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Cover photo by Daisy Li

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MISSION STATEMENT

The Emory Undergraduate Medical Review (EUMR) publishes a semesterly journal that features faculty and student-authored articles on cutting-edge medical issues. Our interdisciplinary articles span various clinical fields and are peer reviewed by medical professionals from more than a dozen leading academic institutions, including Emory University, Yale University and the Mayo Clinic.

In addition to our publication, EUMR hosts various medically-related events on campus, including collaborations with the School of Medicine. Our projects have been featured by Emory's News Center and have caught the attention of President Sterk.

LETTER FROM THE EDITOR

Dear Reader,

As the start to a new decade, the year 2020 seemed inherently destined to be a turning point in history. As of May 2020, this expectation holds true, for better or worse, as we find ourselves in the midst of a global pandemic and a world that has transformed in response to it.

As college students, we reside in a transitory period that straddles different chapters in our lives. We are no longer children, but not quite adults; no longer restricted at home as high school students, but not completely engulfed by the sometimes terrifying freedom of the "outside" world. Instead, we are sheltered in a microcosm that provides us a space to grow and question the world, whilst shielding us from most of the grim effects.

But this pandemic has impacted every population, and college students around the world felt it too as they left campuses in droves this spring, packing bags into cars, booking last minute flights and bidding farewell to friends. Our microcosm has collapsed and we are left with awkward Zoom calls, cancelled internships and the anxious uncertainty of what the fall will bring.

In a time of global crisis, it can seem almost selfish to worry about something as comparatively insignificant as the final grade in a class or the fate of a little university publication, but it is only through the act of carrying on and moving forward that we can endure and recover from this unprecedented time.

Even as the world around us changes in draconic measures, I promise that EUMR will be one thing that stays the same. Hopefully that brings a sense of normalcy, however small, to ground our shifting worlds.

In the meantime, please enjoy the second issue of our sixth volume, and read everything from a timely exploration of the politics of global pandemics to a more whimsical look at the science of dreaming.

Many thanks to our editorial board for adapting to new virtual formats and making this issue possible despite all the unexpected roadblocks this semester. I wish everyone well, no matter where you are in the world at this moment.

And to our dedicated advisory board, know that you have our appreciation and respect. Many of you work as professionals in healthcare and we hope that you stay healthy in these challenging times.

I cannot wait to work with everyone again this fall — count on EUMR happening, no matter where we may end up.

Cordially,

Daisy Li
Editor-in-Chief
EUMR 2019-2020

Understanding postpartum depression in mothers

ANDY CHEN
Staff Writer

Childbirth is a momentous and joyous event — a cause for celebration. The first few days following a positive pregnancy test can be filled with dread or eager anticipation, and the months to come involve careful monitoring of maternal and fetal health by family, friends, and medical professionals.

Unfortunately, the experience of all expectant mothers is not the same. For some, pregnancy and childbirth are not so much jubilant life events as they are nerve-wracking and terrifying. The mere thought of becoming a mother can be a nightmare for those lacking the social and financial means to raise a child. The Diagnostic and Statistical Manual of Mental Disorders (DSM) recognizes the peripartum (during pregnancy) and postpartum (after delivery) periods as higher risk for the onset of major disorders include psychotic and depressive disorders. These include postpartum depression (PPD). The ways in which we understand and study postpartum depression can inform our approach to treating and helping mothers with the condition.

Psychotic episodes associated with postpartum mental illnesses can include thoughts of infanticide.

Although the classification of mental disorders using the DSM has been historically complicated, the current edition estimates that the time period for peripartum onset to be during pregnancy and postpartum onset to be in the four weeks following delivery (American Psychiatric Association, 2013). Using these criteria, the DSM reports that 3-6% of women experience depression, with half of major depressive episodes beginning prior to delivery (American Psychiatric Association, 2013). Other studies on postpartum depression report conflicting statistics. The DSM is more conservative in its classification of PPD, while most researchers use broader time constraints for PPD screening and diagnosis. The margins for classification of postpartum depression are usually between 6 to 12 weeks and suggest that the prevalence of mothers experiencing PPD can range from 5-20%

Figure 1. Symptoms of postpartum depression can be difficult to identify because they can be easy to dismiss, but common symptoms are a good place to begin. This infographic provides a quick overview of common symptoms to look out for. Image from Stone n.d.

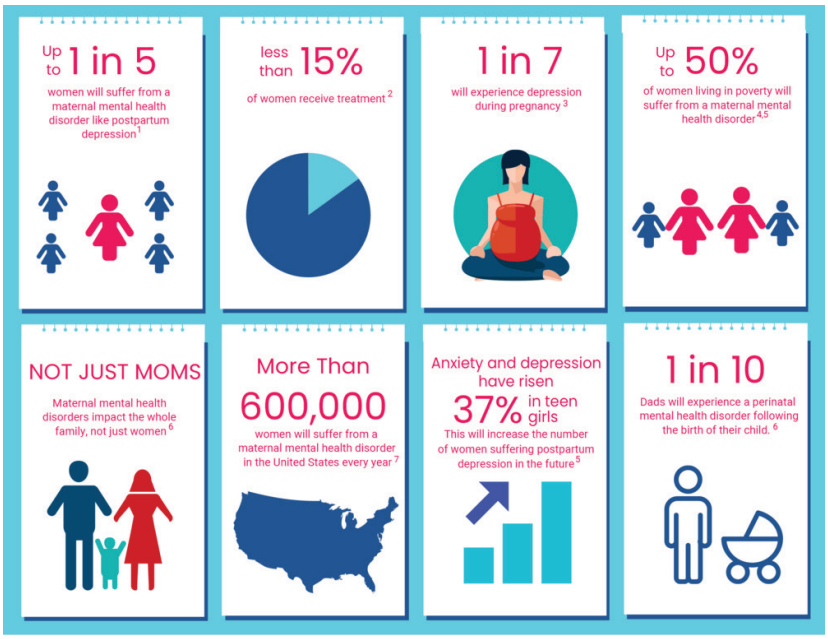

Figure 2. This infographic created by TheBlueDot Project serves to raise awareness and erase stigma surrounding maternal mental illness and in this case, maternal postpartum depression. Image from TheBlueDot Project 2020.

(Eberhard-Gran, Eskild, Tambs, Opjordsmoen, & Samuelsen, 2008).

Due to the constraints of the DSM in diagnosing peri- and postpartum onset of the disorder, most researchers use the Edinburgh Postnatal Depression Scale (EPDS) to detect postnatal depression. The ten-item self-rating scale has been validated in several studies and a meta-analysis of these studies found that the predictive value of EPDS in a clinical setting was much greater than its predictive value when applied to a general population of women (Eberhard-Gran et al., 2008). Symptoms of peri- and postpartum depression can be hard to deal with for mothers and families. PPD can cause anxiety or even panic attacks. In its extremes, psychotic episodes associated with postpartum mental illnesses can include thoughts of infanticide (American Psychiatric Association, 2013). However, not all psychotic episodess involve extreme delusions or hallucinations.

Women pregnant for the first time are more likely to experience mood disorders than those who have had multiple previous pregnancies (American Psychiatric Association, 2013). The risk of mood disorders is also increased in women with prior postpartum mood episodes and those with a personal or family history of depressive or bipolar disorder (American Psychiatric Association, 2013). These findings indicate a possible genetic component to PPD. The risk of recurrence for mood episodes is as high as 30-50% after the initial one (American Psychiatric Association, 2013). Given the dramatic statistics and symptoms of postpartum depression, it is all the more important for more research to be done to encourage more screening and find better treatments for PPD.

Social support during pregnancy and the postpartum time period negatively correlates with the likelihood of developing PPD.

Unfortunately, decades of research on the biological etiology of postpartum depression has been largely unproductive. The role of reproductive hormones in PPD pathogenesis has been studied, but a direct mechanistic association has yet to be clearly identified (Schiller, Meltzer-Brody, & Rubinow, 2014). Because of this, researchers have suggested the possibility of multiple PPD phenotypes, each with their unique biomarkers (Schiller et al., 2014). In other words, postpartum depression resulting from reproductive hormone modulation of the hypothalamic-pituitary-adrenal (HPA) axis is different from PPD resulting from immune dysregulation and would thus require different routes of treatment. Although more research is needed to validate this hypothesis, identifying the existence of multiple PPD phenotypes with distinct etiologies would allow for better diagnostic tools and individualized treatment plans.

As research on the biological mechanisms of postpartum depression pathogenesis continues, social scientists have taken another approach to studying PPD. Anthropologists studying major life cycle changes investigate the role of cultural patternings of the postpartum period that could result in postpartum depression.

Anthropologists Gwen Stern and Laurence Kruckman argued back in 1983 for more attention to be given to effects of social organization and role expectations in understanding postpartum depression (Stern & Kruckman, 1983). Most notably, studies find that social support during pregnancy and the postpartum time period negatively correlates with the likelihood of developing PPD. Accordingly, there is a positive correlation between social support and mental well-being. A study in Malaysia reported that the transition into motherhood after delivery was dependent on the support provided by others (Mustaffa, Marappan, Abu, Khan, & Ahmad, 2014). Women from poor socioeconomic backgrounds and who had low social support were especially at risk for developing PPD symptoms (Mustaffa et al., 2014).

The literature on postpartum depression reveals a significant role for spouses in the transition into motherhood. In a study published in 2016, psychologists studied the ways in which couples communicated about postpartum depression symptoms and how their conversations affected the couples' likelihood of conceptualizing their symptoms as an illness and seeking treatment (Henshaw, Durkin, & Snell, 2016). Their interviews revealed two central questions: "How bad is it?" and "What should we do about it?" (Henshaw et al., 2016). Couples usually worked together to determine if the symptoms were normal, and reported a shared reluctance to seek treatment (Henshaw et al., 2016). Fathers reported feeling unprepared and needing to learn more about supporting their partners through their symptoms (Henshaw et al., 2016). This research reinforces the evidence found by other social scientists in studying PPD, emphasizing the role of spouses. The reluctance of mothers to seek professional help is an obstacle to treatment and can be problematic, leading to increased severity of symptoms, including those that can result in child neglect or abuse.

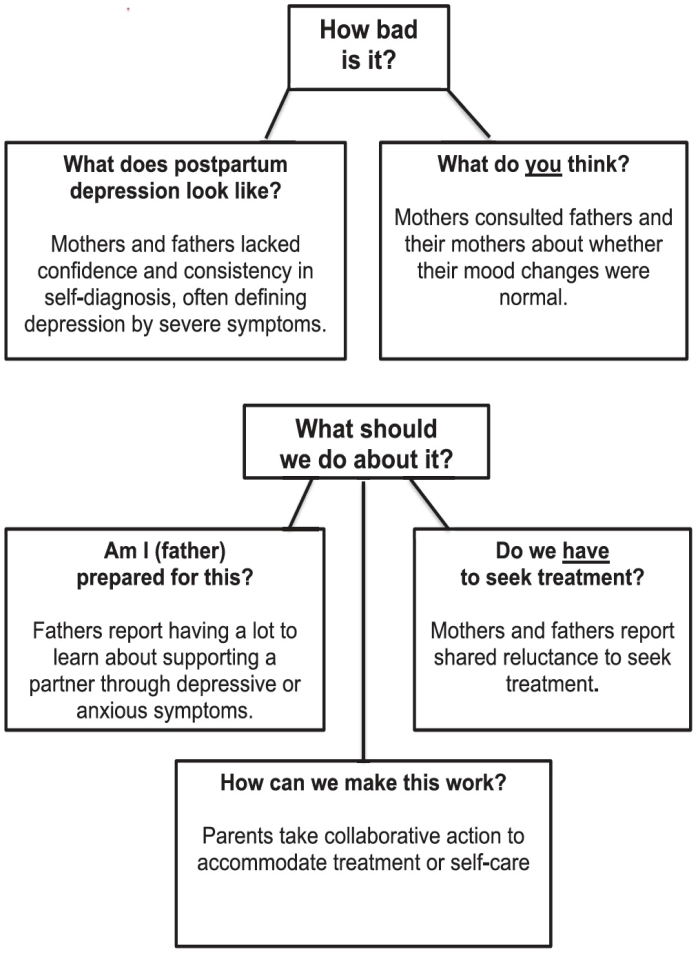

Figure 3. Researchers found these qualitative themes that summarize first-time parents' evaluation of maternal postpartum mood changes and depressive symptoms. Image from Henshaw et al. 2016.

Postpartum depression not only affects the mother, but also her entire family.

While ongoing research on the underlying neurological basis of postpartum depression continues, the first step in navigating a PPD diagnosis is to organize social support for the mother. A study on the type and prevalence of social support at 6 and 12 weeks postpartum found that emotional support, defined as sharing of experiences, and structural support, referring to the social network of the mother, were effective predictors of PPD at 12 weeks (Leahy-Warren, Mccarthy, & Corcoran, 2011). In addition to informal support offered by

the family, formal support in the form of medical care provided by healthcare professionals was also found to be important for first-time mothers (Leahy-Warren et al., 2011).

Because the consequences of postpartum depression affect not only the mother, but also her entire family, PPD must be carefully managed. How these cases are handled, however, may vary depending on the individual's circumstances. In cases where spousal support is available, the need for pharmacological treatments may not be needed. Where spousal support is unavailable, as in the case of single mothers, for example, social support may be found in family or friends. Ultimately, case management should occur on an individual basis and may involve either medical support (i.e. hormone treatments) and/or social support from spouses, family, or friends. ❧

AUTHOR BIO

Andy Chen is a third year in the college double majoring in NBB and Anthropology & Human Biology. He firmly believes in the power of storytelling and the insights we can garner from simply listening.

Edited by Lauren Flamenbaum, Dr. Gregg Orloff, and Bushra Rahman

Placed by Rachel Xue

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Cerebral organoid systems: architectural and philosophical perspectives

Figure 1. A "brain in a vat.": Concerns relating to Putnam's famous thought experiment are being raised in discussions regarding the moral status of cerebral organoid chimeras. Image from Herman 2017.

ANIRUDH RAGHAVAN
Staff Writer

Imagine if a physician could create complex, personalized tissue structures when required that mirrored the patient's own tissues, and then use these cultures to make diagnoses and test treatments. This may soon become reality as a result of rapid advancements in organoid system development. Organoids are a class of self-organized, three-dimensional, organ-like structures that are derived from pluripotent stem cells—which are able to differentiate into a wide variety of cells in the human body. Cerebral organoids are a subset of this broad category, and they are specifically utilized to model human neural development in vitro in both physiological and pathophysiological states. Cerebral organoid research was pioneered by Yoshiki Sasai and his group in 2005. His team successfully created three-dimensional neural tissues in vitro from mouse embryonic stem cells that functionally mimicked the mouse cerebrum. Currently, its applications within disease modeling range from neurodegenerative diseases such as Alzheimer's disease, to neurodevelopmental disorders such as autism, microcephaly, and pediatric gliomas thus far. As researchers continue to develop the architectural complexity of cerebral organoids to more accurately model human neurogenesis and circuitry, questions of sentience, consciousness, and cognition will arise. Some have raised concerns similar to the argument in Hilary Putnam's "brain in a vat" thought experiment, which posits that the envatted human brain (by a supercomputer, or directly by mankind in this instance) may possess the same consciousness capacity as an adult human. Contemporarily, cerebral organoids constitute a promising approach for studying brain development as well as for analyzing neurodegenerative mechanisms. In its current state, however, it is difficult to ascertain whether cerebral organoid research clashes with bioethical guidelines, specifically on the topics of organoid transplantation, chimera generation, and in vitro organoid production.

Human in vitro organoid models have been highly effective in discovering potential therapeutic interventions for a host of neurodegenerative diseases...

Architecturally, the main driving force that leads to 3D tissue formation lies in the self-organizational capacity of pluripotent cells. Pluripotent stem cells are self-renewing cells that can differentiate to become any of the cell types in the three primary embryonic germ cell layers: the endoderm, the ectoderm, and the mesoderm, and therefore can virtually differentiate into all cells of the adult body except extraembryonic structures such as the placenta. Genetic, chemical, and mechanical stimuli can stimulate differentiation of pluripotent cells. An important experimental achievement that made this differentiation possible was the generation of neural rosettes from embryonic stem cells (ESCs) (Zhang et al., 2001). Neural rosettes refer to the radial arrangements of columnar epithelial cells that express many similar proteins to those expressed in neuroepithelial cells of the neural tube, the embryonic precursor to the central nervous system. Neural rosette formation is now recognized as the developmental insignia of neural progenitor cells in cultures of differentiating ESC, and these neural progenitor cells ultimately give rise to virtually all glial and neuronal cell types of the central nervous system.

...the organoid alone cannot be worthy of definite moral status in that there is a lack of sophisticated sensory inputs to human brain organoids that are required for the learning and conditioning that in turn develop cognition.

While structurally cerebral organoids recapitulate the mammalian telencephalon, neural activity in cerebral organoids is largely a grey area. Intracellular calcium waves, post-synaptic potentials, and induced action potentials have been recorded within cerebral organoids thus far (Chen et al., 2019), but there has been no conclusive evidence regarding communication across multiple neuronal networks beyond localized regions. A recent study identified synchronized neural activity in brain organoids and reported on the presence of oscillatory activity in neuron firing, constituting multi-network interaction (Trujillo et al., 2019). However, these may not correlate well with regular oscillatory activity in the mammalian brain, and these organoids also do not display non-oscillatory forms of neuronal activity observed in mammalian brains. Another area that is currently being developed upon is increasing the similarity and accuracy of neurovasculature in cerebral organoids in modeling the neurovasculature of the human brain. Particularly, endothelial cells of the brain form the blood brain barrier (BBB) that is interconnected by tight junctions and heavily regulated by associative astrocyte foot processes that extend to the capillary. Currently, BBB organoids have been shown to retain key barrier properties such as tight junction protein 1 (ZO-1) required for tight junction formation, the P-glycoprotein (P-gp) efflux pump for elimination

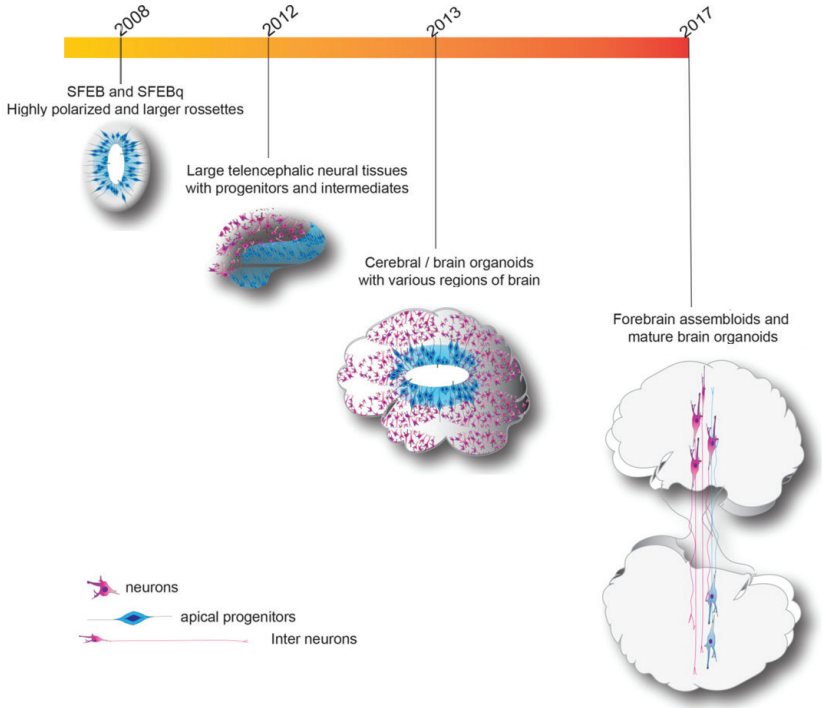

Figure 2. A brief summary of significant experimental achievements in in vitro developmental neurobiology that have led to the current generation of human brain organoids. Apical progenitors are progenitor cells located in the ventricular zone of the brain. SFEB and SFEBq refer to "serum-free culture of embryoid bodies" that utilize various genetic reprogramming factors. Assembloids refer to larger aggregates of progenitors that exhibit distinct cortical layers and resemble the mature postnatal stage of human brains. Image from Gopalakrishnan 2019.

of endogenous wastes and active transport of the peptide angiopep-2 which shows evidence of receptor-mediated transport (Bergmann et al., 2018, Cho et al., 2017). These do not, however, sufficiently characterize a vascularized cerebral organoid system consisting of optimal oxygen supply, nutrient supply and waste elimination. In light of organoid limitations, such as the aforementioned BBB limitations, a wide array of organoid models have been designed to fit various applications (Fig. 3). Human in vitro organoid models have been highly effective in discovering potential therapeutic interventions for a host of neurodegenerative diseases, and have been successfully applied in treating movement disorders, namely Huntington's Disease (HD) and Parkinson's Disease (PD), as well cognitive diseases, namely Alzheimer's Disease (AD), and Frontotemporal Dementia (FD) (Fig. 4). Essentially, these disorders share certain features in their origin and effects, broadly in protein misfolding and consequent aggregation, inflammation, hindered lysosomal function, and altered RNA homeostasis (Faravelli et al., 2020).

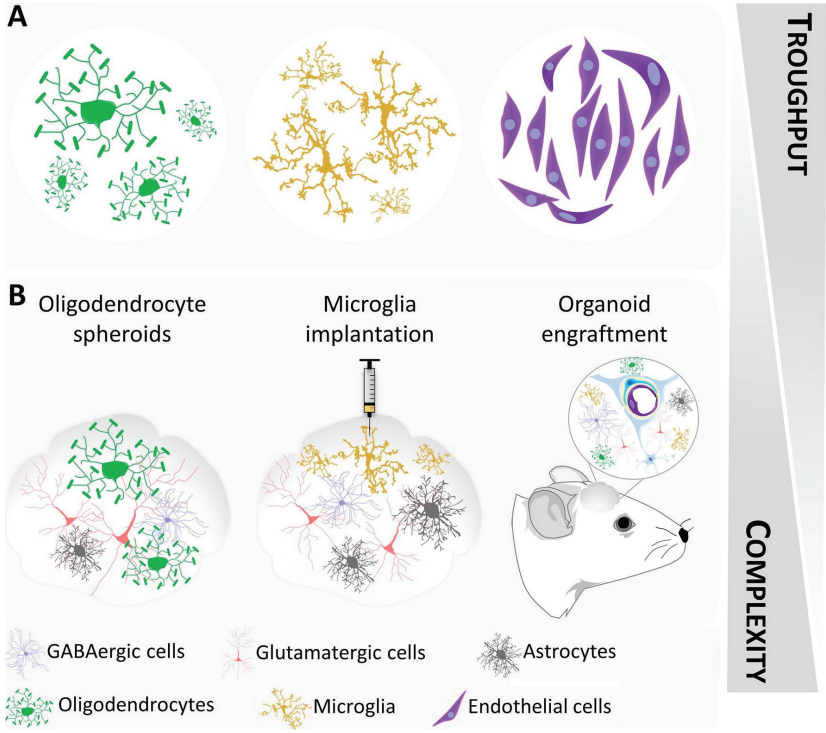

Figure 3. Current advanced models of human stem cell-derived brain organoids. A. Two-dimensional culture systems can be used for drug testing, and are generally appropriate for high-throughput approaches. B. Three dimensional culture systems better capture developmental processes due to increased cytoarchitectural complexity, and the ability to control and manipulate microenvironments to more accurately model cellular interactions. (1) Oligodendrocyte spheroids parallel in vivo neurodevelopment in terms of cellular heterogeneity, and (2) microglia are often implanted due to native scarcity in organoids. (3) Organoid engraftment is essential to model three-dimensional neurovascular systems as accurately as possible. Image from Oliveria 2019.

Huntington's Disease is a dominantly inherited neurodegenerative disorder caused by a mutation in the Huntingtin gene on chromosome 4, which results in a defective protein (Adegbuyiro et al., 2020). Associated symptoms, such as cognitive dysfunction, have been tied to neuron loss in cortical regions. Previous reports have stated that the Huntingtin gene is involved in early embryonic tissue organization and neurogenesis (Barnat et al., 2017, Conforti et al., 2018). One aspect of mechanistic discovery that HD organoids studies revealed was that there was low expression of genes related to neuronal migration and differentiation—namely SOX11, GAP 43 and CELSR3 (Conforti et al., 2018), which was largely determined using organoid protocols modeling 3D spatial cytoarchitecture of neural tissue.

...future efforts may be used in developing methods to increase long-term in vitro organoid survival, in order to decrease organaanoid transplantation and usage of other in vivo organoid settings.

Parkinson's Disease is caused by dopaminergic neuron degeneration in the substantia nigra, a region of the brain involved in modulating motor movement. A deleterious mutation in the gene LRKK2 seems to lead to cessation of neurogenesis, mitochondrial and synaptic vesicular movement, and a disruption of the intestinal microenvironment (Wang et al., 2012). This elucidation of a brain-gut axis that directly links the autonomous enteric system with the central and

peripheral nervous systems was possible due to data collected from LRKK2 patient-derived pluripotent stem cells and human intestinal organoids.

Alzheimer's Disease, thought to be caused by an accumulation of amyloid-β peptides and neurofibrillary tangles composed of highly phosphorylated tau protein (Serrano-Pozo et al., 2011), has been better understood using a human embryonic stem cell based organoid system. A study demonstrated that mutations in the amyloid precursor gene (APP) and presenilin-1 (PSEN-1) gene caused [or 'were associated with] extracellular deposition of amyloid-β and Tau tangles, which further supports the current amyloid hypothesis (Choi et al., 2014). Organoid systems were also used to discover that inhibition of β- and γ-secretases, which are involved in cleaving APP into amyloidogenic fragments, led to decreased Tau protein aggregation, in line with observed patient outcomes (Choi et al., 2014).

Investigation of tauopathy helped to better characterize the pathogenic mechanism of Frontotemporal Dementia, which refers to progressive degeneration of frontal or temporal brain lobes (Bang et al., 2015). Specifically, overexpression of tau regulating proteins such as CDK5 has been associated with increased tau aggregation, and reduced expression ceases neuronal degeneration in Frontotemporal Dementia (FTD) brain organoids.

As brain organoids grow more and more sophisticated and more accurately capture the mature human brain both structurally and functionally, they will not only become more valuable for research and clinical interventions, but will also be increasingly subject to ethical concerns. The "brain in a vat" thought experiment has been invoked in relation to cerebral organoid research, postulating that these organoids may in fact be capable of cognition and perception, but are being held captive in a dehumanizing laboratory setting. Under current research ethical guidelines, there is major agreement that the organoid alone cannot be worthy of definite moral status in that there is a lack of sophisticated sensory inputs to human brain organoids that are required for the learning and conditioning that in turn develop cognition (Chen et al., 2019). However, transplantation of brain organoids into the brain of an animal results in a fully functional, cognitive organism, and concerns have been raised regarding potential humanization of the animal and enhancement of the organism's brain by virtue of bringing about self-awareness. It is imperative to find out whether such consciousness and cognition

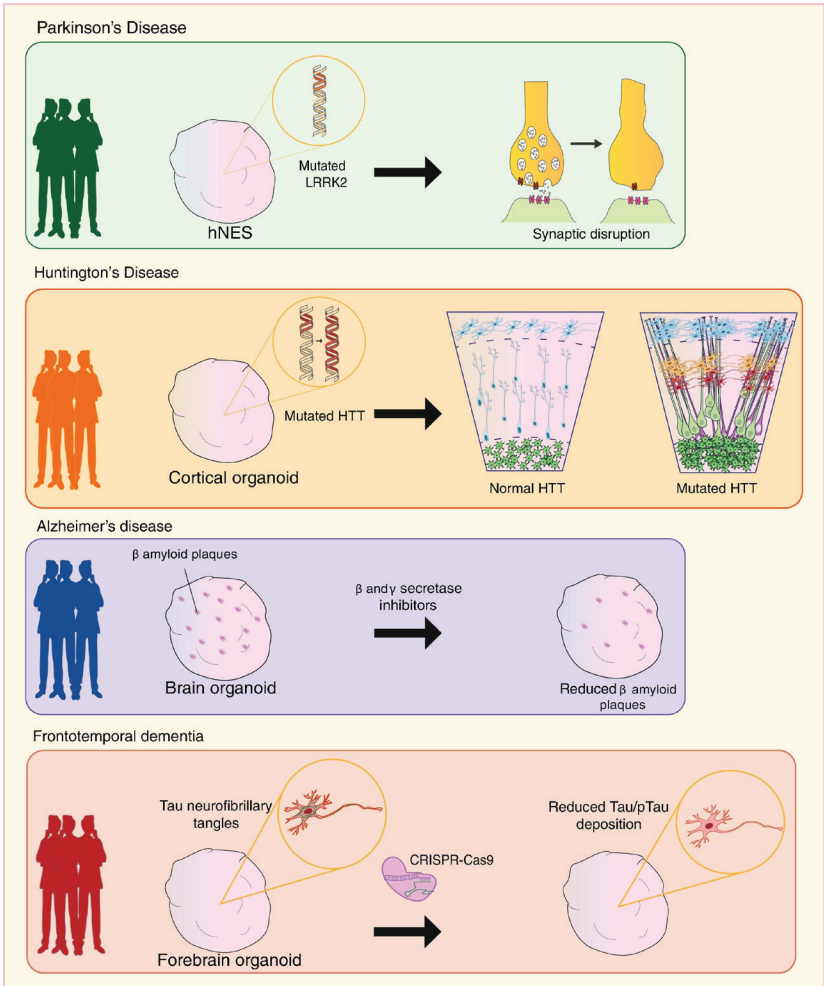

Figure 4. Cellular and molecular phenotypic characterization of common neurodegenerative disorders using 3D human brain organoids: The most investigated diseases are movement disorders such as Parkinson's and Huntington's diseases as well as cognitive disorders including Alzheimer's disease and frontotemporal dementia. Image from Faravelli 2020.

is possible post-transplantation to decide ethical ramifications. One of the only methods that exist contemporarily that test self-awareness in laboratory animals is the rudimentary mirror test, wherein recognition of one's reflected image in a mirror as oneself rather than as another individual constitutes self-awareness. If animals pass this mirror test post organoid transplantation, but had failed it pre-transplantation, this would not only warrant more thorough behavioral testing to assess cognition, but also necessitate consultation with research ethics committees. It is important to keep in mind that the result of the mirror test is imperfect in that there may be various levels of mutually exclusive levels of cognitive ability, such as in the case of the domestic pig. Though pigs do not pass the classic mirror test, they are able to use mirrors to locate hidden food. This cognitive ability may be classified as more highly sophisticated than mere self-awareness.

Extending this discussion further, cerebral augmentation via brain organoid transplantation is not possible, and enhancing the cognitive capabilities of animals such as rats or pigs to human cognitive capacity is likely implausible. Even if such a point is reached, further inquiries such as methods to obtain consent may be necessary to offer transplant chimeras legal protections, such as consent for procedures. Nevertheless, in undertaking research on animals attention should be given to the welfare of these animals to minimize any suffering. It is also prudent that a set of rational, robust thresholds for concern be developed regarding brain organoid enhancement in animals. Architecturally, future efforts may be used in developing methods to increase long-term in vitro organoid survival, in order to decrease organoid transplantation and usage of other in vivo organoid settings (Sawai et al., 2019). Brain organoids may then be able to provide a more accurate snapshot of the cellular composition and microenvironment of neurons within the brain for more effective disease modeling in the future. Further development of cerebral organoids in line with bioethical guidelines can enable physicians and researchers alike to use specific cerebral organoid modes of production to directly and specifically target and treat cerebral deficits. This can enable more efficient diagnoses, treatment protocols, and better prognoses for patients with neural defects due to birth defects, viral infections, neurodegenerative diseases, and even cancers such as glioblastomas. ❧

AUTHOR BIO

Anirudh Raghavan is a second year in the college, majoring in Chemistry and Biology. An interesting fact about him is that he enjoys singing and Indian classical music.

Edited by Aditya Jhaveri, Alexa Rome and Dr. Jesse Soodalter

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(Figure 1) "Belgian researcher Manuel Morrens holds a container filled with a human brain, part of a collection of more than 3,000 brains that could provide insight into psychiatric diseases, at the psychiatric hospital in Duffel, Belgium", July 19, 2017. REUTERS/Yves Herman

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The intricacies of dreaming

VYAS MURALIDHARAN
Staff Writer

Dreams: a shimmery, dark, and colored abyss brimming with possibilities. Much like the very nature of dreams, the various theories vying to explain dreams are contradictory. Whether it be the classical flying dream, being swallowed up by the ground whole, or going on a date with that special someone in your life, a dream is a common experience in sleeping. However, there is no one unifying explanation for why we dream. The brain is among the least understood features in the world, and dreaming only intensifies its mystery. Leading explanations emphasize its important role in memory consolidation and others think of it as purely a byproduct of REM (Rapid-Eye-Movement) sleep. Either way, dreaming provides a unique insight into the inner workings of the mind. Whatever the true nature of dreaming may be, there's no denying that it can play a useful role in our lives. Dreaming can boost our base cognitive abilities and it can even be used to treat psychiatric diseases. It's an incredibly complex, useful phenomenon that involves every part of the brain, and the more one studies it, the more complicated its story becomes.

First, it is important to establish a baseline definition of dreaming. Neuroscientist Penelope A. Lewis at Cardiff University uses the very broad definition of "all perceptions, thoughts, or emotions experienced during sleep." Under this framework, anything your brain experiences while sleeping can be considered a dream. While dreaming can occur during all stages of sleep, it is most vivid during REM sleep. REM occurs within the first 90 minutes of sleep, during which the body is completely paralyzed. This ensures that the body will not accidentally "act out" the dreams that the brain is experiencing. Paradoxically, this is also the period of sleep when the body can be considered "most awake," as the heart rate, blood pressure, and neural activity are closest in relative magnitude to the active/awake state (NIH).

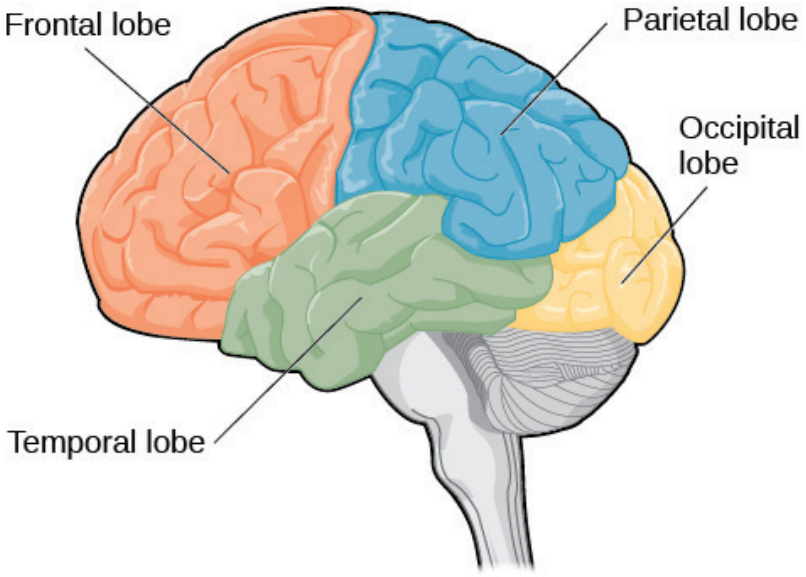

Figure 1: Different regions of the brain. Anterior aspects were correlated with remembering the dream, while posterior aspects of the brain were correlated with the perceptual aspects of the dream. Image from OpenStax 2016.

There are four main regions of the cerebrum, the division of the brain associated with higher order functions and consciousness. The frontal lobe, located at the front of the brain, is responsible for most executive function. The parietal lobe relates sensory information, the occipital lobe conveys visual information, and finally, the temporal lobe processes auditory information.

Dreaming involves all parts of the brain, though some regions are more active than others. More importantly, the activated regions paint a picture that suggests some overlap between the "awake" brain and the "asleep" brain. In the same study, researchers administered an electroencephalogram (EEG) tracking of 46 participants during their sleep with frequent disturbances to answer questions about if and what they were dreaming. This study centered on activated regions of dreaming, and we see that the parietal-occipital cortical area plays a fundamental role in

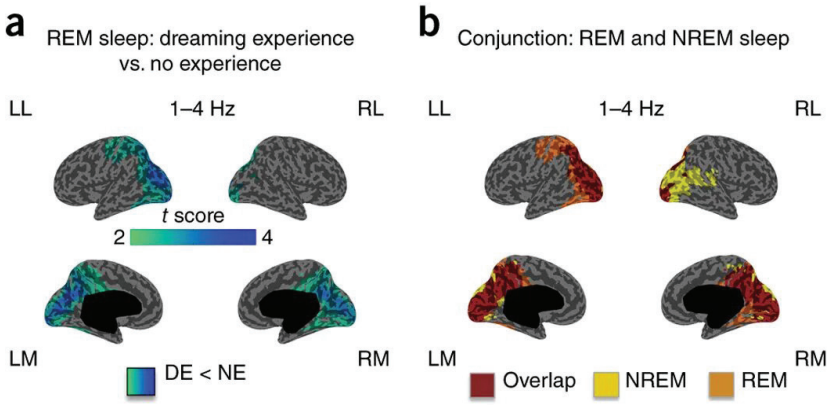

Figure 2: Correlation between dream experience and NREM/REM activation. Image from Siclari et al. 2017.

nearly every aspect of dreaming. In addition, we see that dreaming truly involves every aspect of the brain. Though it may arise in one particular region, for us to truly experience dreaming the way we do, every region must play a role (Siclari, 2017). When we dream about faces, that region of the brain lights up (fusiform face area). When we dream about certain objects, that particular region of the brain lights up (Orbitofrontal Lobe). When we dream about environments, that region lights up. Dreaming, therefore, involves the integration of all our senses.

REM sleep has conventionally been thought to be the source of dreaming. However, there is evidence that non-REM sleep plays an important role in dreaming as well. In fact, similar brain regions are activated between the two as well. In both non-REM sleep and REM sleep, dreaming was marked by reduced low-frequency EEG activity in the posterior cortical region of the brain (Siclari, 2017). This area includes occipital, parietal, and temporal cortices, which relate to visual, spatiotemporal, and auditory activity respectively.

High frequency EEG waves indicate increased neuronal activity in a certain region. In participants experiencing NREM sleep, the parieto-occipital region increased in its activity when compared to participants who reported no dreaming experience, though it "extended superiorly and anteriorly to parts of the lateral frontal cortex and the temporal lobes"(Siclari, 2017). When it came to remembering the dreams, the frontoparietal region showed an increase in activity. In REM sleep, the researchers found something rather interesting: increased dreaming activity indicated high-frequency activity in the frontal brain region and in parietal, occipital, and temporal areas. These regions are ultimately responsible for mediating thought. This suggests that just as in the awake state, the anterior regions help mediate thought, while the posterior regions help modulate the perceptual aspects of the dream state (Siclari, 2017).

...just as in the awake state, the anterior regions help mediate thought, while the posterior regions help modulate the perceptual aspects of the dream state

The same regions that are normally active when awake can also be active while dreaming. This suggests that the divide between the dream state and the awake state is not as concrete as once thought. We can exploit this knowledge to improve our experiences while asleep. The real world can affect how we perceive and remember our dreams. For example, olfaction therapy can change the behavior and sleep patterns of patients (Goel, Kim, & Lao, 2005). In a study done at Wesleyan University, a sleeping group in a lavender-wafted setting experienced "higher vigor" the morning after sleep as well as increased deep sleep compared to the control group given distilled water. Dr. Lewis, in her book The Secret World of Sleep, describes a similar phenomenon that happened to a group of patients who were studied while in REM sleep. One group was wafted with pleasant scents, while the other group was wafted with some rather unpleasant smells (Lewis, 2013). The group that had been wafted with the pleasant scents experienced more positive dreams, while the other group experienced more negative dreams. Olfaction is special; the primary olfactory cortex has strong links to the amygdala and hippocampus, which are responsible for processing emotions and memo-

ries, respectively (Schäfer, 2019). The implications are massive, as this finding can be used in the treatment of psychiatric diseases. One particular disease researchers are looking at is post-traumatic stress disorder (PTSD). A defining feature of PTSD is troubled sleep due to bad dreams and nightmares. Dr. Laura Schäfer at the University of Dresden conducted a study with 40 patients who had been diagnosed with PTSD, half of whom were given a placebo while the other half were given aroma therapy (options included rose, lavender, orange, and peach). Several variables were measured: quality of sleep, recovery after sleep, dream intensity, and general negativity/positivity of the dream. Most significantly, patients who had been given the scents reported having a lower dream intensity (Schäfer, 2019).

However, none of this helps to explain why we dream. As stated before, there is not one single unifying theory. The activation-synthesis theory states that dreaming has no definitive purpose, and that it is simply a byproduct of sleep. However, other neuroscientists believe that dreaming plays an important role in memory consolidation, cognitive function, and mental well-being. Dr. Matthew Walker at the University of California, Berkeley believes that dreaming can be considered akin to overnight therapy, as dreaming is tightly correlated with emotion and memory. He states that "REM-sleep dreaming appears to take the painful sting out of difficult, even traumatic, emotional episodes experienced during the day" (Walker, 2017). Only during REM sleep is the brain devoid of noradrenaline, a stress response hormone. In this biochemical environment, the brain processes emotion and memory without eliciting a stress response. Overall, dreaming seems to be a window into the process by which this consolidation happens during REM sleep (van der Helm, 2010).

...neuroscientists believe that dreaming plays an important role in memory consolidation, cognitive function, and mental well-being.

Dreaming can also play a role in solving complex problems. Because REM sleep blends different memories together, it can provide new insights. Dr. Walker conducted another study, wherein participants were given simple anagram puzzles, then told to sleep. The team woke up half of the subjects from REM sleep and the other half from NREM sleep. The subjects then performed the same tasks. He found that individuals woken up during REM sleep had a 32% better success rate of completing the tasks compared to subjects who had simply been woken up during NREM sleep (Walker, 2002). In fact, subjects would sometimes say that solutions had just "come to them" (Walker, 2017). Though dreaming is most intense during the REM state, we cannot completely minimize the role NREM dreams can play in memory consolidation. In fact, brain regions involved in NREM sleep have a close relationship with hippocampal-dependent forms of memory. Further evidence of dreaming helping with problem solving comes from a different study which looked at a subject's ability to navigate through a virtual maze (Wamsley, 2011). All subjects were initially trained in the same maze navigation task, then retested five hours later. Half of the group slept before the retest, while the other half was simply given a video to watch. Subjects who napped before the task showed much greater improvement . However, participants who stated they dreamed about the maze task performed tenfold better compared to their fellow sleeping participants (Wamsley, 2011).

The brain is vast, and there is so much yet to discover. Dreaming is yet another knot in this tangled web. Dreams are a manifestation of our memories and represent the consolidation of memory and emotions. Dreaming is a small glimpse into the fantastical world of our brain; this view may allow us to treat psychiatric diseases and gain a deeper understanding of how different regions in the brain interact with each other. Regardless of what the true nature of dreaming is, it cannot be denied that it is a fascinating phenomenon. ❧

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The science of epigenetics

LAURA PAULE
Staff Writer

Epigenetics is the study of changes in DNA through the alteration of gene expression, rather than modifications in the genetic code itself. According to the Greek lexicon, "epi-" means above, near to, or in addition to, indicating that the chemical changes involved are external to the DNA sequence. They are added to genes as a means of enhancing or suppressing their expression. As a result, these epigenetic changes often ensure that only the necessary proteins in an organism are produced (U.S National Library of Medicine, 2020). As a 21st-century science, epigenetics is a growing and developing field of research, with studies indicating that traumatic experiences such as the Holocaust and the Dutch famine may have modified the DNA passed down to the offspring. Current research focuses on how to create drugs that can regulate epigenetic modifications in DNA, with the purpose of enhancing the desired genes and suppressing those that are harmful.

Epigenetic changes can determine which proteins are expressed. Although human bodies contain the same DNA in all cells, cell types vary broadly: muscle cells, liver cells, etc. These differences between cells emerge as a result of the set of genes that are turned on or off in a specific cell. Two main ways in which genes are regulated include DNA methylation and histone modifications. DNA methylation, or the addition of a methyl group, affects the structure of the DNA, causing it to interact differently with the nuclear machinery responsible for transcription. Histones are proteins that interact with DNA to create chromatin, a complex that makes up chromosomes. Post-translational modifications of histones affect the expression of genes in the cell. Acetylation, or the addition of an acetyl group to the amino acid lysine in histones, is associated with active chromatin (euchromatin), giving RNA polymerase access to the DNA for transcription of the gene. Deacetylation, conversely, corresponds to the inactive chromatin (heterochromatin), preventing transcription from occurring (Simmons, 2008).

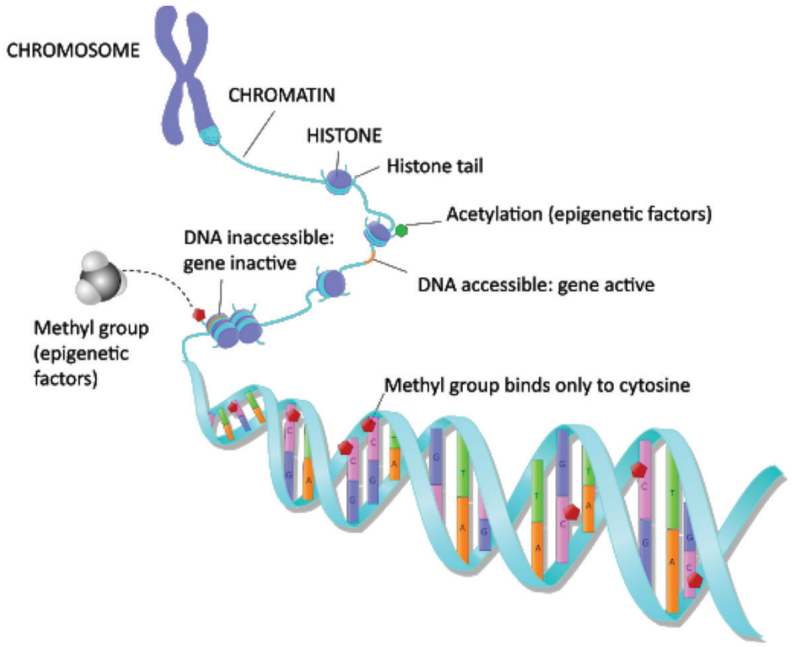

Figure 1. Regulation of gene expression in cells. Image from Wise 2020.

Epigenetically-acquired characteristics have the potential of being transmitted to offspring. The Holocaust, or genocide of European Jews during World War II, was one of the most devastating moments in history. A cross-sectional study that focused on child Holocaust survivors (born in 1940–1945 during WWII) who had been exposed to the Holocaust both pre- and postnatally reported a higher prevalence of cancer in the exposed group (vs. controls: descent, age, gender). These results suggest that exposure to Holocaust conditions before birth and in early life may be associated with a higher prev-

A cross-sectional study that focused on child Holocaust survivors... reported a higher prevalence of cancer...

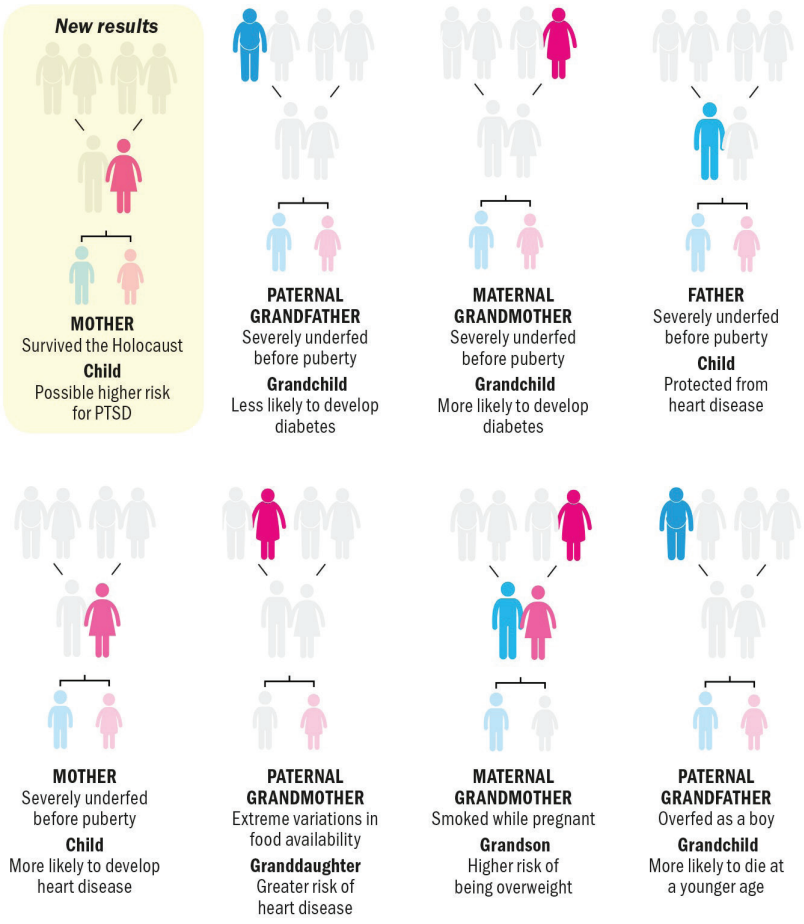

Figure 2. Risk for PTSD among children of holocaust survivor mothers. Image from Rodriguez 2015.

alence of diseases in adulthood (Keinan-Boker, 2018). Besides some of the well-known physical and psychological effects on survivors, including stress and anxiety, there is growing evidence suggesting an impact in the immediate offspring. Children of Holocaust survivors have reported having nightmares in which they are persecuted, abused, burned to death, or exposed to extreme living conditions. This could be the result of marks on the chemical coating of their chromosomes, which created a sort of "memory" that allowed for the reminiscence of past events, to the point of imagining vivid details of hunger and frozen limbs that scarred the previous generations. The fact that children of survivors dreamt of the Holocaust does not necessarily mean the memories were transmitted through gametic epigenetics. "What could have been inherited is the disposition to have nightmares, and of course if they know something about the Holocaust through primary exposure, from stories and so on, the nightmares will take this form" (Kellermann, 2013). Furthermore, Holocaust survivors have been found to have lower levels of cortisol, a stress hormone that controls blood sugar levels, regulates metabolism, and helps the body recover from trauma. Offspring of survivor mothers with PTSD presented lower levels of cortisol, and their hormone profile indicated higher susceptibility to developing PTSD (Rodriguez, 2015). Previous studies have supported this finding by showing how the offspring of Holocaust survivors were more likely to develop stress, obesity, and hypertension (Bercovich, Keinan-Boker, & Shasha, 2014).

The question also arises as to how these experiences from the Holocaust can be transmitted to several future generations, and not just the immediate offspring. Studies of laboratory animals reveal that epigenetics changes induced by stress levels are passed down to subsequent generations. In humans, however, there is scarce evidence supporting the transgenerational transmission of trauma (TTT), although a variety of studies have hinted at this as a possible explanation for observed patterns. For example, a study investigating self-reported health complaints of 82 offspring of Holocaust survivors found that maternal exposure was associated with greater use of psychotropic and other medications, and significantly lower self-rating of emotional and physical health (Flory, Bierer, & Yehuda, 2011).

Studies revealed that women who were pregnant during the months of famine were more vulnerable, and their children were marked for life.

A second event in history

that has been broadly analyzed by scientists in the field of epigenetics is the Dutch famine registered from 1944-1945. The Nazis blocked the food supply to the Netherlands because Dutch railway workers helped the Allied Forces stop the transport of Nazi troops. Subsequently, thousands of people died during approximately 8 months of starvation. The consequences extended further down the line, leaving imprints even on those affected prior to birth. Studies revealed that women who were pregnant during the months of famine were more vulnerable, and their children were marked for life. Once adults, they presented higher rates of obesity and diabetes, and died at a higher rate than people born pre and post famine (Carl Zimmer, 2018). The exact reasons behind these observed patterns are not certain, but researchers have geared their attention towards epigenetic changes that could have arisen during the period of starvation.

A main focus for researchers is on how methylation plays a role in these characteristics that seem to be specific to people from the Dutch famine. By analyzing blood samples from middle-aged subjects, scientists looked for methylation spots that pertain specifically to Dutch survivors born during the famine. Some studies portray a link between a methyl group and people with a higher Body Mass Index (BMI). This methylation could be responsible for silencing a gene called PIM3, which helps burn the body fuel. As speculated, it is possible that a methyl group was added to fetuses of pregnant women during the famine, which led to decreased activity of PIM3 in the children, and consequently higher rates of obesity (Carl Zimmer, 2018).

Offspring of survivor mothers with PTSD presented lower levels of cortisol, and their hormone profile indicated higher susceptibility to developing PTSD.

One second study regarding the Dutch famine was centered around methylation in the IGF2 differentially methylated region (DMR), one of the "best-characterized epigenetically regulated loci." Subjects with prenatal exposure to famine had 5.2% lower methylation in this region, revealing that periconceptional exposure to famine can in fact affect the fetus and impact adulthood (Heijmans et al., 2008). IGF2 plays a key role in human growth and development, opening up the gate to future experiments that determine how lower levels of methylation of this gene alter cell function.

As more associations are discovered regarding the interplay between external modifications to parental DNA and the impact these changes bring to future generations, more research is being geared towards identifying ways to take advantage of the field of epigenetics. For example, there are current methods or drugs used to enhance "good" genes and repress "bad" ones, depending on context. Since errors in the epigenetic process can lead to disorders and abnormalities, scientists are working to prevent these undesired changes in the DNA. Several agents have been found to play a role in DNA methylation and histone modifications, including 5-Azacytidine (used for chemotherapy), and Zebularine (shown to inhibit tumor growth), but they have to be further analyzed (Egger, Liang, Aparicio, & Jones, 2004). Epigenetic therapy is not an easy process, since using certain drugs in humans could not only bring the desired outcome, but also indirectly affect other functional parts of the body. The associations between epigenetic modifications and transgenerational inheritance are eminent, and the studies have controlled for factors such as gender, descent and age. However, a downside

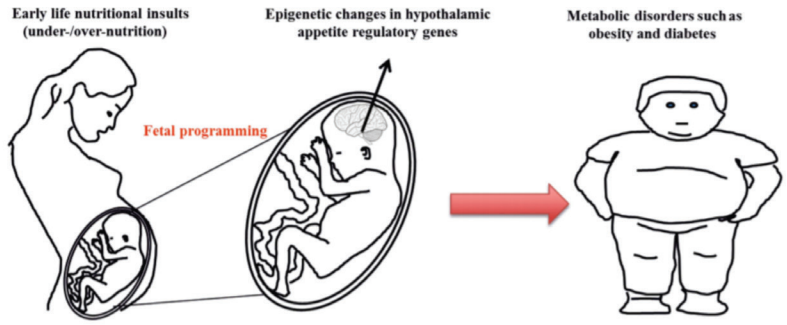

Figure 3.Epigenetic changes could have altered regulatory genes, leading to increased susceptibility to genetic disorders like obesity and diabetes. Image from Ring 2020.

comes from counter-arguments claiming that culture and human interactions could have an impact in patterns observed in subsequent generations. Epigenetics is only in its beginning stages, and much information still needs to be verified and validated regarding these outside modifications to the genome. To further understand transgenerational impacts, controlled and large-scale cohort studies should continue to be implemented, which could potentially allow for the development of tailored measurements of health care. Drugs that are capable of modifying the expression of genes in DNA continue to emerge, and this could provide solutions to ongoing and future detrimental health conditions caused by epigenetic changes. ❧

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Future considerations of the medical field

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Staff Writer

The two main fields tasked with the handling of chronic illnesses are the fields of medicine and public health. Despite sharing the goal of keeping individuals healthy, these two disciplines vary distinctly in their ideologies. The medical field takes a reactionary approach where a provider treats a patient after the development of an illness. On the other hand, the field of public health focuses on the preventative aspect. Public health organizations, such as the Public Health Institute and the Center for Disease Control, work to identify how illnesses develop, research methods to control them and educate the community on these matters. The two fields ideally go hand in hand to form a comprehensive system of care that first treats individuals and keeps them healthy afterwards. Unfortunately, the reality is that patients frequently revisit hospitals for an illness they have already been treated for. According to a paper published in 2015, 23% of the patients who underwent treatment were readmitted into the hospital within 30 days of their procedure (Ziaeian and Fonarow, 2015). In order to reduce hospital readmission rates and help patients remain healthy and free of illness after initial treatments, it is worth establishing a more holistic treatment approach.

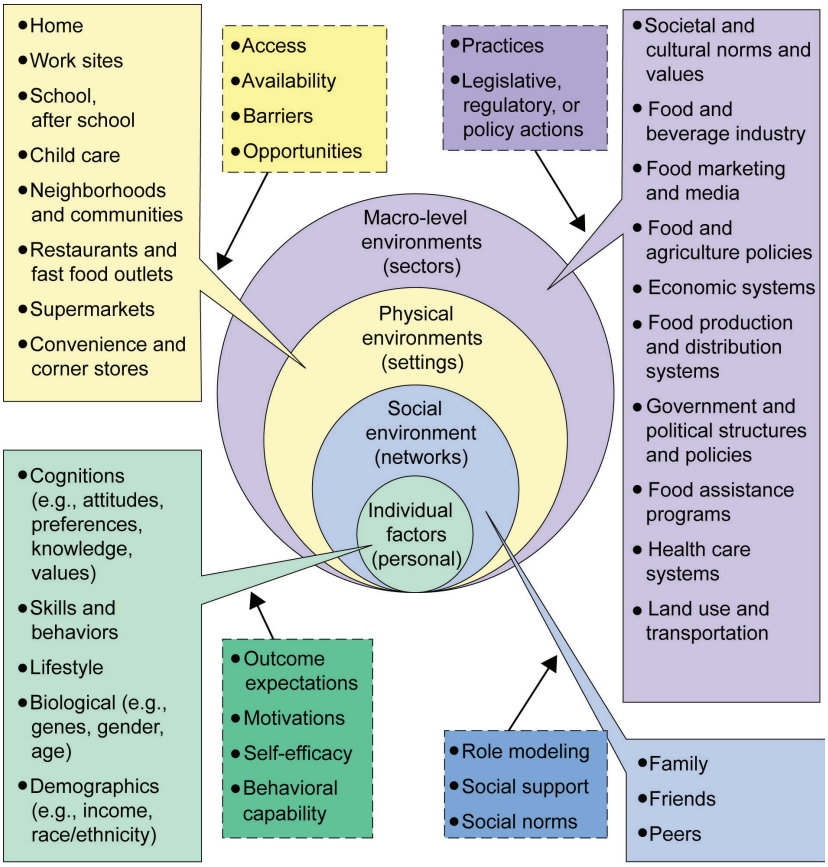

Figure 1. Diagram displays the layers of environmental and social interactions that influence a person's diet. Image from Story et al. 2007.

Holistic treatment methods include considering the patient's community, which actively shapes the health habits of its members. In a study on healthy eating habits, it was found that dietary choices among children are influenced by the people around them in settings such as schools, child care facilities, work sites, and homes. These behaviors are further compounded by socioeconomic variables such as household income and the consumer nutrition environments individuals are exposed to (Story et al., 2007). For example, physicians who solely prescribe eating more vegetables as a form of treatment would not be effectively supporting the patients who do not have adequate access to fresh produce. Similar social determinants of health could be applied to the development of other chronic illnesses as well.

Physicians typically approach treatment as a reaction where medical intervention occurs once the patient is already ill. Since the development of many chronic illnesses are caused by the lifestyle of the patient, treatments that only focus on alleviating the physiological symptoms do not mitigate the fundamental causes of the illness and thereby increase the possibility of recurrence. Instead, evidence has shown that the addition of complex, continuous

care in the form of programs such as Patient Hotspotting and osteopathic treatment have incorporated more holistic aspects of care that the current medical field does not fully incorporate.

The Patient Hotspotting program is designed to identify "super utilizers" — patients who frequently and repeatedly visit the emergency room for conditions that are entirely preventable. These super utilizers are assigned a caseworker who helps them develop a personalized protocol to proactively improve their health and minimize the need to visit the ER. The protocols emphasize the implementation of healthy behaviors to reduce the risk of redeveloping a chronic illness. Most importantly, this program takes into account the social determinants of health, addressing issues such as homelessness, social support, substance abuse, food needs, and unemployment and identifies the best ways to work around them (Matsumoto et al., 2018). The case workers, on their end, are trained in harm-reduction and health-coaching. Harm-reduction is the practice of identifying habits that are harmful to one's health and creating solutions to reduce these behaviors. Health-coaching is the method of guiding the patient towards an achievable goal in reducing said behaviors.

In terms of patient interactions, there is a focus on the COACH method. This acronym reads as follows: Connecting plans with a vision, Observing normal patient routines, Assuming a coaching style, Checking the backward plan, and Highlighting progress with data. Typically, caseworkers first introduce patients to the hotspotting program while they are at the hospital. Once sent home, patients receive further follow up care by a team of registered nurses, health workers, and coaches to help with medical tasks such as medication management, blood pressure and blood sugar management, and helping patients apply for behavioral health programs. Lifestyle goals for the patients are also set during this time. These methods allow for an easier and monitored lifestyle transition.

...treatments that only focus on alleviating physiological symptoms do not mitigate the fundamental causes of the illness and thereby increase the possibility of recurrence.

In data collected from the first 36 patients who received Patient Hotspot Interventions, the average number of emergency visits per month and average monthly cost of healthcare expenditures decreased. Although promising, recent and larger patient hotspotting implementations in New Jersey hospitals have been met with mixed results. One study examined the effectiveness of patient hotspotting with the Camden Coalition methods by measuring the readmission rates of patients (ages 18-80) 180 days after their first emergency room visit. The control group received no additional care while the treatment group received access to patient hotspotting case workers. Results show that the control group had a readmission rate of 61.7% while the patients who took part in patient hotspotting had a 62.3% readmission rate. These numbers seem to suggest that the treatment had no significant effect on readmission rates. However, case workers sometimes encountered patients who did not respond through the hotspotting program, which may have had a part in contributing to the results of the study (Finkelstein et al., 2020). This indicates that although hotspotting programs are a good preliminary initiative in the pursuit to improve the healthcare system, more studies are needed that

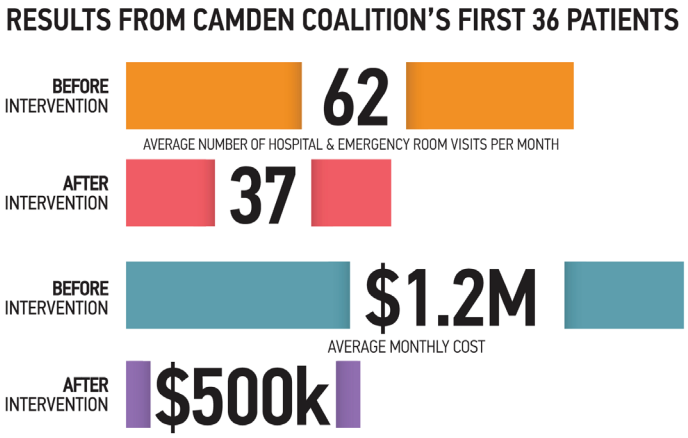

Figure 2. Data collected with early Camden Coalition Patient Hotspot Interventions. Shows decrease in emergency room visits and monthly costs. Image from Camden Coalition 2017.

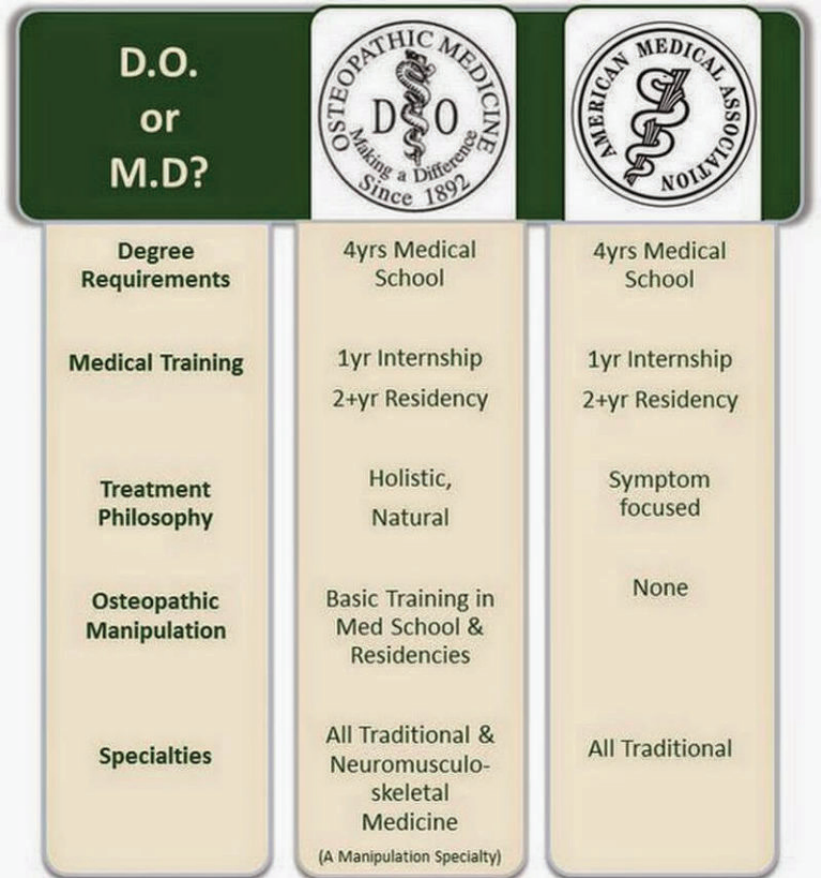

Figure 3. Main differences between D.O and M.D are found in treatment philosophy and osteopathic manipulation. Image from VCU Pre-Professional Health Advising Blog.

delve into the sociological and anthropological implications and identify other relevant social determinants of health. This will better equip hotspotting treatment plans with all the variables that may affect health outcomes in a certain area.

Practitioners of osteopathic medicine are, unsurprisingly, known as Doctors of Osteopathic Medicine (DO), and they follow an approach to care akin to that of patient hotspotting. Compared to MDs, DOs specialize in a holistic approach to healthcare. This type of care not only emphasizes treating the individual by curing the illness at hand, but also focuses on developing tailored treatment plans that accommodate for the patient's needs and take into account his/her available resources. In comparison to MD patient visits, DOs are more likely to discuss aspects of preventive healthcare in areas such as family life, social activity, and emotional state (Licciadorne, 2007). Although osteopathic practices do seem more beneficial to patient outcomes when compared to the more typical medical doctors, more studies need to be conducted comparing the outcomes of allopathic and osteopathic methods to determine the effects of a more holistic approach to care.

...more studies are needed that delve into the sociological and anthropological implications and identify other relevant social determinants of health.

Preventive healthcare in the form of complex and continuous care is indeed an aspect the current medical field needs to consider implementing in order to keep patient populations healthy in the long term. For chronic conditions, it is difficult for providers to manage the health of patients in the traditional ways, since health outcomes are directly dependent on habits and lifestyle choices that are often overlooked by medical professionals. However, this also broaches an ethical argument that questions whether physicians are allowed to dictate how a patient should live his/her life. Furthermore, patients will likely only benefit from these suggestions if the community they live in has the resources to support their attempts to change their lifestyle. Although promising, Patient Hotspotting and the DO philosophy still fall somewhat short in addressing the challenges posed by the social determinants of health. Incorporating aspects of preventive and holistic care into current medical field practices will help reorient healthcare perspectives to set the foundations of a supportive network patients can easily reach out to. ❧

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The good, the bad, and the better of the pharmaceutical industry

Figure 1. A joint effort made by patients, the government, and the pharmaceutical industry may help to reduce negative effects associated with prescription drug use. Image from National Institute of Health 2019.

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In 2016, 148 million people in the United States used some form of prescribed medications (Martin 2019). While the goal of prescribed medications is to maintain or improve health, many feel that their health is not prioritized by the pharmaceutical industry. Large pharmaceutical companies heavily advertise their prescription medications to doctors, making these drugs readily available and seemingly necessary for even the smallest of ailments. As a result, benefits of medication can be counteracted and problems introduced, such as drug addiction. However, the majority of health professionals agree that the medical advantages and treatments that present-day medications provide outweigh the risk of abuse. Therefore, in terms of prescription medications, Big Pharma is implicated both in improvement and impairment of human health. Big Pharma refers to the largest pharmaceutical companies, including Pfizer and Johnson & Johnson, that make the largest contribution to the most commonly used and widely trusted prescription drugs (Llamas 2020). While prescription drugs help save countless lives from illnesses like diabetes and tuberculosis, prices of some drugs are unreasonably high. Fortunately, there is a promising future for changes in the industry. Proper education and government insight into the problem has slightly addressed the problem. Further involvement by the general population, government, and pharmaceutical industry itself can reduce many of the negative effects associated with prescription drug use.

Large pharmaceutical companies... [make] these drugs readily available and seemingly necessary for even the smallest of ailments.

The role that pharmaceutical drugs play in maintaining and improving health has long been recognized by institutions globally (Hepler 1985). In fact, the World Health Organization updates their Model List of Essential Medicines every two years to provide the most current information about the safest and most effective drugs ("Geneva: World," 2019). Many of the pharmaceuticals included in this book have been vital in paving the way for modern

medicine. For example, following the discovery of insulin in 1922, patients with diabetes mellitus no longer had to follow low-calorie fasting diets to slightly reduce the frequency of glucosuria, acidosis, coma and delay death (Quianzon & Cheikh 2012). Penicillin, after being discovered and safely isolated, saved tens of millions of lives in WWII. Manufacturing guidelines in producing penicillin contributed to the discovery of other antibiotics. While current-day penicillin use prevents patient infection during common medical procedures and operations, some scientists argue that increased life span and decreased mortality is not a result of drug development. (Kardos & Demain 2011 and DeNoon). For example, AIIMS cardiology professor Dr. Sundeep Mishra posits that pharmaceuticals should only be used in "extreme cases" (Mishra 2016). However, many ailments are no longer life-threatening or dangerous due to research and creation of pharmaceutical drugs and vaccinations. For example, widespread and easily transferable diseases like tuberculosis, meningitis, and typhoid have been routinely treated and cured as a result of prescription drug development (Marriott 1956). These diseases are not examples of "extreme cases," but ailments that threatened to kill countless lives. Therefore, decreased mortality rates are a result of pharmaceutical development.

Figure 2.While the US economy leaves prescription drug pricing dependent on the competitive market, the US government can still indirectly lower prices by funding personalized therapies and scheduling congressional hearings that focus on pharmaceutical company profits. Image from Gal 2019.

Despite the role they play in saving lives, pharmaceutical companies are often scrutinized on whether they are more interested in saving lives or making money. "In recent years, the price differential has been exacerbated by above-inflation annual increases in U.S. drug prices at a time when governments in Europe have capped costs or even pushed prices down (Hirschler 2015)." Exorbitant prices are partially a result of the competitive market in the United States, combined with limited government involvement. In contrast, many European governments interfere by limiting drug prices. Perhaps drug pricing is more of a political issue than people want to believe. But, while the US does sell a few of the most expensive drugs, it sells significantly more affordable drugs than countries in Europe. Ninety percent of prescribed drugs in the US today are affordable generic brand medications. In Europe, no more than 75% of drugs are sold as generics (Hirschler 2015).

Research that is causing elevated prices of some drugs is also funding the development of less addicative therapies and the study of factors that predispose certain individuals to addiction.

Of course, no discussion of prescription medication can avoid mention of the opioid crisis. Misrepresentation of risk and over promotion of opioid painkillers by Purdue Pharma make Americans feel safe while taking a highly addictive and commonly lethal drug (Van Zee 2009). Furthermore, the high price of Naloxone, a life-saving opioid overdose treatment, seems unreasonable and is one cause of the reduced faith that people have in pharmaceutical companies ("Profiteering from," 2018). Similarly, some of the most expensive drugs in the North American market treat Hepatitis C, which commonly leads to chronic liver failure and death (Morris 2017). Many Hepatitis C patients were originally

infected through use of needles contaminated with the virus. As needle injection is an increasingly common route of opioid administration in cases of abuse, the number of reported Hepatitis C cases grows, especially among opioid drug abusers. Recovering addicts face an additional roadblock on the path of recovery from prescription drug abuse, as they require the financial means to overcome both drug addiction and Hepatitis C ("Hepatitis C"). Non-coincidentally, pharmaceutical companies now charge significantly higher prices for their opioid overdose and Hepatitis C treatment prescriptions.

The necessary research investment to produce any pharmaceutical drug contributes to their high prices. Although the United States Senate discussed mandating price caps on prescription medications, they eventually rejected this notion owing to the opinion that these regulations would severely restrain biotechnological development and hinder research into more life-saving drugs. Furthermore, the profit made by some pharmaceutical companies is sometimes corruptly made, as Purdue Pharma did when they released opioids. The public may assume that all pharmaceutical companies make their money this way, when in actuality, many drug companies fail to make a profit on many of the drugs they release (Chabner & Roberts 2007).

Figure 3. Both governmental agencies and private companies are investing in producing prescription drugs in forms that prevent their misuse. Image from Albert Einstein College of Medicine 2020.

The competitive nature of drug pricing in the United States can also greatly benefit the consumer. More competition between companies will typically drive drug prices down so that these businesses stay relevant. Even more important, advancements in drug production research bring with it more personalized therapies. As a result, drug prices can be decreased since companies are assured that they have a patient population ready to buy their drugs and both parties are confident that the therapy will effectively treat the illness. Drugs that follow this type of development have been endorsed by the National Cancer Institute (NCI) and Food and Drug Administration (FDA), foreshadowing further efforts to develop such drugs. Considering all of this, the United States Congress is still contemplating increased involvement in pharmaceutical therapy price-setting and is indirectly increasing the amount of companies that offer free drug access. Congressional hearings would reveal excessive profiting by Big Pharma on their prescription medications. Therefore, this type of government involvement can serve to reduce patient cost as pharmaceutical companies try to reduce negative connotations with their names (Chabner & Roberts 2007).

While the US does sell a few of the most expensive drugs, it sells significantly more affordable durgs than countries in Europe.

Twenty-one million Americans are addicted to at least one drug, with only 10% of them seeking treatment ("Addiction Statistics"). While thousands of people were lied to in the case of opioid prescription drugs, counteracting the epidemic may be easier than with other addictions since evidence clearly demonstrates the dangers of its misuse. Most addicts and users are now somewhat familiar with the high abuse potential and negative side effects associated with taking any opioid longer than prescribed or without a prescription. Widespread education on these facts, in conjunction with effective and accessible addiction treatment options, is the most effective way to remedy the mistakes already made (Jayawant & Balkrishnan 2005). The National Institute of

Drug Abuse explains that clinical standards are being published for prescription drug use to inform doctors and patients on the best treatment options and doses for certain prescriptions, including opioids. Additional promising measures include making prescriptions harder to misuse. Incorporating aversive substances and chemical or physical barriers to prevent a person from taking the opioid in a different way than it is prescribed have demonstrated some success. Similarly, medical advances now allow attachment of new molecular entities that make the drug inactive in the human body if it is taken in any other way than orally. Most importantly, research that is causing elevated prices of some drugs is also funding the development of less addictive therapies and the study of factors that predispose certain individuals to addiction ("How can"). This gives hope for a future with less drug addiction.

With any great thing comes unwanted or unpredicted side effects. There is clearly a price to pay, both metaphorically and non-metaphorically, for the life-saving abilities of prescription medications. However, the battle is not completely lost as many viable solutions and alternatives are being implemented to make prescriptions safer, more effective, and available to those who require them. Hopefully one day, misuse and unreasonable pricing will no longer overshadow the great things that medications do for many people. ❧

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The sound of music: a bird's eye view

SHREYA RANA
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One of the unique characteristics that enabled humans to surpass other species in intellect and innovation was the gift of vocal communication. It is easy to believe that most people take this simple trait for granted. However, vocal communication is anything but a common phenomenon in nature. Vocal learning and performance requires complex adaptations of the brain that so few species of animals have managed to attain. To study such a vital adaptation in human evolution, scientists have turned to using songbird models to further investigate the specific brain mechanisms that allow finches to not only carefully learn their songs, but to perform their songs to perfection.

To begin understanding the mechanics behind song performance in birds, it is imperative to be familiar with the different stages of song learning. The first stage is sensory learning, in which a young bird listens to and memorizes the songs of the tutor. The tutor, in most cases, refers to the father, as female birds do not sing. This male ability to sing is due to the effects of the hormone testosterone. Studies in the past have shown that injecting testosterone in females induces a temporary singing ability in females as it causes key song-producing nuclei in the brain to enlarge substantially(Nottebohm, 1980). The following stage is known as the sensorimotor learning stage. In this stage, the bird perfects its song through continuous repetition and practice over the span of many weeks (Mooney, 2009). To detect and correct errors in its songs, the bird relies heavily on auditory feedback of which the mechanisms are still unclear. (Brainard, 2002) The last stage is referred to as crystallization, which is the smooth performance of the adult song with minimal vocal errors (Mooney, 2009). As stated earlier, song performance only occurs in male birds with the intent of attracting potential female mates. It is important to note that even after crystallization, birds perform two types of songs due to the fact that they strive to continuously improve their song. These two types of song are referred to as "directed" and "undirected". "Directed" songs are performed directly to the female and have minimal vocal errors, since it is the bird's best attempt at performing the song perfectly. "Undirected" songs are not performed for the female and can be thought of as practice songs where there is a lot more variability in the acoustic features of the notes.

Vocal learning and performance requires complex adaptations of the brain...

The main neural pathway associated with song learning is known as the anterior-forebrain pathway (AFP) which is the main topic of discussion in this paper. In addition, the pathway associated with the mechanics of song performance is known as

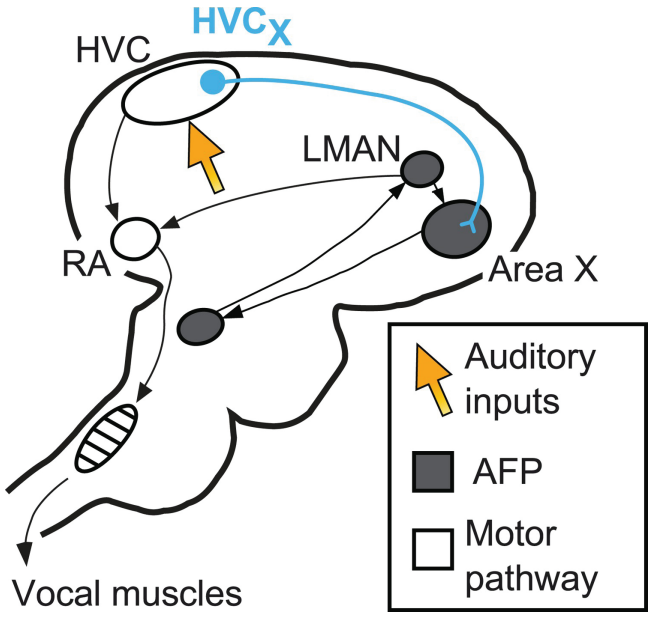

Figure 1. Diagram of the anterior forebrain pathway (AFP) within songbird brain. Image from Sober et al. 2016.

the Song Motor Pathway (SMP). Both pathways begin in the HVc (high vocal center) nucleus, which generates timing signals for songs. HVcx neurons feed into the early parts of the AFP pathway, which also has connections with the ventral tegmental area (VTA). The VTA, as part of the mesolimbic dopamine system, contains dopamine (DA) neurons(Schultz et al., 1997) that are necessary for reinforcement learning and is therefore crucial during the sensorimotor learning stage. The output nucleus of the AFP pathway is the lateral magnocellular nucleus (LMAN) which is responsible for injecting variability into the robust nucleus of the arcopallium (RA). (Andalman et al., 2009) The RA is ultimately responsible for controlling vocal organs and respiration during song, and it receives input from both the SMP and AFP pathways (Mooney, 2009). There are certain neurons, HVcRA neurons, that project song motor commands directly from the HVc to the RA (Mooney, 3). Within the RA, there are different clusters of neurons that influence each other and impact the acoustic features of the song. While researchers have a general understanding of the main pathway involved in song learning, there is still more to uncover in regards to the correction of vocal errors and auditory feedback. There is no consensus about the exact mechanism by which the tutor song is "stored" in the brain so that birds have a reference to which they compare their own songs. In order to improve their performance, birds need to have a sense of the desired song output and a way to detect differences between their own song and the target. Additionally, they must determine how to make those motor changes. (Sober, 2009) There is evidence that HVcx neurons are reminiscent of "mirror neurons,"

The RA is ultimately responsible for controlling vocal organs and respiration during song...

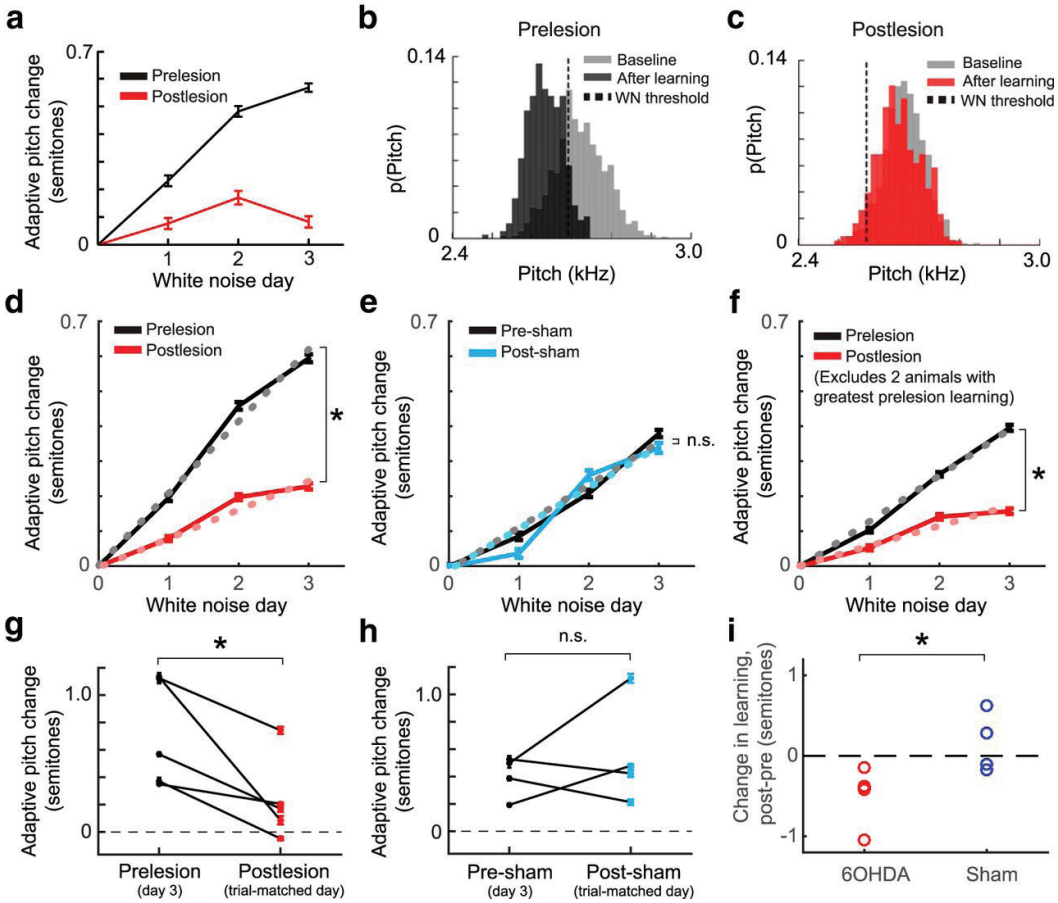

Figure 2. White noise experiment results show a downward trend following negative feedback after high-pitched note and upward trend following negative feedback after low-pitched note. Image from Hoffmann et al. 2016.

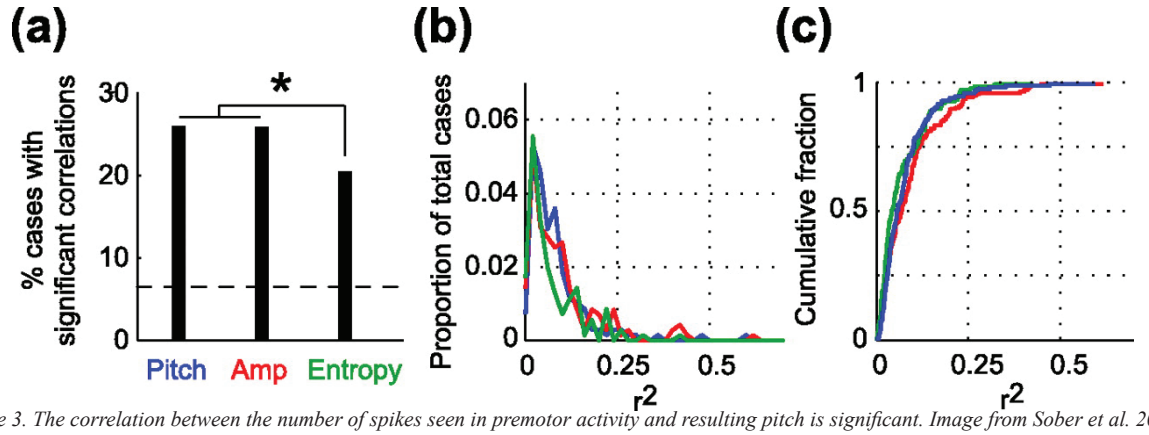

Figure 3. The correlation between the number of spikes seen in premotor activity and resulting pitch is significant. Image from Sober et al. 2008.

which fire when the bird sings its own song and is a reflection of its experience. It is a possibility that these mirror neurons have connections with the tutor-tuned neurons which could offer an explanation as to how the process of auditory feedback is involved.

White noise experiments are a common type of experiment used to study vocal learning through songbird models. White noise experiments function through a negative feedback mechanism in which birds change certain features of their notes due to an unpleasant stimulation, and this process is thought to be analogous to the auditory feedback and learning process (Tumer, 2007). Researchers are constantly striving to figure out which specific nuclei within the AFP is involved in this process. In a certain experiment, Area X within the AFP was the central target as it is thought to be responsible for the degeneration of "adaptive modification"(Hoffmann) in adult bird songs. Past experiments have shown that damage to Area X hinders song learning in young birds. Therefore, an experiment was conducted in which neurotoxin 6-OHDA was delivered to DA neurons within Area X in birds in the treatment group. Birds in the control group were given sham lesions where no damage was inflicted on the brain. White noise was then delivered to both groups of birds immediately proceeding certain high pitched notes. Results showed that the pitches of the birds with the sham lesions significantly decreased, while the pitches of the OHDA-lesioned birds changed minimally (Hoffmann et al.,2016). The inability for the OHDA-lesioned birds to adapt following auditory feedback is evidence that their learning ability greatly diminished following the lesion in Area X. After the white noise effect was removed, the pitches of both groups of birds went back to the baseline pitch. Also, there has been heightened interest in assessing the effect of pre-motor activity in neurons on acoustic features such as, pitch, amplitude, and spectral entropy. To study this, researchers analyzed the number of neural spikes during the 40 millisecond window before the performance of the note. The data suggested that the number of spikes had the most significant correlations with the pitch of the note (Sober et al., 2008). However, other features of premotor activity, such as the spacing between spikes, are still under considerable research.(Srivastava et al., 2016)

The possibilities for vocal learning research in songbirds are endless, as there is still so much to be uncovered. A trait as complex as vocal communication requires considerable adaptations in the brain which would not have occurred if it had not been evolutionarily beneficial. While scientists have a general understanding of the various stages of song learning and the AFP pathway, more research is needed to fully understand the correlation between the two. That is, the weights of the nuclei in the AFP are constantly changing as a bird ages. Other areas of research also include understanding the differences in the AFP nuclei between the two hemispheres of the brain. Such breakthroughs could lead to a general understanding of how human language acquisition and performance works which is one of the hot topics in the field of neuroscience. ❧

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The politics of public responses to global epidemics

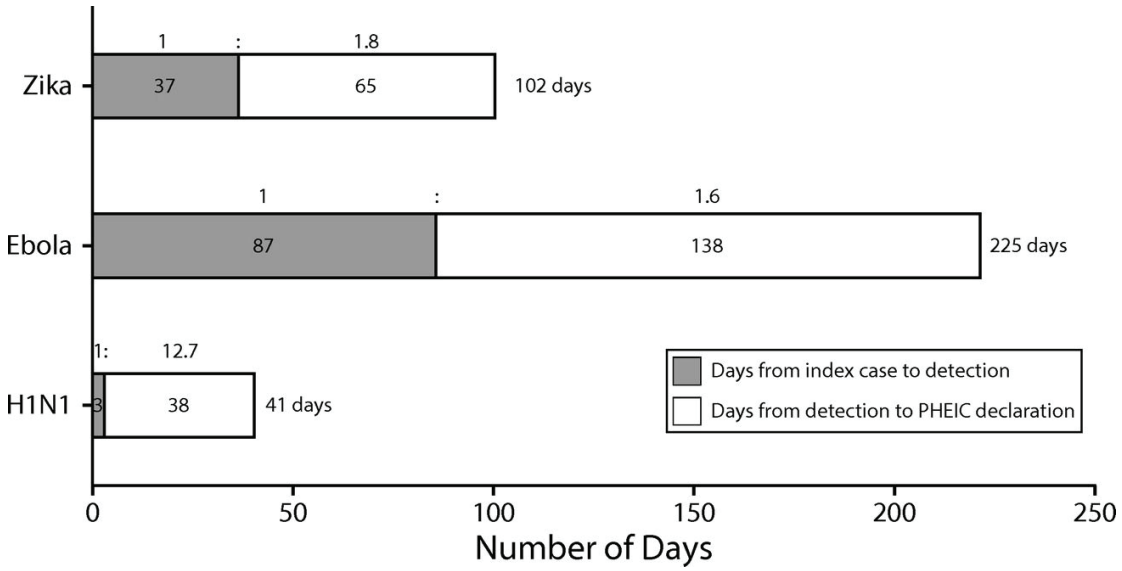

Figure 1. Tracking delays in the last three major epidemics. Image from American Journal of Public Health 2018.

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Since its recognition as a Public Health Emergency of International Concern (PHEIC) on January 30, 2020, the n-COVID 2019 has upended life in the United States. As cases precipitously rise in the United States, among many other nations, and as fear escalates in the public, it is inevitable that scrutiny falls on the governing bodies and on the tactics that they deploy to help ensure the public's health. Of these, governmental transparency and global and domestic politics are of immediate concern. Such issues are, however, not unique to n-COVID, and they draw parallels to Ebola and Zika outbreaks, cases which also saw failures in communication and policy. Underlying these concerns is a broad critique of the government's slow speed of response, a logical concern as the fight against n-COVID seems increasingly like a race against the clock.

The significance of studying political factors and the government's role in public health response merits some preliminary discussion. Epidemiologists often recognize two kinds of delays in response to epidemics: delays in surveillance, or uncovering the disease; and delays in communication or propagation of pertinent information. The two forms of delays are analogous to limitations in technology or politics respectively in the mobilization of a response (Hoffman, 2018). One of the most powerful vehicles to facilitate mobilization is the World Health Organization's ability to declare a Public Health Emergency of International Concern (PHEIC). Therefore, comparing the difference in time between the initial case and its detection - the delay in surveillance - to the detection and its PHEIC declaration - the delay in communication - can be valuable in understanding whether technology or politics plays a larger role in response to an epidemic.

Instead, the data suggests that political factors, and especially failures to establish rapid political mobilization, may be the true culprit in delays.

Given the data in Figure 1, in the last three major epidemics, as paradoxical as it may seem, surveillance and technical limitations can hardly be considered the source of major delays in response. Instead, the data suggests that political factors, and especially failures to establish rapid political mobilization, may be the true culprit in delays. In the world of public health, the importance of these factors must not be underestimated and mitigants to these delays must be sought. A deeper comparison of governmental public health strategies in response to Ebola, Zika, and Coronavirus may provide insights into the ways that the mobilization rate is further linked to global and domestic politics in the face of widespread epidemics.

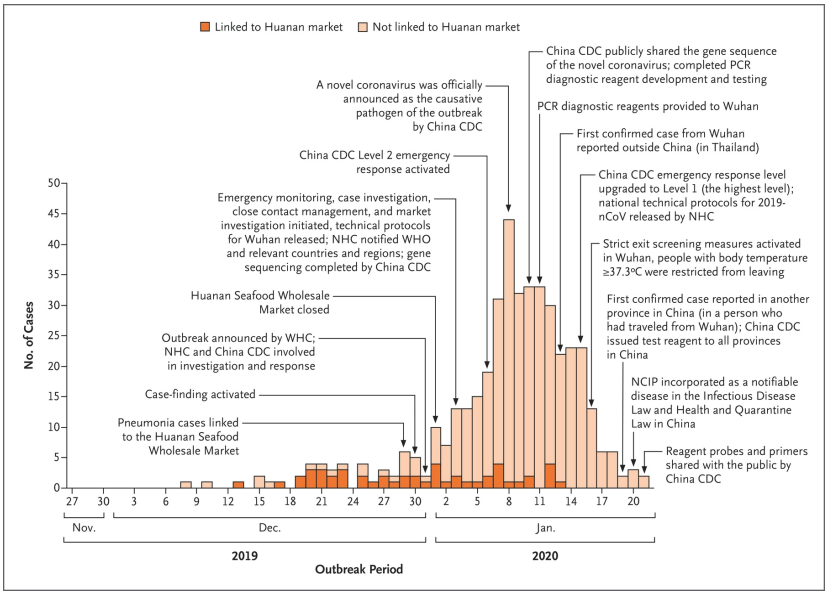

Figure 2. Onset of Illness among the First 425 Confirmed Cases of Novel Coronavirus (2019-nCoV)–Infected Pneumonia (NCIP) in Wuhan, China. Image from New England Journal of Medicine 2020.

Unsurprisingly, issues of transparency issues arise in China, a country whose intolerance of domestic dissent and, indeed, of any discourse that may damage the reputation of the government is well documented. In many ways, the initial outbreak and containment of n-COVID in Wuhan resulted from a lack of transparency. On the 31st of December of 2019, Dr. Li Wenliang, an opthalmologist in Wuhan, encountered strange, SARS-like symptoms in several patients and shared his concerns with his peers. Within hours, Chinese officials questioned his motives and forced him to sign a statement characterizing his behavior as "illegal" (Buckley, 2020). On the very same day, the Wuhan Municipal Health Commission issued a statement claiming the illness was a "viral pneumonia" that was both "preventable" and "controllable," thereby downplaying its severity (Wuhan Municipal Health Commission, 2019; World Health Organization Situation Report).

On January 7th, the identity of the virus was officially confirmed to be a new strain of Coronavirus; yet, the narrative still persisted in a later interview, on January 11th, when officials of the Wuhan Municipal Health Commission claimed that no new cases had been detected and that the virus did not show human-to-human transmission (Wuhan Municipal Health Commission, 2020).

It is likely that political factors, namely forthcoming elections, overshadowed the need for accuracy in public-health decisions and undermined an already strained trust in the government. The Chinese government's failure early on to disseminate accurate information led to a serious delay in public-health responses that could have crucially contained the spread of the disease.

A lockdown was finally issued in Wuhan on January 22nd, but by then the number of cases had grown exponentially and the death toll had begun to rise. In brief, the delay in response meant a response that was too late.

In the case of Zika, the response of the government in Brazil, the main country of outbreak, was similarly flawed. Funding to hospitals in poorer areas, which were the main locations of the outbreak, was deemed insufficient even before the outbreak, suggesting that the infrastructure was substantially vulnerable and funding chronically inadequate (Gomez, 2018). The response was further crippled as many policies were planned without "budgetary allocation for their execution", further hindering the delivery of adequate interventions to those who needed it most. Slashed funding to the

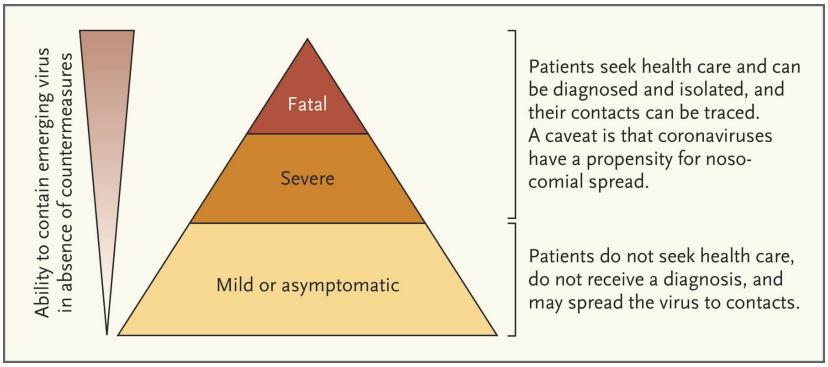

Figure 3. "Surveillance Pyramid and Its Relation to Outbreak Containment." Image from New England Journal of Medicine 2020.

Sístema Único de Saúde, Brazil's universal healthcare system, contributed crucially to the lack of major response (Gomez 2018). In a country rocked with deep political corruption and turmoil, evidence again emerges of the inadequate governmental response to protect the safety of the public. Geopolitical factors also inhibited effective response. For example, the United States's CDC (Centers for Disease Control and Prevention) was initially reluctant to collaborate with Brazilian scientists, instead seeking to independently verify results (Donald, 2017). One especially unhappy outcome was that more than 5,000 symptomatic cases were reported in the United States alone, an outcome that might have been prevented were there given greater collaboration and better-specified responses (CDC, 2019).

Politics and fear were obstacles in the case of Ebola as well. When an American who had returned from Guinea became ill with Ebola, panic ensued. The media in part fueled this panic by presenting dangerous speculations instead of informing the public about the nature of Ebola and how it actually spreads. Furthermore, politicians in the midst of the 2014 midterm election season chose to respond not with science-based policies, but rather with seemingly off-the-cuff, gut-reaction policies whose consequences were not thoroughly considered. For example, strict home quarantine rules may have led sick people to avoid treatment or travelers returning from Ebola-affected countries to misreport their exposure in hopes of evading quarantine (Spencer).

...the Wuhan Municipal Health Commission issued a statement claiming the illness was a "viral pneumonia" that was both "preventable" and "controllable..."

In in each of these cases, political motivations delayed what could have been sound and much more effective responses based on scientifically researched evidence. Instead, fear of panic and backlash from the public clouded judgements and informed crucial decisions. Pre-existing issues regarding governmental organization and funding also hindered any mobilization efforts. However, with each mismanaged government response, public mistrust may only be further fueled, thereby potentially trapping us in a seemingly never-ending cycle. Thus, as we move forward, we inevitably arrive at this question: will future public health emergencies be met with reasoned responses based on the best available scientific evidence? Or will we continue to be lost in the confusion and inefficiency that stems from political tactics and mass panic? ❧

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EUMR's main advisor is Dr. Michael Crutcher, one of the many distinguished faculty members in Emory's Neuroscience and Behavioral Biology Department. Having received his PhD in Physiology from Johns Hopkins University, he joined the Department of Neurology and of the Neuroscience Ph.D. program at Emory in 1991. His research is primarily focused on the neural mechanisms of visually guided reaching movements in monkeys.

Dr. Crutcher has taught many NBB courses over the years such as: freshman seminar courses (NBB 190) on Brain Enhancement, Curiosities of Neurology and Neuroscience, and Neuroethics as well as Perspectives in Neuroscience and Behavioral Biology (NBB 401 SWR), Biology of Movement Control (NBB 370), Neuroscience Research Methods (NBB 221), Functional Neuroanatomy (NBB 470), and Topics in Neuroscience and Behavioral Biology (NBB 270).

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Dr. Soodalter is a hospice and palliative care specialist in the Emory Healthcare network. She also collaborates with physicians from places as far as Pittsburgh where she most recently completed a fellowship in 2019.

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Daisy is a second year pursuing a bachelor of science in Anthropology & Human Biology and co-majoring in Integrated Visual Arts. She originally joined EUMR as a first-year liaison and organized the first Suture Lab with the Emory School of Medicine. Since becoming editor-in-chief, her main goal is to continue expanding EUMR's potential. That aside, there is nothing she loves more than a day with no agenda spent on all sorts of creative endeavors.

NATHAN JACOB

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Nathan is a second year majoring in Biology with a minor in Philosophy. He began as first-year liaison and now as secretary, he does a little bit of everything to ensure that all aspects of the club run smoothly. Outside of EUMR, he is also involved in organizations such as club tennis and Remote Area Medical. Nathan was an extra in Spider-Man Homecoming and you can actually see a blurry image of him during the first ten minutes of the movie!

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Anirudh is a fourth year majoring in Neuroscience and Behavioral Biology with a minor in Predictive Health. As treasurer, he works on budgeting for all the event committees and the club's dealings with SGS. Outside of EUMR, he is also involved in SAHI and The Emory Wheel. In his free time, he enjoys basketball and chess.

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Jinny is a fourth year majoring in Anthropology & Human Biology and looking forward to medical school in the fall. She has been a writer in EUMR since her second year at Emory and took on the role of Managing Editor for EUMR Open Access (formerly the blog) over the past two years. Outside of EUMR, she has also been involved in Emory Bioethics Society. She "peaked" three years ago when she ran a half marathon.

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Anna is a fourth year majoring in Neuroscience and Behavioral Biology. She started EUMR as a first-year liaison, and founded the Emotive Arts Series, a medical humanities conference which is now hosted by EUMR each year. Later on, she advanced into the roles of Copy Editor and Events Chair. Outside of EUMR, she spent a summer working as a science writer composing Wikipedia articles for the military.

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