Hendrick Hudson
High School

Science Research

May 2018

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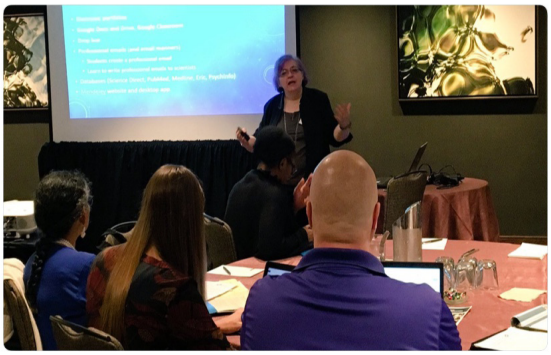
" You are limited only by your imagination"

Society for Science · 14h

Teacher @HenHudSCIRE talks at #SSPteach about setting up a science research program at school.



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Mr. Beau White

Hendrick Hudson High School

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Congratulations to a wonderful group of students.

Melody Munitz received two Regeneron STS badges, for Student Initiative and for her Research Report. She placed Second in the Behavior category for WESEF and Second as a speaker for JSHS, qualifying for the finals. Her work on Aphantasia defined new characteristics of this condition. In addition to her accomplishments in Science Research, Melody is an outstanding actress and singer, who will join the Pennsylvania State University, Schreyer Honors College, to major in musical theater. She is the 2018 Salutatorian.

Peter Manthey placed Second in Tri-County Science Fair in computer science category. His project, modeling the development of birds' beaks, is very important in understanding the epigenetic modifications leading to specific beaks' shapes. Peter is going to attend Colgate University in the fall.

Margaret Quinn Gruber has worked on the effects of radiation on neurogenesis, an important topic not just about our future in space flight, but also addressing the neural degeneration happening in radiation therapy treating brain cancers. Quinn will attend University of Pennsylvania in the fall.

Our Juniors competed this year as well. **Thea Barbelet** took First place for her poster in the Animal Science category on bee pollination at JSHS and got Second best overall grade. **Buu-Hac Nguyen** got First place for her poster in the Neuroscience 1 category at JSHS and got Third best overall grade. She also got the College Admission Central Science Horizon Award at WESEF. Buu-Hac worked on characterizing the Dopamine transporter with nanobodies. **Hailey Kissner** competed at WESEF with her fabulous work on Dyslexia.

We would like to express our sincere and profound gratitude for the work of **Dr. Matthias Quick**, who has been mentoring several of our students over the years, who has acted as judge, advised and helped our students present their research better.

Our collaboration with the Pine Ridge Girls School in South Dakota is continuing. We will be able to pair our Science Research classroom with the science class of **Mr. Beau White** on a regular basis starting in the fall, thanks to the generosity of **Mr. James Mackin**, who equipped both of our classrooms with webcams. This Science Research Program collaboration is part of a developing and pilot program from the Society for Science and the Public to help underserved communities build science research programs.

An Epidemiological Study of Aphantasia by Melody Munitz (STS paper excerpt) (Senior)

Abstract

Aphantasia is a newly acknowledged condition characterized by the inability to form mental images in one's mind's eye. As it has recently surfaced, there has been little research conducted on it. I created a survey and distributed it to groups of self-declared aphantasiacs via social media, and received 395 responses. These responses were compared to a control group of 150 subjects. This epidemiological study of aphantasia is the first of its kind to function on a large scale, providing important information about the nature of the condition and its effects on those who have it. The results suggest that aphantasiacs find mental workarounds to compensate for their lack of visualization skills that allow them to be high-functioning as individuals and in society. One of the most prominent results is that most aphantasiacs have vivid visual dreams, suggesting that aphantasia affects conscious, but not unconscious visualization. Another important result lies in the fact that most aphantasiacs experience diminished imagery of their other senses, not simply visual; i.e., they have difficulty conjuring auditory or gustatory imagery. This suggests that aphantasia is caused by a neurological mechanism broader than those responsible for just visual imagery formation and recall.

Introduction

Visualization, or being able to conceive an image in one's mind's eye, is an impressive and impactful ability. Believed to be the product of frontoparietal and posterior brain processes (Bartolomeo, 2008), this skill has numerous practical implications, such as its assistance in learning, glancing ability and creativity, among other psychological processes. The formation of mental imagery is also linked to memory, as supported by Marks' 1973 experiment in which male and female subjects who claimed to have varying visual imagery capabilities were shown an image and then asked to recall it. The results suggested that the subjects who claimed to have higher visual imagery capabilities were more accurate in their recall of the images they had seen, allowing for the conclusion that "images have an important role in memory" (Marks, 1973). In another experiment relating to the correlation between eye movements and visualization, there was "no evidence that vivid visualizers showed more scanning activity than a group of Ss [patients] operationally defined to be poor at visualizing", suggesting that visual imagery is more than simply eye movements (Marks, D.F., 1973).

Some of the first documented research regarding visual imagery was conducted in 1880 by Sir Francis Galton, esteemed English scientific pioneer of the 19th century, and was geared toward determining how different people's visual imagery skills compare. To assess where each patient lay on the scale of visualization, Galton developed the Vividness of Visual Imagery Questionnaire (VVIQ), which has since become a standard of scientifically quantifying visualization skills. This questionnaire describes several situations and then asks the participant to rate the vividness of their mental imagery on a scale of 1-5. Using the VVIQ and other similar tools and questionnaires, Galton found that not everyone is equipped with comparable visual imagery capabilities. While most people fall somewhere on the high end of the spectrum, having good or even superb visual imagery skills, there is a small percentage of people that possess very poor visualization abilities (Galton, 1880). In similar research conducted by Faw in 2009, assessing such capabilities of 2,500 participants, it was found that 2.1-2.7% of them fell in this small group, claiming extremely poor or absent visual imagination (Faw, 2009).

Aside from Faw's limited work, this phenomenon has not received much scientific exploitation. Recently, however, Professor Adam Zeman at the University of Exeter has begun conducting research on this topic. This condition now named 'aphantasia' (Zeman, 2015), is hypothesized to be the result of either of two different types of neurogenic visual imagery impairments: i) visual memory disorders, or ii) 'imagery generation' deprivation (Farah, 1984). To explore further features of aphantasia, Zeman and his team distributed a shortened version of the VVIQ as well as a supplemental questionnaire addressing additional

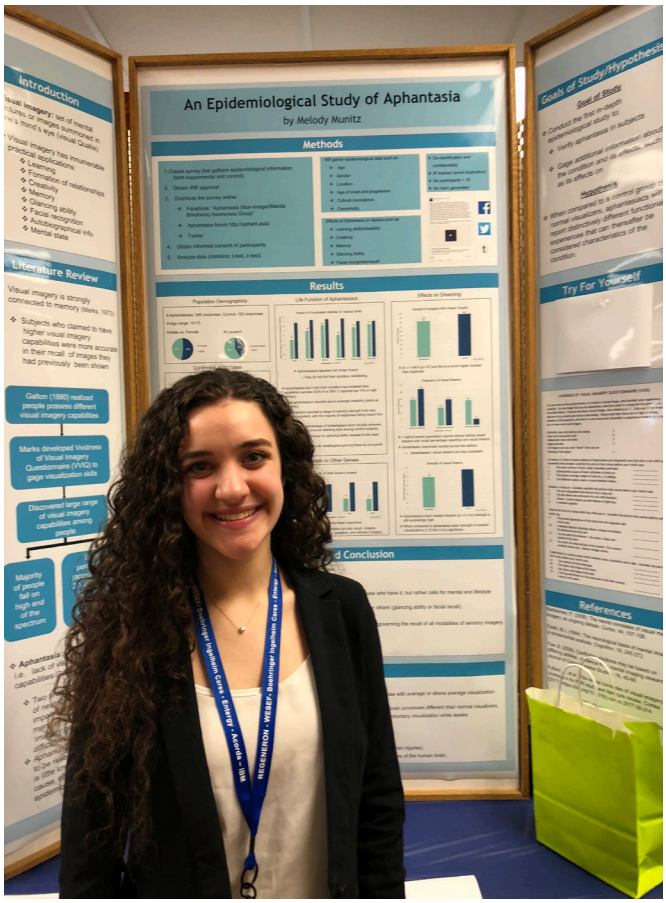
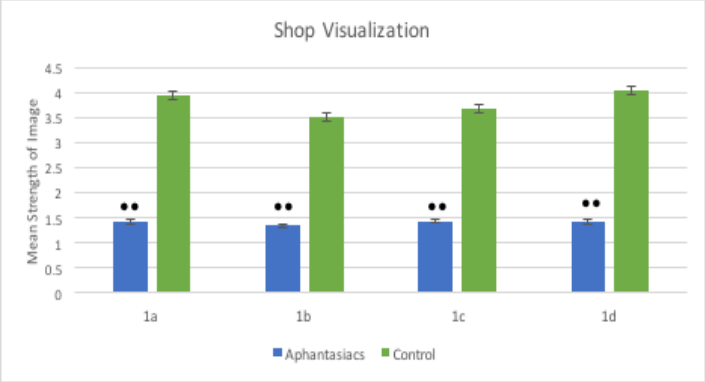


FIG. 1.

Question 1: Think of the front of a shop which you often go to. Try to form a visual image, and rate the vividness of it is using the five-point scale described below.
1a: "The overall appearance of the shop from the opposite side of the road."
1b: "A window display including colors, shapes and details of individual items for sale."
1c: "You are near the entrance. The color, shape and details of the door."
1d: "You enter the shop and go to the counter. You hand the clerk your money, and they give you back change."

5 - Perfectly clear and vivid as real seeing; **4** - Clear and reasonably vivid; **3** - Moderately clear and lively; **2** - Vague and dim; **1** - No image at all, you only "know" that you are thinking of the object

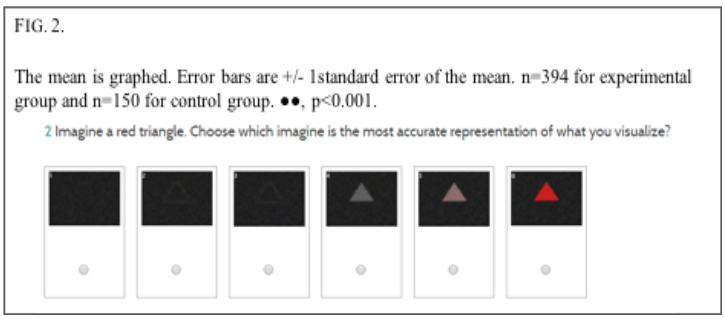
The mean is graphed. Error bars are +/- 1 standard error of the mean. n=394 for experimental group and n=150 for control group. ●●, p≤0.001

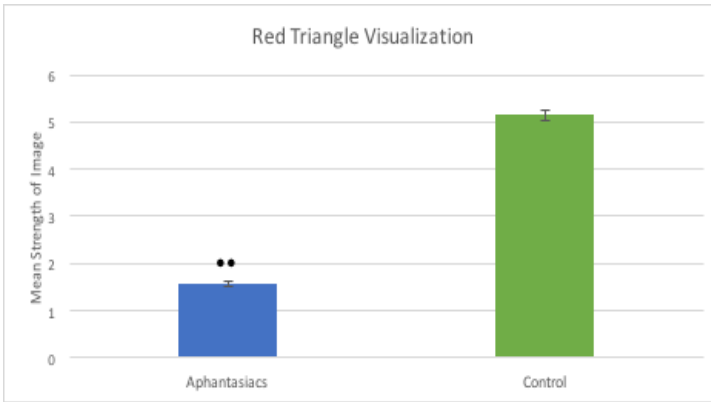


personal information to 21 participants who suspected that they had the condition, 19 of whom were male. This testing generated various results; 5/21 reported having relatives who experience similar symptoms, and most participants claimed having realized their visualizing deficit during their teens or early twenties through conversation with 'normal' visualizers. Interestingly, despite the 21 participants' VVIQ scores being tremendously lower than those of the 121 control patients, many subjects claimed to experience involuntary imagery at various times. This first exploratory study of aphantasia began to define and quantify the condition, and acted as a good basis for further research (Zeman, 2015).

FIG. 2.

The mean is graphed. Error bars are +/- 1standard error of the mean. n=394 for experimental group and n=150 for control group. ●●, p<0.001.





I created a questionnaire and distributed it via the internet to self-proclaimed aphantasia patients to gather additional statistics of the condition. This study gathered demographics of the tested population, as well as information regarding the effects of aphantasia on learning ability, glancing ability, facial recognition ability, creativity, career and memory. This data will facilitate an improved understanding of aphantasia within the scientific community, and act as a base for further studies aimed at determining the cause of the condition.

Goal of Study/Hypothesis

Develop a survey to be administered to self-proclaimed aphantasiacs to verify their condition, as well as gage additional information about aphantasia that will facilitate further scientific investigations. This will serve as the first in depth epidemiological study of this condition, providing useful information about the demographics of the population of non-visualizers, as well as highlighting the effects of the condition on various functions. When compared to a control group of normal visualizers, it is expected that aphantasiacs will report distinctively different functional experiences that can thereafter be considered characteristics of the condition. (...)

Results

Population Demographics:

There was a fairly even spread of ages tested, ranging from 18-75, with the 25-34 range being the most popular. There was a relatively even split between male and female subjects (53% female: 47% male). Subjects were from the United States and other countries (42% US: 58% Other). Of aphantasiacs, 42% reported having been in the academic top 10% in high school, comparable to the 39% of the control group that reported such, showing that aphantasiacs don't feel that aphantasia has hindered their academic success. Most subjects expressed that their visual imagery had been equally weak throughout their life, and did not seem to be the result of an accident or other change.

Confirming Aphantasia:

Since most aphantasiacs were self-identified (only 4% reported that their mind's eye weakness has been verified by a healthcare professional), it was important to verify their standing as aphantasiacs. The first questions of the survey asked subjects to undergo a series of visualizations and record their experience. The experimental group consistently reported low numerical responses, showing their diminished mind's eye and categorizing them as aphantasiacs. The consistently high numerical responses of the control group on the same questions verified them as non-aphantasiacs, making them a viable control population.

Life Function of Aphantasiacs:

The collected data suggests that aphantasiac's diminished visualization abilities affect various aspects of their functionality, specifically their career, creativity, memory, learning ability, glancing ability, and facial recognition abilities. Normal visualizers reported that their visual imagery capabilities had a very strong impact on these aspects of their life, showing that visual imagery is a skill that the normal population relies on heavily for daily function. Thus, it would be expected that those

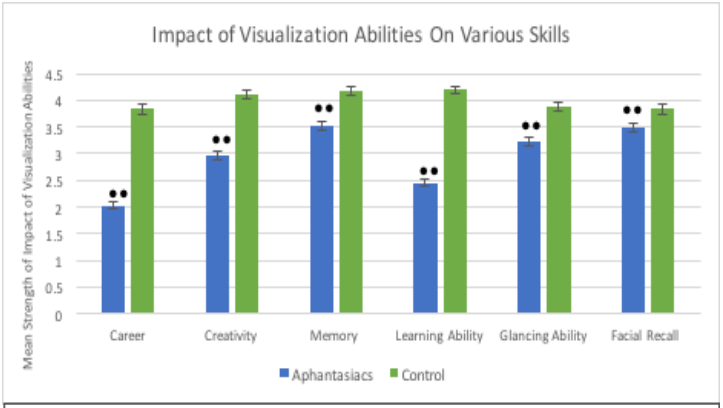


FIG. 3.

"1 = no impact; 5 = strong impact"
The mean is graphed. Error bars are +/- 1standard error of the mean. n=388 for experimental group and n=128 for control group. ●●, p<0.001.

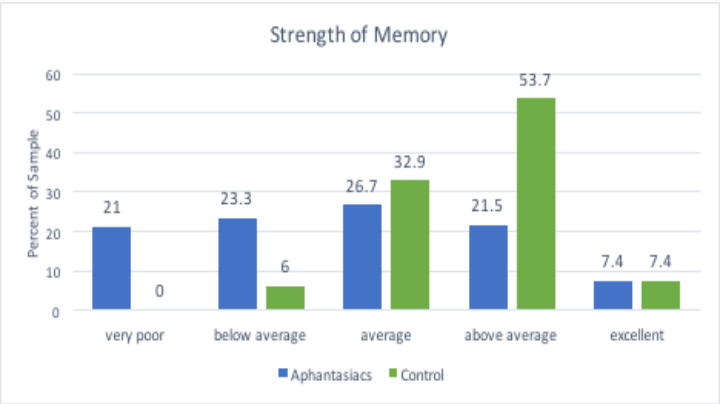


FIG. 5.

Percentages of the sample are graphed. n=390 for experimental group and n=149 for control group.

who do not possess the ability to visualize would experience a noticeable deficit, and would note very high impact of their lack of visualization abilities in Figure 3. However, aphantasiacs reported mid-range impact, suggesting that aphantasiacs do not find their condition debilitating, but rather, something they are finding ways to compensate for.

Considering the reported impact of visualization on creativity, it would be expected that aphantasiacs would experience decreased creativity. However, most aphantasiacs reported above-average creativity, just as the control group did (Figure 4). Here, it is beneficial to consider the varying definition of 'creativity'; these results may either speak to artistic creativity, or to being a creative thinker (i.e. thinking in a creative manner). The latter may be more prominent among aphantasiacs, as their possible compensation for their lack of visual imagery may mean they rely on other, 'creative', methods of thinking.

For memory, there was a spread of strengths reported by aphantasiacs, but very few reported "excellent" memory (Figure 5). Most of the control group reported above-average memory, with very few reporting memory weaker than average. The memory strength reported by aphantasiacs is swayed to the lower end of the scale, whereas the results from the control group are swayed to the higher end, showing that aphantasia does have an impact on memory, but not a drastic one. Since memory tends to be highly dependent on mental images, and aphantasiacs are not reporting an extremely weak memory, they must be finding means of compensation and relying on other methods to remember and memorize.

Since visualization tends to play a large role in learning, it was relevant to assess how aphantasiacs learn. While most control subjects reported being visual learners, this was not the case among aphantasiacs (Figure 6). Rather, most aphantasiac subjects reported being either "kinesthetic" or "read-write" learners, with the smallest percentage reporting being visual learners. This suggests that aphantasiacs are learning differently than the rest of the population, and though they are just as likely to be intelligent and high-achieving, are relying on work-arounds to learn and memorize.

Since glancing ability, the ability to take in information at a glance, relies on taking a mental snapshot for later recall and analysis, it would be expected that aphantasiacs would have weak glancing abilities. Indeed, most aphantasiacs reported either average, very poor, or mildly below average glancing abilities, with very few reporting above average or excellent (Figure 7). These results are significant when compared to the control group's responses of primarily average or above average, with the smallest percentages reporting mildly below average

FIG. 4.

Percentages of the sample are graphed. n=393 for experimental group and n=150 for control group.

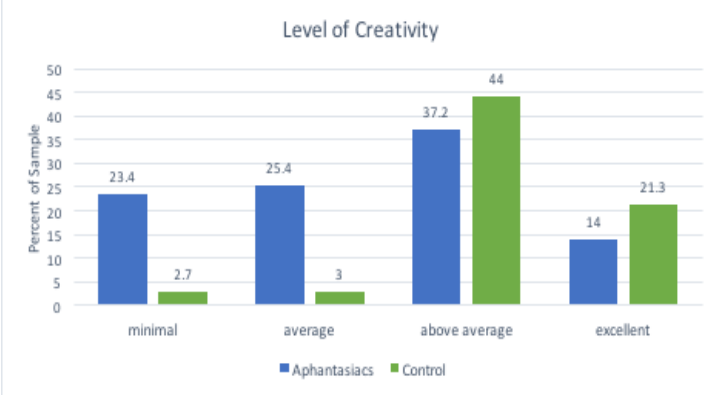
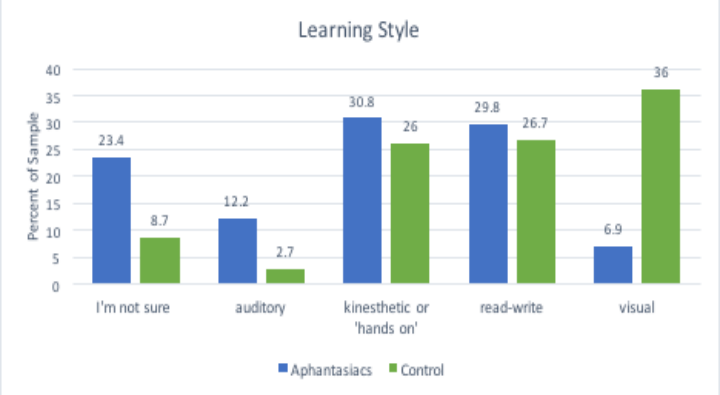


FIG. 6.

Percentages of the sample are graphed. n=393 for experimental group and n=150 for control group.



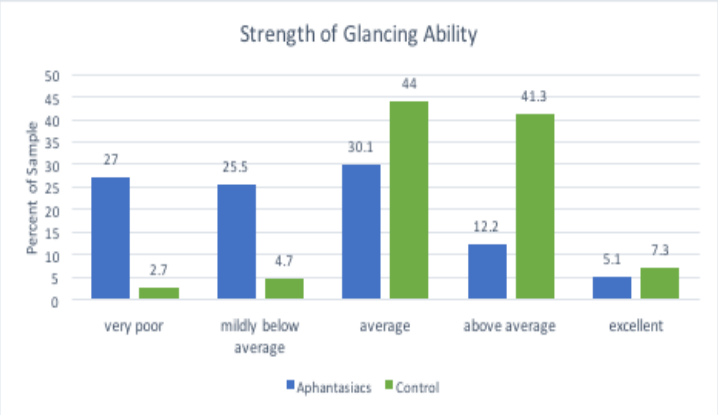


FIG. 7.

Percentages of the sample are graphed. n=392 for experimental group and n=150 for control group.

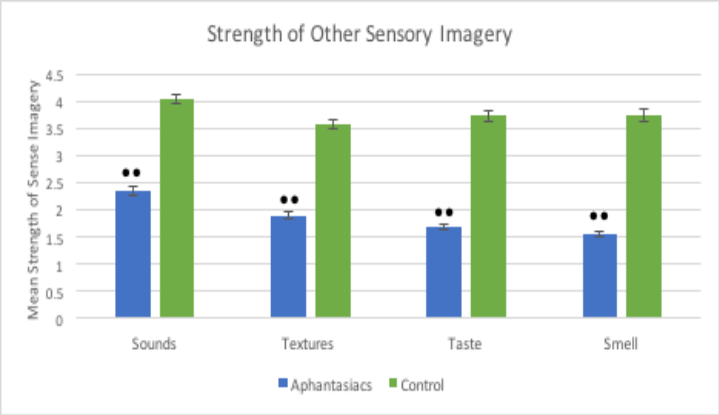


FIG. 9.

The mean is graphed. Error bars are +/- 1 standard error of the mean. n=388 for experimental group and n=127 for control group. ●●, p<0.001.

or very poor. The aphantasiac responses skewed to the lower end of the spectrum, compared to the non-skewed control group responses, suggest that aphantasiacs do in fact struggle with glancing ability.

Facial recall (Figure 8) requires one to capture a mental image of a face, and thus it seemed likely that aphantasiacs would have difficulty recalling faces. Nearly 60% of aphantasiacs reported difficulty with this—a significantly higher percentage compared to the approximately 15% of normal visualizers that reported difficulty recalling faces.

Function of Other Sensory Imagery:

While aphantasia is defined by diminished visual imagery, it was a point of interest to see if other sensory imagery is also affected by the condition. Subjects were asked to rate the strength of their imagery when attempting to imagine, for example, a song, the feeling of a certain fabric, the taste of their favorite food, and the scent of a candle. Compared to the control subjects, the aphantasiacs reported consistently lower strength of imagery for sounds, textures, tastes, and smells, suggesting that Aphantasia is inhibiting not only visual imagery, but also auditory, tactile, gustatory, and olfactory imagery (Figure 9).

Function of Dreaming:

Since visual dreaming requires the playback of visual images in the mind's eye, it was under question if aphantasiacs would be able to dream visually. Surprisingly, many of them can. Because of the large number of participants in the study, the 81.1% of aphantasiacs who dream visually is statistically significant when compared to the 94.6% percent of normal visualizers who dream visually (Figure 10). However, we must look beyond the statistics to understand what this particular data set is truly saying. In actuality, this 81.1% is much higher than expected, as based on their deficit in visualization, it seemed highly unlikely that aphantasiacs would dream visually at all.

Though aphantasiacs are dreaming visually, they seem to be doing so less frequently than the population of normal visualizers (Figure 11). Whereas over half of the control population reports always having visual dreams, and only a small percentage report that their visual dreams occur rarely, the aphantasiacs responses were spread across the options, showing that their visual dreams are less consistent than those of the normal-visualizer population. As in Figure 10, the statistical significance displayed in the data regarding the strength of these dreams can be misleading due to the large population. While the strength of the dreams experienced by aphantasiacs is lower than the strength of dreams experienced by the control group, the aphantasiac strength reported is still surprisingly high. Especially when compared to the mean strength of wakeful visualization reported by aphantasiacs as approximately 1.5 (see Figures 1 and 2), the mean strength of visualization while dreaming reported here as approximately 3.4

FIG. 8.

Percentages of the sample are graphed. Error bars show standard error. n=392 for experimental group and n=150 for control group. ●●, p<0.001 as determined by a z-test.

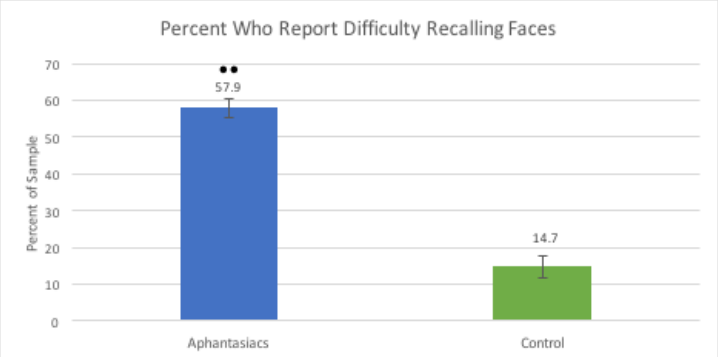
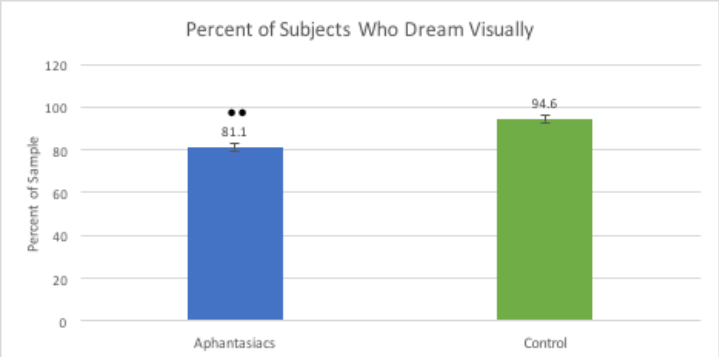


FIG. 10.

Percentages of the sample are graphed. Error bars show standard error. n=387 for experimental group and n=149 for control group. ●●, p<0.001 as determined by a z-test.



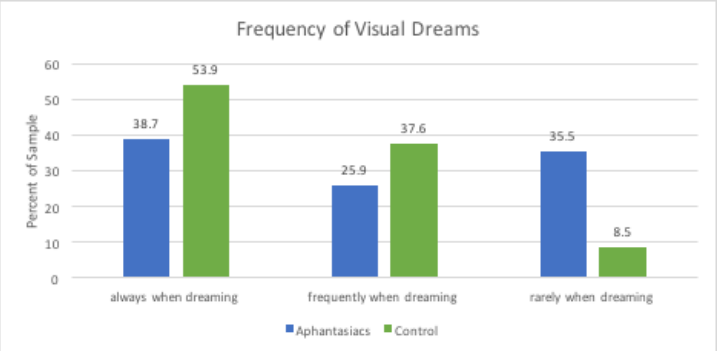


FIG. 11.

Percentages of the sample are graphed. n=313 for experimental group and n=141 for control group. These populations are smaller because only those who reported "yes" to having visual dreams in the previous question were presented this question.

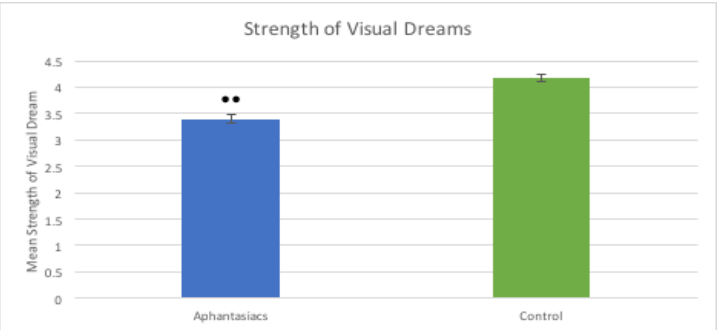
is significantly higher, and should be legitimately considered.

Discussion

This questionnaire yielded many unprecedented results that begin to characterize and explain aphantasia. While this condition does not seem to act as a major deficit to the success of those who have it, it certainly affects the way they function and learn (see Figure 3). Their relatively high strengths of creativity and memory suggest that they must be implementing mental and lifestyle adjustments to compensate for the effects of their diminished visualization abilities (see Figures 4 and 5). However, there do seem to be some functions that aphantasiacs cannot compensate for so readily; they did report significantly weak glancing ability as well as difficulty recalling faces (see Figures 7 and 8). This split between what they can and can't compensate for seems to fall logically, as glancing ability and facial recall are based almost entirely off of the formation and recall of a mental image, whereas creativity and memory are supported by other mechanisms. One of the most fascinating results of this study was that the vast majority of people with decreased visual imagery also have weakened imagery of their other senses (see Figure 9). This leads one to believe that the neural deficit that causes aphantasia is not necessarily based specifically in brain processes relating to visualization or sight, but rather in a more general process relating to the recall of all modalities of sensory imagery. Another surprising and interesting result was that most aphantasiacs (81%) experience visual dreams, and peculiarly, very vivid ones. This result calls for further research to explain what brain mechanism allows for involuntary visualization while asleep, but not voluntary visualization while awake. In providing new and interesting results, this survey adhered to the goals of study and served as the first in depth epidemiological study of aphantasia. Though this survey should not be considered sole proof for the drawn conclusions, it has helped to highlight what areas of aphantasia should receive further research.

FIG. 12.

"1 = vague, lifeless; 5 = extremely vivid"
The mean is graphed. Error bars are +/- 1 standard error of the mean. n=388 for experimental group and n=127 for control group. ●●, p<0.001.



Dr. Adam Zeman, MD

Professor of Cognitive and Behavioral Neurology

University of Exeter, Medical School, Exeter, UK.

Conclusion

Research of aphantasia is important as it appears to be a condition that is affecting a significant number of people, supported by Faw's proposal that 2.1-2.7% of a population are likely to have extremely diminished or entirely nonexistent visual imagery capabilities (Faw, 2009), and recognizing the high number of responses this study received in a short period of time. Overall, this study suggested that aphantasiacs are finding ways to compensate for their visual imagery deficit, as they are high functioning and can even dream visually. The next step in aphantasia research is underway with the recent completion of an fMRI study observing the brain function of poor visualizers. That study found that those with low visual imagery capabilities utilize a more widespread set of brain regions when attempting to visualize than those with average or above average visualization skills (Fulford et al 2017). This result supports the hypothesis suggested by my study that aphantasiacs are utilizing compensatory brain processes different than normal visualizers. Further neuroimaging studies should be conducted to help us understand why aphantasia seems to affect imagery of all the senses, as well as how aphantasiacs are able to dream visually. If a large percentage of aphantasiacs are dreaming in images, often vivid ones, they must be able to create and store visual images that are retrievable during dreaming, but not consciously during wakefulness. Additional brain imaging studies may help to pinpoint the neural pathways that are prohibiting conscious visual imagery recall, helping us to understand how visual imagery is generated in the brain. Such findings can relate to other fields by possibly aiding in the development of therapies for patients with visual recall impairments, (caused by stroke or brain injuries) or by expanding the knowledge base of other conditions pertaining to visual imagery such as synes-

thesia (a crossing of sensory modalities) or schizophrenia (where there may be visual hallucinations). In learning about how visualization occurs, we can expand our understanding of the functions and processes carried out by different structures of the human brain.

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Using Bioinformatics to Model Cell Proliferation by Peter Manthey (STS Paper excerpt) (Senior)

REGENERON SCIENCE TALENT SEARCH 2018 ENTRANT

Abstract

Bioinformatics is the use of computer science, statistics, mathematics, and engineering to analyze and interpret biological data. The advancements in this field are currently being used to produce simulations to analyze dynamic cell to cell interactions providing scientist more in-depth data regarding how different cells and cell groups interact with one another, as well as allowing them to visualize the data. Here we leverage CompuCell3D to analyze genetic and epigenetic data regarding the formation of the beak and facial development of bird embryos. This simulation will demonstrate how an abnormally curved beak shape in chicken embryos can be achieved by altering cell proliferation. Researchers have found that administration of certain chemicals can modify the growth rate of critical regions of the developing bird's beak and facial region. In these simulations the goal is to produce observable changes in the simulation's output graphics that reflect the key features that were observed in the original research.

Introduction

Bioinformatics is an emerging discipline that uses computer technology, statistics, mathematics, and engineering to analyze and translate biological and genetic data, as well as healthcare information. Although bioinformatics has been around since the 1960s, it is now being widely used. In the simplest form, bioinformatics is data that is collected from specific sources, run through unique code and organized by the associated biological macromolecules.

The amount of data being collected today throughout the world is enormous. One of the largest databases being used for bioinformatics is the GenBank, which is part of the International Nucleotide Sequence Database Collaboration. As of December 2015, this database contained over 203 billion nucleotide bases in more than 189 million sequences, collected from daily exchanges of data with the DNA DataBank of Japan (DDBJ), the European Molecular Biology Laboratory (EMBL), and GenBank at NCBI.

"This database is produced and maintained by the National Center for Biotechnology Information (NCBI) as part of the International Nucleotide Sequence Database Collaboration (INSDC). The National Center for Biotechnology Information is a part of the National Institutes of Health in the United States. GenBank and its collaborators receive sequences produced in laboratories throughout the world from more than 100,000 distinct organisms." [1]

As a result, there has been an increase in the application of bioinformatics tools to help medical researchers not only analyze larger quantities of data in shorter period of time, but to also become more precise in diagnosing and determining treatments. One breakthrough is using DNA sequencing to break apart a DNA strand which is made up of four nucleotide bases. By doing this, scientists can determine variations for genetic diseases. Collecting all of this data and using bioinformatics will now allow doctors to break down a person's entire human genome in one day and provide personalized treatment and medication. One bioinformatics software tool currently being tested will automate the interpretation of the genome data by accessing any medical journal, research and articles applicable to the data and allow the treating doctor to reference those sources for potential treatment. In 2003, researchers from several universities in the United States leveraged CompuCell3D, a multi-model framework that simulates morphogenesis, to simulate how limbs form in multicellular organisms during the stages of embryonic development. [2] The program was designed to help researchers better understand the processes of morphogenesis. The program simula-

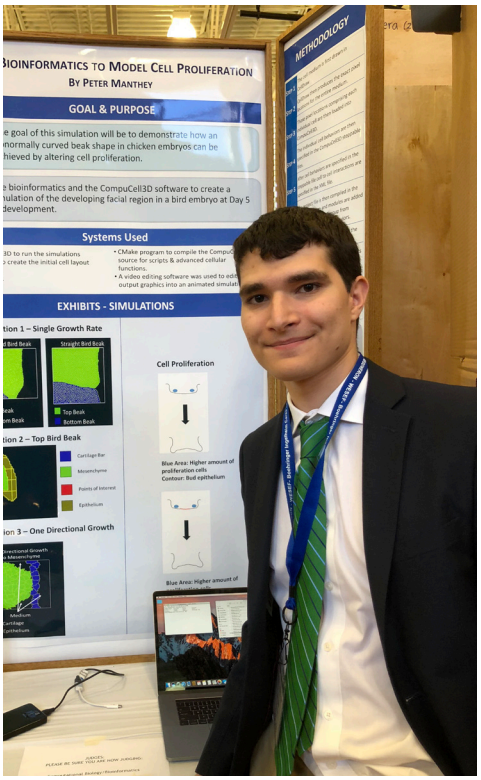
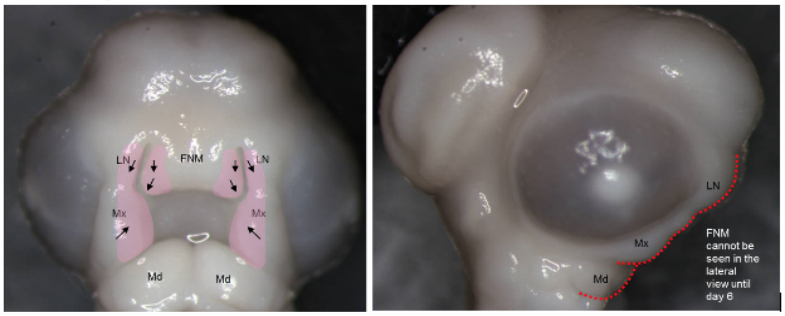


Figure 1 - Day 5 - Mesenchyme and epithelium, not cartilage
Picture courtesy of Dr. Marta Linde-Medina, New York Medical College and University of California, San Francisco



Pink area = > proliferation

No fusion between buds

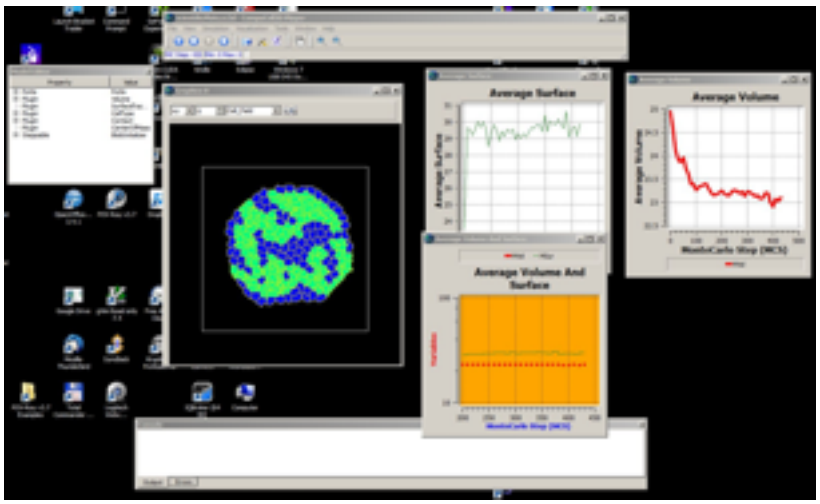
Black arrows indicate the direction of expansion of cell populations. Different buds expand in different directions:

1) FNM and LN expand along a mediolateral axis (in the plane of the screen, towards the lower corners)
2) Mx expands along a proximodistal axis (towards the viewer out of the plane)

tion models the interactions between the gene regulatory network and genetic and cellular mechanisms. This new technology for modeling morphogenesis could help us to better understand defects that occur during limb development.[2] In 2005 additional research was performed presenting CompuCell3D, a three-dimensional, cell-centered, multiscale framework.[3] Today CompuCell3D is being used to in an open source environment that allows for "virtual tissue simulations of development, homeostasis, toxicity and disease in tissues, organs and organisms, covering subcellular, multi-cell and continuum tissue scales."[4]

In October of 2015, a group of scientists in Italy developed a bioinformatics program that is capable of identifying potential biomarkers for diseases and disorders know was SANIST. In this study, researchers used SANIST to identify a biomarker for prostate cancer known as carnitine, an ammonium compound involved in fatty acid metabolism. The research found that carnitine was expressed at lower levels in the plasma of prostate cancer patients and concluded that SANIST was able to accurately identify and separate individuals with prostate cancer from those with benign conditions at a rapid rate.[7]

Figure 2 – CompuCell3D Floating Windows Layout [15]



In late October of 2015 several databases have were created to provide doctors with access to allergen lists, protein classifications and sequence information to be used to determine potential risk of allergenic cross-reactivity. Over 55% of the US population has tested positive for some type of allergy. [8] Allergies are caused by a person's immune system which mistakes an allergen, a foreign body, as a threat and launches and attacks to neutralize it. The researchers used bioinformatics to predict which proteins in parasitic worms would cause a reaction similar to an allergic reaction in humans. They were able to isolate in a parasitic worm one of the most common proteins in pollen. This protein was similar to a protein only known previously in the genomes of plants. Pollen is one of the most prevalent allergens. This bioinformatics tool will allow scientists to predict proteins that cause allergies, and to design protein molecules for treating them. [9]

Right now, research is occurring to find a more accurate detection for ovarian cancer in women. Currently fifty percent of women who have been diagnosed with ovarian cancer do not survive more than five years. The reason this cancer is so deadly is because ovarian cancer is very hard to detect and symptoms present themselves in later stages of development. In 2012, there were over 200,000 documented cases and 125,000 deaths worldwide. Researchers have found that NSC 319726, a small-molecule anticancer, could be used to effectively treat ovarian cancer. This study used bioinformatics to analyze and map the interactions between differentially expressed genes across a network. This allows researchers to find potential targets for NSC 319726. The result suggested that these genes and pathways may be candidate agents for NSC 319726. This is because NSC 319726 has been found to reduce levels of RPS6KA6, a chemical that is found to be overexpressed in patients with cancer due to it influencing the growth of cancer cells.[10]

One of the most important tools in the CompuCell3D program is the chemical field tool. These tools allow researchers to simulate the morphogenesis of multicellular organisms. The "French flag" model displayed how cells placed into varying positions on the chemical field changed their parameters including target volume, shape, orientation and diffusion due to the surrounding environment. One prominent theory surrounding the development of a curved bird beak is that at a curtain point in the beaks development, the cartilage bar will pass through a chemical field that weakens the strength of the bar. This chemical field is stronger though at the bottom of the bird's beak than it is on the top of the beak causing it to develop a hooked shape.

Recent research on the formation of body segments (somites) in vertebrate embryos also utilizes cell growth with multiple parameters dependent of the age of the de-

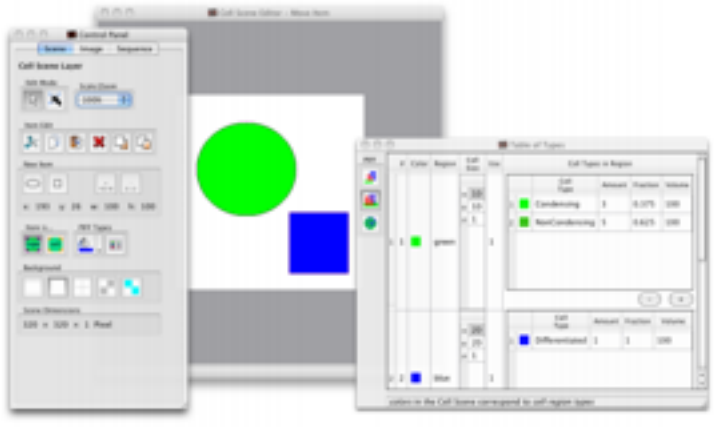


Figure 3 – The CellDraw User Interface [16]

veloping cells. This research used bioinformatics to prove it is possible to model cells with multiple age dependent parameters in the CompuCell3D program by using local cell interactions versus an external segmentation clock. The research concludes that somites are self-organizing structures whose size and shape is controlled by local cell-cell interactions.[11]

Over the last ten years there has also been significant progress in the field of using bioinformatics for epigenetic research. In 2010, Bare Bones Pattern Formation: A Core Regulatory Network in Varying Geometries Reproduces Major Features of Vertebrate Limb Development and Evolution used bioinformatics to "simulated the behavior of the core chondrogenic mechanism of the developing limb in the presence of an FGF gradient using a novel computational environment that permits simulation of LALI systems in domains of varying shape and size." [12] This research concluded when a gradient is present the limb it affects the behavior of the mesenchyme and can form limb-like skeletal structures. Bioinformatics was applied to simulate in vitro and in vivo limb development. This will allow doctors to better understand limb development and any complications that may occur in utero.

In 2012 in the Physico-Genetic Determinants in the Evolution of Development, scientists found embryos exhibit an assortment of stereotypes and patterns during development that have been present for millions of years. This has led researchers to believe the origins of animal development lay in the effects of external forces on how these animals develop. Dr. Stuart Newman believes "that the origins of animal development lay in the mobilization of physical organizational effects that resulted when certain gene products of single-celled ancestors came to operate on the spatial scale of multicellular aggregates".[13]

Researchers compared the embryological processes that shapes the limb bud, teeth and beaks to current theory of bone and cartilage development. Bioinformatics was used to determine that the current theory only applies to limb development. This research has been the foundation for a new therapy regarding the process of evolution in which an organism's genetic expression or phenotype, will often change before there is an actual change in the organism's genetic code of genotype. This theory has more recently been used to examine the evolutionary changes that were first observed by Darwin during his finch study in the Galapagos Islands. Researchers were able to find that by introducing different external factors into the environments of a developing bird embryo, all beak shapes described by Darwin in his studies could be achieved. [14]

Purpose of Study

The purpose of this research is to use bioinformatics and the CompuCell3D software to create a simulation of the developing facial region in a bird embryo at Day 5 in development. This simulation will demonstrate how an abnormally curved beak shape in chicken embryos can be achieved by altering cell proliferation. Researchers have found that administration of valproic acid, a drug used to treat epilepsy in humans, changes the relative rates of growth of the FNM and LN regions of the developing bird face (Figure 1). Researchers theorize that this is most likely due to changes in the chemical fields that control cell division. Success will be determined if the simulation produces a change in the beak shape in the output graphics that parallel those observed during original study.

Systems & Methodology

I used CompuCell3D (Exhibit 1) to run the simulation and produces output graphics. CompuCell3D is a widely used open-source simulation environment for multi-cell, single-cell-based modeling of tissues, organs and organisms. The program leverages the Cellular Potts Model to model cell behavior. Within the program CellDraw was used to create the initial cell layout and Twedit++ to define the cell properties and behaviors, and edit the code. The simulation and related

Baseline Data Analysis Steps (Table 1)

Step 1	The cell medium is first drawn in the CellDraw program.
Step 2	CellDraw then produces the exact pixel locations for the entire medium.
Step 3	Those pixel locations comprising each individual cell are then loaded into the CompuCell3D simulation file.
Step 4	The individual cell behaviors are then specified in the CompuCell3D steppable files.
Step 5	After cell behaviors are specified in the steppable file cell to cell interactions are specified in the XML file.
Step 6	The project file is then complied in the CMaker program and modules are added to restrict specific cell group from performing undesirable behaviors.
Step 7	The project file is then loaded into the CompuCell3D framework.
Step 8	The CompuCell3D program then outputs a PNG or image file of the medium at every specified MSC step or an increment of frames.
Step 9	The PNG files are then edited together in video editing software to animate the simulation.

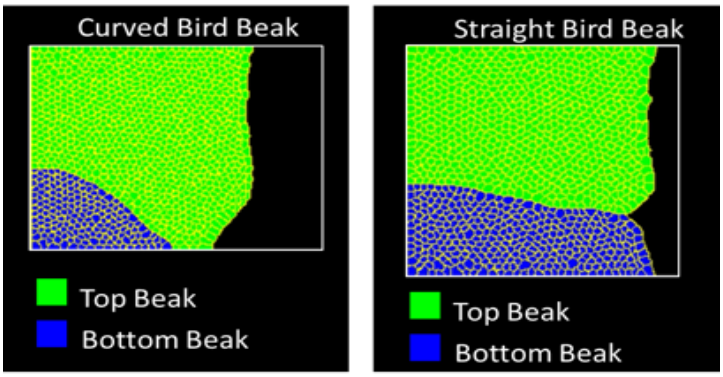


Figure 4 – Cell Simulation 1- Single Growth Rate (Source: Dr. S. Newman)

programs are run through Python 27. I then utilized the CMake program to compile the CompuCell3D source to write scripts for more advanced cellular functions. Then Windows Movie Maker was used to edit the output still graphics into an animated simulation.

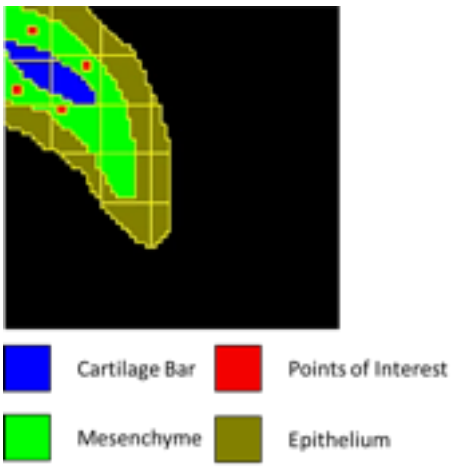
Creating the Baseline Simulations

The recreation of cell simulations requires knowledge several types of code. These codes include Python, C++, Bash, as well as how to incorporate these languages into the CompuCell3D program. To familiarize myself with Python, Bash and C++ I used several online courses and tutorials.

The first simulation attempt was to use CompuCell3D to recreate existing simulations regarding bird beak growth in utero at a single growth rate (Figure 4). These simulations were successful because they only required the modification of the single growth rate and inter-cell interactions of two cell groups – the top beak and the bottom beak.

The second attempt was to use CompuCell3D to model bird beak development of birds with a curved beak. I narrowed my focus to looking solely at the development of the top portion of the beak because it is theorized that the top and bottom portion of a bird's beak grow independent of each other. To accomplish this, I examined areas of beak growth based on significant areas of concentrated cell proliferation. I was unable to get the surrounding areas of proliferation to grow at a correct rate to consistently influence the positioning of the cartilage bar.

Figure 5 – Cell Simulation 2 – Top Bird Beak



In this simulation (See Figure 5) a singular large central cell group, indicated by blue shaded cells, should expand out in a singular direction and should initiate various intercellular reactions as a result of its expansion. Most importantly it should create a disturbance in the surrounding cell group, indicated by the green shaded cells, causing the cells to break apart and eventually drive the expansion of the outer most cell group, indicated by the brown shaded cells, as it stretches to contain the internal cell groups. The inner green cell in this simulation will have an incredibly high growth rate, but will only grow to fill any unoccupied locations in the medium that directly neighbor themselves. The final shape of this simulation should resemble that of the initial shape of the simulation but should be much larger in scale. Additionally, the blue central cell group should take up all spaces from its starting position to the tip of the outer most cell layer, without having broken the outer most cell group at any point during the simulation. Finally, the cell green group should occupy any other spaces inside the outer brown cell group, and all spaces outside the outer brown cell group should remain unoccupied.

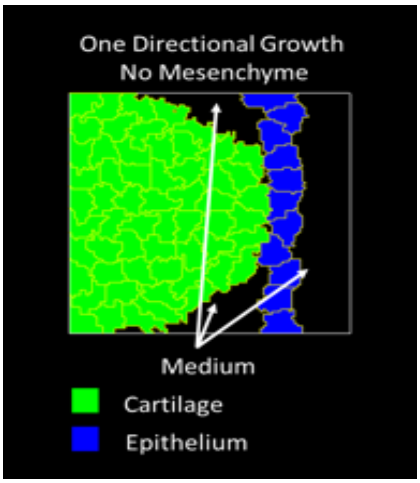
During this process, I also attempted to produce simulations using the program EmbryoMaker on the Linux operating system. The EmbryoMaker modeling framework is designed to better model epithelial cells in a three-dimensional space. However, the program was designed to work on a smaller scale with more complex cell to cell interactions, versus working on large group of cells with identical interactions at the same time.

Based on the results received in Simulation 2, I returned to reincorporate the group of mesenchyme cells into Simulation 1, to make the simulation more accurate and allow me to focus on using cell to cell group interaction to reposition existing cell groups. Simulation 3 represents the development of normal beak growth that includes the presence of an epithelium. This included a similar one directional growth pattern for the beak used in Simulation 1, as well as an outer cell group with extremely strong inter-cellular connections to act as an epithelium. The epithelium of a bird's beak is theorized to play a key role in the development of a bird beak due to possible changes in its elasticity. However, this simulation did not include a group of neutral cells to represent the mesenchyme and instead represented the area the cartilage bar grew into as on an empty space or medium indicated below.

Simultaneously I shifted my approach to focus cell proliferation during an earlier stage of bird beak development. This allowed me create mesenchyme cell in a simpler environment so I could learn how to manipulate their cell properties in my main simulation.

Cell Proliferation Control

Figure 6 – Cell Simulation 3 – One Directional Growth



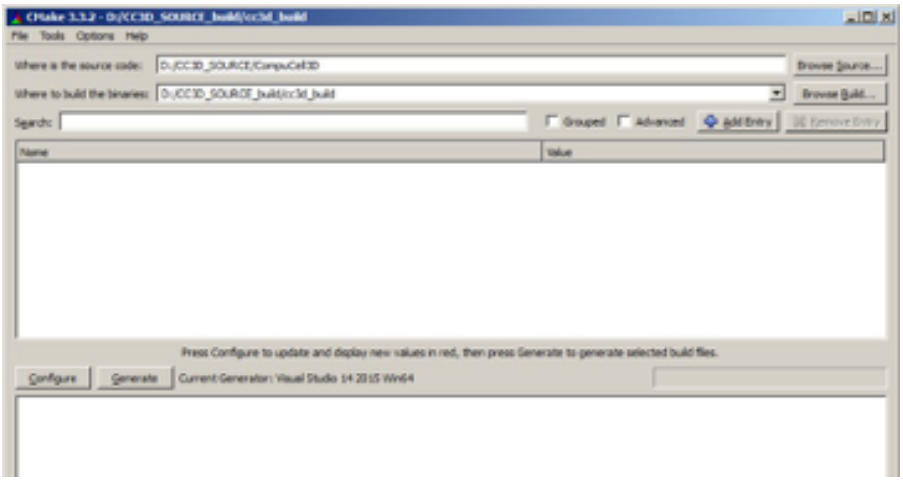


Figure 7 – CMake Interface, Source: Building CompuCell3D on Windows using Visual Studio 2015 [17]

In the Control Simulation I am attempting to model two separate identical cell groups that grow at the same constant rate to manipulate the shape of a singular outer cell group that has an extremely slow constant rate that allows it to fill unoccupied shapes in the medium that appear when it interacts with the other cell groups. There will also be one final cell group that should remain unchanged throughout the entirety of the simulation and should only serve to impede the expansion of the other cell groups. This can be accomplished by creating a cell group with no growth rate and extremely strong cell-to-cell interactions, such that this cell group could not be influenced by the others. In this simulation the two separate identical cell groups are represented by cells that are shaded blue, while the other cell group is represented by the cells that are shaded green. Finally, the group of cells that is intended to remain unchanged throughout the simulation is shaded red.

Cell Proliferation Experimental

The Experimental Simulation should be able to produce a similar, if not identical, final shape to that of the control, but should be able to accomplish this task without the presence of the red shaded cell group. This mean that this simulation will need to create its final shape solely through the use of the properties that are present in the other cell groups. To make comparing these two simulations easier, the color of the cell group will remain the same.

These simulations did not work as anticipated. I was unable to get the mesenchyme cells to interact correctly with other cell groups.

At this point I attempted to go back and incorporate neutral mesenchyme cells into the simulation that would be overtaken by the growing cartilage bar. However, I was unable to accurately simulate the behavior of the mesenchyme cells by using a singular growth rate and varying cell to cell interactions. Numerous attempts were made to produce simulations of cell groups to grow at different rate of growth, but they were unsuccessful. The various approaches that were attempted are detailed below.

The first approach was to create custom module to affect the growth of the specified cell groups. This was done by using Windows to compile the CompuCell13D source code in CMake. The first attempt was leveraging the CompuCell3D tutorial 17 to incorporate SWIG into the environmental variables so that the program could be utilized while CMake compiled the CompuCell3D source code. All attempts to download, install and incorporate SWIG into the environmental variables on both Window and Linux operating systems were unsuccessful.

Simultaneously attempts were made to leverage GIT for Windows, which includes precompiled dependencies to be utilized by the CompuCell3D program. Both GIT and SWIG needed to run simultaneously to accomplish the compiling of the source code, therefore the use of GIT for Windows was abandoned.

The second approach was compile the data using the Linux operating system.[18] Linux is an open source operating system that is available in various distributions, three of which CompuCell3D supports. These distributions would be UBUNTU, RedHat and CentOS. For UBUTU the binaries are provided through the CompuCell3D site, while RedHat and CentOS require you to compile your own binaries. To compile CompuCell3D on these 3 operating systems SWIG is required. After numerous attempts with each OS I abandoned the use of Linux.

The third and final approach was to bypass the issues by using a MAC operating system to compile the CompuCell3D source code because the Mac operating systems does not require the use of SWIG. To compile CompuCell3D on the MAC operating system the programs required include CMake and the CompuCell3D binaries. As well as I downloaded Celldraw.bat through an UNBUNTU Linux VirtualBox so I could create custom PIFF files to run on the CompuCell3D program.

I am now in the process of working with the MAC to write a custom module to interface with CompuCell3D to produce varying cell growth simulations. I am currently coding new modules that will allow me to manipulate multiple growth parameters to a greater specificity than allowed in the basic tools to CompuCell3D.

Results

Although my final simulations are not complete the intent is to produce simulations using bioinformatics and CompuCell3D that successful replicate the cell group formations that were observed on Day 5 in the facial region of the developing bird embryo. This simulation, once complete, will also demonstrated how a certain beak shape can be achieved solely through cell proliferation without the use of restrictive chemical fields.

Conclusion, Implications & Future Research

The establishment of the bird embryonic development simulation demonstrates that it is possible for the facial cell region to develop as

observed in prior research solely through the use of cell proliferation. The success of this project shows that bioinformatics can be used to model sophisticated cell behavior during embryonic development. This method could potentially be used to demonstrate and validate other theories regarding the embryonic development of birds and other animal systems including humans. It is worth investigating whether or not this same method of bioinformatics modeling can be applied to interpret more sophisticated epigenetic data. Because simulations are not technically physically observable data, all conclusion drawn from them are essentially implication.

Because of my interactions with the CompuCell3D research team, the CompuCell3D website was modified to include an area and form where users like myself can now go to for support with issues they may be encountering.

Following the completion of my cell proliferation simulations, I plan turn my efforts to the development of my original simulation of using bioinformatics and CompuCell3D to model simulations to help support the theory that external environmental factors introduced in vitro can have an impact on the development of a chicken embryo.

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The Impact of Thyroxine upon Neurogenesis after Galactic Cosmic Radiation Exposure by Margaret Quinn Gruber (WESEF paper excerpt) (Senior)

Abstract

As long-term space missions to planets such as Mars come closer to fruition, it is essential that astronauts are protected from galactic cosmic radiation on these trips. Galactic cosmic radiation (GCR) poses a risk to astronauts because they do not have the protection of Earth's magnetosphere. GCR hinders neurogenesi, the growth of new neurons in the dentate gyrus, a part of the brain responsible for sorting memories and patterns. Impaired neurogenesis results in cognitive deficits and depression, so steps must be taken to preserve neurogenesis in astronauts. Thyroid hormone stimulates neurogenesis, and GCR leads to hypothyroidism. Thyroxine, a thyroid hormone, was administered to mice in order to determine if it may act as a protective agent against GCR-induced impairment of neurogenesis. Mice were irradiated with 28Si. Doublecortin was used to visualize immature neurons in order to compare rates of neurogenesis between experimental groups. Mice which received thyroxine and no radiation showed the highest number of immature neurons. All groups which received radiation had significantly lower numbers of new neurons than the control group, but there was no significant difference between irradiated mice who received thyroxine and those who did not. Our results support current literature showing the negative impact of GCR upon neurogenesis, but thyroxine does not rescue new neurons and neurogenesis from GCR damage.

Research supported by the National Aeronautics and Space Administration.

Review of Literature

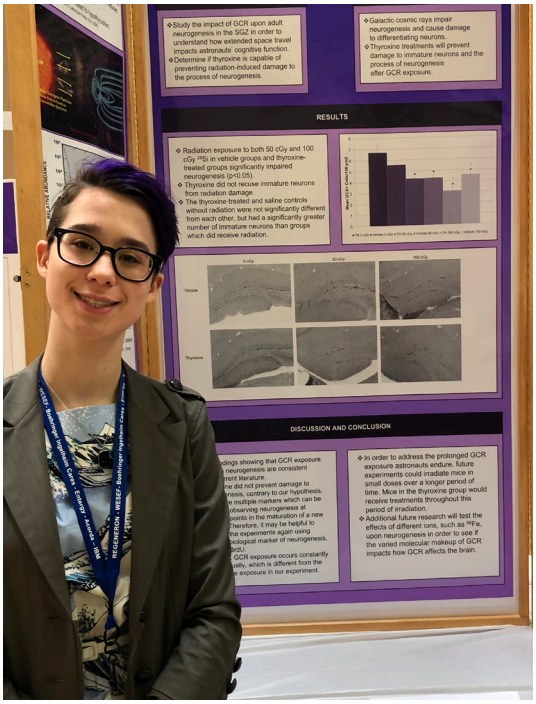
With rapid technological advancement allowing humanity to explore space further than ever before, there is a pressing need for novel ways to protect astronauts from the extreme conditions of the final frontier. One such threat is galactic cosmic rays (GCRs), which are caused by solar flares and supernova events outside of our solar system. Earth's magnetic field protects the planet from GCRs, but on planets such as Mars which lack a magnetosphere, astronauts are left vulnerable to the health risks posed by GCRs (NASA 2002).

GCRs consist of atoms whose electrons were removed as the particles traveled at light speed through the galaxy. The particle makeup of a GCR is eighty-five percent protons (hydrogen), fourteen percent helium, and one percent heavy charged nuclei (HZE) particles, which includes iron, silicon, carbon, aluminum, and other elements. Although HZE particles do not make up a large portion of GCR particles, their high energy causes them to ionize atoms inside the body, causing breaks in DNA strands which are extremely difficult, if not impossible, for the body to repair (NASA 2002; Schimmerling 2011). Therefore, HZE particles pose a great risk to the health of astronauts even though they are fewer in number than other GCR particles.

Astronauts face a myriad of risks other than GCRs on missions. However, if they suffer neurological damage while in space, their ability to handle mechanical issues and other problems will be compromised. Mice exposed to GCRs have been shown to perform worse on novel object recognition (NOR). NOR tests memory retention and degree of hippocampal function by measuring a rodent's ability to distinguish between new and previously introduced objects. Significant reductions in recognition memory were observed in mice treated with 30 centigrays (cGy, grays=Joules/kilogram) 48Ti. Neurons of the medial prefrontal cortex (mPFC) had significantly reduced dendritic complexity fifteen weeks post-irradiation, measured by number of dendritic branches, branch points, and dendritic lengths, indicating memory deficits (Parihar 2016). These results indicate that GCR exposure negatively impacts cognition and memory, so finding a treatment capable of limiting or reversing the effects of GCRs is all the more necessary to ensure the safety of astronauts on long-term missions.

The hippocampus is the section of the brain located beneath the cerebral cortex and is a part of the limbic system, which regulates emotions and memory (Yassa 2009). The dentate gyrus (DG) is a specific section of the hippocampus which is involved in the process of "pattern separation:" the sorting of neural inputs so that memories may be encoded in the CA3.

It is especially important that the hippocampus is protected from GCRs due to its role in adult neurogenesis. The subgranular zone (SGZ) of the dentate gyrus (DG) is one of two sections of the adult brain in which neurogenesis occurs (Zhao 2008). Neural stem cells are the first stage of neurogenesis, dividing repeatedly into clones of themselves until they form neuronal progenitors. Neural progenitor cells (NPCs) cannot renew themselves as stem cells can, but still have the potential to differentiate into different types of neurons. In the SGZ, NPCs most often form dentate granule cells (DGC). Running directly results in increased proliferation of NPCs in the



SGZ and improved cognition, indicating that neurogenesis is correlated with increased cognition. In addition, neural stimuli activate adult-born dentate granule cells at a higher rate than mature granule cells are activated. Models of neuron replacement in the DG imply that new DGCs do not override previous memories, but allow for a greater number of memories to be stored. Adult-born DGCs are less selective in firing, involving them in the process of "pattern integration," which is similar to pattern separation but ensures that similarities between memories are recognized by the brain. Pattern integration links memories encoded at close time points, while memories encoded further apart in terms of time are separated. These models show that DGCS born in adulthood play an important role in memory formation (Deng 2010).

GCR exposure has been shown to have a negative impact upon neurogenesis. Irradiation with either five "fractionated" 20 cGy doses or one "acute" 100 cGy dose of 56Fe particle radiation resulted in a respective 58% and 74% decrease in proliferating neurons in the DG 24 hours post-irradiation. Three months after irradiation, the fractionated radiation group had 36% fewer proliferating neurons than the sham group, while the acute radiation group had 46% fewer proliferating neurons than shams (Rivera 2014). 56Fe particle radiation has also been shown to cause significant damage to DNA, as seen by an increase in DNA damage response protein 53BP1 foci in the DG (DeCarolis 2014).

Cancer therapies utilizing radiation also negatively impact adult hippocampal neurogenesis. Since cancer treatments aim to prevent malignant cells from dividing, but lack the ability to discern between healthy and unhealthy cells, NPCs are also harmed by these therapies. Radiation used for the purposes of treating cancer in the central nervous system increased apoptosis of neural stem cells and decreased production of new neurons by 95% overall. Cognitive deficits resulting from radiation therapy include a slowing of information processing speed, memory impairments, and difficulty with word retrieval (Pereira Dias 2014).

The thyroid gland, located below the larynx, produces hormones which regulate the body's metabolism. Two types of thyroid hormone, triiodothyronine (T3) and thyroxine (T4) are produced from tyrosine and iodine. Thyroid hormones bind to two types of thyroid nuclear receptors (TRs), TRα and TRβ, which affect how genes are expressed depending on their ligand binding. When thyroid hormones bind to their receptors, gene expression is activated. The presence of thyroid hormone receptors in the hippocampus suggests an important regulation of neurogenesis at this level in the adult (Desouza 2005).

Thyroid hormones play a significant role in hippocampal neurogenesis and cognition. Hypothyroidism is linked to higher levels of depression and lowered amounts of new neuroblasts in the DG. The number of proliferating progenitor cells in the SGZ is decreased by 30% due to hypothyroidism; the reduction in progenitor cells was ameliorated with thyroxine treatments (Remaud 2007).

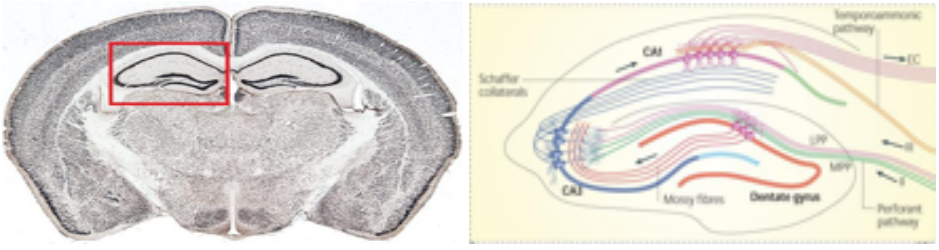


Figure 1: Coronal slice of a mouse brain (Left) The section encapsulated by the red box is the hippocampus (Richards). Detailed diagram of the mouse hippocampus (Right) (Deng 2010)

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Statement of Purpose

We aim to prevent damage to the brains of astronauts due to exposure to galactic cosmic radiation using thyroxine as a stimulating agent of neurogenesis.

(...)

Results, Discussion and Conclusion

The control groups exposed to no radiation showed significantly higher numbers of immature neurons than experimental mice exposed to irradiation, which is consistent with current literature demonstrating the negative impact of GCRs upon neurogenesis (Figures 2 and 3). Thyroxine treatments did not significantly alter the number of immature neurons, and the thyroxine group which underwent 100 cGy of radiation showed a lower amount of new neurons than the vehicle group. Therefore, this data does not support the hypothesis that thyroxine reduces harm to neurogenesis from GCR exposure. Radiation exposure in space takes place at a much slower rate than the radiation used in the experiment, multiple exposures versus one exposure, which may have impacted experiment results. Further experimentation will include examining neurogenesis at a time closer to irradiation.

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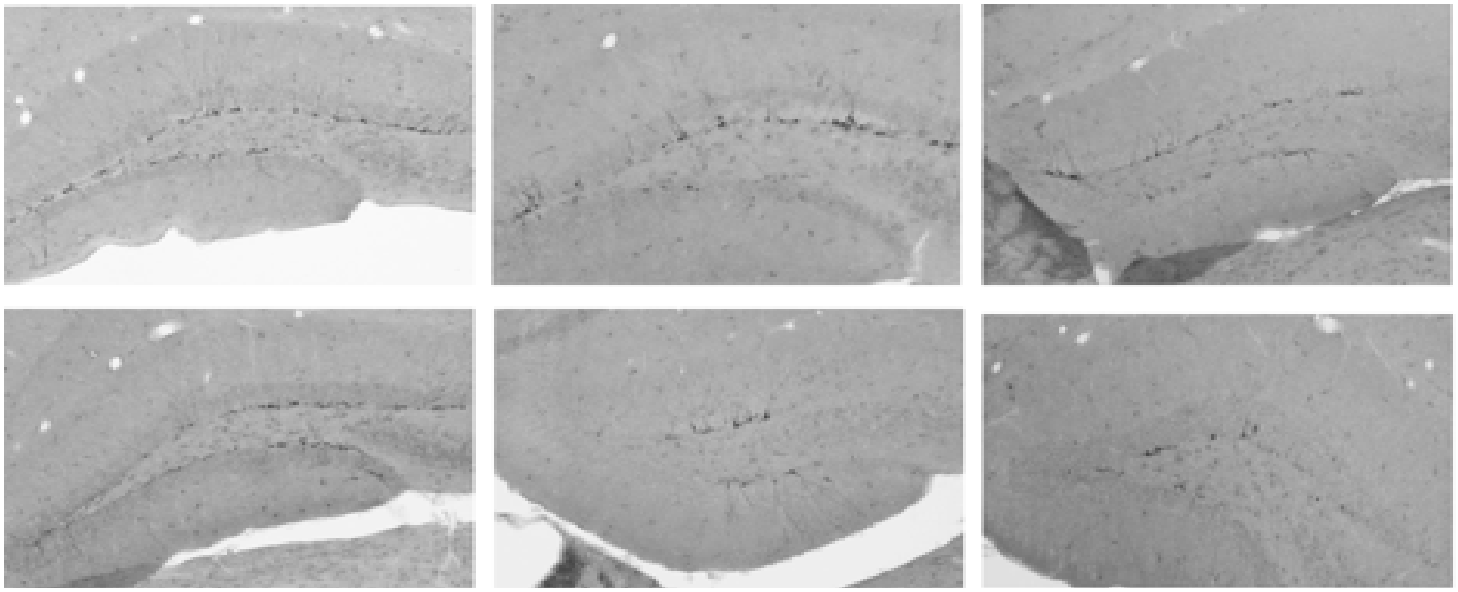

Figure 2: These photos are of the subgranular zones of mice from each experimental group. The first row received saline injections, and the second row received thyroxine. The first column was not exposed to radiation, the second column was exposed to 50 cGy of radiation, and the third column was exposed to 100 cGy of radiation.

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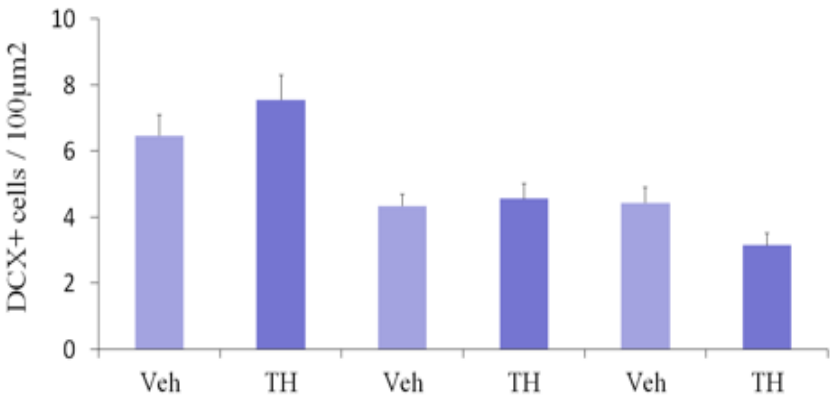
Figure 3: The two furthest left columns received no radiation. The middle two columns received 50 cGy radiation. The two furthest right columns received 100 cGy radiation. The right four columns were significantly lower ($p<0.05$) than the control groups.



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Single-Domain Antibody-Mediated Modulation of Neurotransmitter Transport by Buu-Hac Nguyen (WESEF paper excerpt) (Junior)

Abstract

The human dopamine transporter (hDAT) maintains dopamine homeostasis in the central nervous system. Substances such as cocaine or amphetamines inhibit hDAT, causing an imbalanced dopamine homeostasis that results in severe psychiatric conditions. To counteract the effect of these illicit substances or other therapeutic substances that target hDAT, it would be desirable to have available molecular tools that aid in the regulation of hDAT's activity. One promising approach is the use of small proteins that, in theory, can inhibit or stimulate hDAT function. This study analyzes the effect of nanobodies directed against a homolog of hDAT, LeuT, a bacterial amino acid transporter that serves as model system for hDAT. The performed methods focus on the isolation of two nanobodies, Nb494 and Nb499. Furthermore, the results of this study portray how the addition of nanobodies affect alanine uptake activity by LeuT. In this study, I identified two nanobodies that bind to LeuT and increase or decrease LeuT-mediated alanine uptake activity. With the similarities of LeuT and the DAT, nanobodies can later be directed against DAT to observe the effect on protein activity. If the nanobody and DAT interaction alters the function of the DAT, this may lead to the use of the DAT as a target for nanobody-based immunotherapy.

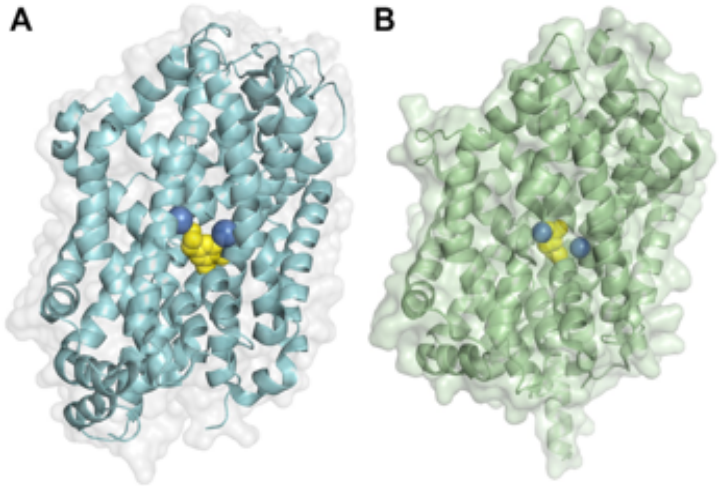
Introduction

Single-domain Antibodies (sdAb), also known as nanobodies, are antibody fragments that are derived from camelids (Cortez-Retamozo et al., 2004). Single-domain antibodies are used from camelids because the antibodies are comprised of a heavy chain homodimer rather than of light chains (Saerens et al., 2010). Studies have shown the antigen-binding portion of the heavy-chain antibodies, which constitutes the complete nanobody, has a greater tendency to interact with parts of the target that are not easily recognized by conventional antibodies because of their smaller size, which allows access to hard-to-reach areas of the target (Saerens et al., 2010). Although these nanobodies are free from light chains, the nanobodies remain fully functional (Cortez-Retamozo et al., 2004). They are stable, highly soluble, distinctly specific and have high affinity (Cortez-Retamozo et al., 2004).

Through these favorable characteristics and their minuscule size, scientists are examining the potential uses of single-domain antibodies in biosensing applications as well as treating diseases through isolating, cloning, and selecting nanobodies with specificity to the desired antigens (Cortez-Retamozo et al., 2004). The results of these studies exhibit the possible use of nanobodies in the dopamine transporter, a protein that catalyzes the neurotransmitter dopamine into presynaptic neurons.

To determine the potential use of nanobodies in biosensing and diagnostic assays, scientists secured single-domain antibodies onto biosensor surfaces with the use of multiple immobilization strategies (Pia et al., 2015). The characterization of the interaction with the single-domain antibodies' specific target was done by Surface Plasmon Resonance (SPR) biosensors, which are used to monitor biomolecular interactions due to their high sensitivity and reproducibility (Pia et al., 2015). Through the immobilization methods, scientists determined the kinetic binding constants of the immobilized nanobodies for their antigens on the different

Figure 1. This diagram illustrates the similar structure of DAT and LeuT.



surfaces. This data was compared to traditional monoclonal antibodies with their kinetic binding constants and showed that the immobilized nanobodies were the most successful in capturing molecules (Pia et al., 2015). Furthermore, the results of this study also revealed immobilized nanobodies with high affinities to their antigens and high resistance to numerous denaturing agents, such as temperature. These characteristics portray the possibility of using nanobodies in the dopamine transporter because the nanobody is likely to identify the dopamine transporter without becoming impaired.

In addition, nanobodies have the ability to treat diseases, such as cancer, by attaching to the tumor site and killing cancer cells (McMurphy et al., 2014). Previous studies have shown that nanobodies specific to carcinoembryonic antigen (CEA), a protein which appears in the blood of cancer patients, targeted a distinct non-overlapping epitope on the CEA molecule (Cortez-Retamozo et al., 2004). An experiment revealed how the nanobody conjugate stopped the growth of the tumor xenograft that was placed in nude mice (Cortez-Retamozo et al., 2004). These results show that the minuscule size of single-domain antibodies alters their biodistribution and distinctly improves access to epitopes (Cortez-Retamozo et al., 2004). The improved access to epitopes further illustrates the likelihood of using nanobodies in the dopamine transporter because of their smaller size, as compared to whole antibodies, which has better access to the dopamine transporter.

Furthermore, a previous study shows the application of specific whole antibodies in the dopamine transporter (DAT) (Ciliax et al., 1995). The antibodies were used for immunolocalization of transporter protein in rat brain (Ciliax et al., 1995). This study showed how the antibodies targeting the N-terminus and the C-terminus were specific to the expressed cloned DAT, recognized the transporter protein and were sensitive to the excess homologous fusion protein (Ciliax et al., 1995). The results of this study prove how the generation of specific DAT antibodies will allow further characterization of the cellular as well as subcellular localization of DAT protein (Ciliax et al., 1995).

Compared to whole antibodies, nanobodies are significantly smaller, which alters the biodistribution of the single-domain antibodies and improves access to the target. Other advantages of nanobodies against regular antibodies are the ability to block certain proteins for biochemical/crystallographic studies, can be screen for specifically desired conformation, and can be produced from libraries in E. coli. Nanobodies also show high affinities for their target and remain stable under denaturing agents; with these superior characteristics, nanobodies portray potential use on the dopamine transporter. The use of nanobodies on the dopamine transporter exhibit promising advancements in immunotherapy.

The other part of the study involves the similarities in structure of the DAT and LeuT (Penmatsa et al., 2013). The DAT functions through cotransport, pumping dopamine out of the synaptic cleft and into the neuron interior. This is important as dopamine plays a critical role in movement, reward, behavior, and more. The DAT allows the conclusion of dopamine neurotransmission and therefore maintains dopamine homeostasis in the central nervous system. The similarity in structure between the dopamine transporter and the leucine transporter provides a reliable template to determine DAT structure-function predictions.

Statement of Purpose

The first goal of this study is to direct the nanobodies against the LeuT, a model similar to the DAT. The second goal of the study is to research the advantages of using nanobodies to characterize the DAT. Additionally, to research if and where the nanobody binds to the DAT and if this interaction alters the function of the DAT, allowing them to be used as immunotherapy agents. If nanobodies are engineered against LeuT, the nanobodies can later be characterized and tested against the DAT. Additionally, if monoclonal antibodies can be used for immunotherapy by binding to the dopamine transporter then nanobodies exhibit potential in the advancement of immunotherapy due to the nanobodies' smaller size, widespread biodistribution, and high stability.

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Results

The Coomassie-stained SDS-PAGE gel of the two purified nanobodies 494 and 499 were subjected to size-exclusion chromatography. Thus, after

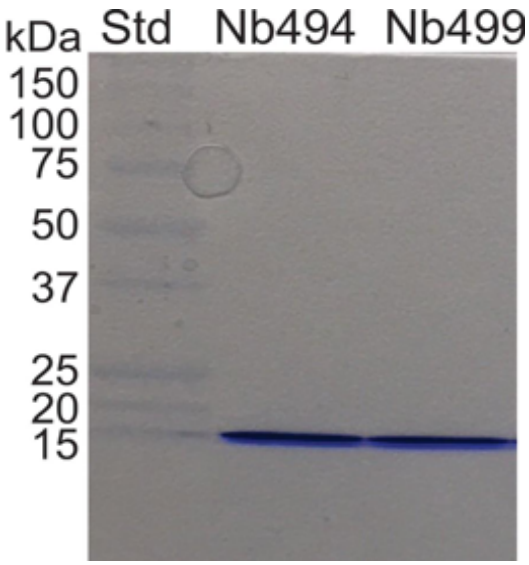

Figure 2. Coomassie-stained SDS-PAGE gel of the two purified nanobodies 494 and 499. The leftmost column provides the standard while the dark blue lanes represent nanobodies 494 and 499.

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the protocol, the proteins are found in a highly pure form as I was able to purify the two nanobodies to apparent homogeneity.

The time course of 3H-alanine uptake was tested in proteoliposomes that contain LeuT. Uptake was performed in the absence or presence of Nb494 or Nb499. With Nb494, uptake of 3H-Ala was almost completely inhibited, whereas, in stark contrast, uptake in the presence of Nb499 was about double of that observed for LeuT in the absence of a Nb.

Discussion

The image of the Coomassie-stained SDS-PAGE gel of the nanobodies 494 and 499 exhibits the proteins after being subjected to size-exclusion chromatography. Thus, the proteins are found in a highly pure form. Referencing the graph displaying the uptake of alanine by LeuT-WT in the presence and absence of nanobodies 494 and 499, the presence of nanobody 499 reaches 20 nmo/mg LeuT which portrays a double alanine uptake. Additionally, uptake by LeuT-WT with the presence of nanobody 494 looks similar to the uptake of the liposomes, the control; this indicates the presence of nanobody 494 inhibits uptake of alanine. Overall, the graph exhibits how the addition of nanobodies affect alanine uptake and increases or decreases leucine activity. Following, nanobodies directed against the LeuT affect protein activity. The results exhibit how nanobody 499 increases the uptake, activating the transport protein more than the normal LeuT-WT. This raises the question of which section of the protein transporter is enhanced. Meanwhile, nanobody 494 shuts down the activity of the leucine transporter. Thus, the nanobodies 494 and 499 have the ability to affect the activity of the transporter. With the similarities of the LeuT and the DAT, nanobodies can later be directed against DAT to observe the effect on protein activity.

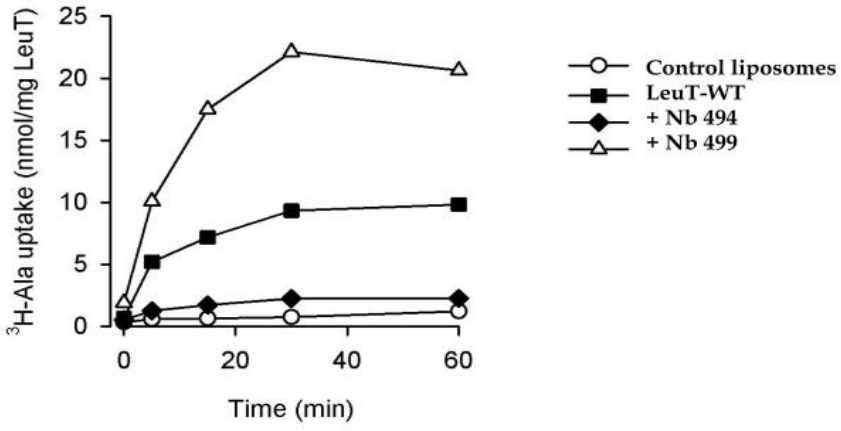

Figure 3. This graph exhibits a time course of the uptake of liposomes, the two nanobodies 494 and 499, and LeuT-WT. As shown, the uptake of the liposomes act as a control. LeuT-WT shows an uptake but then plateaus at 10 nmo/mg LeuT. + Nb 499 reaches 20 nmo/mg LeuT and plateaus. Additionally, + Nb 494 uptake looks similar to the control liposomes.

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Pollinator Landing Frequency after Floral Modification of Tagetes patula, French Marigolds by Thea Barbelet (WESEF Paper) (Junior)

Abstract

Pollination has been occurring for millions of years. Over time, different species of pollinators and angiosperms, or flowers, have adapted to increase the efficiency of the process. Through evolution, angiosperms have developed different ways to draw pollinators in, have them pick up pollen, and then transfer that pollen to another flower, over and over again. Specifically, some flowers began to show close range visual guides in the form of ultraviolet markings to gain the attention of insects. These ultraviolet markings look like dark rings to the eyes of most pollinators, and in this study we evaluate the relationship between the presence of these markings, and the frequency of pollinator visits. Natural sunscreen is used to inhibit the reflectance of close range visual guides on Tagetes patula, or French marigolds, and the results showed that inhibiting these markings decreased the number of pollinator visits. The results of this study may lead to a way to help stop invasive plant species from being pollinated, and therefore limit their spreading.

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Conservation Biology

Director of Environmental Stewardship

Teatown Lake Reservation

Introduction

Fossil evidence dates the first existence of pollinators at nearly 100 million years ago (Peñalver et al., n.d.), and amber from Cretaceous New Jersey holds a 96 million year old member of the Apoidea superfamily (Michener & Grimaldi, 1988). Flowers, or angiosperms, are plants that reproduce using seeds. Before angiosperms, before plants evolved to have petals around their respective sex parts, they would instead release all of their pollen into the wind, and most of it would not reach the desired destination, which was the female sex parts of plants of the same species. If pollen does not reach a plant of the opposite sex, the plants will not reproduce and the species may eventually die out. Clearly, this process was futile, and eventually, evolution resulted in a more effective system. Plants developed white petals, creating early angiosperms, which allowed insects to differentiate plants from the rest of the landscape. Early pollinators would seek out plants because pollen provided a steady food source, but some angiosperms began to also produce nectar, which has a high sucrose content and provided an even more enticing reward. As each insect visited a flower to feed, pollen stuck to its body, and was then transferred to the next visited flower, and with this new method of pollination, pollinators were established (Goulson, 2014).

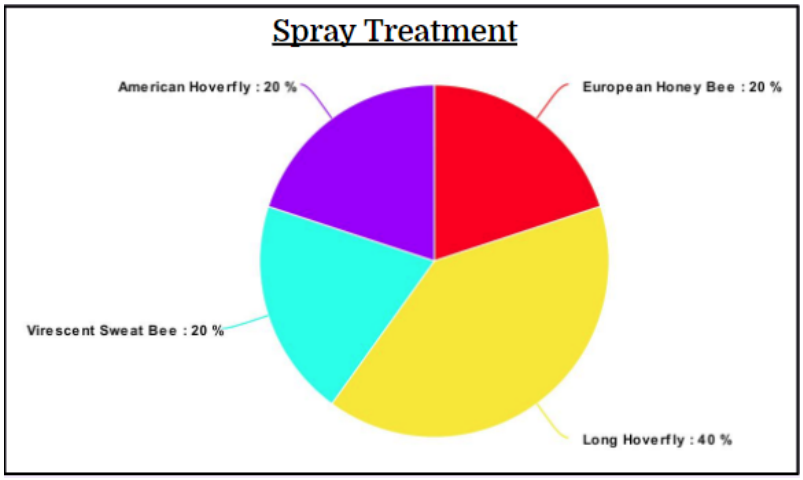
Fig 2: Shows a group of French marigolds
The flowers were temporarily marked with flags to randomly select blossoms for treatment

Since then, both pollinators and flowers have greatly evolved, but the importance of their symbiotic relationship has not diminished. In New York specifically, frequent pollinators include European honey bees, common eastern bumble bees, yellow-masked bees, virescent sweat bees, pearl crescent butterflies, American hoverflies, and long hoverflies (Matteson, 2014). While European honey bees are the most effective pollinators, contributing $20 billion worth of crops to the American economy and $200 billion worldwide (Fairbrother, Purdy, Anderson, Fellk, & Bellevue, n.d.), other pollinators serve more niche purposes and should not be overlooked. Some flowers have developed incentives for specific pollinators, referred to as floral guides (Horth, Campbell, & Bray, 2014). For example, the bucket orchid will attract only male orchid bees with a specialized scent, and the structure of the orchid allows only these male orchid bees to pollinate it (Schnepf, Deichgräber, & Barthlott, 1983).

Furthermore, pollinators have varying types and degrees of vision. Most research focuses

Fig 1: Rudbeckia hirta flower heads under normal and ultraviolet light. The ultraviolet light allows humans to see flowers the same way honey bees do, with a thick reflecting floral guide ring around the center of the floral head, acting as a bull's eye. (Horth et al., 2014)

on honey bees, which see on the same spectrum as humans (Hempel De Ibarra, Vorobyev, & Menzel, 2014). Honeybees can see all parts of the spectrum that humans can see, except for red hues. Honey bees can additionally see into the ultraviolet end of the spectrum, while humans cannot. Most likely not by coincidence, but due to years of adaptation, some flowers have ultraviolet markings, which are visible to bees in a variety of ways, but most commonly as a dark ring around the center of the flower (Orbán & Plowright, 2014). These markings are considered close range visual guides, and serve to draw pollinators into the center of the flower, similar to a bull's eye. Close range visual guides help flowers to be pollinated, and also reward the visitor with nectar (Horth et al., 2014; Menzel & Shmida, 1993).



Statement of Purpose

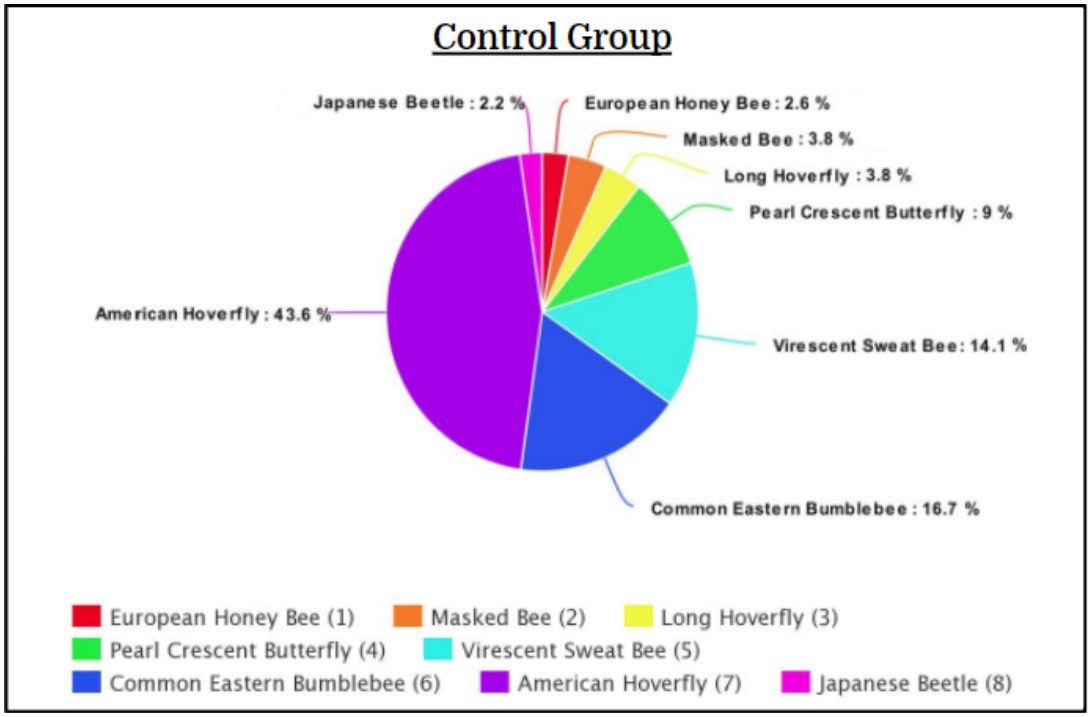
In the present study, we analyze the relationship between the presence of strong ultraviolet floral guides on Tagetes patula, or French marigolds, and frequency of pollinator visits to learn more about how insects see the world. If close range ultraviolet floral guides have a significant role in attracting pollinators, then their modification may affect the frequency of pollinator visits, offering the ability to lessen the pollination of invasive plant species. Removal of close range floral guides on ornamental, or maintained, plants can keep them in gardens and out of the rest of an ecosystem, since they may no longer be pollinated. While each pollinator species has different characteristics, a broad study can offer a basis for further research on each individual species, and also other plant species. Nonetheless, there is always more to learn about pollinators and their respective flora, and any research may stand to offer solutions to current or future problems.

Hypothesis

If the floral guides of the French Marigolds are modified, then the frequency of pollinator visits will decrease, because pollinators rely on vision to effectively find flowers.

Materials and Methods

French marigolds were selected for their strong ultraviolet close range visual guides. A bloom of French Marigolds were commercially purchased, and each blossom was inspected with an ultraviolet flashlight to ensure the presence of ultraviolet markings.



After purchase, the flowers were divided into three groups: two study and one control. Each group contained ten blossoms, with 30 blossoms total. The flowers were taken to a fenced in wildflower garden with a small apiary containing a single European honey bee colony. They were then split into two groups, with 15 blossoms each. One group was placed flush against one row of wildflowers, while the other group was placed on the other side of the row. After random selection, five blossoms were left as controls. The next five blossoms were treated with natural

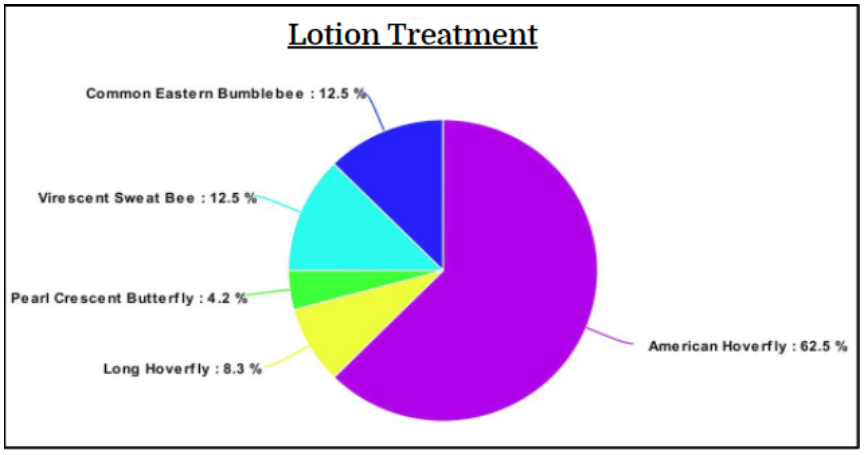
lotion sunscreen, which inhibited the reflectance of the ultraviolet markings, making them invisible. Five more blossoms were treated with natural spray sunscreen, again inhibiting the close range visual guides. Both sunscreens were the same brand, and each ingredient was checked to ensure that the visiting insects would not be harmed. Once both groups were treated with sunscreen, the frequency of pollinator visits was recorded for five minute intervals. After each five minute period, the position of the two groups were swapped, and then after ten minutes, the groups of flowers were moved farther down the row of wildflowers. This process was repeated.

Results

The control group had a total of 78 pollinator landings. The majority of landings were made by the American hoverfly, with 44%, while the European honey bee only accounted for 2.6% of the landings. The lotion treatment group had a total of 24 landings. The majority of landings were again made by the American hoverfly, with 62.5%. Lastly, the spray treatment group had 5 total landings, with the Long hoverfly this time having 40% of all landings.

Overall, the control group had more visits than either of the treatment groups. The Chi-square test was very significant, refuting the null hypothesis of an equal distribution of pollinator visits in each group

Japanese beetle visits were omitted due to being a minor pollinator, but had minimal outcome on the results of both tests. The pollinators accounted for included European honey bees, common eastern bumble bees, yellow-masked bees, virescent sweat bees, pearl crescent butterflies, American hoverflies, and long hoverflies, and the group was diverse.



Discussion/ Conclusion

In this experiment, we compared the frequency of pollinator visits after the inhibition of ultraviolet close range visual guides. Understanding pollination is vital for maintaining our ecosystem. Both species of hoverfly were the most frequent pollinators, despite their ineffectiveness when pollinating. This may have been a result of the additional scent of the sunscreen, which added the smell of lavender and green tea to the French marigolds, and hoverflies have a great attraction to scent (Larson, Kevan, & Inouye, 2001). The European honey bees' flower blindness, the fact that honey bees will not visit a flower until it has been in their environment for some time, may have kept a greater number of honey bees from visiting the flowers, as they were only present in the environment for a short period of time (Orbán & Plowright, 2014). The orange-red color of the French marigold may have also prevented more bees from visiting the blossoms, as mentioned before, they cannot see red hues. Albeit, the color may have attracted more pearl crescent butterflies, who can see the hue (Frentiu et al., 2007).

Some additional problems were encountered during the study that may have led to unsatisfactory results include: overall lack of time, season, weather, financial restrictions, and only one accessible study site. Future studies may be proposed to further investigate the white coloring of the lotion sunscreen versus the clear spray sunscreen, varying eye structure of each pollinator, and a wider set of both flora and fauna subjects.

In conclusion, the hypothesis was supported, but more thorough testing may yield stronger and more reliable results. The revised hypothesis states: if the natural color, scent, and ultraviolet markings of French marigolds are modified, then the frequency of pollinators will decrease, because sight and smell direct pollinators to the flowers.

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Fig 4: Results of the post-hoc test show that the comparison between the control and spray groups was significant

Treatments Pair	Tukey HSD Q Statistic	Tukey HSD P-value	Tukey HSD inference
Control v Lotion	2.8664	0.1342341	insignificant
Control v Spray	3.8939	0.0332603	* p<0.05
Lotion v Spray	1.0276	0.7381012	insignificant

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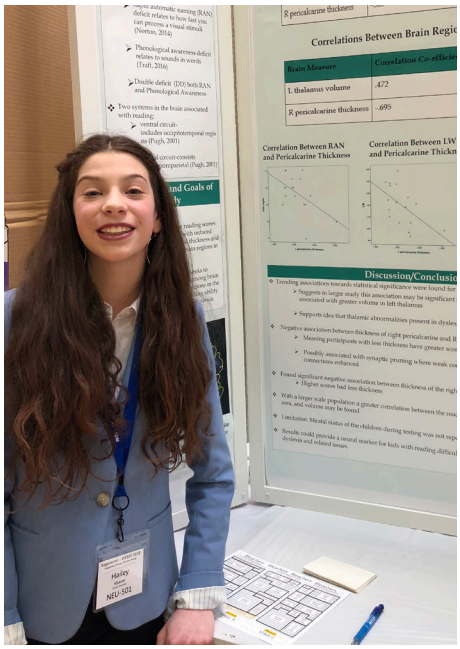
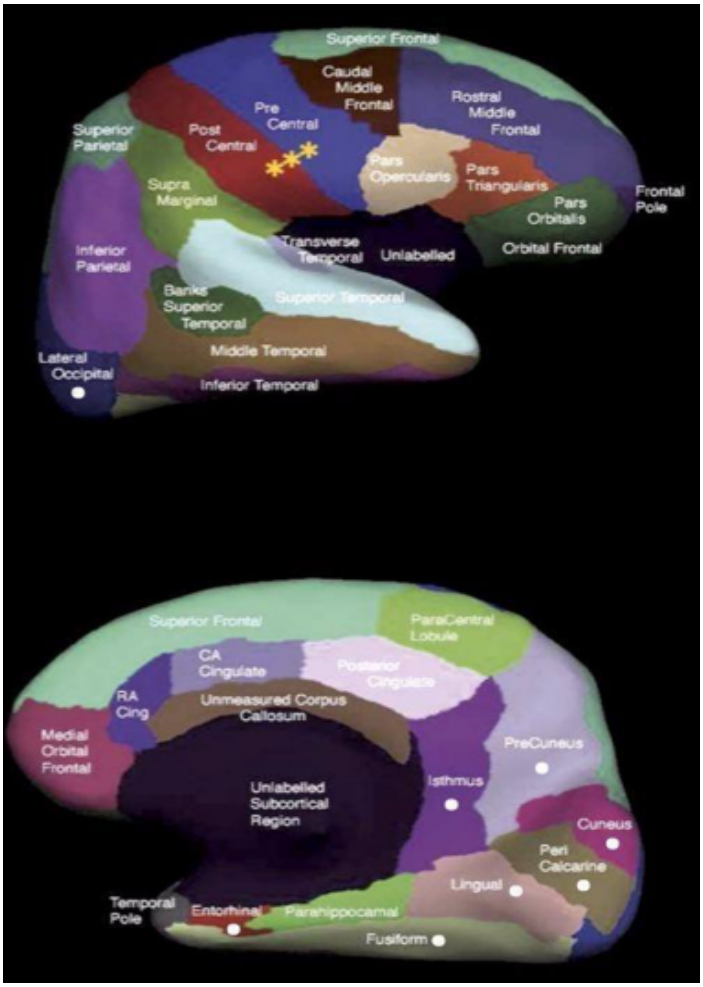
Examining Neural Structure of the Visual System Related to the Reading Ability of Young Children by Hailey Kissner (WESEF Paper) (Junior)

Abstract

This study investigated brain structure as it relates to reading and the dual deficit model of dyslexia. In this research, differences associated with brain structure and reading scores were found, which could relate to dyslexia. Dyslexia is hypothesized to have three subtypes including rapid automatic naming (RAN), phonological awareness deficits, and double deficit consisting of both RAN and phonological awareness. Lower RAN and phonological awareness scores have been shown as a strong indicator of poor reading. Based on current research, MRI results have demonstrated atypical surface area, cortical thickness, and volume in multiple brain regions which have been associated with lower reading scores. Participants in this study were 6-7 years old and had to undergo an extensive set of standardized reading, language, and cognitive measures. An MRI scan was obtained for each subject and analysis was performed on regions of the brain involving the visual system including the precuneus, fusiform gyrus, entorhinal cortex, lateral occipital cortex, lingual gyrus, cuneus, pericalcarine cortex, the isthmus of the cingulate gyrus, and right and left thalamus were analyzed. There were significant negative associations between the thickness of the right pericalcarine region with letter word identification (LW) and RAN. Also, there was a trending association between the volume of the left thalamus and RAN. Children with less thickness in the right pericalcarine regions were found to have higher scores on the RAN and LW tests. However, larger scale studies are warranted to confirm these findings.





Introduction

One of the most One of the most prevalent learning disabilities is dyslexia, affecting 4 – 10 % of the population (Pijpker, 2013). According to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), "Dyslexia is an alternative term used to refer to a pattern of learning difficulties characterized by problems with accurate or fluent word recognition, poor decoding, and poor spelling abilities." (p.67, DSM-5). Although dyslexics struggle with reading and writing, the disability does not impact the individual's' overall intelligence. In fact, many dyslexics are extremely successful despite adversity. Visual processing is one important component of reading that is engaged in both reading and Rapid automatic naming, also known as RAN, so the following study is looking at brain regions and performance on these assessments. Since reading relies on the visual system to process text, I am interested in brain regions related to this aspect of reading.

Literature Review

One leading hypothesis holds that children with dyslexia are made up of three subtypes: rapid automatic naming (RAN) deficit, phonological awareness deficit, and double deficit (DD) consisting of both RAN and phonological awareness. In order to investigate the double-deficit hypothesis, extensive research has been conducted. For instance, researchers have tested adolescents in areas relating to the specified subtypes through color naming, digit matching, and math expression problems and found that dyslexics performed worse than the control group. Children presumed with the DD hypothesis scored significantly lower in the reading and word decoding tasks (Träff, 2016). Additionally, dyslexics completed fewer math problems during the math fluency and calculation tasks and had difficulty with symbolic number comparisons. (Träff, 2016). Norton et al. (2014) assessed a group of poor readers and normal readers while completing tests of phonological awareness and RAN (double-deficit hypothesis) during brain imaging with functional MRI (fMRI). Individuals with dyslexia showed a dissociation between brain regions that were sensitive to phonological awareness (left inferior frontal and inferior parietal regions) and RAN (right cerebellar lobule VI) (Norton, 2014). The authors found that the DD group scored the lowest on the reading ability tasks. There was little difference between the reading ability according to the testing of the DD and single phonological deficit individuals (Norton, 2014).

RAN is one reliable indicator of literacy and is characterized as the capacity to quickly list an assortment of repeating items including numbers, objects, letters, and colors. Amid a RAN test, the time taken to name the visual stimuli shown is recorded and is thought to parallel the cognitive and neural demands for proper reading. In readers, RAN has been shown as a strong indicator of reading achievement (Ozernov, Gaab, 2016) . RAN is known to be associated with brain regions including the left inferior frontal gyrus, left posterior middle frontal gyrus, bilateral inferior occipital areas, and was less strongly correlated with the left parietal and right frontal areas (Pugh, 2001; Norton, 2014). Another strong predictor of reading ability is phonological awareness, a skill used to recognize and manipulate parts of a spoken language such as words and syllables. This skill has been deemed an indicator of dyslexia. During a phonological awareness test, individuals must complete tasks related to the sounds of words like rhyming and decoding. Several studies have looked at phonological awareness and its associated brain regions like the superior temporal gyrus, middle temporal gyrus, superior frontal gyri, and fusiform gyrus (Morken, Helland, 2014; Kovelman, Norton, 2012). Similarly, the left inferior frontal gyrus and the left middle frontal gyrus are both associated with RAN and phonological awareness (Kovelman, Norton, 2012). Other brain regions will be important for various aspects of reading since reading is a complex task that requires the support of many cognitive processes.

The brain has two systems associated with reading, the ventral circuit, and the dorsal circuit. The ventral circuit includes occipitotemporal regions (point of contact between the ventral visual stream and middle-inferior temporal) and is associated with speech, fluency, word recognition, phonological reading, silent reading, and naming. For example, the fusiform gyrus or visual word form area is one such structure in the ventral circuit, this region stretches across the basal surface of the temporal and occipital lobes, it has been found to play an important role in word processing (McCandliss, Dehaene, Cohen, 2003). Also, the lingual gyrus, located in the occipital lobe is a part of the ventral system and plays a role in color perception, and is linked to processing vision, especially related to letters. It is thought to be involved in the analysis of logical conditions (i.e. logical order of events) and encoding visual memories (Bogousslavsky, Miklossy, 1987; Raschle, Chang, 2011). Like the other aforementioned parts of the brain, the lateral occipital cortex (located in the occipital lobe) also in the ventral system and has more general sensory functions, but it still imposes important functions such as the processing of tactile and visual information like object processing (Margalit, Shah, 2016). In contrast, the dorsal circuit is located in the temporoparietal areas of the brain and consists of the supramarginal gyrus and the angular gyrus, which are thought to be associated with phonological processing (Pugh, 2001). Specifically, the precuneus which is located in the dorsal circuit and is a part of the front of the occipital lobe was found to be associated with visual-spatial processing (Trimble, Cavanna, 2006). The isthmus, the posterior portion of the cingulate gyrus is also a part of the dorsal system, this region is located at the junction of the forebrain in the parietal lobe and has been associated with emotion processing, learning, and memory (Webb, 2017; Johns 2014; Desikan, Segonne, 2006).

Other areas used in this study that are not specific to the dorsal or ventral systems, but have more basic sensory functions are the thalamus, cuneus, pericalcarine gyrus, and the entorhinal cortex. The thalamus, the dorsal part of the diencephalon which is mainly interconnected with the cerebral neocortex, is between the cerebral cortex and the midbrain (Bear, 2007). This region is responsible for relaying motor and sensory information (including visual signals) to the cerebral cortex. The cuneus, located between the calcarine fissure and the medial part of the parieto-occipital fissure in the occipital lobe, is responsible for visual processing such as spatial frequency, orientation, and motion (Gray, 1918). Another general sensory region is the entorhinal cortex, located in the temporal lobe serves as the interface between the hippocampus and the neocortex (Joseph, 2000). Additionally, this area is important for processing impulses from eye and ear and plays a role in memory formation navigation. Lastly, the pericalcarine cortex or Primary Visual Cortex is responsible for receiving and processing impulses from optic nerves are located in the occipital lobe (Visual Processing: Cortical Pathways, n.d). The aims of this study are to investigate brain regions that may support visual aspects of reading because deficits in visual processing contribute to poor reading. Therefore a selection of the specified areas of the brain listed above will be analyzed (Margalit,

Shah, 2016).

I hypothesize that MRI results and associated behavioral data with lower reading scores will have less surface area and cortical thickness in the precuneus (Trimble, Cavanna, 2006). In contrast, people who performed better on the reading tasks most probably will have more surface area and cortical thickness in those specific regions. According to other studies comparing normal readers' scores on visual learning tasks to dyslexics, there was a major deviation between the performance of dyslexic individuals and non-dyslexics, therefore, suggesting dyslexics have a deficit with visual-spatial processing (Richlan, Kronbichler, Wimmer, 2013). This deficit in dyslexia may be linked to the reduced gray matter structure of the precuneus. The fusiform gyrus or visual word form area showed more activation in normal readers while reading compared to dyslexics who had a minimal indication of activation in this area of the brain (McCandliss, Dehaene, Cohen, 2003). A lack of activation in this region of a person with dyslexia's brain could be related to reduced surface area and cortical thickness and may look similar to an individual in this experiment with lower scores on reading tests. In one study, lesions located in the temporal lobe (area of entorhinal cortex) resulted in impaired recognition memory for tactile and recurring visual stimuli. Since dyslexics have these impairments, the cortical thickness and surface area of the entorhinal cortex in lower reading scores may be smaller which would explain these symptoms (Schröder, Haak, 2015). The lateral occipital cortex is associated with general visual processing. Since it has been discovered that dyslexia has both an auditory and visual perception deficit (Margalit, Shah, 2016), my hypothesis is that this deficit may be linked to the reduced gray matter structure (surface area and cortical thickness) in the lateral occipital cortex of the poorer readers. Studies have shown differences in brain structure in the lingual gyrus, therefore, I think that both the surface area and cortical thickness are lower with the lower reading scores (Raschle, Chang, 2011). Relating to the cuneus, a study comparing a dyslexic brain to "normal" individuals, activation occurred for the average readers in the cuneus while reading, while there was no activation in the brain of the dyslexic readers. This lack of activation may be related to reduced surface area and cortical thickness and may correlate with lower reading scores (Olulade 2015). In the pericalcarine cortex or Primary Visual Cortex individuals with dyslexia showed reduced activation compared to the control, normal readers (Demb, 1997). Specifically, this lack of activation could account for a lacking amount of surface area and cortical thickness in the pericalcarine cortex and may be associated with the lower reading scores. According to a study, the isthmus of the dyslexic brain is smaller than in typical readers. Therefore, I think the surface area and cortical thickness will be lower with the lower reading scores (Paul, 2011). The Thalamus, the dorsal part of the diencephalon which is mainly interconnected with the cerebral neocortex between the cerebral cortex and is responsible for relaying motor and sensory info to the cerebral cortex. I think that the amount of volume in this region will be lower with the lower reading scores in this region because it has been shown in neuroimaging dyslexia studies that thalamic anomalies are present (Fan, Davis, 2014).

Correlations between RAN and Brain Regions

Control Variables			RAN_digits	lh_thalamus_vol	rh_pericalcarine_thickness
etiCVcm2	RAN_digits	Correlation	1.000	.472	-.695
		Significance (2-tailed)	.	.065	.003
		df	0	14	14
	lh_thalamus_vol	Correlation	.472	1.000	-.205
		Significance (2-tailed)	.065	.	.446
		df	14	0	14
	rh_pericalcarine_thickness	Correlation	-.695	-.205	1.000
		Significance (2-tailed)	.003	.446	.
		df	14	14	0

Goals of Study

The following study seeks to identify associations among brain structure of various regions in the visual system and reading ability. The research will determine if there are structural associations with lower reading scores which could be related to dyslexia. Possibly, these results could provide a neural marker for

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kids with reading difficulties and aid in the diagnosis process of dyslexia and related issues. Additionally, this could help identify aspects of brain structure associated with individual differences in reading. (...)

Hypothesis

I predict that lower reading scores will be associated with reduced surface area, cortical thickness and volume in a set of brain regions in the visual network that may support reading.

Results

Results 1. RAN and Brain Region correlations. There was a significant negative association between thickness of the right pericalcarine region and RAN (R(14) = -.695, p = .003. Also, there was a trending positive association between the volume of the left thalamus and RAN (R(14) = .472, p = .065). This suggests that on a larger scale the association with this brain region might be significant.

Results 2. LW and Brain Region Correlations. There was a significant negative association between thickness of the right pericalcarine region and LW (R(14) = -.585, p = .017).

Result 3: Brain Region areas and Reading Test correlation

As for the cortical surface area, no correlations were found for RAN or LW in any brain region.

Correlations Between Brain Regions and LW

Control Variables			LW_SS	rh_pericalcarine_area
etiCVcm2	LW_SS	Correlation	1.000	-.060
		Significance (2-tailed)	.	.827
		df	0	14
	rh_pericalcarine_area	Correlation	-.060	1.000
		Significance (2-tailed)	.827	.
		df	14	0

Discussion of Results and Conclusion

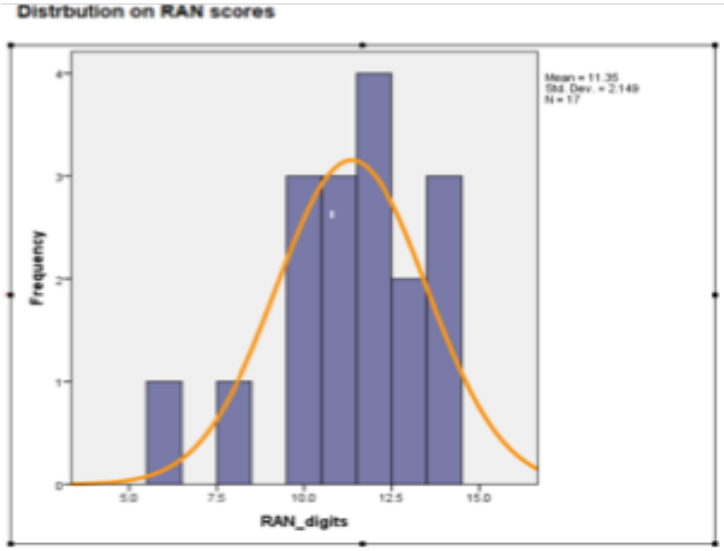
We ran a false discovery test for multiple comparisons to further prove our findings. However, it gave us a p value threshold of .0008, therefore, our results are not corrected for multiple comparisons but they are significant at the standard threshold of .05.

There was a large negative association between thickness of the right pericalcarine region and RAN; what this means is that individuals with less thickness have higher scores on the RAN test. These findings could be associated with synaptic pruning, a process in which weaker synaptic connections are eliminated and stronger connections are preserved and strengthened. In synaptic pruning, the contacts that are enhanced or pruned are determined by experience. In this case, it is assumed that in order to form a more effective pathway pruning cuts away connections in the brain to make stronger ones. There was a trend towards statistical significance between the volume of the left thalamus and RAN scores. This suggests that in a more high powered study, the association of RAN with this brain region may be significant. So in the future, it is possible that we might find that higher RAN scores are associated with higher volume in the left thalamus. This would support the idea that in dyslexia there are thalamic abnormalities and explain speech deficit and RAN deficit in dyslexia since the thalamus is responsible for sending sensory information to the cerebral cortex. The significant negative association between thickness of the right pericalcarine region and LW means that individuals with higher scores on the LW test had less thickness in the right pericalcarine region. A study of sighted, impaired vision, and blind individuals brain structure further supports these findings because more thickness was found in the right pericalcarine of the blind than the other groups (The Brain From Bottom To Top, n.d). Additionally, visual impairments were found to be associated with a lack of synaptic pruning in the visual cortex (Burton, Zhu 2003). As previously discussed in relation to RAN, synaptic pruning may also be responsible for the specified result of the letter word test. For instance, in order to create a more effective pathway pruning eliminates connections in the brain which may account for why there were less thickness and higher scores in the right pericalcarine. As previously mentioned, trending associations could prove to be significant in future studies. Also, trending associations were found between region a with more basic sensory functions not located in the ventral or dorsal circuit, the thamus.

Possible limitations of this study may be that most children had high scores on the RAN and Letter Word tests because the sample does not have a lot of variability in their mean scores (RAN:11.35, LW:119.71) as seen in Figures 3 and 4.

Additionally, the mental status of the children during behavioral testing was not reported; therefore, the test results may not be an accurate representation of their performance. Perhaps with a larger scale population, a greater correlation between the reading tests and cortical thickness, surface area, and volume may be found. Hopefully, these results could provide a neural marker for kids with reading difficulties and aid in the diagnosis process of dyslexia and related issues.

Figure 3



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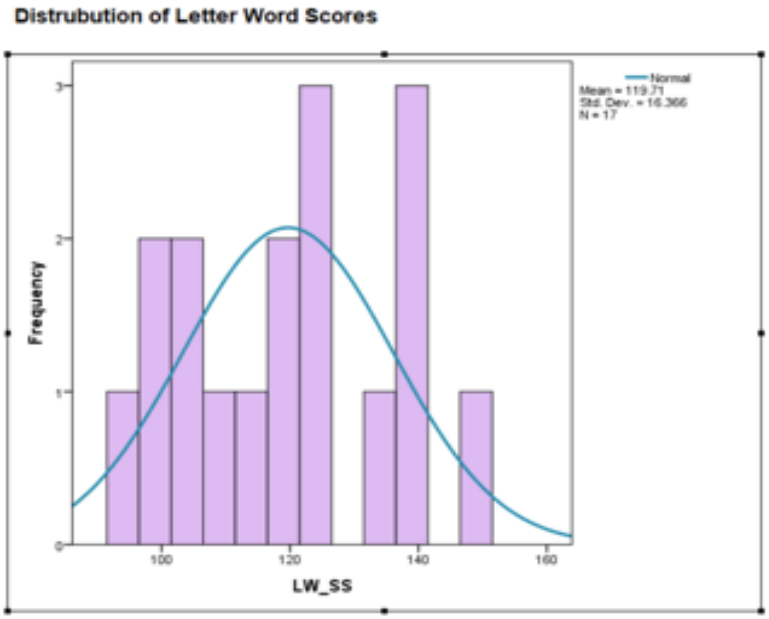

Figure 4

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A Study on Long Term Memory by Supriya Baskaran (Junior)

Long term memory (LTM) is information retained by the human brain for more than a couple of days up until death. The formation and recollection of long term memory is a complicated process that involves several steps including encoding, consolidation, storage and retrieval. The encoding process takes place in the brain, and occurs when neurons fire rapidly, due to your senses perceiving an important or traumatic event (Tulving, Kapurt, Craik, Moscovitch, & Houlet, 1994).When neurons are fired rapidly, the experience becomes more intense and you are more likely to remember that particular event. This biological conceptualization of a memory is referred to as an engram (Ramirez, Tonegawa, & Liu, 2013).

Episodic memory is a type of explicit and long-term memory, that allows humans to recall personally experienced events (Tulving et al., 1994). Although there are several reliable sources that have conducted studies and obtained results about variables affecting the encoding and retrieval processes, scientists needed the positron emission tomography (PET) scan to understand the neuroanatomical correlates of the encoding process (Tulving et al., 1994). Tulving and his associated conducted a study utilizing the PET scan to determine that there was correlation between blood flow and memory encoding. During the study they observed that while the brain was engaging in "deeper" encoding activity there was a prominent increase in blood flow to the left prefrontal region, but no significant change on the right hemisphere of the prefrontal region (Tulving et al.,1994). This helped scientists cement the idea that the prefrontal cortical regions are involved in episodic memory, and that there is a prefrontal hemispheric asymmetry in the encoding and retrieval processes of memory.

Scientists have also conducted studies to determine if individuals are able to recognize explicit memories without awareness that they are doing so (Craik, Rose, & Gopie, n.d.). They conducted an experiment where individuals were had to recognize pictures in a set time constraint, while encoding was performed under full attention, (FA), or divided attention,(DA) (Craik et al., n.d.). During this study they found that individuals were able to recognize more images while encoding was done under full attention however, when individuals were forced to guess about which images they had seen, individuals performed better with divided attention (Craik et al., n.d.). Craik and his associates' study helped identify that attention is a factor that affects the encoding process in long term/explicit memory.

After an engram for long term memory is created through the encoding process, the next step in long term memory is the consolidation process, which is vital for long term memory. Consolidation is the pro-

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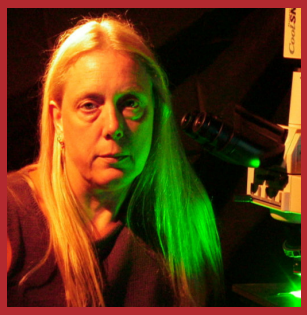

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cess under which a memory trace is stabilized after first being acquired (Ramirez et al., 2013). Studies show that long term memory consolidation is highly dependent on the hippocampal cortex (Moscovitch & Addresses, 1998). The brain contains millions of neurons, and each neuron contains thousands of synapses. All these neurons and synapses are connected together to form a complicated network that can be utilized to store and transport information. New studies have determined that the acquisition and consolidation of memory are dependent on synaptic plasticity (Dudai, 2002). Synaptic plasticity is the ability of synapses to strengthen or weaken over time, in correlation to the amount of activity they endure.

Long term potentiation (LTP) is the specific type of synaptic plasticity associated with long term memory (Oku & Huganir, 2013). LTP is being studied predominantly on in vitro slices of living hippocampus; as the hippocampus is the fundamental portion of the brain involved in memory. New discoveries has proven that long term potentiation requires the postsynaptic Ca2+ entry, activation of glutamate receptors, and intracellular messengers (Bear & Malenka, 1994). AMPA receptors found in the brain conduct most excitatory neurotransmissions in the brain (Oku & Huganir, 2013). NMDA (an amino acid that mimics the action of glutamate) long term potentiation occurs through the trafficking of AMPA receptors (Oku et al., 2013). Scientists conducted an experiment to see the effects of the amyloid β protein (A β) on long term potentiation. They used rats in vivo and injected them with A β oligomer only, to determine that this protein can inhibit long term potentiation (Walsh et al., 2002).

Another protein that inhibits the formation of long term memory is the NF-1 protein (neurofibromin), which is encoded in the NF1 gene (Ho, Hannan, Guo, Hakker, & Zhong, 2007). Researchers used NF1 null mutant and wild type Drosophila Melanogaster and the odor tests and the Pavlovian conditioning protocol to determine whether this protein really had an effect on memory or not. They set up a maze with one tube with the odor of benzaldehyde (BA) and the other tube with methyl cyclohexanol (MCH) (Ho et al., 2007). The BA tube was paired with a shock while the MCH was not, and then the odors were switched and a different group of flies were utilized. Using this method, the flies were taught to associate an odor with shock using spaced training, and then were tested 24 hours later to determine whether the flies remembered to avoid the odor paired with the shock (Ho et al., 2007). The researchers found that NF1 null mutants did not remember while the wild type flies did; cementing the hypothesis that the NF1 gene played a major role in long term memory retention (Ho et al., 2007). The formation and retrieval of long term memory is a complicated process that involves many different steps and proteins. Once a memory is formed the long-term potentiation of that memory determines how long the memory remains. This form of synaptic plasticity is extremely important for long term memory and is studied extensively for this reason. Further research in the molecular biology of memory seems as a promising start to ending many memory related diseases.

One memory related disease that is being looked into more closely is Schizophrenia. This behavioral disorder is characterized by thoughts or ideas that do not seem possible in reality, difficulty with memory, and disorganization in speech or behavior. Although the cognitive characteristics of schizophrenia are well described, the pathophysiology and the etiology are yet to be fully described. Researchers are currently using various animal models to discover the molecular implications of schizophrenia. One common animal used to examine the molecular and cellular mechanisms of schizophrenia is the Drosophila Melanogaster, or the fruit fly (Lessing & Bonini, 2009). This is because, Almost 75% percent of human disease causing genes have a functional homolog in the fly and drosophila also have a relatively low cost and are easy to work with (Pandey et al., 2017). There are also a variety of genetic techniques that can be used to create mutant flies (Jeibmann & Paulus, 2009). Studying human brains is also against ethics, which prevents us from experimenting on human brains.

Although there are many proposed drosophila models to represent schizophrenia, Overexpression of the DISC1 gene is currently being studied to understand behavioral issues at the molecular level (Pandey et al., 2017). The Disrupted-in-schizophrenia 1, or the DISC1 gene, produces the DISC1 protein. Through its interaction with other proteins, it is involved with neurite outgrowth and cortical development (Kamiya et al., 2006). Researchers have introduced the human DISC1 gene in the drosophila nervous system to investigate genetic interactions of DISC1 and psychiatric risk factor genes (Pandey et al., 2017). They then looked at the larval neuromuscular junctions of Drosophila which have several features in common with the vertebrate brain, to obtain results (Pandey et al., 2017). To investigate genes that interact with DISC1, scientists expressed the DISC1 gene in a wild type background (Pandey et al., 2017). They then performed an immunological staining of the glutamatergic synapses on neuromuscular junctions (NMJ) and measured total bouton area, number of boutons, and the number of axonal branch points that are made on the muscle (Pandey et al., 2017). Boutons are also known as synaptic terminals. This is where axons come into contact with and communicate with other neurons. More bou-

tons mean more messages can be transmitted between neurons fast. Scientists observed a reduction in total bouton area, but not number of axonal branch points nor number of boutons in the DISC1 mutants (Pandey et al., 2017). Researchers then expressed the DISC1 mutants in a heterozygous background of fly psychiatric risk gene mutations, and compared their synaptic phenotypes to the DISC1 phenotype in the wild type background (Pandey et al., 2017). Using this method scientists were able to find that a mutation of dnrx1 caused changes to the DISC1 phenotype in the NMJs (Pandey et al., 2017). Dnrx1, which is the Drosophila homolog of the human Neurexin gene, failed DISC1 in causing a decrease in synaptic bouton area, and caused reductions in the number of axonal branch points (Pandey et al., 2017). They then used RNA interference to determine that reduction of the dnrx1 activity led to changes of the DISC1 synaptic phenotypes at a molecular and morphological level (Pandey et al., 2017). These results show an interaction between DISC1 and dnrx1 a molecule that organizes trans synaptic structures and functions.

The DISC1 gene in associated with a wide range of mental conditions, and since NMDA receptor (NMDAR) dysfunction has a lot in common with the mental conditions of the DISC1 gene, scientists examined whether NMDAR is a target of DISC1. Scientists reduced DISC1 levels with RNA interference and examined how NMDA receptors were affected. (Yan et al., 2014). They discovered that DISC1 knockdown led to a significant increase in the NMDAR current density (Yan et al., 2014). By introducing a GluN2B inhibitor and examining the current density mediated by GluN2A, the scientists were also able to discover that NMDAR response induced by DISC1 knockdown is mainly mediated through the use of GluN2A, a NMDAR subunit. (Yan et al., 2014). When scientists then examined NMDAR subunits in DISC1 knockdown neurons, they found that the total and surface levels of GluN2A were elevated whereas the levels of GluN1, and GluN2B were mostly unchanged (Yan et al., 2014). These findings suggest that DISC1 decrease leads to an increase in GluN1 and GluN2A channels, which then elevate NMDAR responses (Yan et al., 2014).

Since NMDA receptors play a major role in controlling synaptic plasticity and long-term memory, it's interaction with the DISC1 gene reveals a possible explanation for the memory loss associated with behavioral issues such as Schizophrenia. DISC1 impairs NMDAR function, and could thus be impairing long term memory as well. Better understanding of the molecular basis and the interaction between DISC1, NMDA and other proteins can lead to faster cure for memory related diseases such as Schizophrenia.

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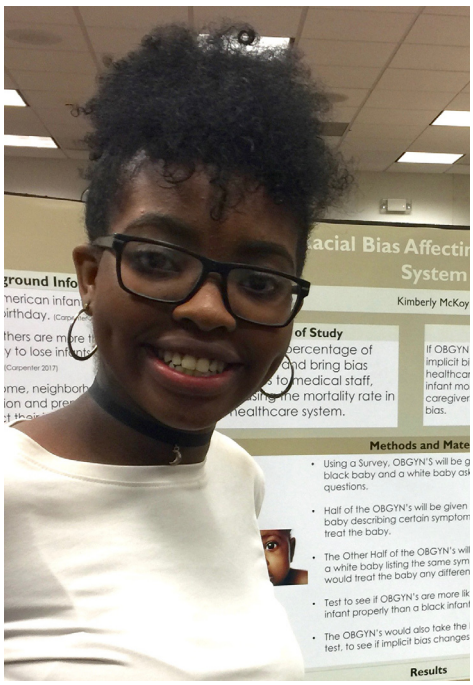
Implicit Racial Bias Affecting The Health Care System
by Kimberly Mckoy (Junior)

More than 2,300 African American Infants die each year in the U.S before their first birthday (Carpenter 2017). It's found that African Americans have 2.2 times the infant mortality rate than white mothers, and are more than six times more likely to lose their infants (Carpenter 2017). The Factors of income, socioeconomic status, and occupation has nothing to do with the infant mortality rate ; and it's actually the factor of Racial Discrimination (Carpenter 2017). Which increases the rate of African American infant mortality rate. And this is contributed through implicit bias (Carpenter 2017).

Vignette-Based Studies Author, year	Outcome Studied	Association between implicit bias and outcome (present or absent)
Charles, 2009	Recommendations for TIIDM treatment	Present
Green et al., 2007	Thrombolysis recommendations	Present
Haider et al., 2011	Pain assessment and management	Present
Katz and Hoyt, 2014	Expectations of therapeutic bonds and patient prognosis	Present
Oliver et al., 2014	Total knee replacement recommendations	Absent
Puumala et al., 2016	Pain and asthma management	Present
Sabin et al., 2008	UTI, ADHD, and asthma management	Present

Table 3.
Association between implicit bias and outcomes.
Abbreviations: TIIDM, type II diabetes mellitus. UTI, urinary tract infection. ADHD, attention deficit hyperactivity disorder.
https://doi.org/10.1016/j.socscimed.2017.05.009

Implicit bias is simply the unconscious bias of someone towards another group. This bias is developed through cultural differences based on stereotypes that our society portrays of different groups. Cultural stereotypes influence information about an individual leading them into an unintended bias. It is found that everyone has Implicit Bias and some people have Explicit Bias. Explicit bias is a intentional bias that someone has to another group and that is derived from personal opinions based on cultural stereotypes. As well this person is considered to be prejudice. Evidently, explicit bias occurs among children as young as three years old of age, and as we get older we start to hide it (Bigler, Liben and Baron, Banaji 2006). Implicit bias is not just entitled to racism but also gender, sexuality, religion and many more. Implicit bias affects everyone and everything that they do. It is shown that as Humans our brains have developed unconsciously in a way that we have developed implicit bias. As we evolved from tribes which gave us the ability to distinguish from other tribes or racial groups as a defense mechanism (Johnston 2017). Implicit bias contributes to health care disparities by producing differences in medical treatment due to racial differences (Biernat M, Manis M 1994).



Differences in medical treatment includes the increase in the rate of infant mortality of African American infants because of racial discrimination. Evidently, Doctors with implicit bias make treatment decisions based on race instead of the patient's description of pain (Cooper L.A, Roter DL, Carson K.A, Beach MC, Sabin JA, Greenwald AG 2012). Results 1 shows the examples of treatments that showed a implicit bias outcome, and 6 out 7 show that implicit bias was present with treatments from doctors. This implicit bias of doctors happens under pressure, which increases the rate of African American infant mortality rate (Carpenter 2017). Implicit bias of Doctors further contributes to the relationship with their patient. Patients who get less health care are found to have less of a relationship with their doctors. The lost of communication has to deal with, racial bias and difference in cultures between the doctor and the patient (Meltzer 2017). And mostly doctors are more likely to not listen to their patients because of a poor relationship. As a result, Black patients are assigned less pain medication compared to white patients but are diagnosed more diseases (Sabin 2016). As an example, a Arizona Mother died from the amount of anesthesia that was given prior to fetal surgery from the implicit bias from the anesthesiologist, who believe that because she wore dreads that she smoked marijuana (Martin 2018). Doctors with implicit bias make treatment decisions based on race instead of the patient's description of pain (Cooper LA, Roter DL, Carson KA, Beach MC, Sabin JA, Greenwald AG, 2012). Which causes constant disparities in the healthcare system and the death of African American infants.

The Hypothesis of my study is if the OBGYNs, Pediatricians, and Fetal Surgeons of different race have a large implicit bias then there will be disparities in the healthcare system causing the increase in the infant mortality rate of Black infants; because caregivers are not aware of their own bias. Using this hypothesis, the goal of my study is to lower the percentage of implicit bias, decreasing the mortality rate in the health-

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care system. Using Vignettes, these physicians will be given pictures of pregnant women of both races during prenatal, pregnancy, and surgery, and as well of black babies and a white babies; who are younger than 1 . These Vignettes would describe certain scenarios of these individuals asking treatment questions on how they would treat them. Half of the physicians will be given pictures of black patients and a list of symptoms. The Other Half of physicians will be given pictures of white patients listing the same symptoms and to see if they would treat the patients any differently. With the given Vignettes this would test to see if physicians are more likely to treat a white infant properly than a black infant. Physicians would also take a demographic survey that would help us see if there is any linking to their bias. And questions that deal with treating the patient any differently by their relationship with the father or, treatment based on the type of insurance the patient has.

Cognitive stress can lead a caregiver to have a large implicit bias (Devine et al., 2012). But a large implicit bias can occur within a caregiver if there is racial differences between them and their patient (Schaa et al., 2015). Furthermore, Pro-White bias physicians show more support towards light colored patients than to dark colored patients (Rossen et al., 2008). Evidently, physicians with implicit bias tend to have different treatment outcomes based on the racial differences of patients (Allport, 1954; Cook, 1978 ; Gaertner et al., 1994). If people are aware of their implicit bias then they can consciously prevent it. In my future studies, I want people to be aware that everyone has implicit bias. And I want To change society's view of one another by making them aware of their own implicit bias and eliminating the disparities in health care system by race and ethnicity.

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The Influence of Gut Microbiota on Behavior and Brain Functions by James Reilly (Sophomore)

In the world today, millions of people suffer from neurological diseases and disabilities such as depression, anxiety, Autism Spectrum Disorder (ASD), and schizophrenia. The prevalence of these such diseases in the United States is very alarming and sparks many people's interest. A study done in 2012 estimated that 1 in 68 children aged eight in the United States have been diagnosed with ASD (Christensen et al., 2012). Along with this, many people diagnosed with ASD suffer from an array of gastrointestinal problems. One study shows that children diagnosed with ASD are three times more likely to experience symptoms such as abdominal pain, bloating, constipation, pain on stooling, sensitivity to foods, and diarrhea than the controls. The severity of these GI issues correlated with the severity of many symptoms related to ASD, including social withdrawal, irritability, and hyperactivity (Chaidez, Hansen, & Hertz-Picciotto, 2014). Other neurological disorders report gastrointestinal issues that also correlate with symptom severity, such as schizophrenia, Rett syndrome, cerebral

palsy, and major depression (Heijtz et al., 2011). These findings support the communication between the gut and brain, known as the gut-brain axis. However, how the gut and brain interact is still unknown.

In the past, studies have further supported the gut-brain axis by exposing the effect that probiotics, live bacteria or bacterial products, have on, both, the brain and behavior. For example, the implementation of Bifidobacteria treatment resulted in reduced levels of 3,4-dihydroxyphenylacetic acid (DOPAC) and decreased levels of 5-hydroxyindoleacetic acid (5-HIAA) in the amygdaloid cortex and the frontal cortex in rats, respectively (Desbonnet et al., 2010). Another study expressed how the introduction of live Lactobacillus plantarum PS128 significantly increased the levels of serotonin and dopamine in the brain. The enhanced locomotor activity observed in this study may have been caused by the increased transmission of dopamine after the probiotic treatment (Liang et al., 2015). On top of this, continuous L. helveticus NS8 treatment resulted in the reduction of biochemical, behavioral, and cognitive abnormalities induced by chronic stress in adult specific pathogen free Sprague-Dawley rats (Liang et al., 2015). Also, the probiotic Lactobacillus rhamnosus was able to modulate behavior in mice by reducing activity related to anxiety. This probiotic also decreased the augmentation of plasma corticosterone levels in mice induced by stress (Cryan & Dinan 2012). All of these findings support communication between the gut and the brain along the gut-brain axis. The consistent demonstrations of probiotics altering brain and behavior provide insight on how our gut and brain interact. More importantly, the results of these studies expose the possible roles probiotic administration may play in controlling and manipulating the gut microbiota, the brain, and the interactions between them.

Bacterial metabolites are substances that act as intermediates and endpoints of biological processes, making metabolites essential to proper function of the body. Metabolites have have been shown to enter the brain, which may be one method of communication between the gut and brain (Hsiao et al., 2013). For example, propionic acid, a stomachic metabolite produced by bacteria, has been shown to access the brain, both passively and actively, by crossing the gut-blood barrier and the blood-brain barrier (Thomas et al., 2012; Conn et al., 1983). The metabolite 4-ethylphenyl sulfate (4EPS) is one metabolite that has been shown to influence behavior. 4EPS is of particular interest due to the potential role it plays in behaviors relevant to ASD. Anxiety-like behavior was observed after naive mice were treated with 4EPS potassium salt from 3 weeks to 6 weeks of age. This behavior of the mice treated with 4EPS was similar to the observed behavior in the offspring of mice injected with the viral mimic poly (I:C) during pregnancy in order to activate the immune system. The offspring of these Maternal Immune Activation (MIA) mice exhibit many behavioral symptoms relevant to ASD. These results suggest that metabolites may cause or influence symptoms associated with ASD and other neurodevelopmental disorders (Hsiao et al., 2013). Additionally, many studies have demonstrated how metabolites have the ability to alter the production of neurotransmitters. One study introduced metabolites produced by spore forming bacteria, such as 4-aminobenzoic acid (PABA), α-tocopherol, and tyramine, to germ-free mice. After the metabolites were introduced, there was an increase in the biosynthesis of 5-hydroxytryptamine (5-HT, serotonin) in specialized endocrine cells, called enterochromaffin cells, in the gastrointestinal tract. It was discovered that these same metabolites increased the expression of tryptophan hydroxylase 1 (TPH1), implying that the metabolites communicate with enterochromaffin cells, signaling the enhancement of 5-HT biosynthesis (Yano et al., 2015). Even the bacteria that produce these metabolites have been shown to influence neurotransmitter production. The absence of the native microbiota that produce these metabolites disrupted the levels of serotonin in the hippocampus, suggesting that the metabolites affect related neural process (Clarke et al., 2013).

Children with ASD have been shown to have some abnormal levels of metabolites mostly due to overpopulation of Clostridium species in the gut. After analyzing the urine of 62 children diagnosed with ASD and the urine of 62 non-ASD children, all 1.5-7 years of age, it was found that the urine of the children diagnosed with ASD had significantly higher levels of the compounds 3-(hydroxyphenyl)-3-hydroxypropionic acid (HPHPA), 3-hydroxyphenylacetic acid (3HPA), and 3-hydroxyhippuric acid (3HHA) than in the controls. After the administration of oral vancomycin treatment to children with ASD, their urinary levels of HPHPA, 3HPA, and 3HHA decreased dramatically, indicating that these metabolites may be produced by the Clostridium species in the gut (Xiong, Liu, Wang, Zeng, & Peng, 2016). The metabolite HPHPA is of notable interest due to its ability to inhibit dopamine beta hydroxylase, a compound required during the process of converting dopamine into norepinephrine. The inhibition of dopamine beta hydroxylase may be related to excess amounts of dopamine associated with schizophrenia and psychotic behavior (Shaw, 2010). The influence that bacterial metabolites have on behavior and brain function suggests that these compounds may be the path of interaction between the gut and the brain.

Metabolites have been found to influence the brain directly. Propionic acid is one such metabolite to do so. Upon entering the brain by crossing the blood brain-barrier, a barrier that tightly regulates the movement of molecules between the blood and the brain (Daneman & Prat, 2015), through the use of high affinity transporters, studies have shown this metabolite affecting an array of neurological functions, including the release of neurotransmitters, mitochondrial functions, and

gene expression (Thomas et al., 2012; Conn et al., 1983; DeCastro et al., 2005; Maurer et al., 2004). Propionic acid has been shown to alter the release of neurotransmitters, including serotonin and dopamine after entering the brain (El-Ansary, Bacha, & Kotb, 2012). These results of the ability of propionic acid to cross the highly restrictive blood-brain barrier and affect neurotransmitter release exposes the possibility of neurotransmitter signaling to be affected by metabolites. One study conducted to discover the effects of antibiotic treatment on the brain also measured the change in expression of neural signaling-related molecules. After antibiotic treatment, the metabolites propionate, p-cresyl, trimethylamine-N-oxide, and deoxycholic acid were recorded at dramatically altered levels. This study tested the expression of different neurotransmitter transporters after antibiotic treatment. Neurotransmitter transporters bind to neurotransmitters in the synapse between neurons, terminating neurotransmission by releasing the binded neurotransmitter back into the presynaptic cell (Rudnik, 2002). Among the tested transporters in the brain was SLC6A4, the serotonin transporter. After the antibiotic treatment, the expression of SLC6A4 mRNA in the hypothalamus and hippocampus was slightly reduced when compared the vehicle-treated mice. On the other hand, the expression of mRNA was increased in the medial prefrontal cortex and greatly increased in the amygdala (Frohlich et al., 2016). A more recent study tested the function and expression of SLC6A3, the dopamine transporter (DAT), after exposure to metabolites. After infecting HEK293-EM4 cells with a recombinant bacmid containing the recombinant dopamine transporter gene, an assessment of the expression and function of DAT as a result of exposure to the metabolites propionic acid, indoxyl sulfate, hippuric acid, and p-cresol was performed. By conducting a bicinchoninic acid assay, western blot, and uptake assay, it was revealed that exposure to these metabolites resulted in altered expression of DAT. It was concluded that the exposure of p-cresol and propionic acid increased the expression of DAT, while indoxyl sulfate and hippuric acid reduced the expression of DAT (Chung, 2017). The ability of metabolites to affect the neurological processes of neurotransmitter release and reuptake sparks the speculation whether or not metabolites play a role in the gut-brain axis.

The expression of monoamine transporters plays a major role in the development of neurological disorders and behavior. Impulsive aggression and its related disorders and behaviors, such as depression, substance abuse, and suicidal behavior, may be related to the altered expression and function of the serotonin and dopamine transporters. Dysfunctional interactions between the serotonin and dopamine systems in the prefrontal cortex may be related to impulsive aggression and the behaviors relevant to it. More specifically, the hypoactivity of the serotonin transporter coupled with hyperactivity of the dopamine transporter may be an underlying biochemical cause of impulsive aggression (Seo, Patrick & Kennealy, 2008). In Drosophila melanogaster, a mutation in the dopamine transporter (dDAT) gene is associated with an increase in dopamine signaling. This could be due to a change in the expression of dDAT. A study done to discover the effects of dDAT expression on behavior found that normal dDAT expression is necessary for normal sleep patterns. A decrease in expression of dDAT resulted in a short sleep pattern, while the overexpression of dDAT abolished olfactory aversive memory (Ueno & Kume, 2014). These results show how altered expression of monoamine transporters results in a subsequent behavioral alteration.

The findings of metabolites produced by gut bacteria affecting the expression of SLC6A3 and SLC6A4 mRNA together with the discovery of behavioral changes due to the overexpression and underexpression of monoamine transporters is very interesting. If a study were to be done in order to test the effects of metabolites on the behavior of Drosophila melanogaster along with an examination of the mRNA expression, the results would provide a better understanding as to how bacterial metabolites of the gut affect behavior and brain function.

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Tumor Targeting Nanoparticles by Paul Williams (Sophomore)

The field of nanomedicine includes a very broad range of studies that seem to formulate new topics based off of eachother. What they have in common is that they work with nano sized structures referred to as nanoparticles typically ranging from 1-100 nm in size to serve many functions as well as topics of study. Many of these studies include but are not limited to, breaking up clusters of bacteria to synthesize treatment, usage for treatment of cardiovascular disease such as atherosclerosis, to serve as an antioxidant to repair damage in the bloodstream or rest of body, increase growth for essential parts of the body, and even cleaning up parts of the environment (Boysen, 2007). Seemingly enough, relatively recently all of these uses came together to treat a disease affecting many millions of people all around the world, and also being one of the largest causes of death in the world, which is most commonly referred to as cancer.

Tumor targeting nanoparticles function to destroy these large cancerous clusters as well as repair their damage that they have done to healthy body cells. The realization that these nanoparticles are known to accumulate in tumor sites is expressed in the phenomenon of the EPR, or enhanced permeability and retention effect. When engineering a nanoparticle, this phenomenon heavily influences what the nanoparticle is composed of, as well as simply the tumor targeting process itself. Upon the synthesis process of the nanoparticle through the bloodstream, it will accumulate and recognize that a cell is cancerous or abnormally growing through it settling in gaps existing between cells in the tumor. This is a reliable feedback system that makes tumor targeting very reliable. Buildup of nanoparticles in the tumor site is the main goal of treatment, leading to the destruction of the tumor (Greish, 2010). This can be done in several different ways, which depend ultimately on the structure and composition of the nanoparticle. Two main methods that have been studied and tested are through thermal ablation, and cellular apoptosis (Cormode et al., 2009). Thermal ablation is the method nanoparticles utilize to heat to solid cancerous mass to such a high temperature where it cannot thrive and function any longer leading to its demise. Cellular apoptosis however a more natural approach, introduces cytotoxic or "toxic to living cells" agents to the tumor which cause it to naturally commit suicide (Gianella et al., 2011). This may seem ideal that nanoparticles can just perform just simply these functions, but they also aid in reversing the damage due to the tumor along the way to the cancer site, or most likely at the site due to the EPR Effect. When a cancer cell is formed somewhere in the body, it's main function is to grow and obtain more nutrients. This is done through the process of angiogenesis, which in part of its process secretes VEGF or Vascular Endothelial Growth Factor protein. Angiogenesis is formally defined as the formation of new cells from pre-existing ones. The VEGF protein is se-

creted as the "signal protein" to stimulate the formation of the new cells which ultimately are created to be sent to the tumor as nourishment for it to grow and flourish. Under ideal circumstances, a tumor can thrive for years and even spread. Abnormal cell growth, angiogenesis and the spreading of tumors is why cancer is so fatal, and often is not dedicated one location. The synthesis of nanoparticles, and creation of nanoemulsion platforms, work to neutralize the negative effects of the VEGF protein, and show a promising future for cancer research. (Gianella et al., 2011).

Most cancer treatments available currently for serious cancer diagnoses are relatively ineffective, due to them often having more negative effects than positive results. Treatment therapies such as chemotherapy, and radiation therapy, introduce very strong toxins in high doses to the body, and most of the time the patient suffers more bodily damage from the traditional devices, than from therapeutic agents and even the cancer itself (Zhu et al., 2014). The immune system is also heavily affected by these treatments, weakening it, and also making it more susceptible to many types of pathogens while on treatment. Nanomedicine for the purpose of tumor targeting, works to exclude most harm from treatment, and just focus on small doses. There are other key benefits attributed to tumor targeting nanoparticles. Cancer has the highest probability of being overcome when it is detected early as possible. This is so because at the earliest stages of development of the tumor, it is the least nourished, and shows the most signs of being an abnormally growing mass. Nanoparticles with the use of certain imaging techniques as well, can detect and diagnose cancer much quicker than most modern cancer treatments (Zhu et al., 2014). The precision of nanoparticle tumor targeting treatment is unmatched for repairing tissue deep in the body, anywhere in it, and for destruction of the tumor mass. Mostly beneficial in terms of cost, the synthesis and engineering of tumor targeting nanoparticles is much cheaper than most treatments available today, due to them being designed with natural and cost efficient components such as iron oxide. They perform better at tumor targeting therapy than treatments most commonly used today (Zhu et al., 2014). As aforementioned, tumor targeting nanoparticles only work for the destruction of cancerous tumor masses and not healthy body cells. All these factors, are why research of tumor targeting nanoparticles have become so popular within the past decade.

Nanoparticles are man made, mainly engineered with natural components. Materials such as iron oxide and quantum dots serve as a natural basis for the structure of them (Jarzyna, P. A., Skajaa, T et al,. 2009). They can also be referred to as a micelle that has a cytotoxic cancer drug encapsulated in to deliver to the tumor (Jarzyna, P. A., Gianella, A., et al., 2011) . This is known as nanoparticle drug-delivery and is a concept that has been studied in much depth over the past decade, and is a recurring concept in most review and research papers. This is so due to the fact that the body's immune system doesn't attack the nanoparticles as they circulate through the bloodstream, and reacts to them as they are a normal body cell. With this fact known, cancer drugs can now be delivered directly to the tumor site, and treat it a known and controlled dosage to make therapy as less toxic to the whole body as possible. The outer portion of the nanoparticle, hydrophilic, and the interior or encapsulated drug hydrophobic, is specific to these qualities in order to get them through the bloodstream which is also an aqueous environment (Cormode et al., 2009). Most of the outer and middle layers of the nanoparticles assist in destruction of the tumor mass through processes such as thermal ablation or cellular apoptosis, and assist in imaging guided therapy for the nanoparticle. At this time these studies are still experimental and have not been expanded or implemented on a larger scale.

Within the past couple years, an experiment was run to test the effect of a nanoemulsion platform on an several experimental cancer mouse models along with imaging guided therapy. "The theranostic platform had oil-in-water nanoemulsions, with Iron Oxide nanocrystals for the purpose of MRI imaging, fluorescent dye Cy7 for Near-Infrared-Fluorescence NIRF imaging, and hydrophobic glucocorticoid prednisolone acetate valerate (PAV) for therapeutic purposes" (Gianella et al., 2011). Fifty-six mice were randomized into seven groups and injected with the tumors in various locations. "Nanoemulsions were administered at a dose of 30 mg FeO/kg and 10 mg PAV/kg", and so treatment began in conjunction with the imaging techniques. The control groups were given the control drug saline, and the experimental groups were treated with the nanoemulsion platform. For the nanoparticles an individual in vitro "outside of the body" and in vivo "inside the body" examinations were performed with the assistance of various molecular imaging techniques. Some of the main in vitro imaging methodities are Dynamic Light Scattering (DLS), and Transmission Electron Microscopy (TEM). The purpose of both of these mainly to get and idea of the structure of the nanoparticles to furthermore understand how they will function and perform with their task to target the tumor. As for the in vivo analysis, the sole purpose of imaging is to track the nanoparticles progress, and make sure upon that it actually makes it to the tumor site. Some of these include, Magnetic Resonance Imaging (MRI), Computed Tomography (CT), and Near-Infrared-Fluorescence imaging (NIRF). With the assistance of these In Vivo imaging techniques, it was noted that the nanoemulsion platform responsible for a large amount of shrinkage of the tumor mass, "this study demonstrated that our nanoemulsions, when loaded with PAV, iron oxide nanocrystals and Cy7, represent a flexible and unique theranostic nanoparticle platform that can be applied for imaging guided therapy of cancer" (Gianella et al., 2011). This is a very large milestone in cancer treatment, especially that angiogenesis was not prevalent with the platform (Gianella et al., 2011). This still however opens room for some future studies, and improvement to incorporate other capabilities to this platform, or use the fundamentals of this formulation, and improve upon it.

One specific type of nanoparticles has attracted a great deal of attention to the biomedical field due to it's duality and multifunctionality. "Gold nanoparticles (AuNPs) have a number of physical properties that make them appealing for medical applications" (Mieszawska et al., 2013). They have ideal properties to be utilized with the specific imaging methods aforementioned and as adjuvants for radiotherapy. Gold nanopar-

ticles can be well utilized for therapy, diagnosis, and imaging which are the three key attributes needed to target a tumorous cancer mass. Gold nanoparticles can be applied to larger structures to deliver more treatment to the cancerous site, and increase the abilities of a nanoparticle itself. They are also considered biocompatible and non-toxic, and can be modified easily (Mieszawska et al., 2013). Gold nanoparticles have quite useful characteristics, and are well worth being considered to being applied to a nanoemulsion platform in imaging guided therapy for cancer treatment.

An effective treatment for cancer isn't as far as it may seem. Due to some nanoemulsion platforms created already, as well as reviews upon more effective nanoparticle components or nanocrystals, studies can just be improved respectively upon the last in order to formulate a treatment that can officially be used in modern cancer therapy. A nanoemulsion platform comprised of nanoparticles with hydrophilic lipids on the outer shell, with the structure of it being of natural compounds such as Aluminum-Oxide, Iron-Oxide, Copper Oxide, or Aluminum Carbonate, and be encapsulated with a cytotoxic cancer drug, favorably, bevacizumab. Bevacizumab is ideal due to its function which is to inhibit the negative effects of the tumorous clusters vascular external growth factor (VEGF), so that way further treatment can be done to the cancerous masses such as thermal ablation, or cellular induced apoptosis from the nanoparticle (Pavlidis et al., 2013). VEGF can be reversed to that way it can only be done with angiogenesis to restore the old body cells to new healthy ones (Pavlidis et al., 2013). Gold nanoparticles to be involved in the system would be essential with the diagnosis, therapy, and treatment. They could potentially be the ones that hold the encapsulated drug and deliver it to the tumorous masses (Pavlidis et al., 2013). With imaging guided therapy in conjunction with this nanoparticle formulation, destruction of a tumorous mass may be possible, and can't harm the body in any way, which is what mainly makes it so beneficial, that even if it fails, it won't have a negative effect on the body. However, this model is based off of previous studies, therefore it will likely represent an effective treatment for tumorous masses, along with imaging guided therapy.

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New Strategies to Fight Antibiotic Resistance by Aiden Breneman-Pennas (Sophomore)

The threat due to bacteria becoming resistant to Antibiotics is increasingly becoming relevant. This major threat may lead to a new age of epidemics and problems if immediate steps to eradicate this problem are not immediately dealt with. "Over the past three decades, antimicrobial resistance in Streptococcus pneumoniae has drastically increased worldwide. Non-susceptibility to penicillin in S. pneumoniae was first discovered in Australia in 1967, and later in New Guinea (1947), South Africa (1977), and Spain (1979). Most of these strains showed resistance to multiple antibiotics." (Liñares, Ardanuy, Pallares, & Fenoll, 2010). Before these incidents, Streptococcus pneumoniae was completely susceptible to penicillin and other antimicrobial treatments, and in the years preceding, drug resistance only amplified with other serotypes of penicillin as well as serotypes of other antibiotic treatments (Liñares et al., 2010). PNSP (Penicillin Non-susceptibility in Streptococcus pneumoniae) was also noted in occurence. "In the USA, the CDC's Active Bacterial Core surveillance reported that 24% of 3475 invasive pneumococcal isolates collected in 1998 were PNSP. Seven serotypes (6A, 6B, 9V, 14, 19A, 19F, and 23F) accounted for 91% of all PNSP" (Whitney et al., 2000).

Serotypes, like the ones mentioned, are increasingly becoming dangerous because of processes that make the bacterial colony stronger. One of these processes undergone by bacteria is auto poisoning of the respiratory chain by a quorum-sensing-regulated molecule favoring bacteria that have formed a biofilm matrix and antibiotic tolerance (Hazan et al., 2016). Auto-Poisoning refers to the fact that the process undergone by some bacteria essentially produce a molecule that "poisoned" the cell. A quorum-sensing-regulated molecule is a molecule that is produced when a certain population density is reached. Altruism is when a few weaker cells of, in this case, bacteria are killed off for the benefit of the colony. "2-n-heptyl-4-hydroxyquinoline-N-oxide (HQNO), a Pseudomonas aeruginosa quorum-sensing-regulated low-molecular-weight excreted molecule, triggers autolysis by self-perturbing the electron transfer reactions of

the cytochrome bc1 complex [of the mitochondria][...], causing bacterial cell autolysis and DNA release" (Hazan et al., 2016). HQNO is released when a population density of 0.8-1.0 OD600 is achieved within a sample. Cell autolysis and DNA release are signs of apoptosis caused by HQNO. P. Aeruginosa cells without a bacterial biofilm, and therefore by extension, without any special antibiotic resistance are primarily the bacterial fatalities caused by HQNO. This becomes a problem first because that means that in this environment, the HQNO regulation promotes more cell viability and then reproduction of cells with a biofilm, and these biofilms can cause major problems. Bacterial biofilm refers to the structure produced when bacterial cells bind together with extracellular polymers that are secreted by bacterial cells. "Bacteria in biofilms can resist antibiotic treatment, host immune responses, and biocide treatment"(Harmsen, Yang, Pamp, & Tolker-Nielsen, 2010). Elimination of cells outside the biofilm matrix, via inhibition of bacterial mitochondrial reaction sites caused by HQNO,promoting a more viable bacteria population, able to resist antibiotics, host immune response efforts and other attempts to kill the bacteria. This coupled with new natural antibiotic resistance within individual bacteria can make for a potentially hard to eradicate population of bacteria.

Viability of these biofilms was tested with the primary immune response cells in the blood, polymorphonuclear neutrophils (PMNs). PMNs kill their bacteria by a process called phagocytosis where they ingest the bacteria through their cell membrane and the proteins inside the PMN dissect the bacteria and kill it.(Meyle et al., 2010). Other ways that PMN cells kill immune threats is via release of cytotoxic entities into the medium, which causes bacterial cell death (Soehnlein, 2009). When a specimen of biofilm positive Staphylococci was introduced, the PMN was able to consume the bacteria with biofilm. However, after prolonged exposure, the PMN exhibited apoptotic behaviors, including a condensation of the nucleus and DNA, causing death. Furthermore, after 30 minutes, 20%-30% death of PMNs to those who ingested biofilm positive Staphylococci cell. After 60-90 minutes, 80% death of PMN to those who ingested biofilm positive Staphylococci. Condensation in the PMNs nuclei was also recorded, indicating apoptosis (Meyle et al., 2010).The PMN was able to break down the bacterial biofilm with release of DNAse 1, and shortly after ingestion of the biofilm, Elastase and Lactoferrin were released, seemingly for transportation of DNAse 1(Meyle et al., 2010). Past trends indicate that the presence of bacterial biofilm matrix can cause a larger intake of antibiotic resistant bacteria than the cell can handle(Liñares et al., 2010).

There are a few innovations that currently exist that could possibly cause the reverse effect needed for the coming years. A human milk protein complex of alpha lactalbumin and oleic acid called "HAMLET", or human alpha-lactalbumin made lethal to tumor cells, has been researched for its applications towards tumor cells, however, there trends of eradication can be seen for bacteria as well. This is because HAMLET causes apoptosis or apoptotic like processes, including mitochondrial permeability (Hakansson, Roche-Hakansson, Mossberg, & Svanborg, 2011). The purpose of additional studies of HAMLET was to see whether apoptosis encompass uniform process to kill prokaryotic cells and eukaryotic cells. A previous examination of the human milk protein showed the apoptotic abilities with eukaryotic cells. However, now it is known that prokaryotes are also able to undergo apoptosis. This is crucial towards understanding the underlying mechanisms in bacteria, like the dangerous multidrug resistant biofilm matrix positive bacteria, and then how to effectively kill them. HAMLET primarily causes apoptosis by inducing mitochondrial permeability, killing the cell (Hakansson et al., 2011). Similar human protein complexes have also been studied, such as MLA, or multimeric alpha-lactalbumin, for their similar apoptosis inducing properties (Köhler et al., 2001). These human milk protein complexes are known not to attack body cells (Hakansson et al., 2011).Bacteria may never develop resistance to HAMLET and other similar milk protein complexes because "The native, folded form of ALA, with lactose synthase activity, has no tumoricidal or bactericidal effect, however" (Hakansson et al., 2011). ALA requires the presence of oleic acid to unfold into the proper protein that can cause apoptosis in onologic cells and bacterial cells. Therefore, for long term application, HAMLET is a likely candidate towards non-antibiotic solutions towards multi-drug resistant bacteria.

Another one of these possible candidates comes from a natural killer of bacteria, silver. "Silver nanoparticles (Ag-NPs) have been known to have inhibitory and bactericidal effects" (Shahverdi, Fakhimi, Shahverdi, & Minaian, 2007). Silver is an effective natural killer of bacteria due to its high specific area and high fraction of surface atoms. Production of the silver nanoparticles was done by introducing Staphylococcus aureus and Escherichia coli to silver nitrate solution. Adding the resulting silver nanoparticles to various antibiotics was recorded. The performance of penicillin G, amoxicillin, erythromycin, clindamycin and vancomycin were recorded with highest performance noticed with penicillin G, amoxicillin and vancomycin (Shahverdi et al., 2007). Silver nanoparticles have not been tested on bacteria with a biofilm matrix, which can be a possible limitation. Silver nanoparticles could be a great

asset towards treatments in the future. One possible use for these nanoparticles could be to combine the human milk protein complexes mentioned before to create a better antimicrobial environment as well as possibly provide ways to combat multidrug resistant bacterial biofilms. I propose to combine these findings to create an additional antimicrobial treatment, hopefully limiting the use of antibiotics as much as possible to avoid producing more of these multidrug resistant bacteria, and avoid possible public health crises.

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Oligodendrocytes and Multiple Sclerosis in the Central Nervous System by Adhithya Rajasekar (Sophomore)

The nervous system uses electrical impulses to communicate with cells all over the body, which is necessary for the body to function. These electrical impulses moves through neurons, starting at the dendrites, moving through the cell body, through the axon, going across the nodes of ranvier, out the axon terminals, and across the synapse to another neuron where the process repeats. These electrical impulses are facilitated by the myelin sheath, which covers the axon.

Myelinated nerve fibers occur predominantly in the cranial and spinal nerves and compose the white matter of the brain and spinal cord. White matter refers to the areas of the nervous system that contain myelinated axons, while gray matter refers to areas in the nervous system in which the nerve fibers are unmyelinated. In unmyelinated nerves, impulses are conducted by the propagation of the action potential along the membrane of the axon. In myelinated nerves, impulses are transmitted by an slightly different process, called saltatory conduction, in which the impulse jumps from one node of ranvier to the next. Impulses in myelinated nerves are transmitted hundreds of times faster and require much less energy than in unmyelinated nerves (Miller-Keane Encyclopedia and Dictionary of Medicine, Nursing, and Allied Health, Seventh Edition).

Oligodendrocytes produce this myelin in the central nervous system. According to an article by Barateiro et al, oligodendrocytes arise from oligodendrocyte progenitor cells (OPCs) that proliferate and differentiate just before and after birth, under a highly-regulated program. Both oligodendrocytes and their precursors are very susceptible to injury by several mechanisms, including excitotoxic damage, oxidative stress and inflammatory events (Barateiro et al. 2016).

In order to make myelin, the glial tongue of an oligodendrocyte surrounds the axon, forming a double-membrane structure which is called a mesaxon. There is an inner mesaxon and an outer mesaxon that ends in a loop, or tongue, of glial cytoplasm. This glial tongue is continuous with the plasma membrane of the oligodendroglial cell through slender processes. One glial cell can myelinate forty or more separate axons (Siegel GJ et al. 1999). There are many disorders, both in the central and peripheral nervous system, that destroy this myelin, and these disorders can

cause disastrous effects in brain function. One such disorder in the central nervous system in Multiple Sclerosis. An article by Khaled Mohamed Mohamed Koriem lists the symptoms of Multiple Sclerosis including muscle weakness, weak reflexes, muscle spasm, difficulty in movement, miss-coordination and unbalance with others. The mechanism underlying MS can be summarized into 2 reasons, " (1) the immune system destroying the myelin sheath, and (2) failure of the myelin-producing cells (oligodendrocytes) to produce new sheathes," (Koriem, 2016).

MS is considered an autoimmune disease, which is when the body's immune system attacks its own cells. The way in which this happens in MS involves T cells, which are one type of white blood cell in the immune system. They become sensitized to proteins in the CNS. It is not known what causes T cells in persons with MS to become activated, but it is postulated that both genetic and environmental factors are important, (National Multiple Sclerosis Society 2017).

The immunopathological events involved in the onset of MS can be divided into 5 steps. First is the initial T-cell priming, which occurs within systemic immune compartments and is initiated by sensitization with myelin antigens including myelin lipids. Next is activation phase of the periphery (thymus and lymph nodes), Antigens presented by antigen presenting cells (APCs) within secondary lymphoid organs induce the activation and expansion of myelin-specific T cells, and these activated myelin-reactive T cells circulate through the body searching for their specific antigens to become re-activated. Next occurs the migration of the proinflammatory T-cells across the blood-brain barrier (BBB). (Engelhardt 2006).

This is a complex multistep process that and occurs via interactions between adhesion molecules found on the surface of lymphocytes and endothelial cells. First, circulating T cells slow in the bloodstream due to contact between distinct adhesion molecules on their surface and on endothelial cells. In the second step, homeostatic chemokines, such as CCL19 and CCL21 are produced by cells and mediate T cell activation, a step followed by third and fourth steps of firm adhesion and final transmigration of the lymphocytes. In the fifth step, CD4+T cells accumulate within enlarged perivascular spaces where they can encounter their specific antigens presented by the major histocompatibility complex (MHC) class II or CD1 on the surface of APCs such as perivascular dendritic cells. This immune synaptic contact reactivates the T cells. However, for complete activation, differentiation and clonal expansion, a co-stimulating process involving additional molecules is required. This antigen-triggered activation enables T cells to traverse the glia limitans and migrate into CNS parenchyma (Engelhardt 2006).

After this comes the amplification of local inflammation and activation of APCs, such as microglia. the autoreactive CD4+T cells initiate the local proinflammatory cascade.

Eventually, a variety of effector mechanisms—including antibody-mediated cytotoxicity, oxygen and nitrogen radicals, proinflammatory cytokines and apoptosis-mediating molecules that damage oligodendrocytes, myelin sheaths and occasionally, at this stage, axons—are induced (Becher 2006). Finally comes the effector phase of the disease, which is invasion of CNS parenchyma resulting in damaging of oligodendrocytes, myelin sheath and axons. Despite this insight into pathophysiology, the cause of MS remains unclear and definitive treatment of this frequent and chronic disease is still elusive. (Engelhardt 2006).

According to a review by Robin J.M. Franklin, disease progression is thought to be compounded from two underlying processes: myelin destruction (demyelination) with failure to remyelinate, and progressive axonal damage with little capacity for recovery (Franklin 2002). The current treatments for MS as listed in a review by Maria Podbielska, Naren L. Banik, Ewa Kurowska and Edward L. Hogan include, " β-interferons, IFNβ-1α (Avonex, Rebif) and IFN β-1β (Betaseron); the synthetic peptide glatiramer acetate (Copaxone); the antineoplastic agent mitoxantrone (Novantrone), and; a very late antigen-4 (VLA-4) blocker natalizumab (Tysabri)". These are only partially effective. All of these drugs are administered by injection and many MS patients prefer oral treatment. There are three new oral medications, already released and approved by the Food and Drug Administration (FDA): "fingolimod marketed by Novartis as Gilenya, dimethyl fumarate (Tecfidera, Biogen Idec, MA, USA), and teriflunomide (Aubagio from Sanofi, Paris, France)" (Podbielska et al. 2013). These drugs mainly affect lymphocyte trafficking and/or differentiation, though more needs to be done to clarify their mechanisms. These therapies aim to reduce the immune response by targeting immunological pathways. They slow down the immune response such that oligodendrocytes have time to catch up and remyelinate the damaged axons, but this treatment method isn't always effective at preventing the onset of disability. They can, however, often leave the body susceptible to infectious diseases. With the immune system slowed, foreign antigens have an easier path into the body.

A focus on remyelination may be a better path of treatment. If a method of improving remyelination can be developed, then patients can be treated without the decrease in immune capability. For that, the specific mechanisms of remyelination that are being blocked in MS need to be found. According to the study by Podbielska et al, there are a multitude of hypotheses as to why remyelination fails in MS, which may reflect either changes in environmental inputs or intrinsic pathways regulating OPCs functions. Several factors are likely to impair the completion of remyelination. Among them are factors related to a defect in OPCs activation and recruitment, or to local inhibitors of remyelination. Theoretically remyelina-

tion can be blocked at any point in the remyelination process: oligodendrocyte survival, proliferation, migration, maturation, and/or myelin sheath formation. In MS lesions late in the course of disease, oligodendrocyte recruitment is deficient and appears to be the primary reason for poor remyelination in late stage MS. In late stage MS, remyelination appears limited by oligodendrocyte density, which could be a product of impaired survival, proliferation, and/or migration of oligodendrocytes. In lesions containing more oligodendrocytes, impaired oligodendrocyte maturation is a major problem for efficient remyelination of lesions. Beyond the oligodendrocyte recruitment and maturation, myelination also requires contact between axons and oligodendrocytes and creation of multiple wraps of oligodendrocyte processes around the axon, culminating in the myelin sheath. Another factor is that repeated demyelinating insults, as observed in the relapse-remitting form of MS, can exhaust the OPCs source so that remyelination failure may be regionally defined due to exhaustion of distinct progenitor pools (Podbielska et al 2013). While this study lists possible aspects of remyelination that could be affected, it is unknown whether it's a combination of these problems, or just one major mistake is occuring in MS. It seems however, that the main problem is less OPC differentiation into oligodendrocytes, which causes a lack of oligodendrocyte density. If the root cause of this problem is found, then a treatment method can be created to combat that and to keep the body's natural remyelination strong to combat the inflammatory effects of the disease.

Research has been done on certain pathways that promote remyelination overall, such as Neurotrophins, Insulin Like growth factors, the Gp130 family of Neurotrophic Cytokines, the gene Interleukin-11, and Neuregulin 1 type III, (Zhang et al. 2011). There has also been research done on certain inhibitors of myelination, such as Canonical Notch Signaling, the Canonical Wingless Pathway, and Bone Morphogenetic proteins (Zhang et al. 2011). Out of these growth factors, Neurotrophins show the greatest promise in terms of increasing functional recovery and remyelination. Neurotrophins (NTs) comprise a family of soluble mediators including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4/5. A study by Christelle Girard et al. found that "transplantation of fibroblasts expressing either BDNF or NT-3 has been shown to enhance axonal growth, OPC proliferation and myelination in adult rat spinal cords after injury. Moreover, transplantation of BDNF or NT-3-expressing Schwann cells into demyelinated mouse spinal cords leads to increased OPC proliferation and differentiation, remyelination and locomotor recovery. Interestingly, studies in the MS model experimental autoimmune encephalomyelitis (EAE) imply a functional role of BDNF in mediating axon protection in autoimmune demyelination. Remyelination and functional recovery have also been reported following transplantation of glial-restricted precursor cells (GRPs) expressing a multi-neurotrophin of BDNF and NT-3 into the CNS of rats subjected to spinal cord injury," (Girard et al. 2005). However, while these studies provide evidence that neurotrophins are effective at promoting regeneration of the injured spinal cord, the relative contributions to these outcomes of effects on neurons versus glia remain to be fully defined. I propose that that we combine the two studies, and research further the full effect of transplanting neurotrophic factors into MS mice models, for if we can use this to increase OPC differentiation, which seems to be the biggest factor preventing remyelination in MS, then we can treat MS without leaving the body susceptible to diseases.

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