Sally's Phantom: A Case Study on Plasticity of Cortical Representation

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Abstract

The brain organizes somatosensory experience based on the body location from which it originated and the pathway by which in arrived. Here, I present a classroom discussion-based activity centered around the concept of a phantom limb to allow students to explore how cortical representation of sensory experience can be altered. The goal of the activity is to allow students to explore concepts surrounding plasticity of cortical representation. The mouse barrel cortex, a common model system for studying these effects, will be presented to explore potential mechanisms of the change. Finally, the students will hypothesis how the mirror box therapy can be used to ameliorate phantom limb pain without the use of pharmacological treatment. The activity is designed for second- or third-year biology or physiology majors and can be conducted in a single class period. Students can work in small groups answering questions before discussing their answers as a class. There are many opportunities to expand the discussion described. https://doi.org/10.21692/haps.2023.022

Key words: phantom limb, plasticity, mirror box, sensory maps, barrel cortex, neuroscience

Introduction

A classic dogma in the field of neuroscience stated that the adult brain was static, meaning that new connections between neurons could not be formed. Studies in animal models as well as with human subjects have proven that this once central tenet of the field is inaccurate. It is now widely accepted that the brain changes itself based on experience. This is most evident in the sensory domain, but these concepts are broadly true of all synaptic connections. In almost every brain area explored, including motor, learning, and even language processing regions, neurons have been identified that reorganize based on activity, or lack of activity (reviewed in Fu & Zuo, 2011).

This new understanding, however, is rarely presented to introductory students, despite its value to a potential future career in healthcare and biomedical research. This article presents an activity to guide students through a classroom discussion of a case study exploring the concept of brain plasticity. Case studies are an effective approach to science education, in general, and specifically useful in engaging students in exploring physiological and medical concepts (Ghosh 2007; Herreid, 1994; Kay & Pasarica, 2019). Additionally, case studies encourage group work and can be effectively used in both large lecture style courses and online or hybrid courses (Herreid & Schiller, 2013; Kibble et al., 2016).

The case presented here allows students to discuss two examples of plasticity in the sensory domain and a behavioral intervention that is based on the brain's capacity for change. Students will explicitly link changes in neuron structure with alterations in human perception. The questions in the activity allow the instructor to direct the conversation based on the interests of the class. The use of case studies to support learning of physiological topics is both perceived as helpful by students (Cliff, 2006; Nasre-Nasser et al., 2022) and has been shown to improve exam scores (Pekary et al., 2021).

Neurons of the anterior gyrus of the parietal lobe, the somatosensory cortex, process touch, pain, and temperature information from the skin. A so-called somatotopic map exists in which neurons are activated in response to stimuli from specific body parts. For example, one population of neurons in the anterior gyrus becomes active when touching the thumb. But the same perception of being touched on the thumb would occur by directly activating the same population of neurons (without touching the skin). The representation of neurons in the anterior gyrus is related to body anatomy: areas of the body close to each other are represented by populations of neurons near each other. Stimulation of a nearby population of neurons would lead to perception of touch on the index finger, and next to those the middle finger, etc. Interestingly, the size of this region (typically the number of neurons representing a body part or region of skin) relates not to the size of the body part but rather to the sensitivity of that region. For example, more neurons represent the tips of our fingers than the tips of

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our toes. This is not fixed, however. The examples provided for class discussion provide evidence of changes in these representations.

In the 1970s H. Van der Loos and T. Woolsey described a region of the rodent somatosensory cortex specialized, both anatomically and functionally, for processing touch of the whiskers (Woolsey & Van der Loos, 1970; Van der Loos & Woolsey, 1973). They found that each whisker on the face corresponded to a specific area of the cortex. The region was named the 'barrel cortex' due to the representation of each whisker being a column that extends down into the brain, like a long, thin barrel. Van der Loos and Woolsey showed that during development the maps could be altered based on changes in sensory input from the whisker. Removing a whisker reduced the number of neurons that represented that whisker and caused the neighboring regions to enlarge and extend into that area of the cortex. It was later found that simultaneous stimulation of two neighboring whiskers causes fusion of their cortical representations (Welker et al., 1989).

Similar to what was observed in the rodent barrel cortex, changes in sensory inputs can lead to changes in cortical representation in the human somatosensory cortex (May, 2011). A dramatic example of this occurs with phantom limb. A phantom limb is the perceived sensation that an amputated limb remains present (Flor, 2002). Often, pain is perceived as coming from the phantom limb. A standard example of phantom limb pain is described as a missing hand that is clenched without any ability to relax the phantom fist. Phantom limbs may occur following surgical amputation or traumatic injury (Flor, 2002).

It was once thought that phantom limbs were purely psychological, but a neurological basis is now widely accepted. The leading hypothesis predicts that a phantom limb results from two interacting processes. First, the sensory neurons representing the now-missing limb reduce their activity due to decreased stimulation (since the limb is gone). This causes a coincident decrease in activity of cortical neurons which previously represented the limb. Then, through an unknown mechanism, nearby neurons representing intact body parts activate the cortical area which previously corresponded to the missing limb. In this way, phantom limbs are a disease of plasticity.

Phantom upper limb pain is often experienced as a clenched fist (Ramachandran & Rogers-Ramachandran, 1996). No specific tests exist to diagnosis phantom limb pain – determination is largely reliant on the exclusion of other disorders (Cleveland Clinic, 2021). Medications aimed at treating generic pain may be effective in some cases.

The classroom activity presented here culminates by discussing an effective drug-free treatment, the so-called mirror-box therapy. A visual-illusion is used to create the perception that the phantom limb returned and is under control of the subject. This is accomplished by placing both arms in a box with a vertical mirror dividing it. The subject experiences the sensation that their phantom fist is relaxing by viewing the reflection of their intact fist opening in the mirror. Despite the subject being aware that an illusion is occurring, an immediate relief of the phantom pain is experienced. With a single 15-minute session, the sensation may last a few minutes once the arms are outside the box. However, with prolonged training the patient may experience permanent pain relief (Ramachandran & Rogers-Ramachandran, 1996).

Here I present an activity designed to introduce concepts surrounding plasticity of cortical representation, including during development and in pathology, for students in an undergraduate anatomy and physiology course. Student learning objectives, classroom strategies, and opportunities to delve deeper into the topics will be described.

Methods

I have used this exercise in a 200-level anatomy and physiology course, a 300-level physiology course, and a 300-level neuroscience course. It is typically facilitated in the final class meeting of the unit on brain anatomy and function and serves as an opportunity to delve deeper into the concepts we have been discussing. I dedicate an entire 50-to-60-minute class period to this activity and do not require the students to read anything beyond the assigned textbook chapters for the class. The learning objectives associated with this activity are the following:

1. *Define phantom limb.*
2. *Describe the relationship between the areas of the somatosensory cortex and body parts those areas are representing.*
3. *Predict how sensory changes may alter sensory maps.*
4. *Discuss one treatment of phantom limb pain.*

Please refer to the Appendix to review the case. The class starts by reading the scenario together before breaking into groups of 2-4 to discuss the questions. The questions on the handout following the case are organized so that all sub-questions having the same number should be answered during a single breakout period. For example, students can work in a group for 5-7 min to answer questions 1a, 1b, and 1c. At this point, the instructor should encourage students to read and make an attempt to answer all of the questions before finishing the small group discussion. Students may ask questions of the instructor, but should work together to find answers. It is helpful to remind the students that each component will be discussed as a class and they should make a best effort before seeking assistance outside the group.

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After students complete the discussion of the first batch of questions, they should return to their groups to discuss the next set of questions. For example, after finishing the class discussion of all of question 1, the students should discuss question 2 in small groups before examining it as an entire class. It is important for the instructor to remain active walking around the classroom to maintain engagement of the students.

Each set of questions is designed to move the students towards an understanding that the somatosensory system changes with experience. Question 1 focuses students on the concept of a somatotopic map – that body parts nearby on the body tend to be represented by neurons in proximity to each other. But also, that the amount of representation (number of neurons) representing a body part is related to the sensitivity of that body part, not its overall size.

Question 2 introduces the rodent barrel cortex. The instructor should emphasize that whisker sensory information is especially important to a rodent and that rodents over-represent this information in their brain. It should be explained that each whisker has a distinct group of neurons encoding it. Whiskers are named by the row and column it falls on the face of the animal; a matching column can be found in the barrel cortex. This exercise examines the whiskers in 'row D' and their associated neurons in the barrel cortex.

Question 3 asks students to describe how the barrel cortex changes when sensory input is altered. Students should notice that barrel D2 has disappeared. But rather than leaving a hole in the barrel cortex representing D2 (or those neurons ceasing their activity altogether), students should also see that the representation of whiskers D1 and D3 have enlarged to include the neurons which formerly represented whisker D2.

It is worth noting that the neurons in the barrel are changing *function* more than *structure*. While some synaptic growth and refinement is occurring, the changes seen are due to the neurons in the barrel cortex that once responded when D2 was stimulated are now responding to stimulation of whisker D1 (or D3), which they previously ignored. The instructor should point out that neurons want stimulation. When the barrel that represented whisker D2 stops receiving input (because whisker D2 is removed), the neurons in that barrel 'seek out' activation elsewhere. However, when whisker D2 and D3 are bound the barrels fuse because the inputs are synchronized. Experience, either stopping stimulation or synchronizing it, will alter the representation in the cortex.

Question 4 requires students to make deductions about the information they learned. First, they should put in their own words the concepts demonstrated by the fact that changing the whiskers changed their representation in the cortex. Then the students will take this knowledge of barrel cortex experience-dependent plasticity to hypothesize the mechanism of phantom limb pain that Sally, the protagonist of the case, is experiencing.

Often, there is a spectrum of understanding at this point. Some students follow the logic and immediately can draw the appropriate conclusions while others need a little assistance. The instructor should gauge the comfort with the concepts for each group by walking around the room. This can allow the instructor to choose the groups best prepared to answer. Typically, a group can provide a reasonable answer that requires minimal supplement by the instructor or another student. After asking the class for additional input, the instructor should provide a more detailed explanation (possibly by reading from the answer key, please see Appendix). The second part of question 4 asks the students to link the data from the animal model to the clinical manifestation of phantom limb. The instructor should similarly prompt students to provide as much detail as possible before explaining (or reading from the answer key).

Question 5 – the final question in the activity – provides an opportunity for the students to think creatively in applying their knowledge of plasticity towards an explanation of a treatment for phantom limb pain. Students are introduced to a chemical-free, non-invasive, and highly effective procedure to reduce phantom limb pain. The mirror-box induces a visual illusion that the patient's clenched phantom fist opens, which leads to the immediate sensation that the patient's phantom fist has relaxed. The instructor should first directly address the question of developing a hypothesis to the potential mechanism. Students generally make the link that there is a latent signal from the missing limb miscommunicating to the brain that the patient's fist is clenched. They recognize that the seeing the illusion of a fist in the mirror open as if it is the phantom fist must be sending a stronger visual signal that is overpowering the latent 'clenching' signal. It is not necessary for the instructor to describe how this occurs on a cellular or molecular level. However, the speed of the response does suggest that whatever neural circuitry is mediating this behavior is already present; new neural connections do not have time to grow and become functional in the time it takes for the mirror-box illusion to relieve the phantom pain.

The instructor can then lead the class down a variety of avenues depending on the interests of the class and comfort of the instructor. For example, a discussion of how phantom limbs are a disease of plasticity can occur. This is an example of plasticity gone awry. While plasticity is often, and rightfully so, thought of as a positive attribute, in this case it is the mechanism of a disorder. The mirror-box treatment fights plasticity with plasticity. The instructor can also emphasize that the mirror-box treatment is effective immediately, and with repetition can have long lasting effects. The class can discuss how this provides a biological mechanism of the idiom 'Practice makes perfect'. Alternatively, students can reflect upon how the most effective treatment for debilitating chronic phantom pain does not involve surgery or drugs.

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Discussion

The discussion of brain plasticity, phantom limbs, and the mirror-box treatment is engaging to students. While no assessment data were collected, the questions the students work through are designed to specifically discuss these points. Upon completion of the provided questions and engagement in the classroom discussion, students typically can provide a concept of phantom limb and can connect it with plasticity occurring in the brain. Moreover, generation of a hypothesis to describe the mechanism of the mirror box treatment allows students to develop their understanding of the relationship between sensory experience and representation in the brain.

In my experience, students who come with previous knowledge are excited to share and those learning for the first time become enthralled in the concept of a hallucination of body image. Through a classroom discussion of these topics one can explore brain plasticity and more generally experimental design, originality in science, or other tangential topics. By remaining flexible, instructors can allow their classes' specific interests to inform the direction of conversation. You may wish to follow up with a discussion (or assignment) exploring a primary literature article on one of the topics. Below are ideas for further exploration and noteworthy papers that can be used to supplement a discussion in an area.

Sensory maps were most famously explored by the Nobel prize winning scientists Hubel and Wiesel. They showed that neurons in particular areas of the brain encode precise types of visual information and that visual experience during particular developmental times (so-called 'critical periods') affected visual processing as adults. The Journal of Neurophysiology has a wonderful essay on six of Hubel and Wiesel's works exploring this topic (Constantine-Paton, 2008).

Many of these papers and concepts, however, can be overwhelming to undergraduate students. I prefer to explore sensory maps via a series of studies utilizing an interesting alterative model organism, the owl. Knudsen and Konishi (1978) recorded from individual neurons in auditory areas of the owl brain while playing sounds from a movable speaker at different locations in a room. They, like Hubel and Wiesel, found a map-like organization of neurons. Neurons responded to sounds relative to the location in the surrounding environment from which each sound emanated. Knudsen also wrote a very approachable essay in Scientific American (1981) in which he summarized his lab's work describing how the relative volume of a sound in each ear and the timing disparity between the sound reaching the ears is used by the owl to determine the location from which the sound emanated. This article can be used to facilitate a discussion on how sensory stimuli are coded in the brain.

Woolsey and Van der Loos first described the one-to-one relationship between the mouse barrel cortex and whisker stimulation in 1970. However, the paper they published is 38 pages and not appropriate for use in-full for an undergraduate class. Consider choosing excerpts or focus on how the style of scientific writing has evolved. If students want to delve into the concepts explored by removing a whisker, the follow-up article (Van der Loos & Woolsey, 1973) is more approachable. Students can examine the photomicrographs of the barrels with and without whiskers to describe the changes. To achieve a broader discussion of the use of the barrel cortex in studying various topics in neuroscience, including topographic development and brain plasticity, consider a historical perspective published in the Journal of Neuroscience on the discoveries found in this model system (Erzurumlu & Gaspar, 2020).

Of the extensions offered here, I most enjoy discussing the original article describing the mirror-box treatment (Ramachandran & Rogers-Ramachandran, 1996). It is unique in so many ways. There are no statistics, no single variable, and no controls. Rather than a typical terse overview of the results of the study, the authors describe the personalized treatment and progress of each of the ten patients in an approachable tone. It is the first-time visual input was shown to overpower a phantom experience. The mirror-box is as simple and low-cost a treatment as can be imagined and, yet, is more effective than any developed and optimized chemical pain killer. Students should appreciate that advances in science do not always require cutting edge technology, but rather thinking about and understanding a problem to determine the most straight-forward solution.

An astute student might point out that the mirror-box treatment is not a panacea. There are very real limitations on the ability to generalize this treatment to other phantom body parts or other diseases of plasticity. The orientation of the eyes, the existing limb, and the mirror must precisely align with the location of the phantom. But other situations, such as double amputations or phantom pain that cannot be pinpointed to a body part, will be impossible to treat using a mirror-box approach. In these cases, the class can imagine how other treatments capitalizing on plasticity could be used to treat other forms of phantom limb pain.

A wonderful way to engage kinesthetic learners is for the instructor to ask the class to fully clench their fist for one minute. While the students do this, the instructor can explain the impact of chronic pain and the benefits of treatment without drugs or surgery. After the minute, the students can relax their fists while the instructor prompts them to imagine the relief the patients must experience as their phantom fist unclenches for the first time in, perhaps, years. This can be a very powerful moment.

In summary, the activity described here can be implemented in numerous ways depending on the instructor's comfort level with the material and classroom practice. It can be adapted for students at different levels with varied expectations in terms of the depth and breadth of solutions in different classes. After all, everyone's brain will be changed a little after participating in the class.

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Acknowledgements

I would like to thank Alex Hernandez for assistance in drawing the rat head and brain used as part of Figure 2.

About the Author

Scott Dobrin is an Assistant Professor of Biology at Eckerd College, where he teaches cell biology, human physiology, neuroscience, and other courses in the discipline of biology. Dr. Dobrin's research focuses on experience-dependent plasticity using a honeybee model. Research in the lab links molecular and structural changes in the brain with changes in behavior. Using insect models that display complex social behaviors, the lab studies the impact of environmental stressors on learning and memory.

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Appendix 1: Case Study of Sally's Phantom

(Answers indicated in italics and blue font.)

Learning Objectives

1. Define phantom limb.
2. Describe the relationship between the areas of the somatosensory cortex and body parts those areas are representing.
3. Predict how sensory changes may alter sensory maps.
4. Discuss one treatment of phantom limb pain.

Sally Moore was cutting down trees to chop for firewood on a breezy fall afternoon that would soon change the rest of her life. After topping a few trees, she dragged them across the field to the waiting woodchipper. Sally, noticing she was late for work, rushed to finish.

In Sally's haste she forgot to check her gloves before operating the chipper. She turned it on and rushed to rapidly push the limbs into the woodchipper. On the final branch, her glove became entangled in the trimmings and Sally's left arm was pulled into the blades of the chipper.

Sally was prepared enough to push the emergency stop on the woodchipper with her free hand. Unfortunately, her trapped hand and lower arm were completely eviscerated. She quickly wrapped her injury tightly and drove herself to the nearest hospital.

The surgeons stopped the bleeding, but unfortunately there was no way to restore Sally's arm and hand. To make matters worse, 6 months following the injury Sally began complaining of excruciating pain coming from her missing limb. She told the doctor that it felt as if the missing hand was clenched in a tight fist and no matter what she did, she could not release that fist. Her doctor told Sally that this was known as a phantom limb (the sensation that an amputated or missing limb is still attached and perhaps even moving). What is going on with Sally?

1. The image (right) represents the somatosensory cortex of the parietal lobe of the human brain.
   a. What is the function of the somatosensory cortex?
   Detecting touch, pain, temperature, and sense of your body in space. It receives this sensory information from every part of your body.
   b. Various body parts are depicted above the brain. What does this represent?
   Each region of the somatosensory cortex represents sensory information from a distinct body part. The pictures represent which body part the nervous tissue beneath them is encoding.
   c. Describe the relationship between body parts close in proximity to each other and the brain areas which represent them.
   Body parts that are close to each other on the body are also represented by nearby parts of the brain. This is referred to as a somatotopic representation. Brain maps, or specific cortical tissue that only represent a subset of the full sensory information, are common to all sensory domains. Furthermore, these maps are not randomly oriented but tend to be established such that nearby brain areas represent similar sensory information. With touch for example, this means the hand and the arm are represented by distinct brain regions – but those areas in the brain are close to each other. For hearing, similar frequencies of sound are represented in neighboring brain tissue.

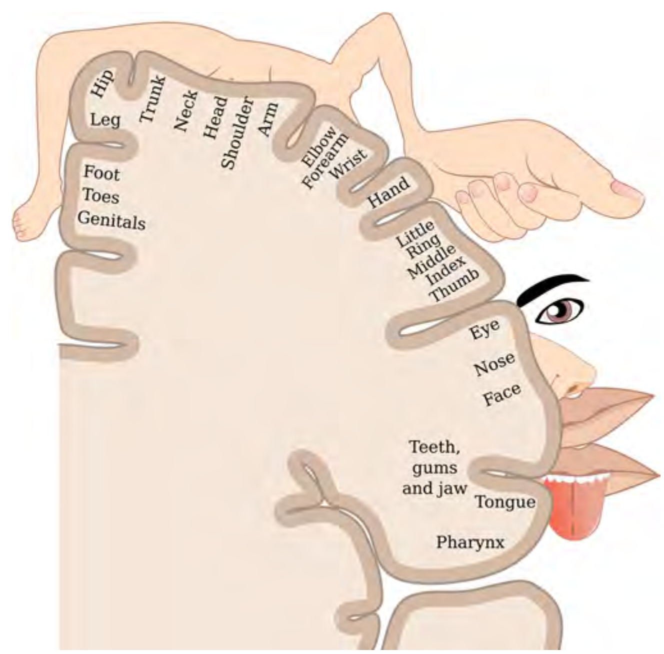

Figure 1. *Somatosensory cortex of human brain. A map of the body is represented in the brain. Body parts which are anatomically close are also represented in nearby regions of the brain. The sensitivity of each body region is related to the size of the representation in the brain. From Wikimedia Commons, File:1421 Sensory Homunculus.jpg: OpenStax College derivative work: Popadius, CC BY 3.0 <https://creativecommons.org/licenses/by/3.0>.*

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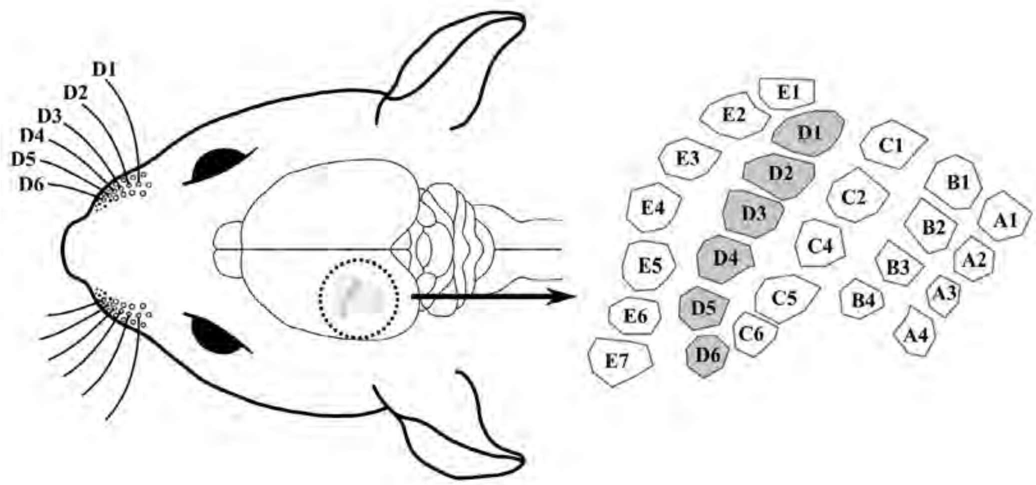

Figure 2. *The barrel cortex of the mouse. Each whisker of a mouse is represented by a distinct area of the somatosensory cortex. The representations are organized into column-like structures giving the brain region the name 'barrel cortex'. Note the relationship between whiskers labels and barrel labels.*

2. In the 1970s, an area of the rodent brain was identified in which each individual whisker was represented by distinct brain areas (Woolsey and Van der Loos, 1970). This area, the so-called Barrel cortex, is depicted on the left side of Figure 2 above.

   One row of whiskers has been labeled D1 through D6 on the right side of the image. What do you note about the relationship between the labeled whiskers and the area of the barrels represented by the labels on the left image?

   There is a mapping of the whiskers such that each whisker is represented by a single neural region and nearby whiskers are represented by nearby regions of brain. This is similar conceptually to the body representation we saw in the somatosensory cortex. Humans do not have a barrel cortex. This is because, despite having hairs on our face, we do not rely on the sensory information from those hairs enough to dedicate the neural tissue to representing it so thoroughly. Rodents use their whiskers to identify the locations of objects near them while in the dark.

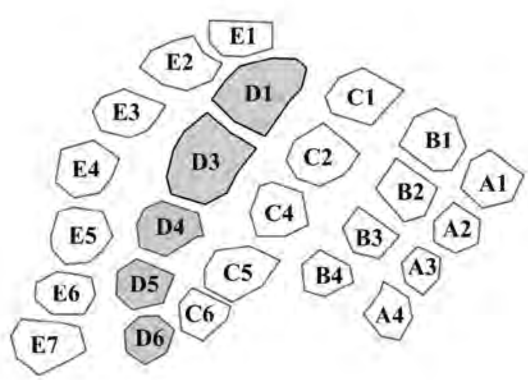

Figure 3. *Barrel cortex after clipping of whisker D2. The representation of whiskers in the barrel cortex is altered as a result of changing the sensory experience of the animal.*

3. Figure 3 represents the barrel cortex of a mouse that had whisker D2 clipped shortly after birth.

   a. Describe how the representation of the whiskers in the barrel cortex of this mouse is different from the "normal" mouse barrel cortex depicted in Figure 2.
   The barrel representing whisker D2 has disappeared. The barrel representing whisker D1 has grown into the D2 space and the barrel representing whisker D3 has also enlarged into the D2 space. Thus, the area of the brain which formerly responded to touches of the D2 whisker would now respond to touches of D1 or D3 whiskers, not D2.

   b. Why do you think these changes occurred?
   While representation of whisker D2 has disappeared, the cells which composed the barrel are still alive and functional. The lack of input to those cells permits the inputs to regions representing whiskers D1 and D3 to 'invade' and input onto the cells which formerly represented whisker D2. This emphasizes the principle that neurons seek activation; when the normal input to an area is removed (during the appropriate developmental timepoints) that area is more likely to be taken over by neighboring regions with functioning inputs.

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   c. What changes in the barrel cortex would you predict if whiskers D2 and D3 were permanently bound together (using tape or glue) shortly after a mouse was born?
      D2 and D3 become represented by the same region; stimulation of either whisker activates the same area. If the whiskers are separated and touched individually, the mouse would not be able to differentiate which whisker was touched.

4. The changes described in the barrel cortex are an example of a brain altering its sensory mapping based on an animal's sensory experience.
   a. Support the statement above based on your answers to question 3.
      Cutting the whisker or taping two whiskers together alter how the world is experienced. When inputs to the brain change, the representation of the outside world by the brain will also change. Removing the input by cutting the whisker permitted regions still being used to invade the input-starved regions. Likewise, linking sensory experience by taping together 2 whiskers alters the mapping because the 2 whiskers are always in synchrony with each other. Donald Hebb famously wrote "Neurons that fire together, wire together" (1949), which succinctly emphases this idea.
   b. Based on how the barrel cortex can change, make a hypothesis about what may be happening in Sally's brain that is leading to the phantom limb pain she is experiencing.
      When Sally loses her arm, the area of the brain which previously represented that area no longer is receiving input. Nearby areas which are still being activated will invade the deprived area. This may cause a stimulus that is coming from another body part (say the face) lead to activation of the brain that formerly represented the arm. Touching that body part (i.e. the face) may lead to the false sensation that her arm is being touched.

Figure 4. *Mirror box therapy for phantom limb. A mirror box allows patients to see an illusion that their missing hand is restored. Using the illusion to provide a visual cue of unclenching the missing hand provides instant relief. Prolonged use extends the relief from phantom limb pain for the patient. Used with permission from BBC News at bbc.co.uk/news.*

5. Rather than drugs or surgery, it was discovered that pain experienced by patients' phantom limbs could be alleviated using a simple mirror (Ramachandran and Rogers-Ramachandran, 1996). An open-topped box was constructed into which patients could insert their existing arm on one side of a mirrored divider and the stump of the missing arm on the other side of the divider. A patient complaining that their phantom hand was permanently clenched (an excruciatingly painful experience) would find the pain instantly relieved when they looked at the mirror image of their existing hand making and then unclenching a fist.
   a. Make a hypothesis regarding the mechanism of this treatment. How might watching a hand (which appears to be the phantom hand) unclench lead to an alleviation of the pain?
   b. What does this mean about the interaction between multiple sensory modalities (touch and vision, for example)
      The visual stimulus that the hand opening is sufficient input to convince the brain that the clenched fist it 'thinks' is occurring has been relaxed.
      This must mean that visual and somatosensory maps overlap and can influence each other. (Any reasonable answer is acceptable.)

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