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SCIENCE, TRANSLATED

BIOLOGY | PHYSICS | CHEMISTRY

The Best of 2022

ORGANIC ROBOTS

Learn about "living robots", heart regeneration, the space age, and so much more in this edition of the Science, Translated summer newsletter!

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Editor's Note

Welcome to Science, Translated's summer newsletter! We hope that browsing Science, Translated will not only be an informational experience, but an enjoyable one. Science should be shared and cherished as a foundation that makes up a great deal of our everyday lives. We hope that this newsletter highlights the work our talented journalists are doing and teach you something about recent research breakthroughs in science! Thank you to the managing editor and copy editors who made these articles the best that they could be:

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Best of 2022

THE FAULT IN OUR SETS

Author: Allison Cartee
Graphic artist: Margaret Cartee

March 14, 2022

I stubbornly resisted watching John Green's The Fault in Our Stars until a midnight flight back from an 8th-grade field trip. Sitting in the middle seat between two pre-teen boys, I dutifully rolled my eyes at the mushy dates, poignant declarations, and tragi-romantic ending. Even if you haven't seen the movie, most people remember Hazel Grace's pre-eulogy delivered to her terminally ill boyfriend Augustus. Pondering their deep romance and its untimely demise, she claims that there are more numbers between zero and two than zero and one. She famously laments some infinities are bigger than other infinities, a beautiful yet erroneous idea. Though some jump to discredit her mathematically flawed statement, I hope to remedy her logic through sets and their sizes, called cardinalities. Georg Cantor's foundationalist set theory ultimately dictates principles that prove how there are as many numbers between zero and one as there are zero and two as well as zero and a million. Building off his principles lets us count to an infinite number or even claim there are just as many even integers as there are all integers.

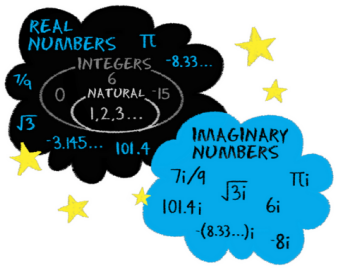

Figure 1. Different types of numbers. Graphic by Margaret Cartee.

To analyze Hazel Grace's complex metaphor between mathematics and mortality, we'll turn to the world's arguably most renowned mathematician, Count von Count of Sesame Street. The Count uses natural numbers starting from one to quantify objects for young viewers (Figure 1). Let's say the Count needs to know how many bats are in a group, called a set. He bijects the natural numbers zero through ten onto his friends and concludes he has ten bats. This bijection refers to the one-to-one correspondence with or bijection from each of the natural numbers up to ten onto each of his bats. Ten therefore represents the cardinality or size of the set [1]. The Count now visits Dracula and his twenty bats. Though Dracula has twice as many bats, von Count makes another bijection of the natural numbers zero through twenty onto Dracula's bats. The cardinality of von Count's bat set is ten while Dracula's cardinality is twenty. For fun and unintentionally for later, the Count decides to count every other one of Dracula's bats to confirm that Dracula has more bats. Von Count's finite sets behave intuitively even to his youngest, most avid fans. However, what if he faces an extremely, inordinate number of bats beyond a Sesame Street episode?

I Von Count travels to Batman's Batcave, which houses as many bats as there are integers. As they fly out of the Batcave single file, von Count bijects the set of natural numbers onto the bats. Exhausted from all that counting, von Count decides to count every other bat as they return and doubles this value to sum the bats. If he could double his bats to compare with Dracula's twenty bats, why wouldn't it work with Batman's integer set of bats? To a mathematician, von Count ponders whether bijecting onto the set of all integers then halving is the equivalent of bijecting onto the set of all even integers. To us, he ponders whether there are exactly half as many even integers as there are all integers. However, the Count finds that there are just as many even bats as there are total bats. Where did all these 'new' bats come from? The difference between Dracula and Batman's situations distill down to how mathematicians classify types of sets. Dracula possesses a countably finite set with a cardinality of twenty bats. Batman, however, has a countably infinite set of bats with a cardinality of all the integer numbers. This term seems paradoxical: how can we count to an infinite number? And how is a sub-set of even integers the same size as the full set of all integers?

The befuddled batmen seek out mathematician Georg Cantor to explain set theory. Cantor postulates that von Count could theoretically count Batman's bats with natural numbers, but it must have taken him forever. As von Count successfully bijected a natural number onto all of Batman's bats counting both every single and every other one, Cantor claims that Batman has aleph-null (א0) 'number' of bats. Yet, aleph numbers are not true numbers like von Count's twenty bats, integers like 0, 1, 2, 3...etc. π , e or any imaginary number and certainly don't behave like them (Figure 1). Aleph numbers describe the cardinality of sets with sizes that exist beyond any large, finite countable number. Aleph-null represents the smallest, first aleph number where you can bject a natural number onto each element of your set. Cantor proved that the set of all integers has the same aleph-null cardinality as the sub-set of all even integers. In other words, there are indeed just as many even integers as there are all integers. His work establishes:

$$\aleph_0 + r = \aleph_0 \text{ for any number } r,$$
$$\aleph_0 \times r = \aleph_0 \text{ for any } r > 0,$$
$$\aleph_0{}^r = \aleph_0 \text{ for any } r > 0 \text{ [2]},$$

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March 14, 2022

demonstrating aleph numbers and their algebra do not behave like classical finite numbers. By the second line, it doesn't matter if von Count counts every single, other, third, fourth, or tenth bat: Batman always ends up with aleph-null bats simply because he's Batman.

Where does this leave Hazel Grace? Unlike the sole infinity, ∞, some aleph numbers are indeed larger than others. While Dracula and Batman have finite and countably infinite sets, Hazel Grace's set extends beyond countably infinite. The batmen biject natural numbers onto concrete objects like bats you, me, or a toddler can physically count. However, Hazel Grace's numbers between integers zero, one, two, or a million delineate number lines with decimal values intermediate to these whole numbers (Figure 1). There's a stark difference between the batmen's natural numbers and Hazel Grace's real numbers. As opposed to aleph-null, the next smallest cardinality א1, aleph-one, describes this cardinality of a set of all real numbers between any two for number line sets [3]. Mathematicians later proved 2 א0 or that 2 raised to the power of aleph-null, the number of natural numbers, gives aleph-one. Put simply, there are more real than natural numbers. The Count can biject natural numbers onto the integers to derive aleph-null, but he would run out of integers to biject onto the real numbers. Assuming Hazel Grace's first set between zero and one has aleph-one cardinality, Cantor's equations state that there are just as many real numbers between zero, one, two, or a million. Sadly, scientists reserve infinity to describe functions' end behavior, boundless limits, or projective geometry, not love. That is unless any of those topics scream love to you.

f von Count, Batman, and Cantor wrote The Fault in Our Stars, Hazel Grace would opine that some cardinalities are bigger than others, even though her sets between zero, one, two, and a million all have size aleph-one (א1), the cardinality of real numbers. Because א0 < א1 < א2...אn, she's now correct that some relationships and cardinalities measured by aleph numbers are larger than others. Aleph numbers may not wax as romantic, but they give her statement a more optimistic perspective. Extending this metaphor between relationships and cardinalities implies it's always possible to find another just as meaningful. There are many aleph numbers compared to the traditional concept of a singular infinity.

Some relationships are countably short, others countably infinite or truly uncountable. Yet, each is distinctively unique for the numbers and memories they contain. Even if both time and aleph-numbers face some distant unseen end, such limits should encourage us to celebrate finite moments and the people within them in the great sets of life.

Acknowledgments:

I would like to thank my professor Dr. Jeffrey Yelton for reviewing, editing, and guiding my work.

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EATING AWAY AT ECOCIDE: ORGANIC ROBOTS USHER IN A GREENER WORLD

Author: Jane Nguyen

April 22, 2022

In 2020, scientists developed organic, biocompatible robots that independently moved and interacted with other objects. This breakthrough design revolutionized approaches to environmental care, drug delivery, along with countless other applications.

Think of a robot. Did you imagine R2-D2? Maybe even a Roomba? We often think of robots as chunks of metal and grinding gears with the occasional flickering bulb atop an antenna. We don't imagine something organic or biological. Robots thrive off synthetic fuels and electricity, not cells and nutrients. However, innovations in artificial intelligence (AI) change this.

AI has come a long way since the times of Ferranti Mark 1 – a machine of the 1950s that bested masters of checkers. As we step into a new decade of the 21st century, AI has helped transform robots into our personal assistant Alexa and social-learning companions like Moxie. While we're distracted by Alexa's ability to know our favorite song or Moxie's cute animated face, we forget their environmental impact. Stripped down, Alexa and Moxie are chemicals, metals, and plastics that release toxins into the environment as they degrade.

This begs the question: Can AI be incorporated into a biodegradable robot? Xenobots say yes.

Robots made of cells

Xenobots are programmed from stem cells harvested from their namesake – the African clawed frog (Xenopus laevis) [1]. Stem cells are unspecialized cells; meaning, unlike oxygen-transporting blood cells or sensory neurons, they don't have specific functions. Instead, their ability is to differentiate or transform into virtually any other cell type. Remember how Ditto can become any Pokémon? Same concept. This makes stem cells, and Ditto, pluripotent.
Pluripotent stem cells self-organize [2]. They innately assemble to grow and morph into any tissues in the human body. Scientists utilize this pivotal ability to design xenobots that can virtually take on any shape and form.

The algorithm

Created from frog-derived pluripotent stem cells, xenobots are programmed by an evolutionary algorithm. This algorithm was developed by a collaboration between the University of Vermont, Tufts University, and the Wyss Institute for Biologically Inspired Engineering at Harvard University.

Evolutionary algorithms are AI-based calculations that use mechanisms of biological processes – think reproduction and Darwinian evolution – to find solutions for a given problem or goal [3]. In this case, the goal is to engineer a functional robot, defined by its ability to independently move.

Once optimal designs for the xenobots are calculated, they're put to the test on a petri dish. The bots' behaviors are observed and compared to the goal. If the goal is not met, the designs are plugged back into the algorithm with new constraints. These constraints help the algorithm reconfigure the robot to yield better designs.

Compare evolutionary algorithms to playing Wordle. Your objective is to guess the secret word. Each guess is your design of what the word might be. If it's the wrong design, you try again, but now you know your constraints – the letters that don't belong in the word or letters that are in the wrong space. Scientists carry out these iterative processes until they achieve the optimal design for a functional xenobot.

Coming to life

A xenobot's design is brought to life through two basic components: passive blocks (green) and contractile blocks (red). The passive blocks do not move. These blocks made of stem cells act as a body, while contractile blocks are the legs. The contractile motions are achieved through a layer of frog heart muscle cells attached to the underside of the body. The biological function of heart muscle cells is to form cardiac tissues that pulse as heartbeats. These cells lend their contractile abilities to xenobots, enabling them to slide across surfaces. Micro-tweezers were used to manipulate the blob of cells into a replica of the simulated design.

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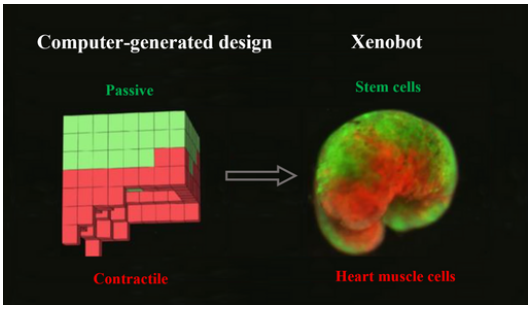
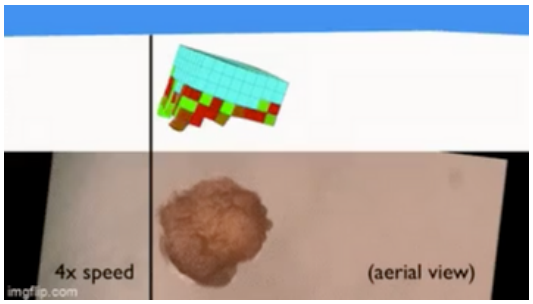
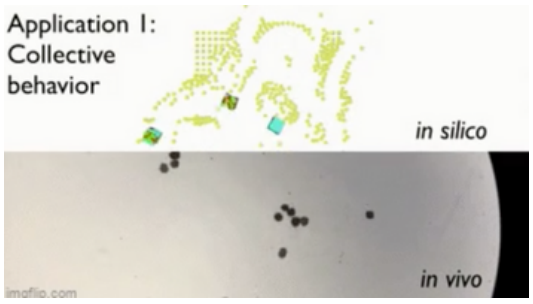


Live xenobot model translated from a computer-generated design using evolutionary algorithms. Adapted with permission from Kriegman et al. [1] under the Creative Commons License 4.0.



Comparison of simulated and observed xenobot movements. Adapted with permission from Kriegman et al. [1] under the Creative Commons License 4.0. See live image on sciencetranslated.org.

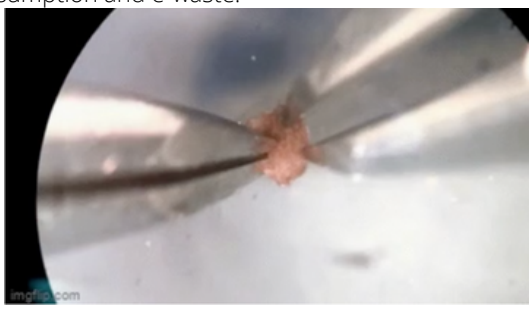
The xenobots' movements were tested in three applications: swarming, manipulating their surroundings, and transporting objects. With these foundational movements, xenobots can gather plastic pollutants from oceans, precisely administer medical drugs, and travel throughout the human body to remove toxins or buildup [1].



Xenobots successfully display movements and behaviors predicted through AI simulations. Adapted with permission from Kriegman et al. [1] under the Creative Commons License 4.0. See live image on sciencetranslated.org.

Self-sustainability

Unlike our phones after a shocking drop onto the concrete, xenobots are self-repairable. When torn apart by micro-tweezers, these bots can completely heal themselves. Wound healing is something that is unique to complex cellular processes – a space where metal, plastics, and glass can't compete. This maximizes the xenobots' lifetime use while minimizing resource consumption and e-waste.



Xenobot repairs itself after injury. Adapted with permission from Kriegman et al. [1] under the Creative Commons License 4.0. See live image on sciencetranslated.org.

Just one year after these bots debuted, the same research group discovered that xenobots can also reproduce, just not in the traditional sense. We typically associate reproduction with two parents producing offspring. Some of us may remember more self-sufficient methods from biology class like budding in yeast or binary fission where bacteria asexually reproduce by splitting in half.

Xenobots reproduce by means of kinematic self-replication. When placed in a petri dish filled with their own base composition (single stem cells), the bots spontaneously swarm. The circular motions aggregate the single cells into spheres that form more xenobots within a matter of days.

This type of propagation has never been seen on the scale of whole organisms until now [4].

Not all xenobots are created equal. For kinematic self-replication to work, the bots must be reconfigured into a specific shape and given just the right amount of building materials and nutrients. In this case, the T. rex-looking xenobot with big legs and tiny arms developed a year ago would not work.

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We need a shape that can corral the dispersed stem cells. With this goal, AI tells us a xenobot taking on the form of Pac-Man is our best bet [4].

An ethical dilemma?

Just the phrase "living robots" instills fear of humanity being surpassed and ruled by our own technological creations. These fears are not irrational. In an interview with Forbes magazine, Micheal Levin, co-author and director of Tufts University's Center for Regenerative and Developmental Biology, reveals, "When we start to mess around with complex systems that we don't understand, we're going to get unintended consequences" [5].

Scientific discovery is a double-edged sword. Before we jump to conclusions and become apprehensive of starring in the next episode of Netflix's Black Mirror, remember, the most that xenobots can do right now is spin and scuttle around. These rudimentary actions do not pose threats to us. In fact, such simple actions have already inspired solutions to many of our problems. Unlike Alexa and Moxie, xenobots are made of biodegradable materials. They're easier to break down and will not release toxins, in contrast to their plastic and metal counterparts.

Xenobots are biocompatible because of their cellular composition. Since stem cells may also be sourced from human tissues, xenobots can advance patient-specific therapeutics. Their form and function rely on the native pluripotent and self-organizing capabilities of stem cells. No genetic modifications required. This means xenobots can't independently take off and evolve, as co-author Douglas Blackiston reports to NPR [6].

At 1 millimeter, xenobots are smaller than the thickness of your credit card, making them ideal for solving problems in tight spaces which may include removing plaque buildup along your arteries [1]. This is a big step in preventing cardiovascular diseases – one of the global leading causes of death [7]. When hooked up to the right sensors, they can pinpoint hard-to-reach areas of radiation and remove toxic waste [1].

With limitless resources, their autonomous abilities to self-propagate and heal make them robust and scalable for regenerative medicine, tissue repair, and more [1]. However, the caveat is these limitless resources. Without a long-term supply of cells and nutrients, these bots would cease to function. Another checkpoint is the AI algorithm. It lets us control and predict the bots' behaviors, ensuring they do not go beyond the scientist's intentions.

Xenobots are malleable and can take on virtually infinite forms. Each form is a potential solution and the list of applications goes on. As robotics expert, computer scientist, and corresponding author Dr. Bongard shared with CNN: "Most people think of robots as made of metals and ceramics but it's not so much what a robot is made from but what it does, which is act on its own on behalf of people" [8].

As it stands now, exploring the benefits of xenobots helps us more so than harms us. From curing diseases to protecting the environment, they can be good for us. After all, they are organic.

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HOW TO MEND A BROKEN HEART: FROGS AS MODEL ORGANISMS FOR HEART REGENERATION

Author: Madison Balagtas

April 10, 2022

Cardiovascular disease is the #1 cause of death in the world [1]. Cardiovascular disease results from the deterioration of heart tissue – an irreversible disease due to our inability to regenerate our heart tissue. There are model organisms used in science with regenerative capabilities, but they have some limitations. Mice have cardiac regenerative abilities one day after birth but lose it at seven days [5]. Adult zebrafish and salamanders can regenerate their hearts as adults but are considered lower vertebrates [6]. Humans are higher vertebrates and have more complex systems, so research on lower vertebrates can only tell us so much. In an article titled "Fosl1 is vital to heart regeneration upon apex resection in adult Xenopus tropicalis," Hai-Yan Wu and Yi-Min Zhou from Jinan University focus on the X. tropicalis, or the western clawed frog, a vertebrate with a closer evolutionary distance to mammals [3,7]. Previous data demonstrated that one-year-old X. tropicalis could regenerate their hearts but did not dive into the mechanisms [3]. This more recent paper uses fully developed frogs matured at six months to show that the protein Fosl1 plays an important role in heart regeneration in vertebrates. Additionally, the authors propose X. tropicalis as an ideal model organism for heart regeneration.

WORD BANK:
α-actinin+: positive expression of protein that contributes to the formation of cardiac muscle filaments
cardiomyocytes (CMs): Cells specific to the heart
cTnT+: Cardiac Troponin T; used as a marker for acute myocardial infarction
EdU: 5-Ethynyl-2'-deoxyuridine (EdU) ; incorporated into DNA to label dividing cells and is commonly used in pulse-chase techniques.
in vivo: Experiments and tests conducted in an entire living organism
Fosl1 vs. Fosl1: It is important to distinguish between the formatting of gene and protein names. Proteins and their encoding gene share the same name. To tell the difference, gene names are italicized while protein names are not. In this case, Fosl1 is the protein and Fosl1 is the gene.
Ki67+: Positive expression indicating the cell is actively dividing
luciferase assay: Determines if a protein can turn on or off the expression of a target gene. If the protein can increase expression, cells will express luciferase and glow, if the protein decreases expression, cells express less luciferase than normal.
myocardial infarction (MI): Heart attack
pH3+: positive expression of dividing cells
pulse-chase: Technique to analyze cellular processes over time. Cells are exposed to a labelled compound (pulse) that is incorporated during DNA synthesis. The pulse is "chased" by the same compound, but unlabeled. The compounds are present to track the replication of cellular DNA.This is monitored to see how long the labeled compound lasts in cells.
Quantitative polymerase chain reaction (qPCR): Measures expression of DNA
RNA-seq analysis: Sequencing technique that analyzes RNA to determine what RNAs are present within a sample, which is used to conclude what genes are expressed or suppressed.

Frog heart tissue can regenerate!

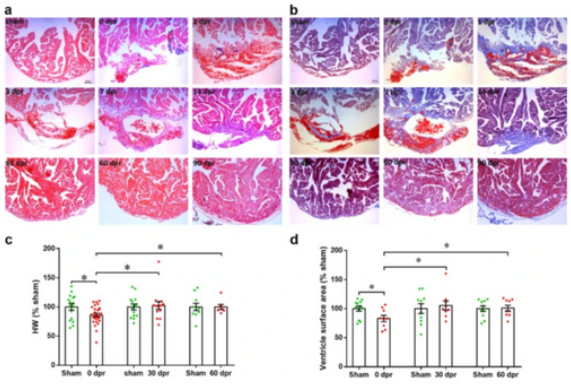

Fig. 1: Regeneration of ventricular myocardium of X. tropicalis.

The researchers' first goal was to compare X. tropicalis with another species X. laevis since previous work showed the latter lost cardiac regenerative capability after 6 months [4]. After cutting the tip of the heart in a surgical process called apex resection, tissue staining showed 6-month X. tropicalis can regenerate heart tissue, with full regeneration 30 days post resection. They also confirmed that there was no significant difference in the heart weight or surface area between the resected hearts and sham (control) hearts. Successful regeneration was characterized by contraction at 30 days post resection.

Author: Madison Balagtas

April 10, 2022

Heart regeneration is successful through cardiomyocyte division

Next, the scientists wanted to rule out the possibility that the **cardiomyocytes (CMs)**, the cells that make the heart contract, were simply getting bigger as opposed to actually dividing. They did this by staining the heart tissue with pH3+ and α-actinin+. They found that there was an increase in dividing cells 1 to 14 days post resection. They again confirmed this by measuring the uptake of EdU, a DNA synthesis marker. If a cell were simply expanding, the DNA would not need to divide and no EdU would be incorporated into the cells. However, they saw a significant increase in EdU, confirming the cells were, in fact, dividing. They show a significant increase in EdU+ α-actinin cells 3 to 14 days post resection. Finally, the researchers used another method to confirm proliferation using another DNA synthesis label, proliferation cell nuclear antigen (PCNA). While EdU specifically labels the S stage where chromosomes are duplicating, PCNA is expressed in all stages of cell division. The S stage is only the replication of DNA, so using PCNA as well ensures the increase is in cell division and not simply an increase of DNA in S stage.

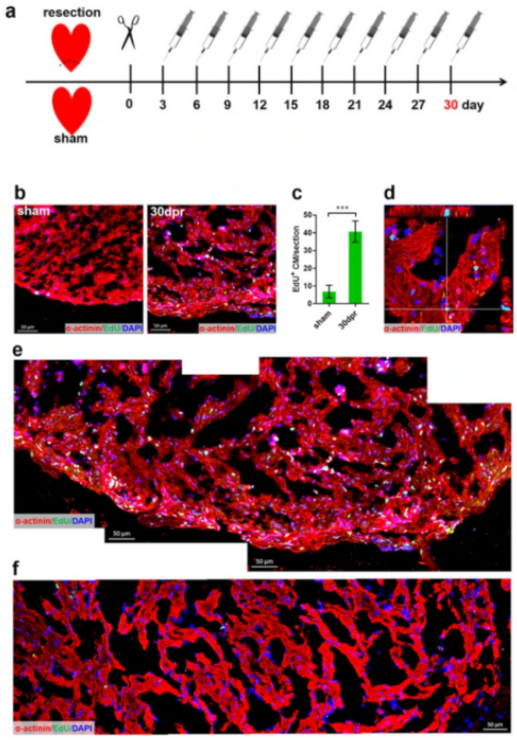

Fig. 3: Proliferation of cardiomyocytes contribute to the regenerated ventricle apex in X. tropicalis.

Now that it is known the CMs are dividing, the researchers asked if the new heart tip was made of newly formed CMs. They prove this using a **pulse-chase experiment.** The CMs are exposed to EdU for a brief amount of time (pulse) which is incorporated into cells. There is a limited amount of EdU given so when the cells are "chased" by unlabeled compounds. This is monitored to see how long the labeled compound lasted in the cells. EdU+ CMs were seen in the new tip 30 days post resection but are absent elsewhere. This shows that regenerated heart tissue is made up of dividing and newly formed CMs. If there were EdU+ CMs in tissues other than the tip, that could suggest that CMs have a broader role and are not the main cells responsible for heart regeneration.

Fosl1 gene is necessary for cardiomyocyte division

Now the authors want to find target genes involved in heart regeneration. They collected cut heart ventricles and did RNA-seq analysis (technique that analyzes RNA to determine which genes are turned on or off and by how much). They found that genes related to cell growth and cell cycle regulation were increased in cut hearts versus the controls. The control frogs underwent the same surgical procedure of the incision but their ventricles were not cut. The gene Fosl1 has known roles in cell proliferation. qPCR showed an increase in Fosl1 after the heart tip was cut. To determine what type of cells expressed Fosl1 during heart regeneration, they examined the pattern of Fosl1 in CMs and non-CMs. They showed Fosl1 expression levels were higher in CMs compared to non-CMs, indicating CMs are responsible for the increase.

To determine target genes or genes affected by the protein Fosl1 during heart regeneration, they used qPCR and screened 7 targets. Using a luciferase assay, they show Fosl1 interacts with JunB, another player in cell proliferation, to activate all 7 genes. One gene, ccnt1, was shown to be directly regulated by Fosl1. This makes sense because the ccnt1 pathway is known to be related to heart injury and regeneration. These results suggest that Fosl1 promotes CM division by increasing ccnt1 expression by interacting with JunB, contributing to heart regeneration.

Author: Madison Balagtas

April 10, 2022

Fosl1 protein is necessary for cardiomycote division

Researchers asked next if the protein Fosl1 influences the proliferation of CMs. Using a rat CM cell line, H9c2, they transfected the cells with a virus that overexpresses Fosl1 protein, meaning that Fos11 will be expressed more than the natural amount. After a cell count and EdU incorporation assay, they found overexpression of Fosl1 promoted cell growth. Short interfering RNA (siRNA) is very specific and is used to cut out instructions for a gene, thereby "silencing" it. When they silenced Fosl1 protein using siRNA they saw a decrease in proliferation (decrease in cell division), as they did when they used Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technology to knockdown the Fosl1 gene. siRNA silenced Fosl1 by generating knockdowns at the mRNA level, while CRISPR generated knockouts at the DNA level. The researchers concluded that Fosl1 protein is necessary for proliferation of CMs.

To see if the gene, Fosl1, influences proliferation, the authors isolated CMs in neonatal mice which lose heart regenerative abilities 7 days after birth. They compared proliferation between mice with and without Fosl1 silencing. Silencing Fosl1 suppressed the amount of Ki67+ cTnT+ cells. Ki67+ is the textbook marker for cell proliferation and has been heavily researched and PCNA is a newer cell proliferation marker [2]. The reduction in PCNA in the active phase of the cell cycle suggests Fosl1 is extremely important for the proliferation of primary CMs.

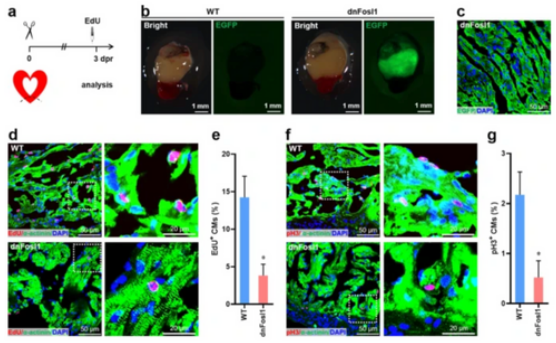

Fig. 8: Fosl1 function is required for cardiomyocyte proliferation during X. tropicalis heart regeneration.

To look at the in vivo Fosl1 function in X. tropicalis, a dominant-negative transgenic line of Fosl1 (dnFosl1) was made.

This specifically blocks the function of Fosl1 while leaving other Fos members intact. After cutting the tip and looking at CM proliferation 3 days post resection, they saw that the percentage of EdU+ α-actinin+ cells (proliferating heart cells) were significantly lower in dnFosl1 hearts compared to the controls. They also used pH3/α-actinin staining to show CM proliferation was significantly lower in dnFosl1 hearts compared to controls. This data shows that loss of function of Fosl1 causes a defect in CM proliferation during heart regeneration in X. tropicalis.

Loss of Fosl1 function decreases neonatal mice cardiomyocyte division

The authors were able to show similar results in neonatal mice and used a virus to silence Fosl1 as opposed to creating a transgenic line. They repeated this in mice because they are mammals and more closely related to humans. If the mechanism wasn't the same in mice, studying heart regeneration in frogs would not be very beneficial for human therapeutic use. Suppression of CM proliferation following Fosl1 silencing is shown by a decrease in EdU+ cTnT+ cells.

Fosl1 improves heart repair in adult mice!

Lastly, the researchers wanted to determine if Fosl1 had any roles in heart repair in a non-regenerative model. They used adult mice to observe the expression pattern of Fosl1 after a myocardial infarction (MI). They saw Fosl1 expression decreased in hearts up to 3 days after the MI. They next wanted to see if overexpressing Fosl1 in these adult mice's hearts could improve heart repair after an MI. Mice were injected with AAV9-Fosl1 for 30 days to overexpress Fosl1 and then had surgery to induce a heart attack. AAV9 is a virus that has been repurposed to be like a delivery vehicle. Instead of the original viral DNA, the authors replaced it with Fosl1 and used the machinery already in the virus to make abundant copies of Fosl1, leading to overexpression. Overexpression of Fos11 significantly improved cardiac function, which was confirmed by an increase in how much blood could be pumped out of the heart, increased change in the diameter of the left ventricle, and reduced scarring.

It is important to do cardiac regeneration research on model organisms so that we can develop therapies for heart damage in humans.

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While there are several model organisms with better regenerative capability than X. tropicalis, they are farther away evolutionary-wise to humans. X. tropicalis has the ability to regenerate spinal cord, tail, eye and limbs. This lab has successfully proved that adult western clawed frogs can regenerate their hearts at 6-months. In the past, the authors proved this with 1 year-old frogs. Decreasing the experiment timeline by half a year can be useful in the future for testing therapeutic treatments quickly and speeding up the process of clinical trials. This paper shows Fosl1 plays an essential role in CM proliferation and heart regeneration in vertebrates. This includes interacting with JunB – a gene activity regulator – to increase expression of cell cycle regulators such as Ccnt1. Ultimately, the authors show 6-month X. tropicalis is an ideal model organism for studying heart regeneration in vertebrates. This puts us closer to fully understanding the mechanisms of vertebral heart regeneration, which will allow us to develop therapies to treat cardiovascular disease.

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THE PRECIPICE OF THE SPACE AGE: HOW WE GOT HERE, WHERE WE ARE, AND WHERE WE'RE GOING

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Throughout history, the sun, moon, and stars have been humanity's companions. The next time you are outside, look up. The lights that shine down upon you now are the same that have guided sailors, mystified fortune tellers, and inspired populations. Those celestial bodies, both incomprehensible and oddly familiar, are embraced by our love and curiosity. Yet, for all of human history, the night sky's immensity and distance has challenged our exploratory capabilities. At least for now. With the rise of technological and, subsequently, human capability, the future that lies ahead of us is dominated by space. In short, we live on the precipice of the space age. But, to examine where we are going, we must first uncover where we've been and understand where we are.

How We Got Here.

Sight plays a pivotal role in the human experience. Whether it's examining the deepest depths of our oceans or gazing towards the night sky, sight capably embodies our curiosity. Yet, with the night sky being so challenging to properly observe, humans have long imagined the celestial bodies that lay beyond Earth's borders. That is until the development of the telescope.

While lenses had been around since the time of ancient Egypt, no one had turned their uses towards the night sky until the early 1600s (1). Enter the astonishing Galileo Galilei, a renowned astronomer whose immense contributions to astronomy would further humanity's understanding of its place in the universe, whether or not it liked the new knowledge (2). Galileo's development of the telescope enabled the observation of celestial bodies in a manner never done before. The subsequent telescope revolution and innovations enabled the onset of the sight humanity sorely needed to expand its understanding of the universe. Moreover, contributions from physicists and astronomers like Isaac Newton and Johannes Kepler ushered in a new study of the heavens, one dictated by math and scientific observation (1, 3).

These developments set the groundwork for physicists in the 20th century, perhaps most notably Albert Einstein. This broader understanding of physics and the universe culminated in the Apollo missions (4), which, to date, have been our most comprehensive and daring project of human exploration. In putting man on the moon, humanity has demonstrated a small extent of its capabilities.

Where is Here?

In the years since the Apollo missions, humanity has, for the first time, sent space probes to beyond our solar system (5), rovers to the surface of another planet (6), and telescopes to gaze into the deepest depths of our universe (7). In the time since the Apollo missions, humanity has developed more capable technology, a deeper understanding of the universe, and, perhaps most of all, a cautious optimism towards the space programs of the future. Our current state in the age of space exploration is still in the womb. Presently, this time has been dominated by the International Space Station, Hubble Telescope, and Curiosity and Perseverance, the most recent Mars rovers. More recently, private enterprise has entered the fray for vying for space exploration. While long thought a possibility (8), companies like SpaceX, Boeing, VirginGalactic, and Blue Origin have all demonstrated remarkably capable vehicles for space exploration.

While the Apollo age is in its twilight, his sister, Artemis, is at its dawn. In the next few years, the moon mission Artemis will launch, fostering a new age of lunar and interplanetary exploration (9). Similarly, the James Webb Space Telescope has recently been deployed to study the universe, hoping to further shed light on our ancient celestial origins. Hopefully, this age will soon reach interplanetary travel, with the arrival of humans on Mars.

Where Are We Going?

While those may be some short term goals, the technologies that will characterize humanity's expansionary period still exist only in the pages of science fiction novels. There are three of these technologies that I would like to briefly touch upon.

Solar Sails:
Solar sails, which is, simply put, a sail using radiation as propulsion (much like a sail on Earth uses wind), is perhaps our most easily "accessible" form of interstellar ravel (10). These characteristics function on using differential in radiation pressure as a means of propulsion (11). In fact, the late renowned physicist Stephen Hawking was a notable backer of the technology (12). Hawking backed Breakthrough Starshot, an effort to reach a near star named Alpha Centauri through a system of lightweight space vesicles, lasers, and space sails (13).

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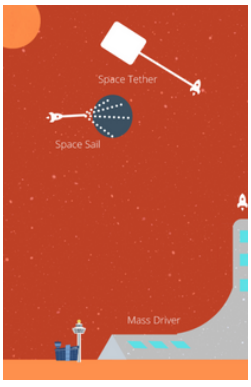
Solar sails represent a promising means of propulsion, so much so that NASA has begun missions to test out its viability (11).

Space Tethers:

Space tethers are, effectively, a large spinning rope in space. While no tethers have actually been built, this theoretical technology is physically possible, and NASA is exploring the possibility of sending a mission to test it out (14). Should this technology be developed, it would provide spacecraft with immense acceleration capabilities without carrying extra propulsion. A tether works by staying stationary around a point in space while the two ends of the rope spin around that axis, picking up spacecraft and other shipments along the way. This provides both acceleration and shortens the distance for spacecraft. In the book Seveneves, science fiction writer Neal Stephenson artfully constructs a form in which space tethers can be utilized, to improve access to low earth orbit (15). Regardless of the future applications of space tethers, it is likely to be a vital part of our future in space exploration.

Mass Drivers:

Mass drivers (see figure 1) use electromagnetic fields to send objects into space (16). Interestingly, due to the acceleration forces passengers would feel, mass drivers are not feasible for passengers. That said, mass drivers serve an important role in bringing raw materials to space at a low cost. On large scale projects, like the terraformation of planets, mass drivers would be immensely beneficial. Much like space tethers, mass drivers have yet to be proven economically viable but remain physically possible (17). They will likely represent an extensive part of our capabilities as humanity develops into a space-faring nation.



While we have a long way to go, these technologies will become a key part of our future. The development of space technology should remain a priority of governments worldwide, as it would be a disservice to all humans, past, present and future, if we fail to expand our technological capabilities. So let's reach for the stars.

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THE RIGHT TO DIE

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In the Carter v. Canada case, the Supreme Court of Canada ruled that consenting and competent adults suffering from serious and irreversible medical conditions should have access to some format of medical assistance in dying [1]. Most Candians support medically assisted dying for patients with terminal/physical illnesses that often lead to some form of physical decline. In fact, a 2016 Angus Reid poll found that 90% of Canadians believe that some form of assisted dying should be legalized in the healthcare system [2]. However, the same poll found that Canadians perceive a clear distinction between psychological suffering and physical suffering, as nearly 75% of respondents agreed that assisted death should be granted to patients with non-terminal injuries/diseases that are in severe physical pain, whereas almost 80% believed that individuals suffering from psychological illnesses should not have access to assisted suicide [2]. The topic of allowing similar access to assisted dying for patients suffering from severe mental disorders is considered extremely controversial and a source of tension for many individuals in Canada [3].

There are many different forms of euthanasia that are dictated by actions a doctor takes (or doesn't take) and a patient's consent. In an essay published in the New England Journal of Medicine, ethics and animal rights philosopher James Rachels stated that active euthanasia is where a doctor does some form of "direct action designed to kill their patient" (assisted suicide/dying) [4]. Passive euthanasia is the act of witholding life-prolonging treatments, allowing the patient's death to take its natural course (it is the absence of life-saving action) [4]. Euthanasia can also be voluntary, involuntary, and/or nonvoluntary. Voluntary euthanasia, the most common for of euthanasia, is when a person give consent to be euthanized. Involuntary euthanasia is when someone who does not want to die is put to death (a form of murder). Nonvoluntary euthanasia is when a person is when a person is put to death without their wil (e.g., taking a comatose patient off of life support).

In an assessment of the legal and ethical dilemmas of euthanasia, forensic psychiatry professor Alexander Ian Frederic Simpson explains the perspective of those opposing euthanaisa for people with mental illness. These proponents would argue that mental health disorders cause people to make distorted judgments and that suicide is often a desperate step made by those who consider their situations to be hopeless and irreparable [5]. These arguments against allowing people with mental illness to be euthanized are true, in some cases. However, it is questionable to deny everyone with a mental disorder the "right to die" based solely on these reasons. It is often inaccurate to equate having a mental disorder to not being sane or of sound mind. In reality, there are plenty of mental disorders that cause mental suffering to a person while leaving them fully rational to make decisions for themselves and others (e.g., depression, anxiety, eating disorders, etc.) [5].

Dr. Simpson points out that another reason why individuals are against euthanasia for people with mental illness is because they themselves cannot justify wanting to die due to mental suffering [5]. It is far easier for people to understand someone's desire for death when they are in constant pain, with medication having little to no effect in relieving their distress, compared to when a person is suffering mentally. This is especially true when the individual did not suffer through a (mentally) traumatic event to cause the mental disorder in the first place (e.g. traumatic event(s) that cause PTSD). With physical illnesses, we can see what is happening to one's body and sometimes imagine what they are going through to the point in which we physically "feel" the pain they are experiencing (to a certain degree). Mental illnesses do not always have physical manifestations meaning most people who have a mental illness are able to conceal their disorder from others. Some even taking drastic measures to do so in order to avoid stigmatization and discrimination from the general public.

When the argument for assisted suicide is proposed for people with mental illness, the focus is largely geared towards severe depression [1]. This focus, however, has proven to be too narrow and fails to take into account other mental disorders that are real (physical and mental) threats to patients with mental illness [1]. If psychiatric conditions were to be considered in terms of assisted dying, severe depression would not be the only mental disorder that would be examined [1].

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An example of this comes from Belgium and the Netherlands, medically assisted suicide is being provided to people with chronic schizophrenia, posttraumatic stress disorder, severe eating disorders, autism, personality disorders, etc. [1]. Most people (with a mental illness) that request assisted suicide have compromised abilities to cope with adversity [1]. This in turn causes them to suffer as they do not know how to manage difficulties that occur in their lives. Jeanette Linda Hewitt, a nursing professor at the University of Swansea and a registered mental health nurse, defines suffering as "any enduring experience of pain or distress that significantly impairs a person's subjective satisfaction with his or her quality of life [2]." This definition of suffering illustrates that the impairments caused by mental illness are just as harmful as the one's caused by physical illness [2]. The suffering caused by depression or PTSD can be just as bad, if not worse than that caused by cancer and should not be dismissed or downplayed [2].

Mental illness affects people to varying degrees and not everyone will (knowingly) suffer from a mental disorder or explicitly know someone that does. Due to subtle and often overlooked symptoms of mental illness, those not affected have a hard time sympathizing with mental suffering and don't holistically understand the pain it causes. Based on this inability to understand the adversity people with mental illnesses face and misinformation of the capability of rational thought from individuals with mental disorders, the public often believes that people with psychiatric conditions do not/should not be given access to medically assisted suicide. The "right to die" is a component of a person's right to bodily autonomy. Yet, this concept repeatedly excludes individuals with mental disorders.

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THE PSYCHOLOGICAL EFFECTS OF PCOS

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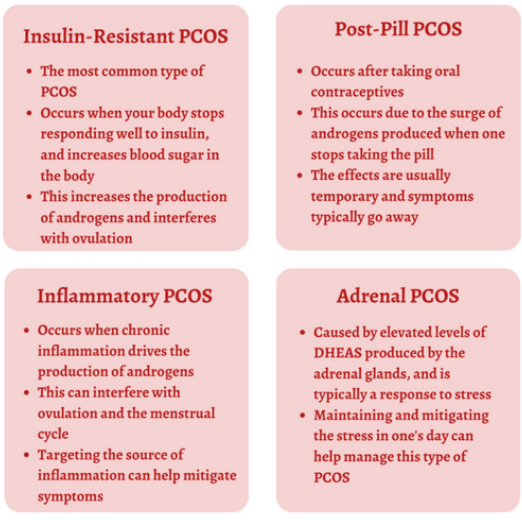
With polycystic ovary syndrome (PCOS) being the leading cause of infertility and hormonal imbalances in women worldwide, it is quite puzzling why this condition has not been further studied and understood. While some of the physical symptoms of this condition have been briefly studied, the psychological effects of PCOS are overlooked by healthcare professionals [1]. Whether women are trying to conceive or just take care of their health, PCOS can be an ongoing struggle for many, affecting their daily lives.

What is PCOS?

PCOS is a condition in women that can cause an imbalance of reproductive hormones. This imbalance can cause a plethora of different health issues, such as:

- Infertility
- Irregular menstrual cycles
- Cysts on the ovaries
- Fluctuated weight gain and loss
- Acne and unwanted hair growth
- Mental health issues
- Increased levels of testosterone and other androgens

There are four main types of PCOS that women can be diagnosed with, each with a different subset of symptoms and treatments [2].



The Psychological Effects of PCOS

The psychological effects of PCOS have largely been glossed over and most women go years without a diagnosis or, more often, get misdiagnosed. In fact, according to the National Institutes of Health, less than 0.1% of funding is allocated towards PCOS research, despite it being the leading cause of many health issues in women [3].

- The Development of Eating Disorders:
  - Many women diagnosed with PCOS, especially the insulin-resistant type, can struggle with their weight, as well as the correct types of food to eat to manage their symptoms. But with that comes the increased risk of developing an eating disorder.
  - Healthcare professionals who treat women with PCOS often disregard underlying hormonal issues and immediately put their patients on a diet. Whether it be a restriction or an introduction to new foods, it can all be overwhelming. In fact, a study published in the Indian Journal of Psychological Medicine found that PCOS can cause changes in eating patterns, which can increase the risk of developing an eating disorder [4].
- Struggles with Body Image:
  - Along with fluctuations in one's weight, issues such as unwanted facial hair and darkness in different parts of the body, also known as hirsutism, can be a source of struggle for many women. These symptoms are usually due to the elevated presence of androgens as a result of certain types of PCOS. Chaudhari, et al, concluded that women who had these symptoms not only suffered from low self-esteem, but their attempts to cover up excessive hair growth and darkness in and of itself was stressful, and overall, it was reported that they experienced a lower quality of life [4].
- Increased Risk of Anxiety and Depression
  - A study in the Neuropsychiatric Disease and Treatment Journal found that women diagnosed with PCOS are three times more likely to be diagnosed with anxiety [5]. Issues relating to fertility, one's menstrual cycle, and other physical manifestations of PCOS all significantly increase the risk of developing anxiety and depression.

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- Women with PCOS are even at a greater risk of developing other conditions such as diabetes and endometriosis, a condition where the tissue that lines the uterus begins to grow outside of it due to hormonal imbalances [6]. In fact, a study done by the Department of Obstetrics and Gynecology in China found that the imbalance of hormones due to PCOS can cause other issues in the body, one of which is the disruption of the normal lining of the uterus [7]. All of these conditions that can result due to PCOS all increase stress on the body and the overall well-being of women who are diagnosed with these conditions.
- The same study dives deeper and explains that chemical imbalances due to PCOS are also directly correlated to the risk of developing depression and/or anxiety. The hypothalamic–pituitary–adrenal axis, or the HPA axis, was found to be disrupted due to PCOS. The HPA axis is responsible for the body's reaction to stress, so when stress levels are elevated, the signaling that is required for the HPA axis to function is disrupted. (Figure 1).

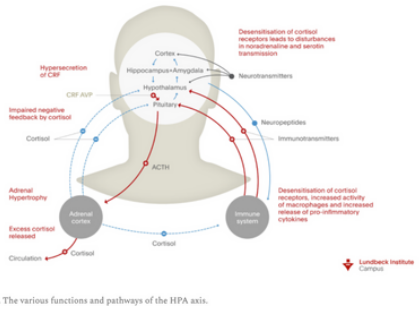

Figure 1. The various functions and pathways of the HPA axis.

- The maintenance of the HPA axis is necessary for homeostasis, which is disrupted by PCOS due to changes in androgens and cortisol levels. A study found that when androgen and stress levels are elevated, it leads to the overactivation of the HPA axis since it relies on feedback inhibition. This increase in the overactivation of the HPA axis further causes imbalances in hormone levels, further disrupting homeostasis in the body [8].

Where do we go from here?

Healthcare professionals have frequently neglected the very real and debilitating symptoms of PCOS.

Too often, birth control is used as a band-aid solution, or the symptoms are ignored in younger women. The lack of research and funding towards PCOS has been detrimental to improving diagnoses and the quality of life of those who are diagnosed. Though there are different types of PCOS, all of its symptoms and diagnoses are often lumped together without providing individualized solutions to each patient.

Dr. John Nestler, the chair of the department of internal medicine at Virginia Commonwealth University, explains that the little funding that does go into PCOS research mostly focuses on understanding why women with PCOS struggle with fertility and ignores the plethora of other symptoms and effects that PCOS can have [9].

Most women either go years with their symptoms being ignored, or they are only diagnosed with PCOS when they are much older and trying to conceive. Though there is not a direct cure for PCOS, the symptoms can be managed when found earlier. Care should be holistic. There are a lot of mental stresses that come with PCOS, ranging from imbalances in hormones to struggles with body image and the development of various other disorders, and healthcare workers must take those concerns into account when developing treatment plans for their patients.

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THE BEST OF TWO WORLDS: HOW MUSICAL TRAINING AND VIDEO GAMES CAN IMPROVE LITERACY SKILLS IN DYSLEXIC CHILDREN

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Dyslexia is a common neurobiological learning disorder that is characterized by difficulty reading with accurate/fluent word recognition and spelling [1]. These difficulties, such as mispronouncing words, hesitant/punctuated speech disfluencies, difficulty reading new/unfamiliar words, and spelling errors, result from deficits in the phonological component of language (see Figure 1) [2]. Existing studies show that, in dyslexia, there is less activation in certain regions of the brain responsible for reading and rhyming tasks. Some studies find that dyslexic individuals have greater activation in some areas of the brain than non-dyslexic individuals to compensate for the weakness in brain areas that are typically involved in reading [3]. The diverse functions of these brain regions make it difficult to understand their exact role in dyslexia; however, it is likely that dyslexic individuals rely on different brain processes/pathways to read, as indicated by the over-activation of atypical brain regions.

Figure 1. Phonological components of language

Musical training has been widely known and accepted as a remediation and therapeutic tool for children with dyslexia as it helps to improve their ability to perceive sound, also known as temporal processing [4]. Past research shows that tapping the number of syllables in a word to a steady beat can improve spelling in dyslexic individuals. In one study, poor readers who received six months of musical training, specifically aimed at developing auditory, visual, and motor skills, performed significantly better on a standardized reading test than a similar group who received discussion training instead, which involved discussing certain topics [5]. Evidently, there is a strong relationship between musical discrimination abilities (tonal/melodic and rhythmic tasks) and language-related skills in dyslexia [6].

There are many different musical training methods used as therapeutic tools for dyslexic individuals, many of which are supported by literature.

For example, the Cognitivo-Musical Training (CMT) method consists of musical tasks and exercises based on an auditory component, a motor component, and a cross-modal component (integrating auditory, visual, sensory, and motor modalities) [4]. For example, exercises combining both sensory and motor components included tapping the written notation of a rhythm or learning to play a small melody and correcting other children's performance [4]. The way CMT can enhance the reading abilities of dyslexic individuals is through boosting their phonological awareness (sound structure of words), word segmentation, and working memory [7]. These are all deficits that dyslexic individuals have as a result of poor temporal processing, both in language and music [7].

There is also growing literature on the use of action video game (AVG) training as a remediation tool for dyslexic children to improve reading ability [8]. Not only is this a low-resource-demanding therapeutic tool, but it also reveals significant improvements in dyslexic children's literacy skills [9]. AVGs have been linked to improving the function of specific brain networks that are implicated in spatial attention and reading. A recent 2021 study by Bertoni et al. was conducted on 14 dyslexic children to investigate whether AVG training compared to non-AVG training improved attentional control [10]. Participants played AVG and non-AVG on the commercial Wii for 80-minute sessions over nine days for each condition and were tested before and after the training [10]. Video games were classified as AVGs if they possessed the following characteristics: fast speed in terms of events and moving objects, a high degree of motor load, unpredictability in both sound and moving parts, and an emphasis on peripheral processing [10]. Testing consisted of a variety of reading tasks and visual search tasks [10]. Findings show that, after only 12 hours of AVG training, children who underwent AVG training performed better on tests, which was measured by their improved attentional control and phonological decoding (ability to sound out words to understand them) speed [10].

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Figure 3. Combining musical training with action video games

The literature supports musical training and AVGs as therapeutic tools in helping to improve literacy skills in dyslexic individuals. Musical training has consistently improved temporal processing, which is necessary for phonological awareness and word segmentation in reading. Furthermore, AVGs have been shown to improve attentional control among other neural networks involved in spatial attention and reading ability. Combining these practises (musical training and AVGs) may reveal even more improvements in working memory and, as a result, reading ability. Further studies would be beneficial and can potentially pave the way for more effective remediation tools/programs, therapy and early intervention programs, and educational tools for dyslexic individuals.

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Abstracts

Demystifying the science behind love

By - Inara Nanji

More often than not, individuals assume that love is rooted in the heart. However, it is much more complicated than that. In fact, the brain is the central aspect involved in love. Several mechanisms are entailed in romantic love such as lust, attraction, and attachment. Each has its own role to play. Lust is solely sexual based and can be short-term, attraction is arousing interest, liking, or desire, attachment is the fostering of strong connection between individuals that can be long-term. Understanding each of these paints a bigger picture of love and its forms. There exist multiple myths about love that continue to persist, including women are more romantic than men, intense love dies down quickly, and the most well-known – opposites attract. The article attempts to address these three myths and how they influence our thought processes, mindset, and predispositions.

Art Therapy to Prevent Elderly Cognitive Decline

By - Leanne Ahra Menguito

Once dementia has set in the elderly, interventions to slow or stop its onset have little benefit. However, art therapy can prevent this cognitive decline in the elderly with mild cognitive impairment (MCI). Mahendran et al. designed a randomized control study of art therapy (AT) and music reminiscence activity (MRA) groups led by trained therapists. AT consists of the evaluation, production, and discussion of artworks. In contrast, MRA consists of recalling and discussing music-related memories while listening to music with accompanying photos or videos. Cognitive tests, psychological tests, and telomere length measurements were collected three and nine months into the study to determine if there were any improvements in cognition. Mahendran et al. found that AT showed more significant cognitive improvement than MRA. This result could be due to the different mental processes involved in the evaluation and creation of art, which could lead to changes in brain connectivity. There was a decline in mild depression and anxiety, but the results are not statistically significant. Similarly, telomere lengths decreased, but the results were not statistically significant. The control group also showed cognitive improvement, but this could be due to the cognitive stimulation caused by their continued daily routine, such as going to work. The study was not perfect, however. Interviews were not conducted before the study to assess their mental state. Mental health cannot be measured with only numbers. Furthermore, the number of participants was tiny, at 68 people, and localized in Singapore, leading to doubts about its application to a larger population.

The best of two worlds: How musical training and video games can improve literacy skills in dyslexic children

By - Lior Boguslavski

Dyslexia is a very common learning disorder among school-aged children. It is characterized by mispronouncing words, hesitant/punctuated speech disfluencies, difficulty reading new/unfamiliar words, and spelling errors. All these deficits stem from the different brain structures that dyslexic individuals have, and the different brain processes they use to read. Musical training is widely known and used as a therapeutic tool for children with dyslexia. Research studies have shown that various musical tasks, such as tapping the number of syllables in a word to a steady beat or learning to play a melody and correcting errors in others' performance, are shown to improve dyslexic children's reading and spelling skills. Additionally, action video games are used to improve the function of specific brain processes to enhance reading abilities and visual search tasks. Overall, research supports musical training and action video games as therapeutic tools in helping to improve literacy skills in dyslexic children and this can potentially pave the way for more effective remediation tools/programs.

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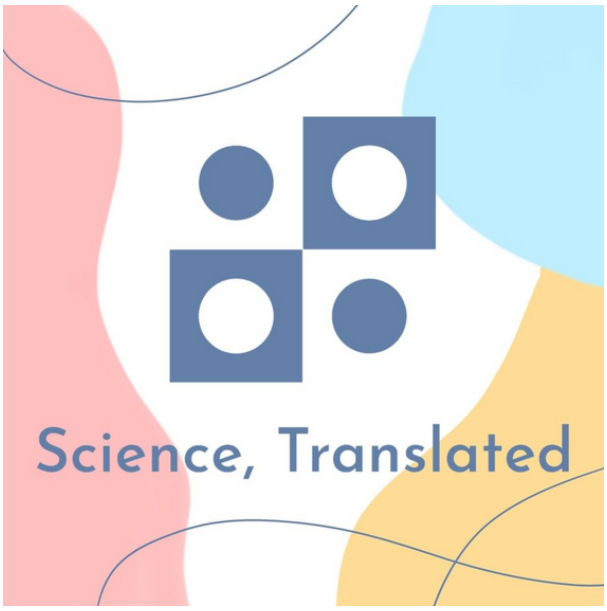

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