rep. 9(1):16479.

This is a one-of-a-kind case report of a 2-year-old rat (known as R222) with spontaneous and severe hydrocephalus which was serendipitously identified from among a cohort of rats undergoing extensive MR imaging and behavioral testing. Using 7 Tesla MR imaging, the authors demonstrate extensive dilation of the lateral ventricles in R222, causing increased brain volume with neocortical thinning and apparent loss of subcortical structures such as the hippocampus, amygdala, and striatum as well as compression of the thalamus, hypothalamus, and midbrain. The manuscript describes results from behavioral assays probing learning and memory and sensory-motor function and statistical comparisons with age-matched control rats. Despite the severe hydrocephaly, R222 demonstrates normal performance on spatial learning and memory, balance, and motor coordination tasks. In contrast, R222 displays robust anxiety in a novel object task. Consistent with normal performance on several behavioral assays, blood-oxygen level-dependent fMRI in R222 shows brain activation in response to odors or tactile stimulation, indicating sensation of sensory stimuli.

Like the case reports described above in humans, this paper allows for much student discussion in spite of being a case report about a rat. In particular, students can discuss in more detail the different behavioral tasks used in the study such as the Barnes maze, novel object task, balance beam, and rotarod tasks, and explore how these tasks seek to assay specific neural systems. For example, the Barne Maze is known to require intact hippocampal function while the rotarod requires intact cerebellar function. Like the case of hydrocephaly in human patients described above, the anatomy of the ventricular system and the different types of hydrocephaly can be discussed. Finally, students can discuss the principles of fMRI and the hemodynamic signals that are used to identify brain activation.

Vetting of papers by undergraduates at University of California, Irvine (UCI)

We sought to evaluate whether students would find the papers described above interesting and a challenge to their views of brain structure and function relationships. Due to the COVID-19 pandemic, an upper-level biology course which focused on various topics in neuroscience (fear, sleep, consciousness, plasticity, etc.) was offered remotely via Zoom. The course had a total of 90 students, the majority of whom were 3rd or 4th year Human Biology majors with previous completed coursework in lower division biology and neuroscience. The course met 3 times a week; two days were synchronous interactive lecture sessions while the third day was an active learning discussion session. During discussion sessions, students were divided into groups of approximately ten, where they worked in Zoom breakout rooms with their assigned teaching assistants.

Students were given access to the MR images from the papers described above via an online data drive. Students were asked to review the MR images before coming to the discussion session and to hypothesize on the type of preserved and impaired brain function that would be present in each patient based on their understanding of neuroanatomy. Thus, this exercise was designed to engage the brain structure-function relationships that the students had developed during earlier lectures and coursework in neuroscience. During the discussion session, students discussed and justified their hypotheses based on the MR images. After this part of the discussion, which lasted ~15 mins, short case vignettes/summaries of the patients in the above papers were presented to the students and they were asked to match the vignette with the MR images they had previously reviewed. Case vignettes were prepared by the teaching assistants. This part of the exercise challenged and (to an extent) confused students who anticipated greater deficits and disability in the patients. After this portion of the discussion, which lasted ~15 mins, multiple breakout groups came together to discuss their experiences and reactions to the cases for the remainder of the session.

A brief survey of students conducted at the end of the week was used to determine whether the use of these papers were valuable in learning more about brain structure-function relationships. A majority (74.7%) of students indicated that the activity improved their understanding of structural-functional plasticity with 80.2% of students reporting that this exercise identified preconceptions of the brain. A majority (83.7%) of students thought that the activity would be helpful for future undergraduates who will take neuroscience courses. Overall, 98.8% of students enjoyed the activity. Open-ended comments provided by students regarding the papers described above included the following: *"I think the concept of brain plasticity overall changed the way I thought about the brain. When I learned about the brain in other classes, it was mostly based on memorization and seeing what different parts of the brain regions did. Although the information was important, it was harder for me to remember what each part of the brain did without a concrete example. The different scenarios that we saw in the activity really helped me understand the concept of brain plasticity and allowed me to see how brain development can help someone adapt to brain damage."*

VALUE, AUDIENCE, AND IMPLEMENTATION

The clinical neuroscience papers described above were selected primarily because of the dramatic brain changes observed in the patients (and R222) despite relatively normal behavioral and cognitive function. A critical requirement in the selection of these papers was therefore the presence of imaging, figures, and/or videos that clearly demonstrated the anatomical deficits as well as detailed description of tasks/tests used to asses brain function. Thus, the value of these papers lies in the potential for many different topics for further discussion among students, especially since the preserved behavioral findings are unexpected based on the anatomical changes. Educators seeking to use the papers described above should emphasize to students that these papers are not in conflict with the well-known lesion studies in animal models or classic human brain injury literature which have been seminal in shaping our understanding of brain structure-function relationships. Instead, the papers described above serve as important examples of remarkable brain plasticity in the face of dramatic anatomical deficits and remind students (and faculty), that there is still much to learn about the brain and behavior.

We describe our approach to understand the impact of these articles in one remotely-taught course at one institution. Based on that approach, we have first-hand experience that the students enjoyed the clinical subject matter of these papers and were stimulated by the task of trying to determine what deficits each patient might have. This may relate to the fact that many neuroscience majors have career aspirations in medicine (Ramos et al., 2016). We observed that the students enjoyed the small group discussion format and the collaborative, problem-solving approach that using cases stimulated among the students. We also observed that these papers challenge the rigid ideas of brain structure-function relationships that students generally have and that these papers foster a greater appreciation of brain plasticity present among different individuals.

We anticipate that the use of these articles could have broad application in a variety of settings and with diverse student groups. For example, students with varying degrees of previously completed coursework can successfully read, digest, and understand these articles with only a modest amount of consultation of other resources when they encounter unknown terminology, techniques, methods, analyses, etc. Because these articles are clinically-related, strong background in cell and/or molecular neuroscience or neurophysiology may not be needed. In contrast, some background in neuroanatomy would be highly recommended for best use of these papers for instruction. One possible approach could be to include these papers as a module in a neuroanatomy course. Whether used for in-person or in virtual/remote settings, we believe the above papers could be used to achieve diverse content learning objectives such as review of brain structure-function relationships and behavioral assessment of brain function. In addition, use of these papers can increase skills-learning objectives including reading and analysis of primary literature as well as participation in small group discussion sessions.

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