Lesson and experiment guide: The Building Blocks of the Brain

Overview

This unit is structured as a two-lesson extension to curricula on the fundamentals of neuroscience. It also includes a short optional extension for advanced students that explores single-cell RNAseq data. It helps advance students' understanding of neuroanatomy and genetics in the brain with real data and drives students to evaluate types of data, data interpretation, and experimental design.

The content of this lesson develops the link between gene expression, explores the functions and specialization of various brain regions, and compares studies of the brain at the level of genes, neurons, and regions. It also introduces open research questions in the world of neuroscience. Students are guided through a data set that is under active development and are encouraged to consider current and future research.

The datasets used in the virtual experiment portion of this unit come from the Allen Brain Atlas, a group of open datasets encompassing gene expression in the brain, visual behavior, properties of neurons, neural development, and more. This lesson concentrates on some of the resources related to the human brain. Students will learn what kind of data is collected in research settings and begin learning how it can be used.

Grade level

AP/IB/Honors Biology, or introductory level college

Existing student knowledge

Before starting this lesson, students should already have a basic understanding of:
- Neurons as the primary unit of cognitive function in the brain
- Central dogma of molecular biology and the relationship between gene expression and proteins

Students do not already need an understanding of many topics covered in this lesson, including:
- Neuron signaling
- Synapses as the interface between neurons
- Neuron classification methods
- Neuron morphology, or shape
- Electrophysiology of neurons

Learning objectives

- Students can describe key open questions in the field of neuroscience.
- Students learn about central dogma and gene expression as it relates to neuroscience.
- Students interact with data demonstrating how gene expression varies across the human brain and understand how gene expression and the function of a brain region are related.
- Students can name key features of individual neurons that can be used to categorize cells into types and understand why categorizing neurons is a useful research goal.
- After completing the experiment, students are able to design their own experiment that uses the same type of data.

Curriculum outline

1. Assignment (in class or homework)
2. Class discussion
3. Pre-lab (in class or homework)
4. Virtual experiment
5. Lab report (in class or homework)
6. Optional: Transcriptomics addendum (additional download from the lesson web page)

The experimental portion (pre-lab, virtual experiment, and lab report) can be used as a stand-alone unit and is applicable to teaching gene expression in neuroscience and more broadly.

Equipment

Computers, tablets, or other devices for students to work in groups of 2-4

Contents

Teachers are welcome to adapt the lesson to suit their classes and curriculum, but may not share modified lessons. If you develop your own lesson plan using Allen Institute resources, we invite you to share your experience with us at communications@alleninstitute.org.

Standards alignment

Next Generation Science Standards

Science and Engineering Practices	
Asking questions and defining problems	X
Developing and using models	
Planning and carrying out investigations	X
Analyzing and interpreting data	X
Using mathematics and computational thinking	X
Constructing explanations and designing solutions	X
Engaging in argument from evidence	
Obtaining, evaluating, and communicating information	X

Crosscutting Concepts	
Patterns	X
Cause and effect	
Scale, proportion, and quantity	X
Systems and system models	
Energy and matter	
Structure and function	X
Stability and change	X

Disciplinary Core Ideas – Life Science	
HS-LS1: From Molecules to Organisms	X
HS-LS1-1: Construct an explanation based on evidence for how the structure of DNA determines the structure of proteins which carry out the essential functions of life through systems of specialized cells.	X
HS-LS1-2: Develop and use a model to illustrate the hierarchical organization of interacting systems that provide specific functions within multicellular organisms.	X
HS-LS2: Ecosystems	
HS-LS3: Heredity	
HS-LS4: Evolution	

Standards alignment

Advanced Placement Biology

Big Ideas	
The process of evolution drives the diversity and unity of life.	
Biological systems utilize free energy and molecular building blocks to grow, to reproduce, and to maintain dynamic homeostasis.	
Living systems store, retrieve, transmit, and respond to information essential to life processes.	X
Biological systems interact, and these systems and their interactions process complex properties.	

Science Practices	
The student can use representations and models to communicate scientific phenomena and solve scientific problems.	
The student can use mathematics appropriately.	
The student can engage in scientific questioning to extend thinking or to guide investigations within the context of the AP course.	X
The student can plan and implement data collection strategies appropriate to a particular scientific question.	X
The student can perform data analysis and evaluation of evidence.	X
The student can work with scientific explanations and theories.	X
The student is able to connect and relate knowledge across various scales, concepts, and representations in and across domains.	X

Teacher guide

The Allen Institute is a nonprofit biomedical research institute located in Seattle, Washington. Our four divisions – Allen Institute for Brain Science, Allen Institute for Cell Science, Allen Institute for Immunology, and The Paul G Allen Frontiers Group – are dedicated to answering some of the biggest questions in bioscience and accelerating research worldwide. We share all of our data and research findings with the scientific community and general public. Launched in 2003 by founder Paul G. Allen, the Allen Institute is supported by government, foundation, and private funds to enable its projects.

The Allen Institute for Brain Science creates large-scale, open datasets that address fundamental questions about the brain's components and functions. These datasets and other tools form the Allen Brain Map, and are publicly available online at brain-map.org.

Key neuroscience concepts underlying this lesson:

- All human brains have the same general organizational patterns – variation occurs on the level of single cells and their connections.
- The brain can be divided into regions, each of which is associated with a specific function, such as V1 in the occipital lobe (primary visual processing), precentral gyrus (issuing motor commands to the body), or hippocampus (memory processing, navigation).
- The adult human brain includes between 85-100 billion neurons, each of which can form up to hundreds or thousands of connections, called synapses, with other neurons.
- There are more support cells in the brain, such as helper cells called glia, than there are neurons.
- Modern neuroscience requires scientists to integrate information from different levels – from single cells to entire brain regions containing hundreds of millions of neurons. At each level, scientists also have to integrate different types of data, such as electrophysiological records, 3D images, behavioral data, and genetics.

This curriculum uses two datasets from the Allen Brain Map at brain-map.org: the Allen Human Brain Atlas and the Allen Cell Types Database.

Allen Human Brain Atlas

- The Allen Human Brain Atlas is a comprehensive review of gene expression across the healthy adult human brain.
- Over 25,000 genes' expression levels were surveyed across the whole brain with over 62,000 gene probes.
- Gene expression is recorded on the level of brain regions, which can include tens to hundreds of millions of neurons.
- This study was performed with six postmortem whole brains that were donated.

Allen Cell Types Database

- The Allen Cell Types Database investigates various properties of individual neurons that can be used to define neuron types.
- The cells used in this lesson plan are associated with data on the location of the cell in the brain, its shape (also called morphology), and its electrochemical properties (electrophysiology).
- Single cell RNA sequencing data is used in the optional transcriptomics addendum to this lesson.
- All data is on the level of individual cells, and does not include interactions between neurons (which is the subject of related research at the Allen Institute) or region-wide data.
- These cells come from tissue donated by individuals who were undergoing brain surgery to treat glioblastoma or severe epilepsy – the tissue would have been medical waste otherwise, and the patients consented to donate it for research.

Open research questions and applications for resources

These two datasets, along with the rest of the Allen Brain Atlas resources, can be used to address a wide variety of open questions in neuroscience. Allen Institute staff and other scientists around the world conduct research using the data we collect. Some of the broad open questions are addressed in the students' homework reading, Five unsolved mysteries about the brain.

Additional articles about breaking discoveries, the process of research, and more are available here and may be of interest for advanced students to pursue further reading.Core to the mission of the Allen Institute is our open sharing of data worldwide, and thousands of scientists use our resources in their research every day. Notable projects where other research teams have used these datasets have included:

- Data Stories: A Tiny Brain Structure with an Outsized Role in Neurological Disorders showcases several uses of the original Allen Mouse Brain Atlas, the first project of the Allen Institute for Brain Science
- Data Stories: Addiction and the Visual System dives into research to find new ways of treating addictions by understanding the brain's computation

The breadth and depth of the Allen Brain Atlas provide opportunities for advanced students to pursue additional projects, such as independent science fair projects, multi-week class experiments, and computer science-oriented projects. Data Stories: Decoding the Brain features a high school student who used the Allen Brain Observatory for an independent science project. Teachers who use this curriculum or other Allen Brain Atlas resources in their classrooms, or who have students who pursue advanced independent projects, are welcome to share their experiences with us.

Expected time for lessons

This lesson is meant to help teachers integrate Allen Institute datasets into their classrooms. Teachers are welcome to modify the lessons to suit their classes. In particular, the experimental portion (pre-lab, virtual experiment, lab report) can be used separately from the other lessons and assignment.

Assignment #1: Introduction

- If you choose to use it, this assignment was designed to be completed before the second in-class discussion period. It takes approximately 30-45 minutes to complete. See section Copy Masters for worksheets for students and reading.
- Reading: Five unsolved mysteries about the brain and The genes that build our brains
- Worksheet: Students begin to think about the relationship between genes, gene expression, and diseases

Lesson #1: Class discussion on research methods, topics, and unknowns

- 60 minutes
- Video: Sorting Cells with Genes
- Small-group class discussions using worksheet with guiding questions
- Introduction to experiment as a class

Assignment #2: Virtual experiment pre-lab

- 15-30 minutes
- Pre-lab review of experimental design
- Students read experimental design for virtual experiment and scroll through explainer on Allen Cell Types Database
- Pre-lab worksheet questions on the type of data involved in the virtual experiment and how it was collected

Lesson #2: Virtual experiment

- 60-90 minutes
- See next page for detailed outline of experiment

Assignment #3: Complete virtual experiment report

- 30-45 minutes
- Students complete the data analysis and additional questions from virtual experiment

Optional transcriptomics addendum

- Separately downloaded worksheet available on the lesson web page
- 30-45 minutes
- Students explore additional single-cell RNAseq data and answer more analysis questions

Outline of virtual experiment for teachers

Equipment needs:
One computer or tablet per student or group of students. We recommend students work in groups of 2-3.
Whiteboard, form, or other method of collecting data from students

Part 1 (15 minutes):
Students choose three genes and three brain regions from the list of options in their packet, creating a matrix of nine gene-brain region combinations. They look up the proteins and functions associated with each gene in the National Institutes of Health gene database.

We recommend that students start with the selected genes and brain regions because we have confirmed that all data types are available; students with strong interest may choose to continue with other genes or brain regions independently.

Part 2 (30 minutes):
Students access the Allen Human Brain Atlas microarray data. They search for each gene using the search box and explore gene expression across brain regions and individual brains in the database. They record the z scores for gene expression across genes, regions, and individual brains.

Part 3 (15-30 minutes):
Students access the Cell Feature Search page on the Allen Cell Types Database. They search for individual neurons' electrophysiological properties and shapes in the database for the same three regions they examined in Part 2. They record these cell properties and sketch the shape of the cell.

Any remaining time:
Students work on analysis questions in packet.

Optional transcriptomics addendum (30-45 minutes):
Students explore transcriptomics data and complete additional analysis questions.

Worksheets - copy masters

The following pages include masters of materials to be copied for students.

1. Assignment #1 worksheet for students
2. Discussion questions for lesson period #1
3. Pre-lab, including questions on experimental design and data used
4. Virtual experiment packet, data collection instructions for students and worksheet (in class experiment periods), data analysis and additional questions (assignment #3)

Note that if you plan to use the optional transcriptomics addendum to this lesson, it is available as a separate download from the lesson web page.

The Building Blocks of the Brain: Introduction

Introduction and goals:
In this assignment, you will study gene expression in the human brain. All of your DNA is present in all of your cells (except reproductive cells and red blood cells), but only some genes are active in each cell. When a gene is active, the cell transcribes the gene as mRNA (gene transcription) and produces the protein associated with the gene from the mRNA (gene translation). The overall process is called gene expression.

Studying what genes are active in different regions of the brain, as well as in single brain cells from specific brain regions, can tell us about the relationship between your genes and your brain function. In this experiment, you will start by studying gene expression across parts of the human brain.

Reading:

Five Unsolved Mysteries About the Brain

Questions:

What surprised you in the article? What do scientists know more about in the brain than you expected? What do scientists know less about?

What is a research question related to these unsolved mysteries that you are interested in the answer to? When you write your research question, make sure that it asks something that it is something you can measure in a lab.

A neuron can be categorized by a combination of its location in the brain, connections, shape, electrical properties, and gene expression. Explain one way you might group neurons into types using these properties, and why you would want to identify groups of neurons.

Reading:

The genes that build our brains - and may drive neuropsychiatric diseases

What did you find surprising or interesting in the article?

Imagine you have just conducted an experiment on the link between neuron types and neuropsychiatric disorders, as described in the story. How would you interpret data that shows such a link? Can you think of implications the finding in the article has for developing treatments for neuropsychiatric disorders?

The Building Blocks of the Brain: Class Discussion Questions

Learning goals:
Understand how the gene expression of neurons is related to their function in health and disease.
Design a real neuroscience experiment.

In small groups, answer these discussion questions. Think about the homework reading and the video to help you with your answers.

Knowledge check:

What does "gene expression" mean? In 10 words or less, what happens when a gene is expressed?

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Knowledge check:

Draw a neuron and label five main features. For each feature of the neuron, list one way that it might vary between neurons. If you need hints, look at your classroom posters or search online.

Design your own experiment:
Outline an experiment studying gene expression in a neuropsychiatric disease. Describe the rationale and focus of your experiment. You may need to research some background information online about the disease you chose to complete your answer. Include your citations at the bottom of the page. (Hint: Think back to the article you read for homework.)

Example:
Disease: Epilepsy
Neuron function affected by disease: Excitability, membrane potential
Brain region affected by disease: Any, frequently temporal lobe or hippocampus
Research question: How is the expression of genes that code for calcium ion channels different in the temporal lobe in people with epilepsy relative to people without epilepsy?
Data you would collect: Relative gene expression levels in temporal lobe in people with epilepsy, and in a control group. In this case, the control group includes tumor patients without epilepsy. This experiment would use the Allen Cell Types Database. This database does not include epileptic or tumor tissue - the data come from tissue removed so the surgeons could access the target tissue.
Prediction: Expression of genes for some ion channels, which are related to excitability, will be higher in the temporal lobe relative to other regions in epilepsy patients than in control patients.

Disease: ____

Neuron function: ____

Brain region: ____

Research question:____

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Data you would collect: ____

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Prediction: ____

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Citations:

The Building Blocks of the Brain: Virtual Experiment Pre-Lab

Learning goals

The goal of this experiment is to study gene expression in regions of the human brain and in individual neurons. By the end of this experiment, you should understand the ways gene expression varies across the brain, some of the basic properties of neurons, and why it is important to study the brain at different scales from single cells to whole regions. Read more about one of the most important ways of categorizing cells, by their gene expression, here.

For Part 1 of the experiment, you will choose brain regions and genes to study. In Part 2, you will find the gene expression in whole brain regions. In Part 3, you will look at some other properties of single neurons. This includes the cell's electrophysiology, which is its electrochemical properties related to its firing, and its morphology, the cell's shape.

Part 1: set up experiment
- Choose three genes from list
- Choose three brain regions from list
- Use online database to look up the function of your genes

Part 2: Gene expression by brain region
- Find the relative gene expression of your genes in your brain regions of interest
- Interpret the data on relative gene expression

Part 3: Properties of single cells
- Examine the electrophysiological properties of single neurons
- Examine the morphology of single neurons
- Calculate some statistics on neurons' electrophysiological properties

Knowledge check:

How do you interpret a Z score? (Hint: research the formula for a Z score, or think about what you might know about distributions.)

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Questions:

The gene expression data in this experiment is in the form of a Z score for each gene in each brain region. The Z scores represent the relative expression of that gene in that region, compared to the expression of that gene in all the other regions. Z scores range from -3 to 3 and are not normally distributed.

Imagine you have found that the gene expression of a gene is -0.254 in Region A and 2.831 in Region B. Explain how you interpret these scores, in the context of both the meaning of gene expression and Z scores.

What is a step in the experimental protocol that you expect to find challenging? How will you work through the challenge?

The Building Blocks of the Brain: Virtual Experiment

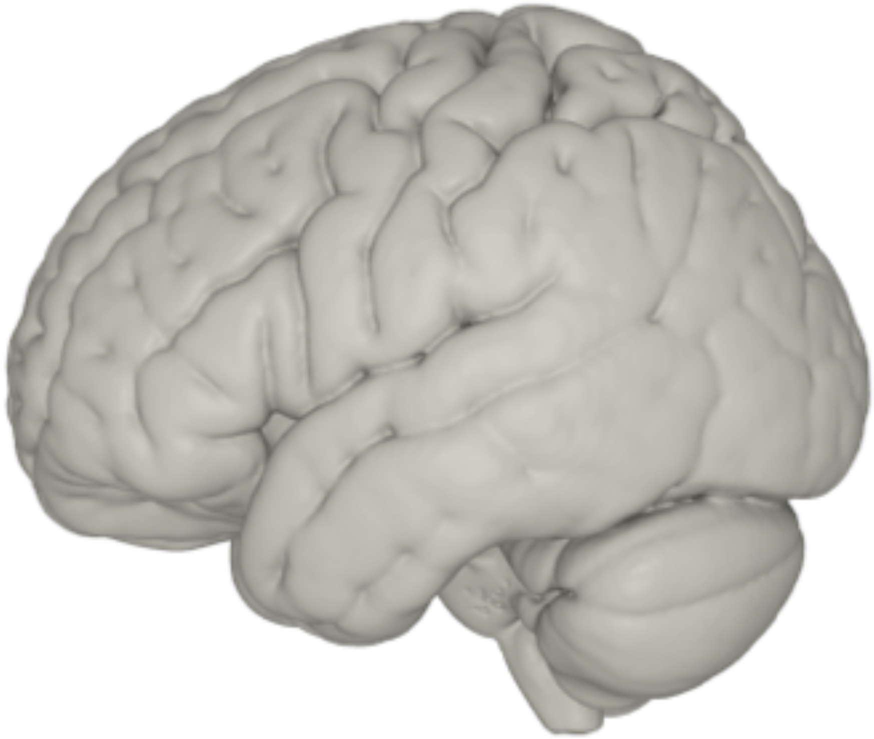
Links for experiment:
Main page: brain-map.org
Allen Human Brain Atlas: human.brain-map.org
Allen Cell Types Database: celltypes.brain-map.org

Part 1: set up experiment

In this experiment, we will be investigating the relationship between gene expression and brain regions, and also looking at some individual neurons and their properties from different regions.

1. Choose three brain regions from this list to investigate in your experiment:
    - Middle frontal gyrus
    - Inferior frontal gyrus (divided into two sections in Allen Human Brain Atlas: use orbital part; listed as one area in Allen Cell Types Database)
    - Middle temporal gyrus
    - Inferior temporal gyrus
    - Angular gyrus

2. Mark your brain regions on this image. (Hint: visit celltypes.brain-map.org and scroll down.)



Want to see more detail? Visit atlas.brain-map.org, click on "Human Gyral Atlas," and type the brain region into the search box. It will be highlighted in purple.

3. Choose three genes from this list to investigate in your experiment.
   - Gene GAD1, probe A_23_P209578
   - Gene DRD1, probe A_23_P388061
   - Gene NPY1R, probe A_23_P69699
   - Gene GRIN2A, probe A_23_P100278
   - Gene SCN1A, probe A_23_P28224

Just make note of the probe name for now - you'll use it later.

4. Look up the function of your genes in the NIH gene list. Click on the blue tags to see function. Remember to look at results for the human genome!

Gene	Function

Knowledge check:

In this experiment you are studying gene expression, which is the mechanism of the central dogma of molecular biology. Summarize the central dogma.

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Part 2: Gene expression by brain region

1. Access the Allen Human Brain Atlas microarray data: human.brain-map.org.
2. Enter your first gene into the search box. The data is organized by gene, probe (the chemical the scientists used to measure the gene expression), and brain donor.
3. Find the gene/probe combination you picked – there may be several probes for the gene, so make sure you have the right probe.
4. When you click on the gene name, an info box will pop up above the heat map. Click on either the gene symbol or gene name to go to the detailed data page.
5. The gene expression data comes from six donated human brains. For at least three of the six brains, find the three brain regions you chose (hint: go back to your brain diagram to remind you where that brain region is).
6. Each region will have a Z score for that gene's expression. **Record the Z scores for at least three brains, to two decimal places.** Fill in the Z scores for your genes in each brain region in the charts.
7. Repeat the search for your three genes. To return to the search screen, click on the word Microarray in the site header.

Gene #1: ______________________________

Brain ID (choose at least 3)	Your brain region 1: ______________________	Your brain region 2: ______________________	Your brain region 3: ______________________
Donor H0351.2001			
Donor H0351.2002			
Donor H0351.1009			
Donor H0351.1012			
Donor H0351.1015			
Donor H0351.1016			

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Gene #2: ___________________________

Brain ID (choose at least 3)	Your brain region 1: ____________________	Your brain region 2: ____________________	Your brain region 3: ____________________
Donor H0351.2001			
Donor H0351.2002			
Donor H0351.1009			
Donor H0351.1012			
Donor H0351.1015			
Donor H0351.1016			

Gene #3: ___________________________

Brain ID (choose at least 3)	Your brain region 1: ____________________	Your brain region 2: ____________________	Your brain region 3: ____________________
Donor H0351.2001			
Donor H0351.2002			
Donor H0351.1009			
Donor H0351.1012			
Donor H0351.1015			
Donor H0351.1016			

Part 3: Properties of single cells

Access the Allen Cell Types Database: celltypes.brain-map.org. Click on Cell Feature Search. In the search panel, select:

- Human
- Your first brain region
- Reconstruction type: Full

Cells that are from your brain region will show up below. Click on Electrophysiology or Morphology to see more data from that cell.

We are researching the cell's shape, its firing rate, and its resting potential. These basic properties tell us about the cell's function and role.

- The cell's shape tells us how it physically reaches out to its neighbors. It is related to its function and connectivity. There are many different shapes of neurons. Neurons are sometimes categorized by shape, but shape doesn't tell the whole story of the cell.
- The cell's firing rate represents how many times it fires in one second. The firing rate is related to many properties of the cell, such as how excitable it is. All of your thoughts and experiences are encoded by many neurons firing at different rates and patterns. Its units are in hertz (Hz), or times the cell fires per second. More details of firing patterns are shown in the plot associated with each cell.
- The cell's resting potential is the value of its membrane potential, or electrical energy, at baseline without any firing happening. The membrane potential is set by the concentration of charged ions inside and outside of the cell. If the membrane potential depolarizes enough, the cell will fire. This is called an action potential. Its units are in millivolts (mV), 1/1000 of a volt.

Record data from at least 3 cells in each region, depending how much time you have and how many cells there are from that area. Some data points may not be available for every cell. Just record the data that is available. The cells in this data set are from live brain tissue that was donated by neurosurgery patients.

For the firing rate, record the average value reported in the info box at the top of the page. The membrane potential is also reported in this box. For the morphology of the cell, you can use either the top view or reconstruction view to help you sketch – whichever is easier for you.

Calculate the mean and (optional) standard deviation for each measure after you have collected all the data. We usually need more data points to calculate a standard deviation, but it's good practice to learn how to calculate it.

Record at least 3 cells per brain region.

Brain region 1: ________________________________

Cell ID number	Firing rate	Resting potential	Sketch of cell
Mean			
Standard deviation (optional)			

Optional: record additional cells below.

Record at least 3 cells per brain region.

Brain region 2: ___________________________________

Cell ID number	Firing rate	Resting potential	Sketch of cell
Mean			
Standard deviation (optional)			

Optional: record additional cells below.

Record at least 3 cells per brain region.

Brain region 3: ________________________________

Cell ID number	Firing rate	Resting potential	Sketch of cell
Mean			
Standard deviation (optional)			

Optional: record additional cells below.

The Building Blocks of the Brain: Virtual Experiment Report and Analysis

Learning goals:

Analyze neuroscience data with methods used by scientists. Explain why scientists are interested in gene expression and systems for categorizing neurons. Apply your knowledge to design experiments and interpret data.

Questions on Part 1 of experiment:

You looked up the functions of your genes. When you are interpreting the expression pattern of a gene, how does knowing its function influence your interpretation?

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Questions on Part 2 of experiment:

For each of your three genes, describe how the expression varies across the three brain regions. Think about each gene individually for now.

Pattern for gene 1: ____

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Pattern for gene 2: ____

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Pattern for gene 3: ____

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What does the expression level of the genes tell you about each brain region? Think about the relationship between genes' expression and their function.

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Pick one of your three brain regions. Describe how the expression of your three genes is different in that brain region. Remember that the Z scores compare gene expression of one gene across brain structures, so you should give your answer in relative terms and not compare values across genes (e.g. Gene 1's expression is far below its average, Gene 2's expression is around its average, etc.).

Brain region: ____

Gene expression pattern for your three genes:

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The six brains used in this data set do not have identical gene expression patterns. List two reasons why gene expression might vary between individuals other than genetic disorders.

1. ____

2. ____

Questions on Part 3 of the experiment:

Explain why it is useful to study both an entire brain region and individual cells from that region.

You calculated some statistics on firing rate and resting potential. The firing rate of the cells varied a lot, but the resting potential did not vary much. Think back to the definitions and roles of the firing rate and resting potential. Think of a hypothesis for why the firing rate varies a lot, but the resting potential is fairly consistent.

In this experiment, we were studying healthy neurons (even in part 2, where the healthy neurons came from diseased brains, the cells included were all healthy - they were adjacent to the disease site and had to be removed to access the tumor or epileptic focus). How can we use what we learned about healthy neurons to better understand diseased neurons?

Design your own experiment:
Think back to the article "The genes that build our brains" that you read for homework. Design an experiment using one or more types of data from this experiment to study a disease of the nervous system. You may need to do some additional research about the disease or disorder you choose to complete the questions. When you write your research question, make sure it is something you can measure in a lab.

Disease or disorder: ______________________________

Brain region or cell type affected: ______________________________

Research question:______________________________

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Data you would collect: ______________________________

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How you would analyze or examine data: ______________________________

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Predicted results: ______________________________

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Citations:

The Building Blocks of the Brain: Above and beyond

Complete these questions for an added challenge.

Imagine you are a researcher studying the link between a gene and a disease. You have collected data on gene expression only from individuals who have the disease, but not any healthy individuals. Describe how you would use the data from from the Allen Human Brain Atlas or Allen Cell Types Database as part of your experiment. What comparisons would you perform?

In Part 3 of the experiment, you looked at data on individual cells from the same areas that you looked at as whole regions in Part 2. Compare what you observed about each region by looking at the gene expression in Part 2 to what you see in individual cells in Part 3. How do the data types complement each other? What additional data would you find useful in your comparison?

Using a labeled dataset to make rules for classifications is one way that computers learn to sort things automatically. We sorted these cells by what brain region they came from. Using the data you collected or other data in the database, name some other ways of sorting neurons. Recommend one way of sorting – why would you be interested in sorting cells using that feature?

Why do we want to sort neurons into categories?