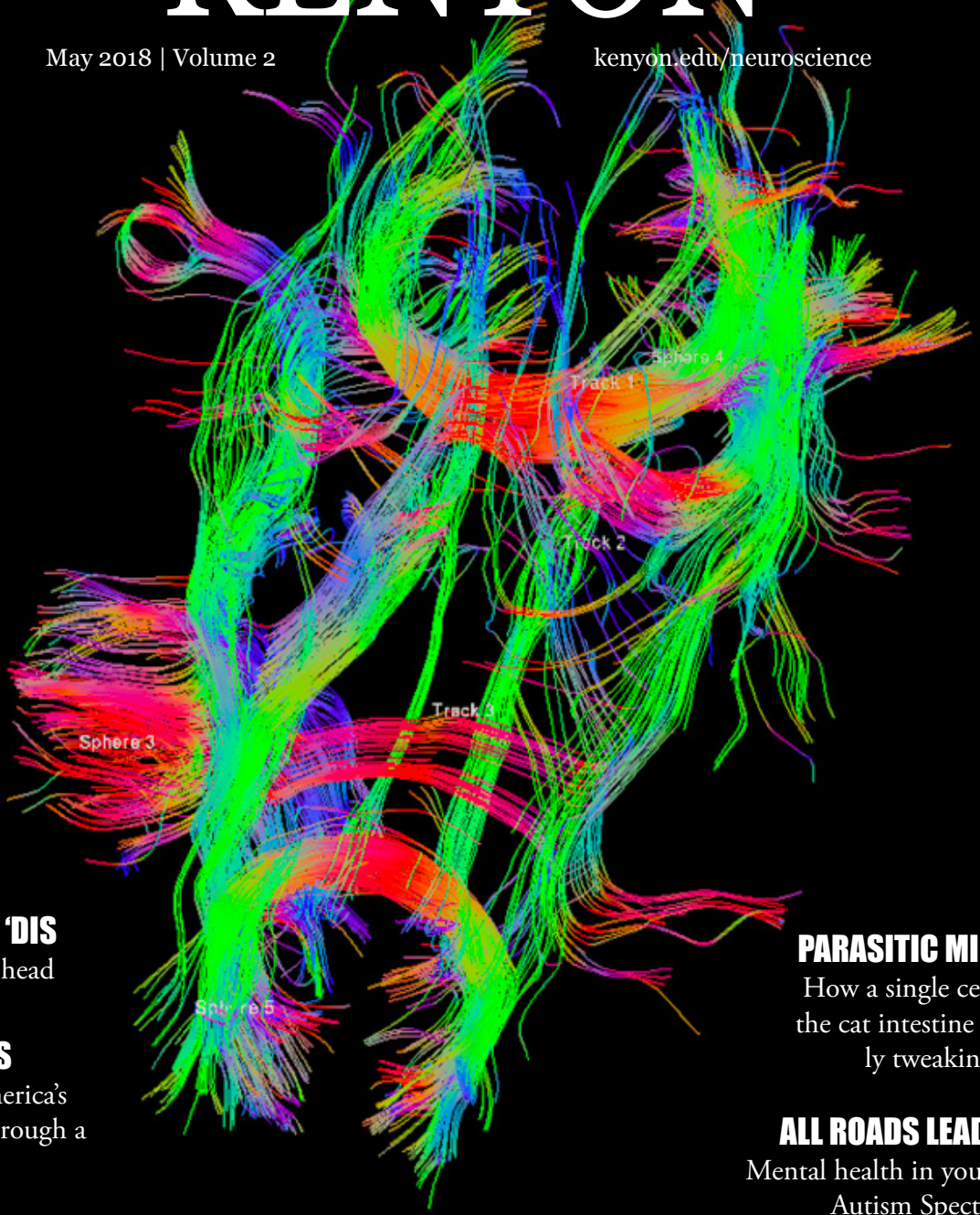
NEUROSCIENCE EDITION

SCIENTIFIC KENYON

May 2018 | Volume 2

kenyon.edu/neuroscience



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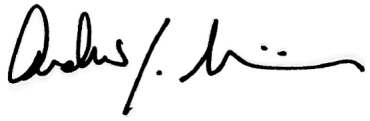
LETTER FROM THE PROFESSORS

On being an ambassador for science to the world.

Class of 2018, you have the distinction of being the largest graduating class in the history of the Kenyon Neuroscience Department/Program. Your dedication to excellence and hard work means that despite this phenomenal growth, we, the faculty, have been able to both maintain and build on the high standards that we have set for you and ourselves. As a result, we are confident that you received a superb education and looked forward to hearing of your future achievements. In the last few years, we recognized that although you, our students, are well trained to write for your scientific peers, we had, like many science training programs, neglected to push you to develop your abilities to communicate science to the public. This skill is essential, especially in the current socio-political atmosphere. More and more we see scientific ideas and facts marginalized in favor of financial and political expedience. One needs only to look at the climate change "debate" to see a perfect example of this trend. We think that the answer to this problem is a better educated public; that the average voter should have the opportunity to have a clear understanding of current scientific issues and trends, even if they themselves are not scientists. The burden of providing that education falls on us, members of the scientific community. We must find a way to communicate to our fellow citizens the complexity, excitement, and wonder of science. Most importantly, we must do so with respect, grace and humility. We must share out knowledge and discoveries with our fellow citizens by inviting them into the scientific world though our engagement with the public. One way is to write about science in everyday language for general consumption. That is what we asked you to do in your senior seminar and those articles are presented here in Volume 2 of *Scientific Kenyon: Neuroscience Edition*. You chose topics that anyone would be excited to read about; from head transplantation to synesthesia to animal linguistics and so many other wonderful topics. We, the faculty, are inspired by the range of your interest as well as your knowledge and the nuanced way in which you tell your stories. This is precisely the kind of public communication of science we had in mind when we set you to this task. We hope that after you leave Kenyon, you will continue serve as ambassadors for science in whatever way you see fit. Whatever path you take, we are confident that you will represent the Neuroscience Department, Kenyon College, and yourselves with grace and distinction. We wish you well.

Sincerely,

Hewlet G. McFarlane
Professor and Chair
Department of Neuroscience
Kenyon College



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Current Topics in Neuroscience
Drs. Hewlet G. McFarlane &
Andrew Niemiec &
The Class of 2018

Special Thanks to Ashley Butler, Digital Media Instructional Technologist, Kenyon College

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Cover image created by
Mary Sawyer

PARASITIC MIND CONTROL

How a single celled parasite carried in the cat intestine may be quietly tweaking our behavior

By **Sophie Letcher**

On November 30th, 2012, Jonah Evans* fell from a 30-foot ledge in Rock Bridge Memorial State Park, landing in a bed of leaves at the foot of a cave called "Devil's Icebox." The Missouri native teen was hiking with a friend when he got carried away jumping from rock to rock along the trail - ultimately leading to the disastrous accidental slip. Jonah was airlifted to the local hospital and made a full recovery, but this kind of behavior was not unusual. Jonah is an extremely intelligent, thoughtful, and kind hearted person, but as his mother, Emily*, attested after the accident, he tends to put himself in reckless situations - jumping atop slippery rocks along a ledge perhaps the most devastating example. As mothers do in these situations, Emily searched for some way that she was at fault for Jonah's fall.

Sitting around a table of friends discussing the horrific accident (post recovery), Emily mulled over why Jonah could be so reckless when he's generally such a clear-headed person. "I did spend a lot of time around cats when I was pregnant with Jonah - maybe he contracted that parasite that makes you crazy," she half-joked. The parasite Emily was referring to is called *Toxoplasma gondii* (*T. gondii*, for short), and it was around this time that pop science was picking up the idea that many

*Names have been changed to protect privacy

Pregnant? Steer Clear of Litter Boxes

If you've ever heard of *T. gondii* or toxoplasmosis, it was probably in the context of cat litter and pregnancy. That's because if the parasite is acquired *while* pregnant, it can be transmitted to the fetus and cause some nasty side effects in the child: eye defects and potential blindness, mental disabilities, low birth weight, jaundice, and in rare instances, stillbirths.[3,20] The CDC suggests taking precautions while expecting: avoiding changing cat litter, avoiding stray cats, cooking meat thoroughly, keeping cats indoors, and feeding cats dry/commercial cat food and not undercooked or raw meat. In the unfortunate event that a pregnant woman is infected (detectable through a blood test), there are medications available but both the mother and the baby will have to be closely monitored.[3]

cats carry a mind-altering parasite (*T. gondii*) that can infect humans and manipulate them into illogical risk taking behavior.[1] Although the idea seems like science fiction, mounting evidence suggests that Emily may have been onto something. While she isn't at fault for Jonah's fall, infection with *T. gondii* may very well change one's behavior - uncharacteristic recklessness being just the tip of the iceberg.

What is *Toxoplasma gondii*?

T. gondii has been on a list of major pathogenic parasites since the 1920s[2] but until fairly recently, knowledge of the effects of infection on humans halted after the initial stage of infection. Acute toxoplasmosis, infection with rapidly dividing *T. gondii*, is usually asymptomatic in healthy humans, sometimes causing mild flu symptoms such as swollen lymph nodes, muscle aches, or fatigue.[3] However, when the immune system is unable to quell the rapidly dividing invaders, as is the case with the immunocompromised (such as people who are HIV positive), infection can lead to severe fever, nausea, confusion, headaches, or seizures; potentially life-threatening situations.[3] Acute toxoplasmosis is also a risk factor if acquired while pregnant.

As the host's immune system starts to halt rapid division of *T. gondii*, the parasite switches gears and barricades itself in intracellular cysts that are safe from the host's immune response. It remains inside these cysts, slowly dividing, throughout the host's lifetime.[4] Parasite-filled cysts can be found in all types of host tissue, but seem to have a higher affinity for neural and muscular tissue.[4] Though this slowly dividing stage was initially thought to be asymptomatic, evidence now suggests that the parasite may be quietly tweaking our behavior and underlying some of the most devastating neurological diseases.

T. gondii life cycle: from cats to rats and back

To understand these parasite induced behavioral changes in humans, it is important to understand why *T. gondii* may have evolved the ability to change host behavior - and the parasite's complex life cycle is at the root of it. *T. gondii* can only reproduce inside the cat intestine - but because sexual reproduction is slow and costly, the parasite outsources itself to an intermediate host where it can asexually reproduce. Dormant forms of the parasite leave the cat through its feces and are ingested by other mammals (the intermediate hosts). During this period of the life cycle, *T. gondii* divides rapidly, proliferating for as long as it can until ultimately returning to the cat intestine to sexually reproduce again and complete its life cycle. How does the parasite find its way back to the cat intestine? Although it is able to infect any warm-blooded mammal, it makes the most sense for *T. gondii* to infect mammals that will be eaten by cats - and this is where it gets interesting. When *T. gondii* is ingested by rodents (common cat prey), the parasite manipulates the rodent's behavior in a way that makes them easier prey for cats; Infected rodents experience "fatal feline attraction"[5,6] where they lose their innate fear of cats, spend more time in vulnerable positions,[5] and are even sexually attracted to cat urine.[7] So what does this have to do with humans? As mentioned before, once *T. gondii* is shed from the cat in its feces, any warm-blooded mammal is susceptible to infection - and it turns out that humans can contract the parasite

through many means, leading to a 30-70% infection rate worldwide.[8,9] The life cycle of *T. gondii* is summarized in Figure 1, including possible routes of transmission to humans. It seems as though the behavioral manipulation that *T. gondii* induces in rodents to facilitate its life cycle may go slightly haywire when the parasite finds its way into human tissue.

From cats to...humans?

From *T. gondii*'s perspective, infection in humans is a dead end - unless we have really powerful, sadistic pet cats or find ourselves in the presence of a hungry lion it is unlikely that we will be eaten by a cat and thus return *T. gondii* to the cat intestine. Nonetheless, the manipulative parasite still finds its way into a large proportion of the human population. Although cats play a pivotal role in *T. gondii*'s life cycle, most of the transmission to humans happens through consuming undercooked contaminated meat, contaminated water, or eating unwashed vegetables.[3] A study done in 2002 found that 38% of British commercial meat was contaminated with *T. gondii*,[8] and countries such as France that prefer meat undercooked have a higher rate of infection.[9] Unwashed

"Cut up steak" by Van Robin is licensed under CC BY-SA 2.0.

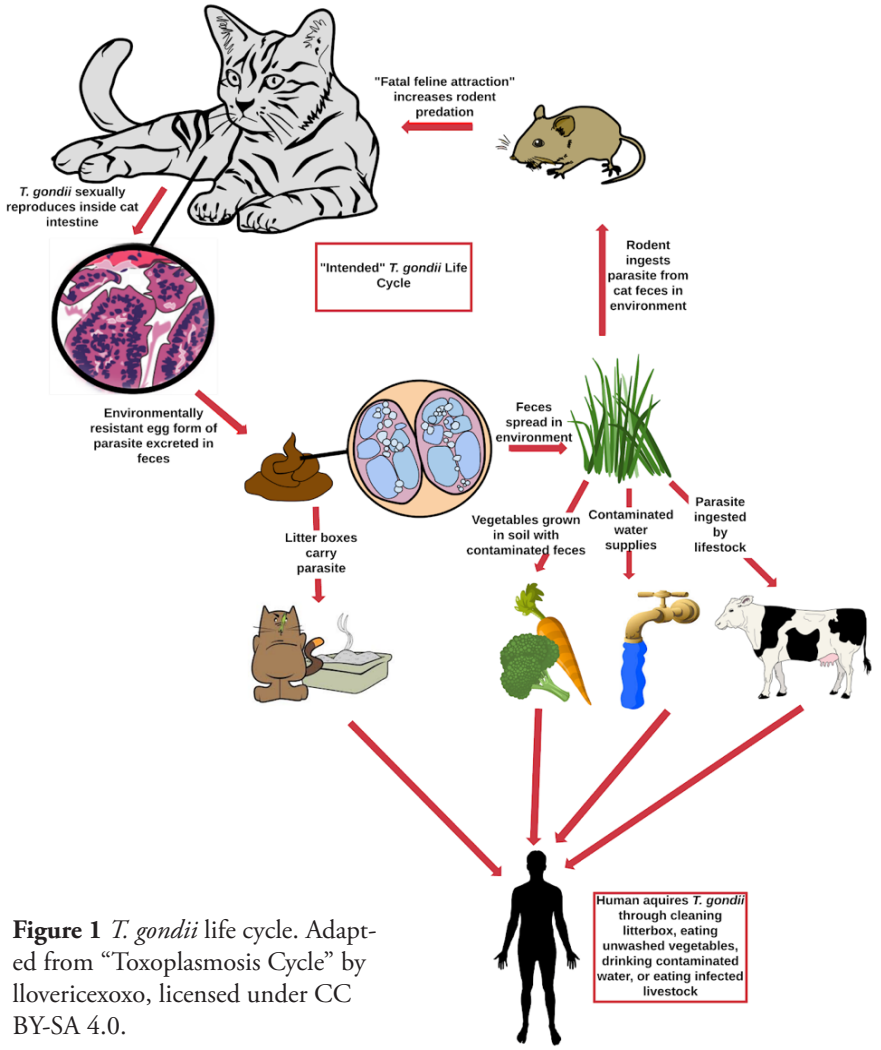


Figure 1 *T. gondii* life cycle. Adapted from "Toxoplasmosis Cycle" by llovericexoxo, licensed under CC BY-SA 4.0.

vegetables carry the parasite when grown in dirt with cat feces containing *T. gondii*, and parasite-laden feces also find their way into water supplies.[3] Lucky for cat lovers, it seems as though domestic cats have a very low chance of carrying the parasite, negating the *T. gondii*-based "crazy cat lady" theory.[1]

Strange Behavioral Changes

The acute symptoms of *T. gondii* infection are easily digestible - the fact that single-celled organisms such as viruses and bacteria can bring us physical harm is accepted and understood. The behavioral changes, however, are far more complex and as such much more terrifying. As humans are "accidental hosts," it seems as though the behavioral changes are spin-offs of the manipulation seen in rodents to make them easier prey for cats.

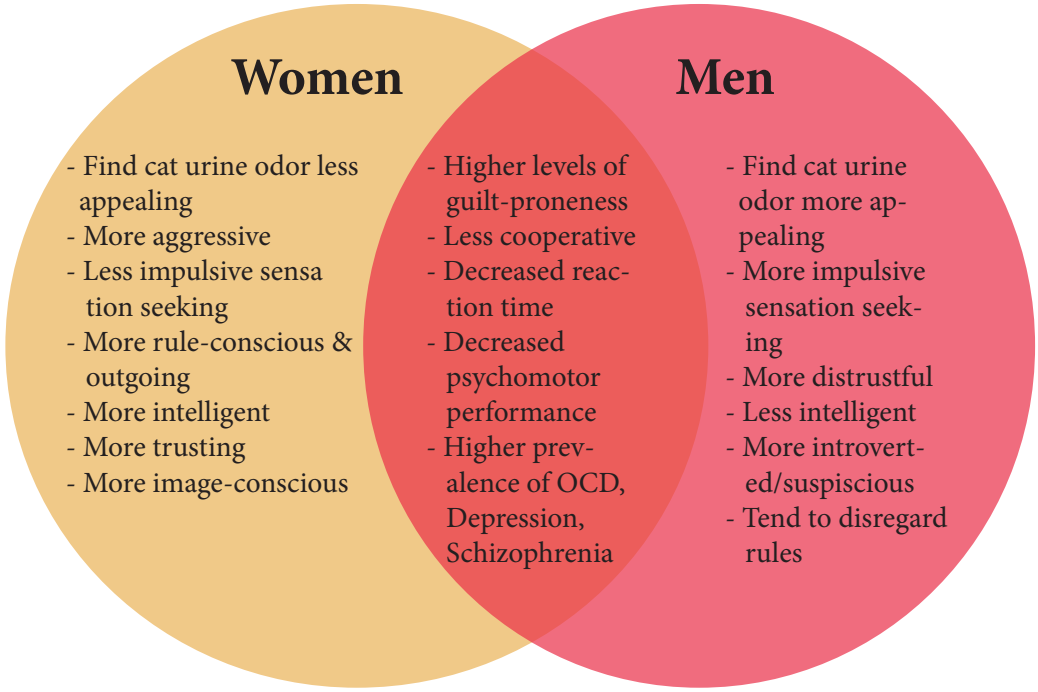
One of the pioneer studies in uncovering behavioral changes in humans with chronic *T. gondii* infection was done by a Czech scientist named Jaroslav Flegr, who wanted to see if the reckless behavior observed in infected rodents translates to humans. Indeed it seems to - Flegr found that a potential combination of reckless behavior and decreased reaction time in infected individuals lead to a greater like-

lihood of getting in a car accident. More specifically, infected individuals are 2.65 times more likely to be in a risky crash, an odds ratio that may contribute to up to one million car crash-related deaths per year.[10] Crazy as it sounds, this study has been replicated in other countries and the theory holds in context of further studies on *T. gondii* induced behavioral changes.[11]

Interestingly, many *T. gondii*-induced changes seem sex-specific, as summarized in the figure to the right. One of the most fascinating differences is that while men seem to retain the "fatal feline attraction" seen in infected rodents - perceiving the smell of cat urine as more pleasant compared with uninfected controls - infected women are the opposite, finding cat urine less appealing than uninfected controls.[12] Though there hasn't been an explanation for this sex-specific difference in odor perception yet, some of the other differences may be explained by the fact that *T. gondii* infection leads to increased testosterone (the male sex hormone) in males but not in females. Many scientists also speculate that differences occur simply because the male and female brains are wired differently, and thus may react to the parasite-induced neurological changes in different ways.[13]

What does appear to be conserved throughout infected humans regardless of sex is the correlation between seroprevalence (detection of immune response to *T. gondii* in the blood) and various neurological disorders. Numerous links have been made between infection and depression, suicides, personality changes, bipolar disorder, OCD, and, most prominently, schizophrenia.[13] Recent studies have also found correlations between infection and epilepsy14 and certain types of cancers.[15,16] Putting together all the indirect ways *T. gondii* infection could kill you, the parasite may be one of the most successful undercover assassins that most people have no idea exists!

Sex Differences in Behavioral Changes With Chronic Infection
Adapted from Flegr 2007, Flegr et al. 2003



How? Putting together pieces of the puzzle

How can a single-celled organism cause us to crash our car or even drive people to schizophrenia or suicide? Although there isn't a single satisfying answer as to how *T. gondii* is able to elicit such complex and specific alterations in the minds of hosts, multiple lines of evidence are beginning to chip away at how the parasite changes host behavior.

Immune response

One of the primary explanations for *T. gondii*-induced behavioral changes in humans is the indirect effect of the immune system working to keep the parasite "dormant." The constant production of chemicals needed to keep infected tissues safe from total destruction by the parasite are also involved in other essential processes. For example, the immune response leads to breakdown of a key precursor of serotonin, a "feel good" neurotransmitter that is often lacking in the brains of those with depression.[17] Constant activation of the immune response also messes with the glutamate pathway, a neurotransmitter involved with anxiety.[17]

Parasite localization

Another plausible way that *T. gondii* manipulates hosts is simply through residing in the right areas of the brain. The brain is an extremely complex organ, and disrupting proper functioning of a specific place may be enough to elicit a specific behavior. Cysts seem to preferentially form in areas of brain associated with emotions, fear, and odor processing (olfactory bulbs, amygdala, and nucleus accumbens).[17] Further, studies have indicated that rats only have "fatal feline attraction" and associated anxiety behaviors when the parasite is localized to certain areas of the brain involved with higher cognitive processes.[18] However, because most physical and cognitive functions of the host are left intact, it seems unlikely that behavioral changes are solely due to *T. gondii* localization. It is more likely (and perhaps more terrifying) that the parasite manipulates specific cells and neural circuits in just the right way where behavior is altered but physically the host is unchanged.

Neurotransmitter modulation

Neurotransmitters are the chemical messengers of the brain, running the show of emotions, actions, and everything in between. One of the most studied and most accepted neurological changes in the brains of *T. gondii* infected animals - rodents and humans alike - is the increase of host dopamine levels.[19,20] Dopamine is a neurotransmitter involved in the reward pathway and motor control,[21] and increased levels of dopamine relate to many of the observed behavioral changes, from movement issues to hyperactivity to schizophrenia. Although the mechanism by which *T. gondii* changes host dopamine levels isn't clear, genomic analysis has revealed that the parasite may synthesize proteins that are critical in the production of dopamine.[22] These studies imply that *T. gondii* uses these proteins to speed up dopamine production inside infected brain tissue, facilitating the increased global dopamine levels that alter behavior.

T. gondii and Schizophrenia

Schizophrenia affects about 1% of the population and is one of the least understood mental illnesses, mystifying neuroscientists for ages.[23] Symptoms of schizophrenia vary, but generally include hallucinations, disordered thoughts, and losing touch with reality.[23] Strangely enough, *T. gondii* infection is the greatest risk factor for developing the disease, bypassing genetic and environmental factors.[24] Patients with schizophrenia have a higher prevalence of *T. gondii* infection across a range of meta-analyses,[25] and some rare cases of acute toxoplasmosis have been documented with symptoms that are very similar to schizophrenia - auditory hallucinations, thought disorders, blunted affect, etc.[24] These cases are especially prevalent in infected immunocompromised individuals, where *T. gondii* has free reign of host tissues.[24] Scientists speculate that infection may switch on predispositions for developing schizophrenia - meaning that *T. gondii* infection doesn't directly cause schizophrenia, but if genes, brain structure, or environmental conditions make one more susceptible to the disease, *T. gondii* may simply flip the switch that effectively "turns on" the disease.

So how does *T. gondii* flip this switch? A hallmark of a schizophrenic brain and likely the underlying cause of many behavioral deficits is an increase in neural concentrations of dopamine -

Manipulation Hypothesis

The activity of *T. gondii* seems to fit perfectly with the "manipulation hypothesis," which holds that some parasites manipulate host behavior for their own evolutionary benefit - often helping the parasite pass through the food chain when a parasite has a definitive host (where it can sexually reproduce) and intermediate hosts (where it can reproduce asexually).[10] Other parasites that follow the manipulation hypothesis can be found infecting a wide range of organisms. For example, Malaria parasites (*Plasmodium*) lead mosquitoes to bite more humans per night. Another fungal parasite, *Ophiocordyceps unilateralis*, selectively infects ants and leads them to clamp down on leaves or twigs, remaining there while being consumed by the fungus - lending them the name "Zombie Ants".[11]

"Man Women's Fragrant Flower Smell" by eommina is licensed under Creative Commons CC0.

and as discussed before, increasing host dopamine levels also seems to be *T. gondii*'s forte.[20] Interestingly, antipsychotic drugs used to treat symptoms of schizophrenia that target the dopamine system (haloperidol, valproic acid) also seem to inhibit *T. gondii* replication and ability to get into the brain, harboring the idea that antipsychotics may be at least partially effective as antiparasitics.[26] Another interesting connection is that many schizophrenic patients experience deficiencies in their olfactory systems - if *T. gondii* is a causative factor for schizophrenia, this could be explained by the olfactory manipulation involved with "fatal feline attraction."[12,27] Though the connection between *T. gondii* and schizophrenia is still fairly recent and not well understood, it creates exciting opportunities for the generation of novel therapeutics for one of the world's most devastating neurological diseases.

Like the smell of cat pee?

One of the most fascinating manipulations that occurs in rodents and seems to be (at least partially) conserved in humans is the selective change in the perception of cat odor. The olfactory system is one of the most intriguing and complex sense systems - each "scent" (chemical) has a specific wiring and a specific receptor that tells the brain what scent was picked up. Webster and McConkey (2010) speculate that *T. gondii* may specifically trip the wiring for the "cat odor" pathway and make the host no longer perceive cat odor. Thus, if a cat is stalking an infected rodent, the rodent will not sense the cat approaching and will make for extremely easy prey. Alternatively, the parasite may target the innate pathway in the olfactory system - the wiring that rodents are born with that sends alarms to the fear response pathway when predator odors are sensed.[17] Further, this fear pathway may be rewired in a way that ties it together with the sexual arousal pathway - meaning that when rodents sense something that they should fear (cat odor), instead they feel sexually aroused. Interestingly, this specific rewiring of fear and sexual arousal also appears to be conserved in humans. One study of 36,564 participants found that those infected with *T. gondii* (both men and women) have increased attraction to sexual masochism and BDSM-related practices.[28] While this behavioral manipulation does not have to do with odor detection, it may be another example of a human spin-off of rodent targeted *T. gondii* induced changes.

What does this mean for you? Is there a cure?

Because the behavioral changes associated with chronic *T. gondii* infection are not well understood,

Humans as Superorganisms

Although there are more single-celled organisms living inside us than there are human cells, these freeriders are seldom considered when thinking about humans as a whole.[28] But what about the fundamental biological idea that the entire *point* of being an organism (be it a single celled parasite, bacterium, or human) is to survive and reproduce in the best possible way? Now think about those billions of individual organisms, each with their own evolutionary strategy - it's unlikely that they all line up, so what gives?

Kramer and Bressan (2015) bring up the idea of humans as "superorganisms," and that when these "selfish entities" (i.e. Brain microbes, components of the gut microbiome, exogenous viruses, foreign human cells, etc.) integrate into the human body, the evolutionary strategies clash - possibly explaining why humans do things that do not promote our fitness. Thus, our behavior may be guided by both human evolutionary strategies *and* microbial evolutionary strategies.[29] *Toxoplasma gondii* may be just one example of a "selfish entity" that is part of our superorganism.

there isn't a specific cure for targeting chronic infection - and as discussed, the encysted form of the parasite that occurs with chronic infection is extremely difficult to target and out of reach from antibiotics or other typical antiparasitic drugs. The most effective combat against infection is prevention: fully washing vegetables before eating, ensuring meat is fully cooked, and being careful around outdoor/stray cats.

If you're like me, learning all this information will immediately make you question if we actually make any of our own decisions, or are simply a puppet of the parasites residing in our brains. Even scarier, *T. gondii* is just one of the millions of organisms we host in our bodies - where do our thoughts and desires end and microorganisms' begin, and how can we tell the difference between the two? For now, we may as well accept the fact that we are not alone in our bodies - and next time you do something reckless, just blame the *T. gondii*!

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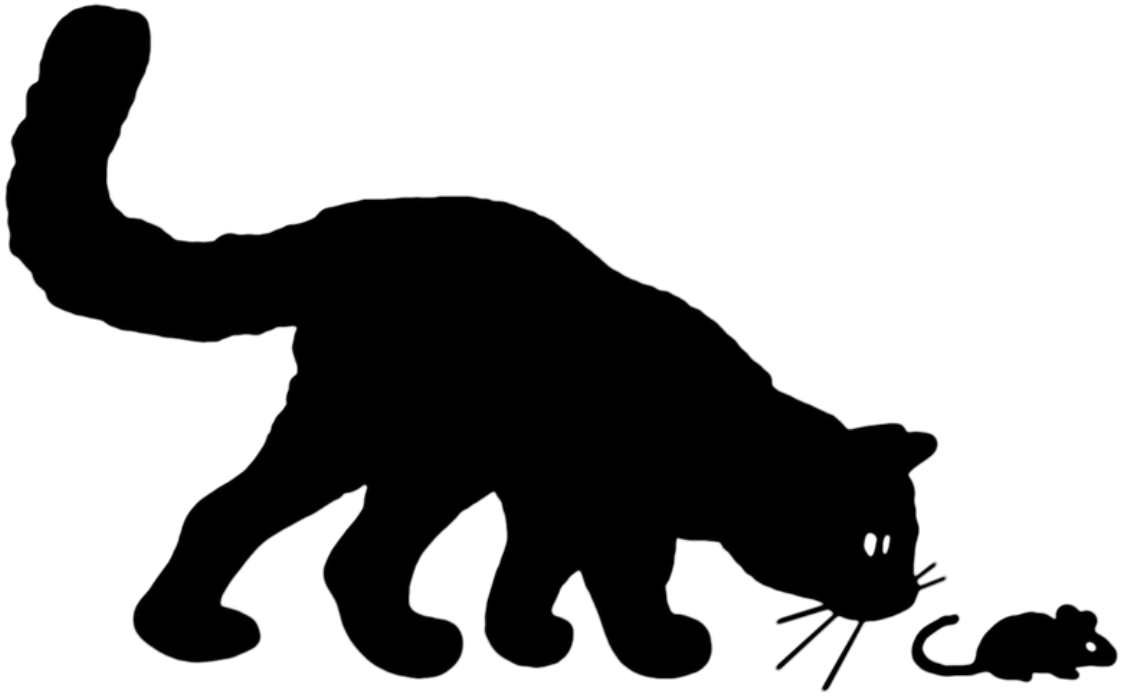


Synesthesia

Sometimes, you really do eat your words

By **John Wilhelm**

As far as State of the Union speeches go, you have a few clear favorites. In short, Harry Truman's 1946 address was cogent—he balanced partisan tensions and maintained a lighthearted, likable demeanor. Franklin Delano Roosevelt's 1941 address on the immediate cusp of WWII was no less impressive; you might argue it formed the backbone of modern liberalism. But nothing compares to Abraham Lincoln's speech on December 1st, 1862. When the country needed it most, Lincoln stepped in to announce the emancipation proclamation. His writing was eloquent, his delivery was immaculate—or so say the first-hand accounts. The most impressive, though, beyond all of Lincoln's talents, was his ability to write a speech that tasted just like a home-cooked thanksgiving dinner. He was great at keeping consistent taste throughout his speeches. FDR, on the other hand, while his verbiage wasn't bad, he could never keep his flavors cohesive. When he discussed international relations, you couldn't help tasting overdressed salad, excess bleu cheese, and flour. While Truman's commentary on military management was great by all accounts—it just tasted like onions, onions, onions.

If nothing struck you as odd halfway through that last paragraph, then congratulations—you might be a lexical-gustatory synesthete! It is not often that words carry a palpable flavor, but this is nothing out of the ordinary in lexical-gustatory synesthesia—a condition where written or spoken words elicit an involuntary association with a specific taste.[1] Of course, this is not limited to food-related words; if I said 'delectable filet mignon,' I would not blame you for getting a hint of tender steak—but any lexical-gustatory synesthete could feel the same way about the word 'bunion.' It is also worth noting that, in reality, it would be quite rare for an entire speech to taste so cohesive to a lexical-gustatory synesthete. Often, words have very distinct, disparate tastes; the word 'woman' might taste like potato chips, where something as innocuous as the word 'by' could taste like sewage gas.[1] In that case, a single one of FDR's sentences in a State of the Union address

Type of Synesthesia	Lexical-Gustatory	Grapheme-color	Ordinal Linguistic Personification	Mirror-touch	Spatial Sequence	Tone-color (Chromesthesia)
What neural pathways are combined?	Words & taste	Words & color	Words & sense of identity	Vision & touch	Temporal & spatial	Sound & color
How does the synesthete experience it?	Synesthete tastes words, either spoken or read aloud	Synesthete sees letters as colored	Synesthete sees individual letters as having personalities	Synesthete feels physical touch that they observe	Synesthete sees time as a spatial construct	Synesthete sees music notes as having a specific color
How common is it?	Very rare, *far* less than 1% of population	Common; roughly 1% of population	Often co-occurs with grapheme-color synesthesia, fairly common	Second most common type of synesthesia, 1.6%	Prevalence unknown; few studies	Rare; under 1% of population; but more common in musicians

could jump from completely palatable words to absolutely repulsive ones in a matter of seconds; but, in my defense, this makes for a more confusing introduction.

Lexical-gustatory synesthesia is far from the only condition of its type. Broadly, synesthesia is a phenomenon in which two neural pathways form a "long-distance relationship"—stimuli of one perceptual pathway elicit a response in another.[1] There are more than 60 documented types of synesthesia.[1] For example, of a word or letter might provoke the feeling of a certain color (grapheme-color synesthesia), as could hearing a specific music note (tone-color synesthesia). The associations in synesthesia tend to be bidirectional, so for a tone-color synesthete, musical tones elicit colors and colors elicit musical tones.[3] Previously, synesthesia was thought to be an incredibly rare condition affecting less than 1 in 2000, people, but it is now known that roughly 4% of the population has some type of synesthesia.[4] Though they are grouped under the same name, types of synesthesia can look very different. For example, visualization of time as a spatial construct around the synesthete (Spatial Sequence Synesthesia), and associating concrete personalities with letters and numbers (Ordinal Linguistic Personification) are also considered synesthesia.[5,6] Types of synesthesia also vary greatly in how common they are, and how much scientists understand about them. So, how does synesthesia work? What is going on in the brains of synesthetes?

Lexical-gustatory synesthesia

As types of synesthesia go, lexical-gustatory is on the uncommon side, affecting very few people—less than 1% of the population.[4] Lexical-gustatory synesthesia is so scarce that there are next to no aggregate studies of individuals with the condition; all of them take the form of case studies—or long-term, in-depth analyses of a particular individual. While a case study might not have the explanatory power of a hundred-participant meta-analysis, they provide a detailed picture of the individual in question. The major risk of a case study is generalizing the results beyond the appropriate context, so it is important to be measured when extrapolating from case studies.

At this point you might be wondering how researchers verify that a person has lexical-gustatory synesthesia in the first place. It is hardly as simple as putting up a "volunteers wanted" sign at your local community center. This is a concern when studying any type of synesthesia—verifying that an individual is indeed a synesthete can be a difficult task, since synesthesia is an internal, perceptual phenomenon. Nonetheless, synesthesia researchers have developed many paradigms to this end, which vary widely between types of synesthesia. In the case of lexical-gustatory, researchers verify an individual's synesthesia by a months-long 'pop quiz' model.[7,8] They begin by establishing a list of ~100 word-taste associations with the synesthete. Months later, they quiz the synesthete on the same associations without prompting—the synesthetes are almost always 100% accurate, except in cases of synonyms (e.g. the synesthete might claim the word 'table' elicits the taste of 'biscuits' instead of 'wafers'). Researchers have extended this paradigm by decades. In one case, a lexical-gustatory synesthete had 100% consistent answers 27 years after the initial study.[8]

It is difficult to generalize the nature of lexical-gustatory synesthesia from any individual

"Word cloud of apple." Pixabay, 23 June 2015, cdn.pixabay.com/photo/2015/06/22/15/38/tag-817712_960_720.jpg.

case study, but most have a few things in common. For instance, lexical-gustatory synesthetes' tastes tend to be quite distinct, including texture and temperature sensations—e.g. a synesthete would not just taste "beer," they would taste "bitter, flat beer."[7] Most lexical-gustatory synesthetes also have "tasteless" words, though the amount of tasteless words varies between synesthetes—one synesthete might "taste" every word in a 100-word sample, but another might only taste 44%.[7] Additionally, the semantic meaning of the word seems to influence taste associations for most synesthetes. Generally, food-words taste like the food they describe ('cabbage' tastes like cabbage), but this extends to indirect semantic associations ('newspaper' tasted like 'chips' to a UK synesthete, where chips are often eaten out of newspaper.[8]

The actual sound of the word appears to influence taste association, as well. For lexical-gustatory synesthetes, the taste sensation provoked by real words ('beach') can also be provoked by similar-sounding 'non-words,' ('keach'). Additionally, lexical-gustatory synesthetes seem to link specific individual sounds to specific flavors.[1] A case study of synesthete "JIW" demonstrated that his synesthetic flavors were connected to specific phonemes (indivisible units of sound, like the /t/ in table). Of the 17 words which elicited the taste of 'cake,' 10 of them contained the /m/ phoneme. This means that words containing the sound /m/ (as in 'mice') were highly associated with the taste of cake for JIW, significantly more so than any other individual sound. Other tastes were linked to sounds in the same manner—for example, the taste of 'yogurt' was highly linked to the sound /g/ (as in gosh) and the taste of 'egg' was linked to the sound /k/ (as in 'key').[8] The reason for these associations is unclear, but it is peculiar that words containing /m/ taste like cake, but the word "cake" does not contain /m/—this holds true for most lexical gustatory associations.

Because of the scarcity of lexical-gustatory synesthetes, little is known about the neural basis of the condition. Of the few neuroimaging studies available, preliminary evidence suggests that the "taste" experienced by synesthetes has a different neural basis than the taste experienced by eating food. When observing the neural activity of a synesthete in response to taste-inducing words, researchers did not see activity in the orbitofrontal cortex or anterior cingulate cortex, regions responsible for processing "normal" taste.[9] The researchers did observe that displeasing synesthetic tastes induce activity in the left anterior insular cortex—a region associated with emotional responses to sensory experiences, particularly smell and taste.[9,10] This could indicate that while the neural basis of synesthetic taste is not the same as "normal" taste, the disgust experienced upon hearing the name Derek[1] is just the same as an individual tasting earwax.

1 "Derek Tastes of Earwax" (September 2004) is a BBC horizon documentary about a lexical-gustatory synesthete - apologies to all the Dereks out there.

Culture and upbringing are two additional but poorly understood factors of lexical-gustatory synesthesia. Synesthete PS, a native English and French speaker, experienced gustatory sensations in both languages, but not in Spanish, which she picked up at the age of 9.[11] On one hand, this could support the idea that synesthesia arises due to associations formed in childhood. On the other hand, perhaps her lack of synesthesia was due to her level of fluency; after enough Spanish work, "Otorrinolaringólogo" might start to taste like pizza. Likewise, the exact stimuli required to elicit a gustatory response are ambiguous—for instance, PS did not experience taste when listening to an individual read words in quick succession, but other synesthetes experience taste from spoken words, written words, and even ambient noise. As fascinating as the condition is, much remains to be discovered about lexical-gustatory synesthesia.

Grapheme-color Synesthesia & Ordinal Linguistic Personification

"'One day,' I said to my father, 'I realized that to make an 'R' all I had to do was first write a 'P' and then draw a line down from its loop. And I was so surprised that I could turn a yellow letter into an orange letter just by adding a line.'"[39]

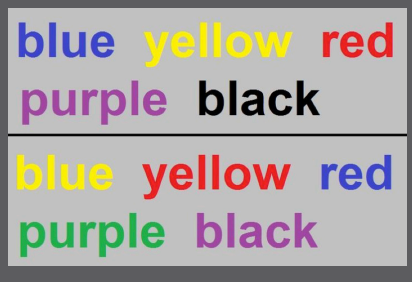
Patricia Lynne Duffy, both a researcher and synesthete herself, remembers discussing her synesthesia with her father at the age of 16. Her father was completely

baffled by Duffy's account of her synesthesia—and she was equally baffled that he did not see letters as colored. While it would be unlikely for a lexical-gustatory synesthete to spend decades of their life without realizing they have synesthesia, it isn't uncommon for grapheme-color synesthetes.[1] Grapheme-color synesthetes associate graphemes (the smallest units of written language, e.g. letters, numbers, symbols) with a distinct color, regardless of the physical color of the grapheme.[1] These colors are quite specific to the synesthete with the exception of a few letters—across synesthetes, "A" is often red, "B" is often blue, and "C" is often yellow.[12] Grapheme-color synesthesia affects 1% of the population, making it one of the most common types of the condition.[4] Like most versions of visual synesthesia, grapheme-color synesthetes can be broken down into two categories: "projective" and "associative." When viewing a grapheme, associative synesthetes have a strong internal feeling of a particular color, but projective synesthetes see the color physically represented on the grapheme. Associative synesthesia is much more common than projective.[13] Grapheme-color synesthesia frequently co-occurs with a type of synesthesia called "ordinal linguistic personification" (OLP). To an OLP synesthete, graphemes have distinct personalities, identities, and motivations—for example, "3" might be a concerned businesswoman working hard to support her child's education, while "5" is a young, bright-eyed rock musician and "Q" is a kindly grandmother.[1]

"ABC-Kids." Public Domain Pictures, www.publicdomainpictures.net/pictures/210000/velka/abc-kids.jpg.

To verify that an individual has grapheme-color synesthesia, researchers employ an altered version of the Stroop task (depicted below) which you can try now, for yourself.

For most individuals, reading the color of the ink in the incongruent condition (below the black line) is harder than reading the color of words in the matching condition. This occurs because of "semantic interference," where the semantic meaning of the word makes naming the physical color more difficult.[14] In an altered Stroop task, synesthetic participants name the synesthetic color of the individual graphemes in the word.[15] This is easier if the graphemes in the word match its semantic meaning (e.g. a synesthete who sees "e" and "l" as blue reads the grapheme colors of "blue") and harder if they are inconsistent (the same synesthete reads the grapheme colors of "yellow"). For an OLP synesthete, an altered Stroop task consists of quickly stating the gender of names, in rapid succession.[6] A synesthete who considers "J" a female letter is quicker to identify "Jillian" as a female name than "James" as a male name. While the altered Stroop paradigm serves to verify synesthesia, it can also demonstrate its intensity. Recording the change in participants' response time between normal and altered Stroop tasks provides a picture of how much synesthesia interferes with participants responses—a high level of interfer-



1) Read the words above the black line
2) Read the words below the black line
3) Read the colors of the ink above the black line
4) Read the colors of the ink below the black line

"Stroop Test 2." Wikipedia, the Free Encyclopedia, 18 Nov. 2012, en.wikipedia.org/wiki/File:Stroop_Test_2.jpg.

ence indicates strong synesthesia.[15]

Owing to its commonality and long history (descriptions of grapheme-color synesthesia date as far back as 1812) most neuroimaging research on synesthesia has been carried out in grapheme-color synesthetes.[16] Unfortunately, meta-analyses show that the lion's share of neurophysiological studies have been inconclusive, inconsistent in methodology, or statistically erroneous.[17] As a result, it remains impossible to conclusively define any neural correlate of synesthetic color. Despite this, there is one peculiar result—research has shown that the synesthetic colors evoked by graphemes do not change activation of the visual cortex. One explanation for this is that real and synesthetic colors are processed differently altogether, similar to how the synesthetic taste of lexical-gustatory synethetes differs from "normal" taste. This could also be explained by a difference in connectivity, e.g. in a grapheme-color synesthete, the regions responsible for color processing have a stronger connection to word-processing areas than in a normal individual.[1]

Mirror-touch Synesthesia

"...[She] has a form of synaesthesia in that she experiences touch from purely visual input. She experiences tactile stimulation on the part of her body that mirrors the body part she observes being touched. [She] has spent the whole of her life experiencing touch when she observes touch on others, unaware that the vast majority of the population do not experience similar sensations."[20]

On the list of "Top 10 Types of Synesthesia That Make it Difficult To Watch An Action Movie," Mirror-touch synesthesia clocks in at #1. Mirror-touch is a variant of synesthesia in which watching another person being touched—tapped on the shoulder, poked in the cheek, punched in the face—elicits a similar tactile feeling for the synesthete in the same area. Unsurprisingly, mirror-touch synesthetes tend to score higher than controls on tests of empathy.[18] Researchers have tried to elicit tactile sensations from mirror-touch synesthetes in various ways, but it seems mirror-touch synesthesia is highly specific to observation of physical touch on another human.[19] Flashes of light on an individual do not elicit tactile sensations, nor does observed touch on an inanimate object.

The first formal study of a mirror-touch synesthete occurred in 2005; this makes it one of the more recently characterized variants.[20] Despite this, mirror-touch is among the most common types of synesthesia. A study of more than 500 people at University College London revealed a prevalence of 1.6%.[19] Much like a Stroop task, researchers verify mirror-touch synesthesia by examining response time on a test where two neural pathways are concurrently activated: researchers have synesthetes report the location of touch on their own face while observing touch to another person's face. Specifically researchers look for "mirror-touch errors" (e.g. a synesthete is poked

"Hand in Mirror." Pxhere, 22 Mar. 2017, pxhere.com/en/photo/1229143.

in one cheek while watching someone be poked in the other cheek, and they report a sensation in both cheeks) which are unique to mirror-touch synesthetes.[19]

Now, imagine yourself as a mirror-touch synesthete. You are facing someone who is tapped on their right shoulder—do you feel the sensation on your right shoulder, or your left shoulder? As it turns out, either answer is correct. There are two categories of mirror-touch synesthesia: "specular" and "anatomical."[19] Specular synesthetes feel a sensation as though they are looking in a mirror—a tap on someone's left shoulder elicits a feeling in their right shoulder; while anatomical synesthetes feel a sensation on the observed side. The specular subtype is roughly four times more common; researchers hypothesize that this choice of mental frame may be driven by individuals viewing their own reflections.[19,20]

Unlike other types of synesthesia, the neural basis of

mirror-touch synesthesia may lie in a recently discovered type of neuron, a "mirror neuron." Completely independent of synesthesia, mirror neurons were first discovered in Macaque monkeys, when researchers noticed a peculiar pattern of neuronal firing.[21] Mirror neurons are understood to fire both when an observer watches an action being performed, and when they perform the action themselves.[22] It has been hypothesized that over-activation or an abnormally high amount of mirror neurons could account for mirror-touch synesthesia.[23] While appealing, this explanation incorporates two poorly understood concepts, and mirror neurons are a topic of heated debate in the neuroscience community. A great deal of further research is necessary to support a hypothesis linking these two phenomena.

Origins & Neural Basis of Synesthesia

Beyond those that we have briefly discussed, dozens of synesthesia variants exist. Other prominent types include tone-color synesthesia, where music notes have a specific color, day-color synesthesia, the most common type of synesthesia (prevalence of 2.8%), and auditory-tactile synesthesia, where sounds result in a feeling of touch on the body.[1,4,24] The vast and varying types of synesthesia make it a difficult condition to study. Currently, a major question for researchers is whether or not the varying types of synesthesia are caused by similar mechanisms.

Broadly, proposed mechanisms of synesthesia all suggest that synesthetes have atypical connectivity between brain regions associated with their synesthesia. Though this is the prevailing mentality in the literature, there has yet to be conclusive evidence in this regard. Despite claims of individual studies, a 2015 meta-analysis of neuroimaging literature concluded that "most published studies to date show, in fact, that the brains of synesthetes are functionally and structurally similar to the brains of non-synesthetes."[17]

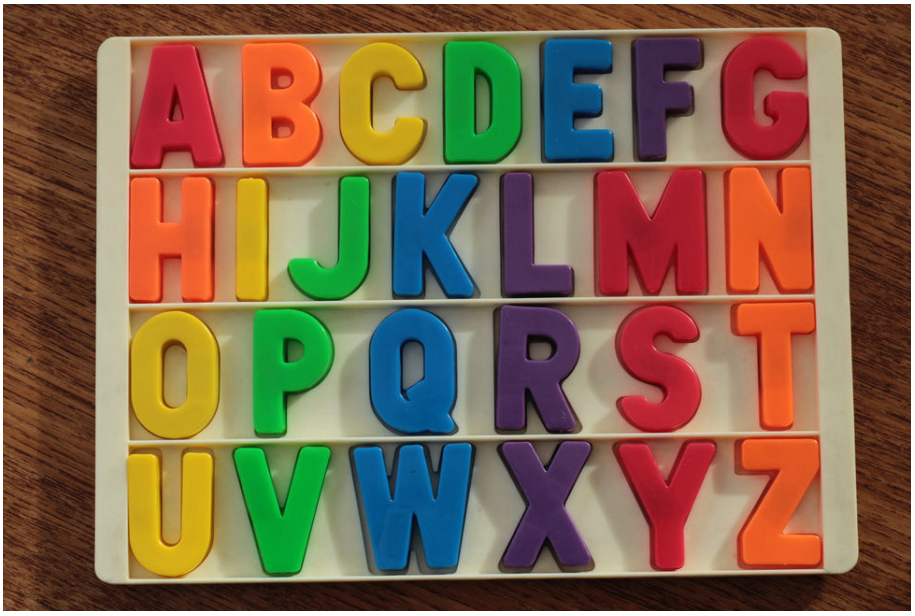
The origins of synesthesia are not completely ambiguous, though. There is a clear genetic component to the condition, multiple studies have found that roughly 40% of synesthetes have another synesthete as a first-degree relative.[25,26,27] Specific types of synesthesia do not appear to be genetically linked. Having a relative with grapheme-color synesthesia makes you more likely to be a synesthete, but not a grapheme-color synesthete; this could support the idea of a shared neural basis between types of synesthesia.[27] Of course, it is also possible that the familial synesthesia reflects a cultural influence, owing to a shared upbringing, or even knowledge of the existence of synesthesia.

Additionally, the evolutionary advantage conveyed by synesthesia may indicate a genetic basis. If synesthesia is an evolutionarily advantageous trait, then it should be preferentially selected for, which could explain the genetic origins of synesthesia. So, what advantages are conveyed by tasting words, hearing colors, and seeing sounds? As it turns out, quite a few. Multiple studies of grapheme-color synesthetes indicate that they have superior color discrimination than non-synesthetes.[28,29] Tone-color synesthesia often co-occurs with perfect pitch, and the prevalence of synesthesia among artists and musicians is at least twice as high as in the normal population.[4] But the benefits of synesthesia aren't limited to creativity. From a very young age, synesthetes tend to have superior memories than non-synesthetes, even if the topic has nothing to do with their synesthesia.[29,30] In particular, spatial-sequence synesthesia—where time is visualized as a spatial construct, normally around the synesthetes' heads—has been studied as the basis for remarkable memories.[31,32] Researchers at the University of Edinburgh propose that spatial-sequence synesthesia is linked to "hyperthymestic syndrome"—an incredibly rare condition where an individual can recall every day of their life in perfect, excruciating detail.[31] Since many individuals with hyperthymestic syndrome are also spatial-sequence synesthetes, it may be that the extra memory cue of spatial-sequence synesthetes' mental maps allows them to remember far more about their lives.

Of course—if synesthesia is governed strictly by genetics, and conveys creative, artistic, and memory benefits, we ought to all be synesthetes by now, surely. But it is unlikely that genetics are the only component of synesthesia. Considering cases of identical

twins where only one twin was a synesthete, it is clear that synesthesia has a social component.[28] In particular, the individual differences in synesthetes—the specific color of their letters, sounds, tastes—seems to be greatly influenced by experiences early in life.[33] For instance, many lexical-gustatory synesthetes' taste associations are foods which were commonplace in in their childhood.[1] Colored alphabets from early childhood also seem to influence the letter-color associations of many synesthetes. In one intriguing case, a grapheme color synesthete's associations were traced back to a Fisher-Price™ magnetic alphabet set, recovered from her parents attic. Her associations almost perfectly matched the color of the magnetic letters, with the exception of the letter "B," which happened to be missing from the set during her childhood.[34] Interestingly, when the same individual moved to Russia at a young age and learned the cyrillic alphabet, she developed synesthetic associations based on her prior associations in the latin alphabet. Cyrillic characters which closely resembled latin characters took on the same color as their latin counterpart ("Б" and "b" were both blue).[34] This was the same for characters with phonetic counterparts ("Ф" makes the same sound as "F", they were the same shade of purple).[35] The fact that old colors were mapped onto new graphemes—rather than new graphemes inducing new colors—strongly supports the idea that synesthesia reflects unique memories developed during early childhood.*

"Fisher-Price Magnet Set." Flickr, 20 Jul. 2015, https://www.flickr.com/photos/joybot/19150803152.



Much of the secrets of synesthesia have yet to be uncovered. Though culture and upbringing are important aspects of the condition, scientific understanding of synesthesia across cultures is quite limited. Despite years of effort, structural and neuroimaging studies have not discovered a neural basis for synesthesia. Nevertheless, a great deal of progress has been made in understanding the behavioral correlates and internal experience of synesthesia. The condition is absolutely intriguing, and provides a unique opportunity to study perception. Some researchers posit that the study of synesthesia will help to discover the neural correlates of consciousness.[37,38] Regardless, synesthesia research will certainly continue to reveal more about this unique condition. Perhaps the researchers will arrive at an earth-shattering conclusion about consciousness; perhaps they will shape cognitive neuroscience for years to come. Or maybe they'll end up eating their words.

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DEMENTIA GONE VIRAL

How years of research linking Alzheimer's Disease and infections has been lost in translation

By **Mary Sawyer**

The Diagnosis

The tangles in the brain begin slowly, like vines in a jungle. They feed, engorging themselves as they expand and grow. They bend back and forth, in and out, becoming entangled like the roots of a tree digging deeper and deeper into the ground. Soon the vines become so entangled that they are no longer individual vines clinging to one another, but rather a single mass taking up the space that used to exist. This space in the brain once filled by cells called neurons and glia has now fallen victim to the grip of the tangles. Typically masses of tangles are observed in brains infected with Alzheimer's Disease, but it turns out they play a role in the pathological development of bacteria and virus induced dementia. These tangles, also called neurofibrillary tangles (NFT), are composed of tau proteins in an abnormal state. Normally, tau proteins stabilize neuronal structures within the brain.[1] Thus, abnormal tau proteins deteriorate networks of neurons, which are typically created from neurons communicating with one another via synapses.[2] These synapses are at the end of neurons and enable neuronal communication through the release of chemicals, ultimately allowing neurons to "talk" and create a network. Through the work of Dr. Alzheimer, we found another key player in the destruction of neuronal networks, aside from NFTs. In 1907 Dr. Alzheimer discovered NFTs during an autopsy of the brain of his patient who had progressive cognitive decline. Confused by his clinical observations and unable to determine the cause, he investigated his patient's brain further. In addition to the observed NFTs within the cells, he found clumps of proteins in

regions of the brain where he had expected to find cells and brain tissue.[3] These "clumps" were actually amyloid-beta plaques (Aβ). Existing concurrently, NFTs and Aβ plaques deprive brain cells of the oxygen and cortical space they need to survive, forcing the cells into a neurodegenerative state (Figure 1). This pathology of AD manifests in a loss of memory and cognitive function, leading to heavy burdens of this disease across thousands of families all over the world.[4]

Over 100 years later, a speculative AD diagnosis is made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and the National Institute of Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders working group.[6] AD is a specific type of dementia for which an official confirmation of the disease still requires an autopsy of the brain after death. Five million Americans are living with AD, and at the current disease rate there could be as many as 16 million people affected by the year 2050 .[7] Described as one of the "holy grails of science", AD research has gained momentum as scientists search for a cure. Most recently AD made headlines because of Bill Gates' donation of 50 million dollars in funding.[8] Despite advances in research and technology, a cure for AD remains an enigma.

Imagine a 90 year-old man wandering the streets of a neighborhood in which he has lived for over 30 years. Every few feet he stops and looks around him with a confused look on his face. Everything is unfamiliar, even though he has lived in the same place for several years. This man suffers from sporadic AD, also known as late onset AD (LOAD).[6] His brain has lost a significant amount of neurons, leaving gaping holes where Aβ plaques now form. Neural networks have been destroyed by the intracellular NFTs. The disease started slowly, creeping in on his memories, settling in to stay. While many experience the cognitive decline that comes with age, there is a difference between the aging process and the disease this old man suffers from. Most notably, the pathology of his brain is unique to those with AD in that he has significant neuronal loss, as well as NFTs and Aβ plaques present. Elderly individuals having trouble recalling memories or thoughts may have changes to their neuronal networks, including loss of synapses.[9] Although this aging person has synaptic loss, they do not have significant neuronal death and therefore, do not have dementia.

Dementia is an umbrella term for diseases classified as a disturbance to cognition and memory in such a way that interferes with daily activities suitable for the age of the person presenting symptoms.[4] Thus, AD is a type of dementia defined by the presence of NFTs and Aβ plaques; AD is further split into two types: LOAD and Early-Onset Dementia (EOD).[6] LOAD, also called sporadic AD, develops in individuals with no family history of the disease. Typically genetics are discussed relative to EOD, or familial AD; however, genetics may also play a role in LOAD. Scientists found that mutations of the Apolipoprotein E (ApoE) gene are associated with LOAD. In healthy individuals this gene codes for a protein that performs many functions. One of these functions is to clear Aβ from the space between cells, ultimately preventing plaque accumulation.[10] Thus, with a mutation to this gene, some individuals may be more susceptible to build up of Aβ plaque. One study looked at the brains of 39 individuals with a confirmed AD diagnosis and 35 healthy individuals; 62% of AD-infected participants had an ApoE mutation, compared to only 20% of the healthy participants.[11] This indicates that genetics likely play a role in the development of LOAD. Many of us are familiar with the unique emotional weight an individual and their family must shoulder upon a diagnosis of AD. However, few of us understand how years of research has connected this disease to bacterial and viral infections.

There is a tendency to as-

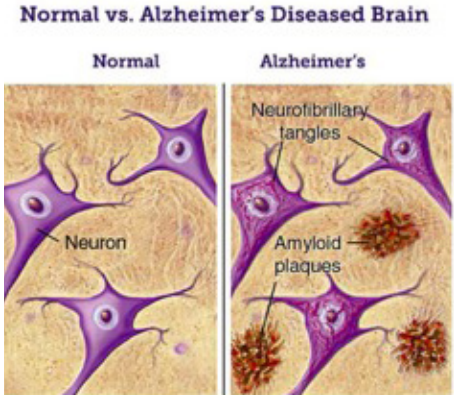
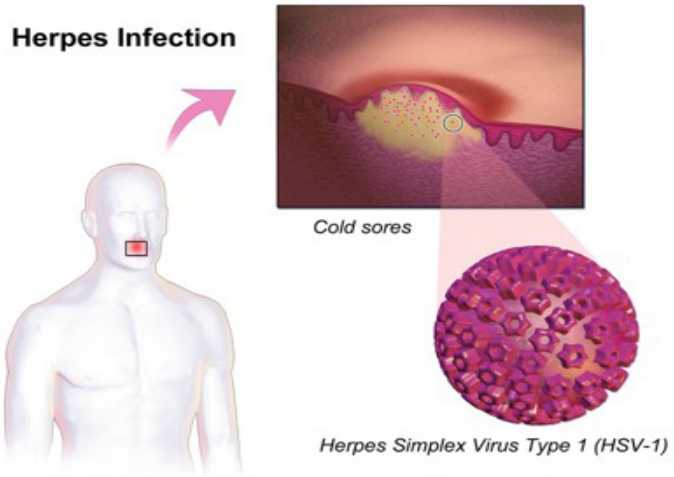


Figure 1 Neurofibrillary tangles (NFTs) and Aβ plaques affect intracellular space (within the cell, or neuron) and extracellular space (between cells in the brain).[5]

Figure 2 A depiction of cold sores caused by HSV1 [15].



sume that each disease is special – that each disease is diagnosed by specific characteristics, leaving us with a false sense of closure when we can finally name our pain. This is rarely the case. Dr. Alzheimer said himself "how difficult it is to define diseases with respect to their clinical features".[12] For decades scientists have recognized NFTs and Aβ plaques as characteristic of some chronic viral and bacterial infections. Certain pathogens can remain dormant in the central nervous system for years, and often a lifetime. These pathogens include herpes simplex virus type 1 (HSV1), C. pneumoniae (pneumonia), Borrelia burgdorferi (Lyme disease), and other spirochetes (spirally shaped bacteria).[6]

Herpes and Alzheimer's

The Center for Disease Control estimates that about 90% of American adults are exposed to the herpes simplex 1 virus (HSV1) by the age of 60. This virus most commonly manifests as cold sores (Figure 2). The second form of the herpes virus is the herpes simplex 2 virus (HSV2), which gets its reputation from self-help books like "how to live with herpes," appearing in the form of genital sores. About 1 in 6 people are estimated to have genital herpes, according to the CDC.[13] Hearing the word "herpes" makes many people run for the hills. However, the reality is that many of us have been exposed to herpes and it now quietly resides in our CNS.[2] HSV infection often lasts a lifetime and can reactivate, producing cold sores. Another more extreme form of HSV1 is herpes encephalitis, which is when the virus inhabits the brain and induces dementia with clinical features similar to AD. Because of these similarities, researchers have been hypothesizing a potential connection between infections and AD for years.[3]

Researchers found that AD-infected patients had less degeneration in brain regions containing more amounts of HSV1.[14] This suggests that the presence of the virus evoked some physiological response that was ultimately protective. In contrast, Aβ was found to prevent and reduce the amount of HSV1 DNA replication. This would suggest that more Aβ plaques reduces the viral infection, yet also spurs on the neurodegenerative process as the plaques accumulate.[16] These results may mean that the presence of HSV1 beneficially produces Aβ and leads to greater preservation of the brain. Seemingly contradictory results like these have left scientists with inconclusive data. Epidemiological studies advance this discussion, further explaining the link between infection and AD. In a study following 360 patients over 6 years researchers found that those who were previously exposed to herpes were twice as likely to develop AD compared to those with no prior infection.[17] Similarly, scientists followed an elderly population for 14 years, examining cognitive function every few years. Baseline blood samples showed who had been infected with HSV prior to the 14-year investigation. They found that HSV infection and the development of AD were correlated, hinting that early exposure to HSV may lead to AD; however, it is also important to remember the old saying that correlation does not necessarily equal causation.[18] Though a causative relationship should be taken with a grain of salt, another group of researchers discovered that HSV DNA is co-localized with Aβ plaques in AD-infected brains, further strengthening the association between infections and AD.[19]

Additionally, HSV1 and AD have been linked genetically. Mice with an ApoE genetic mutation had 13.7 times more HSV1 viral DNA present in their cells compared to mice without a mu-

tation.[20] This genetic mutation, as discussed before, is a risk factor for AD. Thus, these data create an interesting story illustrating how a risk factor for developing AD could also dictate the amount of virus present in an individual. Despite the interesting story being told by years of research, no one has explored the clinical implications of HSV and AD concurrency; could anti-viral HSV treatment cure AD?

Pneumonia and Alzheimer's

Pneumonia is a lung infection that is currently the 6th leading cause of death in America. While not as common as herpes, community-acquired pneumonia (CAP), or pneumonia acquired outside of the hospital, still affects about 5.6 million Americans each year. C. pneumoniae is a specific bacteria that often causes CAP; however, those infected with this bacteria do not always develop symptoms [21] Multiple studies found that the bacterium was present in most of the AD-infected brains and in few of the healthy brains, implicating the bacteria as a risk factor for AD. Researchers also found that the bacterium was more prevalent in areas of the brain most affected by AD, such as the frontal, temporal, and parietal cortex (Figure 3).[3,23,24] Research linking C. pneumoniae to AD started in the 1990's, yet little has been done to develop this idea that the bacteria may be causative. There is even research showing how the bacteria is able to spark cell death in the brain. Despite these pivotal findings, no research has been done to determine if vaccines can improve or prevent AD.

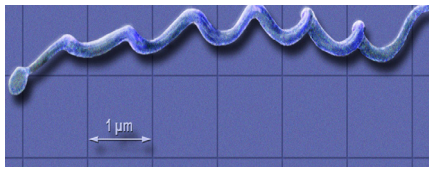


Figure 4 An image of a spirochete bacterium. Notice the spiral-shape, almost like a corkscrew.[26]

Spirochetes and Alzheimer's

The tick crawling on the floor may seem harmless, but it could be carrying bacteria called Borrelia burgdorferi, most often referred to as Lyme disease. Lyme disease infects approximately 300,000 Americans each year, and this number continues to grow.[25] B. burgdorferi is a spirochete, meaning it is long and spiral shaped (Figure 4). There are many types of spirochetes – a form of sexually transmitted disease that causes dementia, one of which is responsible for neurosyphilis.[13] This bacterial-induced dementia has similar pathological characteristics of AD, including a build-up of spirochetes that are indistinguishable from AD plaques.[6] Spirochetes have been detected more frequently in AD-infected brains than in healthy brains. The bacteria were also found in the same areas as Aβ plaques in AD-infected brains, similar to findings previously observed with HSV1 and C. pneumoniae.[27] It seems obvious that something is happening between AD and infections.

In addition, the number of spirochetes in the brain increases as the severity of dementia increases in individuals with an atrophic form of general peresis – a disease that leads to muscular weakness from nerve damage. This was first discovered in the 1920's.[3] The connection between the pathology of infection-induced dementia and AD pathology is apparent. It is peculiar how such convincing data and trends have been discussed for decades without any progress towards improving AD treatment. Individuals with a higher infectious burden have an increased risk of cognitive decline. Elderly patients exposed to multiple viruses were 2.5 times more likely to develop cognitive impairments.[28] A number of other epidemiological studies found that patients at risk of developing AD or with a confirmed AD diagnosis were likely to have been exposed to an infection at some point in their life.[14,18,25]

AD is defined by standards set in the 1900's and confirmation of diagnosis is still performed in the autopsy room. After years of research, it seems crude to diagnose AD based on clinical

Figure 3 Research has shown that the frontal (red), parietal (yellow), and temporal (purple) lobes are most susceptible to AD and bacterial infection.

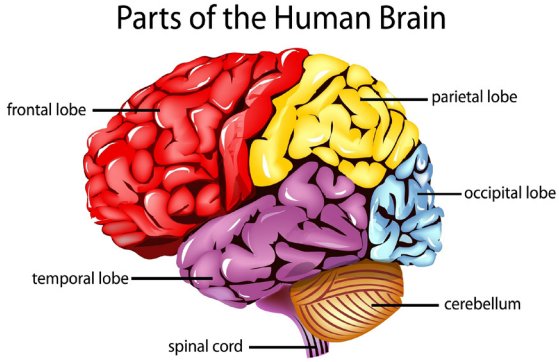
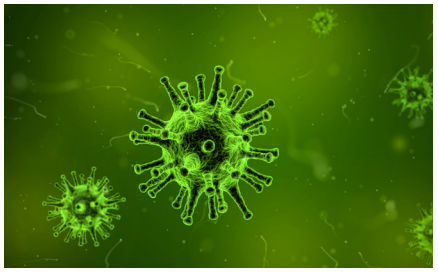


Figure 5 A beautiful yet daunting microscopic image of a virus.



features so similar to those present in infections. How can this diagnosis be so confidently made when symptoms across AD, herpes encephalitis, and neurosyphilis are so similar? These diseases may typically affect different populations, but that does not excuse the potential confound during diagnosis. A key piece to the puzzle connecting pathogens to AD is the innate immune system.

The Innate Immune System

Living in a world full of viruses and bacteria, the human body comes well equipped. Our bodies are able to endure such trauma, including microscopic trauma that may go unnoticed. How do our bodies endure? The innate immune system protects both the body and brain through activation of various cells and proteins that fight foreign pathogens. Scientists are increasingly confident that Aβ is part of the innate immune system. As mentioned previously, Aβ prevention of HSV1 DNA replication suggests a protective role of the protein.[16] Shockingly, Aβ has also been found to reduce bacterial growth and protect against microbial infection.[30,31] It turns out that the protein that goes haywire in AD actually protects our brain from harmful pathogens.

If you recall, ApoE genetic mutations are risk factors for AD. Interestingly, ApoE genetic mutations similarly play a protective role. Children with heavier burdens of diarrhea actually performed better on cognitive tests if they had a genetic mutation of ApoE.[32] Thus, this risk factor for AD can be protective depending on the circumstances. While this may seem surprising, the idea that characteristics of a disease may be protective is not novel. For example, sickle cell anemia protects people from malaria in some parts of the world.[33] In order to find a cure for AD, and the "holy grail of science" we need to consider all possibilities, including the idea that AD treatment might include anti-viral treatment or vaccination (Figure 6).[8]

Over the range of pathogens aforementioned, one thing remains a common denominator. After decades of research and numerous published reviews of research describing the potential role of infections in AD, few strides have been made to clinically study these momentous scientific findings. Finally, the first study will be conducted in Sweden using herpes anti-viral treatment for AD patients (Figure 7). Prior research suggests that if Aβ accumulates around the virus, then killing the virus will also reduce the Aβ plaques and potentially ameliorate symptoms of AD.[34] They started enrolling participants in December 2016, but have not released outcomes of their clinical trials. If there is such a link between AD and infections, why are we now just trying anti-viral treatment to cure AD? Why has it taken so long to test this hypothesis given the decades of research? Potentially, it is the stigmatization of sexually transmitted infections that has prevented a full scope of research. Maybe we have become blind to solutions that have stared us in the face for years. With vaccinations for C. pneumoniae and anti-viral treatment for HSV1, it seems

Figure 6 "The grail may be closer than meets the eye" by Mary Sawyer. Adapted from "Cartoon scientist with magnifying glass" by Boris Klissourski.

Figure 7 Image of the Swedish flag overlaying the country of Sweden.[35]

to be an obvious next step to test whether these could slow the progression of AD in people. In fact, research published in 2011 even showed how antiviral treatments reduced the amount of Aβ plaques and NFTs in cells.[36] It seems that Sweden is leading the rest of the scientific community in this race to find a cure. Hopefully, their clinical trials will pique the curiosity of other scientists around the world and advance the field of AD research. As a captivated audience, we must remember the role we play – clinical trials are nonexistent without willful participants. Not only that, but a public engaged with the sciences will encourage funding for the most sought after research. While AD research is currently caught in the public eye, a link between the disease and common infections is not exactly what people want to hear. That being said, science is not about sharing pleasantries, it is about finding the truth however hard that may be to digest. For now I propose a call to all scientists: it is time to follow Sweden's lead and take this work to the clinical realm.

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Animal Linguistics

HOW HUMAN LANGUAGE DEVELOPED FROM ANIMAL COMMUNICATION

By **Fritz Josephsen**

Living in the middle of a consciousness revolution, new insight comes from the strangest of places. In the past few decades, geneticists, neuroscientists, psychologists, sociologists, economists and others have made huge progress towards understanding the inner workings of the human mind. The pieces of information presented now give us a better grasp of human character, emotion, social bonding, and human communication. In many ways, the gap left void by theology and widened by philosophy is being filled by brain science.

To give us a sense of this consciousness revolution let's consider human language. The leading authority on language development, MIT scientist Noam Chomsky, hypothesized that a specific aptitude for language is encoded in the human brain at birth. According to Chomsky, this so called 'language organ' is responsible for the human brain's capacity to understand complex communication. Possessing the language organ is to be equipped with a type of universal grammar, a set of rules that is shared by all languages.

A distinction between communication and language must be established. Communication encompasses all exchange of information that is verbal and non-verbal. Facial expressions, body gestures, visual art, mimicry, and even odor signals are methods of communication. Language, however, is a tool invented by humans in order to communicate more effectively. Chomsky and other psycholinguists have studied the properties of human languages to gain an understanding of specific characteristics of human intelligence. This effort by linguists is an attempt to learn something about human nature. Now, looking towards animal communication, the very foundations of human language can be assessed. Aside from humans, many animals have relied upon communication systems to form complex social bonds, and thereby create intricate societies. Studying communication by

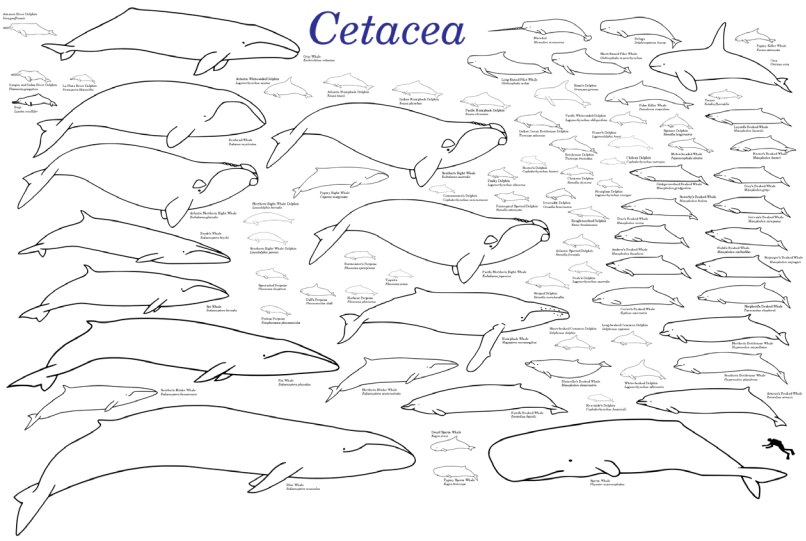
animals reveals the workings of simpler brains, which has the potential to teach us about our own brains.

For ages, language has been described as a talent unique to human beings. This ability to transmit encoded thoughts from one individual mind to another is perhaps the basis for all human advancement. Human beings sharing ideas has led to a larger, species-wide awakening. Sharing ideas caused an enlightenment that gives us an advantage over other creatures and has given birth to the modern day. But how are we so adept at sharing thought? Where did this "language organ" come from? Can archaeological research elucidate an understanding of language's birth, or is it lost to time? Attempts to teach other great apes language has generated more controversy than it has illumination; how then, can we go about discovering this foundation of language?

The first hint of an early human tongue may not lie in an ancient African tomb, but in another living animal. Perhaps that animal is swimming in the oceans. Maybe it's flying in the air. Clearly, forms of animal communication fall short of language, but their feats of socialization warrant attention by the larger scientific community. These beasts of the wild have communication systems advanced enough to both utter and perceive specific sounds. Some species can even learn new units of sound then combine these sounds to create new meaning!

"The first hint of an early human tongue might not lie in an ancient African tomb, but in another living animal."

Vocal learning is a remarkable ability that is rare amongst the animal kingdom. Most communicative animals have a sound's meaning pre-recorded from birth; very rarely are sounds learned after birth. The vervet monkey is famous for its use of distinctive alarm calls.



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These alarm calls indicate specific predators, such as leopards, eagles, or snakes, to be in the area. These alarm calls are learned just after birth and are never relearned or replaced throughout life.[1]

While vervet monkeys represent vocal learning animals that acquire knowledge of vocal calls during a single period of life, other animals learn and relearn vocal signals throughout their lifespan. Cetaceans are a clade of 89 extant species of aquatic mammals that are experts at learning signals.[2] This clade includes: porpoises, dolphins, and whales. Baleen whales have been found to learn songs after birth and learn new songs seasonally. Toothed whales use learned auditory signals to maintain their social relationships which change daily for hunting purposes. Likewise, bottlenose dolphins' use learned sounds referentially to determine individuals within a pod.

One incredible aspect to bottlenose dolphin communication is their signature whistle. In a pod of dolphins, each dolphin will call out a distinctive whistle representing an individual dolphin's name.[2,3] In the deep murky waters of the ocean, wild free-ranging bottlenose dolphins will call their

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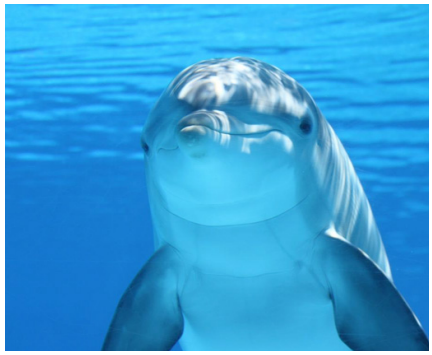

signature whistle to alert others in the pod of their location. Dolphins familiar with the caller will repeat that signature whistle, as if echoing another's name. If a dolphin hears it's own signature whistle it is very likely to respond. Whereas, if a dolphin hears the whistle of a familiar dolphin it is slightly less likely to respond. Dolphins will never respond to unheard whistles.[2,3] This name-calling behavior is the foundation for every dolphin pod's unique hierarchical structure.

Still, dolphin communication is not limited to name-calling. Dolphins frequently emit their whistles and clicks to communicate with one another, but they also are able to use echolocation to communicate. Echolocation enables all cetaceans to send out sound waves, which allow them to identify location, shape, and size of distant objects in the water. This biological sonar allows cetaceans to orient themselves, detect their prey, and coordinate hunting tactics. In fact, echolocation allows dolphins to hear and produce some of the highest frequency sounds of all mammals. In perspective, humans have a hearing range from about 20 Hz to 20kHz, whereas dolphins have a hearing range that exceeds 150kHz.[4] This intense range of sound detection has led many scientists to speculate that dolphin communication is more advanced than previously thought. Some have even argued the possibility of dolphins having a language system of their own, a language system which humans would be unable to detect.

A recent study popularized by the Ted Talk, "Could we speak the language of dolphins?", looked into the question of dolphin's having the capacity for language. Performed in collaboration between leading researcher of cetacean intelligence Denise Herzing, and computer scientists at Georgia Tech, a device was created to bridge the gap between human language and dolphin communication. The device called CHAT (Cetacean Hearing and Telemetry) contains a microphone able to detect the entire acoustic range of dolphins. Furthermore, with the touch of a button, this device can repeat any signature whistle recorded in the wild.[4] Using this device, free-diving researchers were able to communicate with dolphins to form temporary alliances with the pods of dolphins in the wild.[4] Using this communication the divers were able to play games with the dolphins, such as passing a scarf from one individual to another. Shockingly, the animals began to reference the researchers with signature whistles! In this way, the human researchers were integrated into the pod, and even assigned names by the dolphins.

"Dolphins familiar with the caller will repeat that signature whistle as if echoing another's name."

There are many theories regarding how cetaceans developed complex communication systems. Morphological studies have compared dolphin brain cryoarchitecture to that of other highly social aquatic and terrestrial species. These studies have shown that cetaceans posses the largest brain in absolute size related to body mass.[5] There have been several confounding theories presented to explain their brain development as being distinct from other mammals. Many of these theories assert that readapting to an aquatic environment has influenced their brain development; however, the scientific community now largely refutes these theories. After whole and sectional morphological analyses the structural complexity of their brains has been linked with sociality and cognition. In particular, the high density of Von Economo neurons, characterized as having extended axons for fast neural information transfer, has been credited as being highly involved with aquatic mammalian learning, memory, and spatial navigation pathways.[6] This finding is notable, as a quality of human brain communication areas are a particularly high density of Von Economo neurons.[6] The high density of these neurons is a quality of human brain language centers that is shared by the ceta-

cean brain.

However, dolphins are not the only animal to display complex social behavior, nor are they the only animal to have the ability to communicate using ultrasonic frequencies. Indeed, bats are equipped with this same biosonar and can produce and detect up to 250kHz soundwaves. Evolutionary scientists believe these two animals convergently evolved,[7] or independently developed these traits. That means these two animal groups having the ability to produce, detect, and interpret ultrasonic waves does not give evidence of a similar lineage between these two animal groups.

Bat vocalizations have been shown to be even more complex than dolphin whistles,[8] and for good reason. While bottlenose dolphin pods may merge to form superpods with over 1,000 individuals, a bat colony can contain up to a million bats! Remarkably, bats make up a quarter of all mammalian species on Earth. These highly social animals need to communicate amongst their colonies to cooperate on migration patterns.

To compare bat vocalizations with human language, first, human sentences must be broken down into discrete parts. In a single sentence, a human can: distinguish another person's voice, understand meaning from words spoken, and understand a speaker's intention by tone of voice. Human speech parallels bat vocalizations on a number of levels. A single Egyptian fruit bat vocalization has been shown to include

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information about: the identity of the emitter, context of the call, behavioral response to the call, and even the addressee of the call.[8]

In morphological studies comparing the brain sections of bats, shrews, mice, rats, and humans, the organization of calbindin-cholinergic cells shows a marked difference in bat and human brain than that of the rodent brain.[9] In bat and human brains, cholinergic innervation avoided calbindin patches, this showed intermittent entorhinal theta activity, whereas rodent brains entorhinal theta activity features cholinergic innervation within calbindin patches.[9] A common factor between bats and humans caused selective pressure for this conservation of cholinergic stellate and pyramidal cells avoidance of calbindin patches. This means that bat brains have developed more complex brain structures than their more related cousin species in order to allow for more advanced social behavior. Still, in comparing cell distribution patterns, bat brains are not as advanced as human brains. Between human and bat medial as well as caudal entorhinal cortices, relative neuron numbers of these calbindin patches was not constant.[10]

How have bat brains become more advanced than closely related rodent species? A species' brain morphology is almost entirely dependent upon that species' genetics. Even the amount of a gene expressed during an individual animal's development can alter that animal's brain structure. New research is ending the idea that the origins of language are lost in time. Linguists can no longer ignore the archaeological clues emerging from genetics.

Almost two full decades ago the gene related to a developing brain's communication center was identified. The FoxP2 gene has been recognized as the gene involved with development of speech and language areas of the brain.[3,11,12] This gene displays extreme conservation in sequence across all bird species having very low rates of substitution. In fact, all animals show high conservancy of this gene. Between zebrafish and humans, the FoxP2 gene has been shown to be 98% similar.[11,12] This gives evidence suggesting its huge involvement in animal development. Avian species have shown location dependent and seasonal dependent expression of this gene. Meaning, whether the songbird is in its mating season, FoxP2 will be more or less expressed. Differential expression of FoxP2 in avian vocal learners is associated with vocal plasticity.[3]

While, as one might expect, dolphins and bats do not have special versions of this gene, they do however, express higher

levels of FoxP2 genes during fetal development than comparative animals. During brain development, dolphins and bats have similar FoxP2 relative expression patterns as humans.[11]

Dolphins and Bats are two examples of animals that have developed complex communicative behaviors. These behaviors have become essential parts of these animals' lifestyles. We now understand the behavioral, morphological, and genetic conditions that animals must meet in order to possess a capability for complex communication.

These two animals live in social groups and depend upon these groups for their longevity. Dolphin and bat brains feature large centers that are used for communication. Perhaps given another few thousand years for these animals to develop, a definitive language will be created. Indeed, the only key element of language these animals seem to be without is what linguists call "recursion," or the mind's ability to create a phrase based off another into the syntax of an elaborate sentence. It is believed that early humans attained this ability from the use of another brain system, such as the system animals use for navigation.

For a long time biologists and linguists have purposefully inhabited different worlds, because linguists take little interest in evolution, which is the fundamental theory of biology. Any hypotheses put forward regarding the evolution of language, therefore, is promptly contested. However, since the FoxP2 gene breakthrough shook science nearly two decades ago, a solid hypothesis regarding the origin of language has been put forward.

"New research is ending the idea that the origins of language are lost in time. Linguists can no longer ignore the archaeological clues emerging from genetics."

The evolutionary theory of the origin of complex human language follows the gradualism model of evolution, meaning that language developed gradually over time, without rapid bursts on the evolutionary time scale. The "sexual selection information-sharing hypothesis" states that vocal learning causes more selective mating preferences.[13] These selective mating preferences, in turn, cause the next generation of offspring to produce equally or more complex vocalizations. This hypothesis hinges upon information-sharing from one generation to the next occurring during the language acquisition period.[13,14] The human language acquisition period peaks at around six years of age with the window of opportunity to naturally pick up on a language declining after this age. This hypothesis was imagined after better understanding the foundations of language, that is, after understanding other forms of animal communication.

The age-old mystery, "Where did human language originate?" is being solved. With new insight from genetics, and an understanding supported by observing animal forms of communication, human language can be traced back to the time before our globalized world's effective communication. Back to a time before the consciousness revolution, before written, or even, spoken history was recorded.

Only after making sense of animal communication can we imagine the pre-neolithic world:

"Bats, flying, sunset" by Ann Froschauer is licensed under PIXNIO Public Domain.

early hominids communicating abstract thoughts vocally, but not yet speaking a set language. Entire generations of early hominids lived within a community and underwent vocal learning during their language acquisition periods. With each generation, an expansion arose in the community's vocal repertoire. Within-group communication became easier while between-group communication became more difficult. Hence, sexual selection favored information sharing.

This pre-neolithic world is analogous to the pre-globalized world, which had many distinct languages, limiting genetic information transfer. This theory states that for much of human history, kin selection has been determined by an individual's ability to communicate with one another, which was determined from birth. Finally, amongst these early hominid groups, different vocal repertoires further increased and diverged. Communication better represented complete thoughts until, tremendously, it happened. Language was born.

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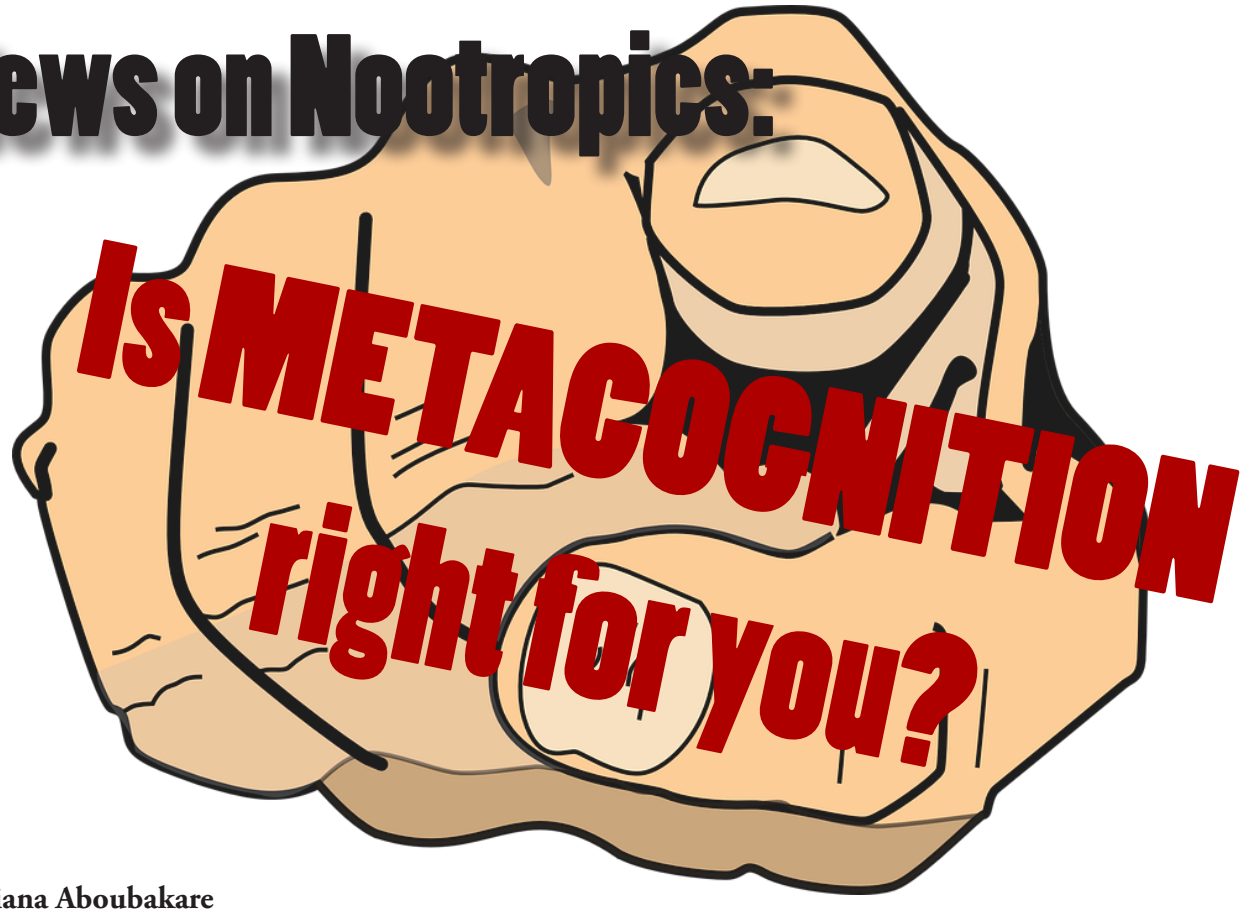
News on Nootropics:

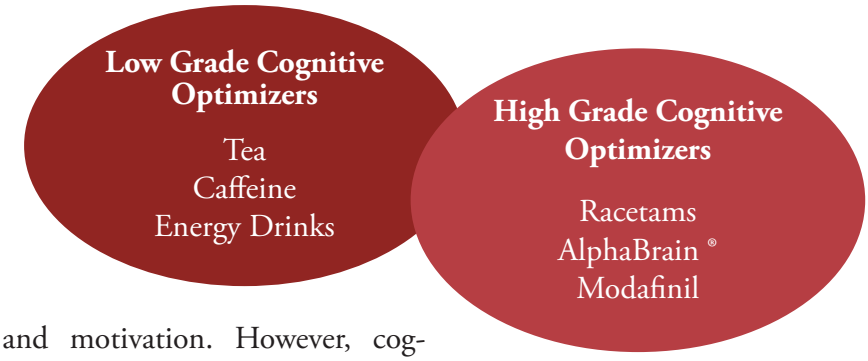


By **Diana Aboubakare**

Animals exhibit cognition – humans exhibit specialized cognition.[1] What makes us so special? One might theorize that the human brain is constructed differently: do structural differences separate us from other animals? Human brains possess a prefrontal cortex whereas other animals lack a brain area that resembles the prefrontal cortex.[2] Could it be our big brains? While this argument works for some animal model comparisons, humans do not own the title of having the largest brain. The biggest known brain belongs to sperm whales. In fact, the average human brain mass pales in comparison to the brain mass of other animals. Given this, some have theorized that perhaps it is our brain to body mass that makes us unique, the graphic also mentions this idea. A more concrete argument actually ties all of these ideas together. Although neuron counts vary between individuals, we on average possess an astonishing number of neurons compared to other mammalian brains. The brain of an African Bush Elephant weighs two times more than the human brain but the human brain has a whopping 16.3 billion neurons while the brain of the elephant has 5.59 billion neurons.[3] The neural networks exhibited in human brains make our cognitive abilities reach beyond all other animals and give us a unique complexity. Having such complex neural networks allows us to change our preferences and gives us the capability of processing massive amounts of information which we can further use for other applications.[4] In fact, we use our cognitive abilities without even realizing it: memory, attention, executive tasks, perception, language, and psychomotor functioning are all processes that require higher cognitive areas.[4] While there are clinical reasons for seeking out cognitive enhancers, individuals with an average capacity of cognitive performance experience societal pressures and exaggerated standards that cause us to strive for an altered, enhanced potential.

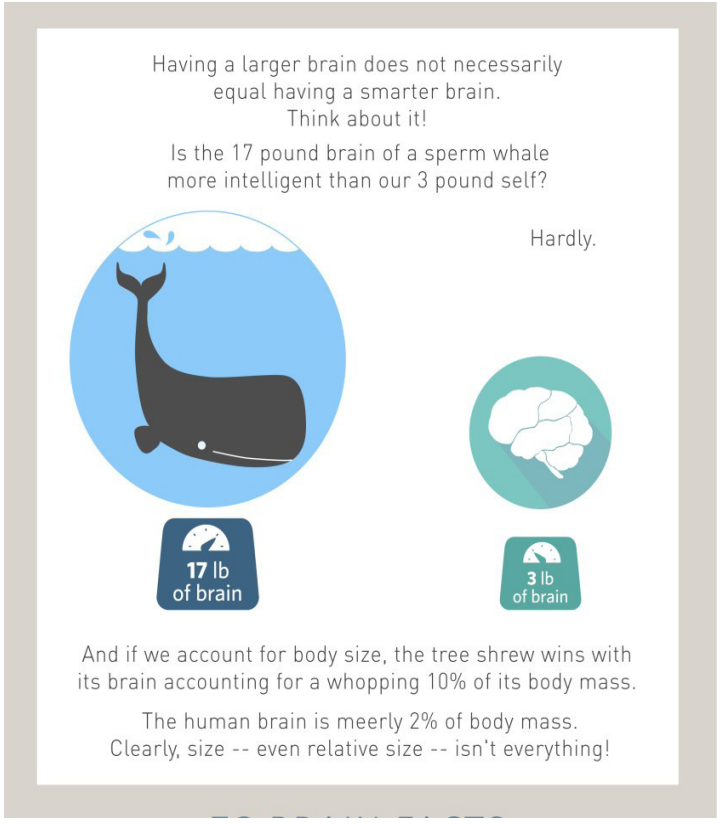
If you went onto your smartphone, tablet, or computer and searched "how to improve cognition", approximately 28 million results are generated. You might find articles that suggest ex-

ercising, playing games and downloading apps that stimulate your brain, or engaging in other intellectual activities. There are movies that sensationalize being better and smarter than we currently are. They display catchphrases like: "The average person uses 10% of their brain capacity. Imagine what she could do with 100%." and "Everything is possible when you open your mind." (Both of which are not factual, more on this later. But give yourself 10 brain points if you can guess those movies.) We are constantly searching for ways to enhance our cognitive abilities. Of the 28 million results, there appear to be a few repeating buzzwords. One buzzword commonly used amongst cognitive enhancement enthusiasts is nootropic: supplements that enhance cognition.[4] The claim behind nootropics is that they boost memory, focus, and motivation. However, cognitive optimizers come in many other forms – some of which you may already consume; for the purpose of this article, these different forms will be categorized as high-grade cognitive optimizers and low-grade cognitive optimizers.



Low-Grade Cognitive Optimizers

Tea. The Tea Association of the USA shared a statistic stating that Americans consumed more than 3.8 billion gallons of tea in 2016; over 158 million Americans are consuming nootropics daily without realizing it![5] The dorsolateral prefrontal cortex, an area within the executive control center of the brain, has been studied in regards to activation caused by green tea extract. This area is believed to be involved in working memory and cognitive processing.[6] A neuroimaging study was completed while participants performed a working memory task after they were given 250 or 500 ml of a milk based whey drink either with or without the addition of green tea extract. It was found that activation of the dorsolateral prefrontal cortex increased when participants consumed the concoctions with green tea.[7] This means that green tea extract has a modulatory effect on the dorsolateral prefrontal cortex, facilitating memory.



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Caffeine

Many people believe that caffeine helps get their day going, and for some, it is an essential staple in their daily routine. It is actually the world's most widely consumed psychoactive drug. Generally believed

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to improve performance on simple tasks, consumers use caffeine to aid them in improving focus and alertness. This logic is not unwarranted. In fact, research claims that caffeine improves performance on simple and complex attention tasks that require executive control networks suggesting that caffeine does affect alertness by antagonizing adenosine receptors meaning that caffeine works against the depressive effect of adenosine when it binds to its receptor.[8,9] Therefore, caffeine works as an attention enhancer. However, there is also evidence that causes one to refer to the phrase "too much of a good thing". Caffeine in higher concentrations has been shown to have anxiogenic affects: consuming too much caffeine leads to feelings of anxiety caused by a reduction of oxygenated hemoglobin in the prefrontal cortex.[10] This being said, there appears to be a way to combat this and actually amplify the positive effects of caffeine.

Caffeine + Tea

To fully realize the potential of caffeine, researchers suggest combining caffeine and tea to create a synergistic affect. Tea is an anxiolytic, an anxiety inhibitor. Because of this characteristic of tea, the anxiogenic effect of caffeine is attenuated when taken in conjunction with tea. L-theanine, a compound found in tea products, combats the anxiety produced by caffeine and actually helped to improve reaction time during an attention-switching task.[11] This makes sense given the implication that caffeine increases attention and alertness. With this study, it was not the result of reaction times that was crucial, but the accuracy expressed by the participants during the task. Participants that were administered l-theanine with caffeine experienced greater accuracy while those that were given the tea alone had lower accuracy during the tasks.[11]

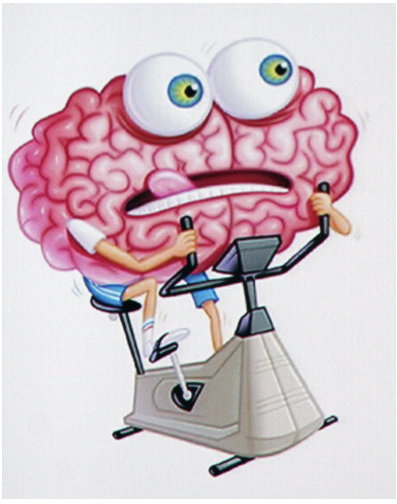
Energy Drinks- Monster, Red Bull, and Rockstar, CC BY 4.0, https://www.flickr.com/photos/aukirk/8170825503

Energy Drinks

Within the last 14 years, the worth of the global energy drink market has risen from $3.8 billion to $27.5 billion.[12] They are trendy and typically come in fun looking cans. What could go wrong? The three most popular energy drinks consist of five (Red Bull), twenty-three (Monster), and twenty-two (Rockstar) ingredients, respectively. Not many consumers are aware of the effects of these ingredients. Shared ingredients amongst popular brands are: l-theanine, glucose, ginseng, guarana, tyrosine, gingko, theophylline, flavanols, creatine, l-tryptophan, St. John's wort, and yohimbine. While an individual can look at the nutrition facts on a can and recognize some of these ingredients, consumers blindly intake energy drinks because of promised affects. Interestingly, of the 12 ingredients listed, research suggests that three of them: St. John's wort, yohimbine, and l-tryptophan are detrimental to mood and performance.[13] And this is just what has been researched, fortunately, the remaining nine were observed to be relatively beneficial to mood and performance.[13]

High-Grade Cognitive Optimizers

History. This category of cognition enhancers was initially used for clinically treating cognitive deficits such as those seen in patients with Alzheimer's, schizophrenia, stroke, and ADHD.[4] Pharmacological enhancers, or synthetic stimulants, were designed to improve the brain functioning of individuals that suffer from diminished brain functioning. The advancements made in cognitive enhancers for the purpose of treating cognitive deficits has led to the creation of supplements and other synthetic stimulants for improving cognition despite an observable lack



"Cerveau & Cognition" by Lorena Biret is licensed by CC BY-SA 2.0.

of deficits. Nootropics of this nature are colloquially referred to as "smart drugs" and are typically taken by young and healthy patients. Piracetam. A stimulant belonging to the class of synthetic stimulants known as Racetams, Piracetams are said to enhance neuronal function by increasing membrane fluidity in the brain.[14] Studies of this drug date back to 1960; these studies investigated the use of Piracetam as a counteractive measure to memory dysfunction in depressed patients and as a prophylaxis against delirium.[15,16] Clinical studies of this drug were done in children with dyslexia and elderly individuals. Age plays a strong role in overall cognitive decline. However, elderly individuals that underwent a regular dosing regimen of Piracetam also experienced positive affects reported as "greatly improved" brain functioning. A possible explanation for this is that dysfunctional mitochondria (mitochondria: which we all know is the powerhouse of the cell and creates energy) treated with Piracetam experienced a nearly complete recovery in membrane potential. In other words, Piracetam elicits an improvement in the brain functioning of elderly individuals because of its ability to stabilize and protect mitochondria.[17] In a more specific application, children with dyslexia also received Piracetam treatment. The children were administered two reading tests, the Gray Oral Reading Test and the Gilmore Oral Reading Test. On these tests, they exhibited an improvement in their nonverbal skills, demonstrating heightened reading and comprehension abilities after 12 weeks of treatment.[18] While affects were only seen after 12 weeks of treatment for children with dyslexia, one study reported that "normal" adults treated with Piracetam showed a significant increase in verbal learning after just 14 days.[19] Modafinil. Although Piracetam indicated similar efficacy in both young and old individuals, Modafinil (commercially known as Provigil) demonstrates a higher efficacy in younger, healthy patients. This drug is similar in its profile to methylphenidate, more commonly known as Ritalin. The "beauty" of Modafinil is that it works like an amphetamine but without the side effects.[20] Participants that were administered Modafinil reported feelings of being more alert, attentive, and energetic, demonstrating that the drug exhibits a positive effect on neuropsychological task performance.[20] The effects of Modafinil on wakefulness are so strong that one study gave sleep-deprived doctors the drug and tested their performance.[21] The doctors were given a placebo or 200mg of Modafinil and then subjected to neuropsychological tests and a Minimally Invasive Surgical Trainer Virtual Reality Machine (MISTVRM) that tested psychomotor performance. The researchers found that despite being sleep-deprived, the doctors that were given Modafinil worked more efficiently when solving memory and planning problems, exercised less impulsive decision making, and were better at redirecting their attention.[21]

AlphaBrain. Web. https://www.onnit.com/academy/alpha-brain-nootropic-shows-statistical-significance-in-groundbreaking-clinical-trial/

The MISTVRM showed that their psychomotor performance was unaffected. Another occupation that requires strict attention to detail and wakefulness is pilots. On Modafinil, pilots remained awake for 40 hour periods while maintaining full mental capacity during simulated flight performances. The results of this study demonstrated that after 25 hours without sleep, the performance of the pilots significantly improved on a 100mg dose of the drug with sustained brain activity.[22] AlphaBrain®. Sixty-three individuals were orally administered AlphaBrain® to investigate the efficacy of this supplement. The experiment was designed so that volunteers were treatment naïve (it was not revealed that they were being given the supplement or a placebo). After six weeks of taking AlphaBrain®, the volunteers returned and took neuropsychological tests; their results were compared to the results of the initial testing. The participants showed markedly improved performance in tasks that required delayed verbal recall and executive functioning.[23] AlphaBrain® works through the mechanism of increasing ace-

tylcholine in the brain by provide raw choline through alpha GPC as well as provide acetylcholinesterase inhibitors (these inhibit the degradation of acetylcholine).[24]

What do users think?

Many users who have experimented with synthetic nootropics have shared their testimonies. Piracetam. One user, an 18-year-old male weighing 196 pounds, shared that he took 2.4g/day.[25] He reported that the best effects he experienced were: long term memory improvement, linguistic ability, memory recall in a conversation, and logic improvement. The user also reports that "slight details of sound and sight are noticed more." The only side effect he experienced was decreased focus.

Modafinil. This individual identified himself as an "enthusiastic amateur" experimenting with Modafinil.[26] Highlights of his usage:

"The biggest effect is that it obliterates the need for sleep … For me, it brings a sharp and clear awakeness similar to a non-caffeine user having a large coffee, except the effect is larger and there is no jitteriness or agitation."

He also shared negative aspects of the drug:

"I really lose track of time, and have to set alarms. I will look around and it will be 5AM, and 8PM was not that long ago" and "I have had bad experiences when taking Modafinil in a particularly bad mood. If I was ruminating…taking Modafinil made me get deeper into the rut and accomplish nothing."

Another Modafinil user says he discovered the drug through an underground entrepreneur's forum and was so convinced that he purchased it online immediately after.[27] He writes how his focus on Modafinil was "[…] breath-taking. It is like being on a train, going through a tunnel. There is no way to go but forward and there are no distractions." He further shares that he often goes until 5pm without eating while on the drug. The testimonial concludes with his experience post-Modafinil: "there are no nasty side effects, there is just back to normal." This testimony for Modafinil comes from a college student.[38] The user created two simple lists, a pros list and a cons list. His pros:

1) "you can concentrate for hours and get [a] lot of work done, and remember it all afterwards", 2) "it helps you wake up early", and 3) "quite subtle: this is not an overwhelming experience".

His cons:

1) "makes you unsociable", 2) "you can become too focused" and so you must "be careful when crossing the road", 3) "your mood tends to swing a little bit up and down while you are on it", and 4) "lots of trips to the loo".

AlphaBrain®. One user shared a review of after being on the supplement for a month. [29] He shares his experience as being "remarkable" and that the drug had a positive effect on his disposition. A highlight of his review: "turned my daily activities from an almost catatonic and quite semi-depressive state into much the opposite". One user did not share such a glowing review.[30] They shared that they used an entire bottle of the supplement "….and nothing. [I] did not feel even the slightest bit different".

So What?

Per the U.S. Food and Drug Administration, Piracetam has not been approved for medical use nor is it permitted to be sold as a dietary supplement.[31] Modafinil is a Schedule IV Controlled Substance; according to the Drug Enforcement Administration, Schedule IV drugs have a low potential for abuse and a low risk of dependence.[32] The current med-

The popularity of Modafinil has skyrocketed for recreational use, even being cited by CNN as "perfection in a pill".

"Perfection in a Pill". Web. Youtube Screengrab. https://i.ytimg.com/vi/ZaZp6X-fqYf8/hqdefault.jpg

ical application for Modafinil is treating patients with multiple sclerosis. Modafinil can easily be found online for purchase even though Schedule IV drugs require prescriptions. The popularity of Modafinil has skyrocketed for recreational use, even being cited by CNN as "perfection in a pill". Natural nootropics belong to the low-grade cognitive optimizers while the high-grade cognitive optimizers are synthetics. The availability of these synthetic supplements is concerning. AlphaBrain® boasts clinical trial results; other supplements are not regulated and can be sold without any verification or certification. General consumers can go online and purchase anything. Some online vendors make claims of being certified and state that their product improves athletic performance as well as the classic cognitive improvement claims of nootropics. Many consumers believe the labels displayed on the bottles (or in some cases, bags). You may think "what is the harm?" when it comes to self-prescribing and purchasing synthetic stimulants, but they as the user testimonies suggest, there are pros and cons.

Conclusion

While these supplements should be taken at your own risk, there appears to be more to gain from experimenting with high-grade cognitive optimizers than fear the risks involved. Because the risk of dependence is low for these substances, the question is less of a "why not?" but more of a "why?". If one is already performing at a level that is above being deemed deficient, then for what purpose does an individual need to take cognitive enhancing supplements? Humans already possess highly complex neural networks that give us a specialized cognitive system. In a sense, it almost seems as if you are cheating yourself of a character-building experience necessary for bettering society. If we truly used only 10% of our brains, perhaps I might understand conceding to these high-grade cognitive optimizers. The only reason one might identify with this and take this myth as truth is because we see our own shortcomings and think "I could be so much better…if only I could use all of my brain." In fact, neuroimaging studies have demonstrated that brain areas are continuously active over a 24-hour period.[33] In conclusion, I would like to add one last personal anecdote. In completing research on this topic, I found myself wanting to experience the effects of these cognitive optimizers (Modafinil, right?!) but had I not written this organically, I would have cheated myself out of the opportunity of learning that I can put together 2,832 words (up until this point) into a relatively cohesive article on a plane from California to Ohio. Without any cognitive optimizers. So yes, although my cognition does experience occasional lapses, I accept my shortcomings and I feel more accomplished in writing this article than I might have if I had used a high-grade cognitive optimizer.

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The Curious Question of Social Synchronization

By **Jennifer Cabiya**

Have you ever clapped in time with an audience at a concert or sporting event? Have you ever fallen into step with your friend on your way to class the way marching bands do? Then you've experienced a phenomenon known in the neuroscientific field as "social synchronization." This term refers to the experience of matching your actions to a tempo set by another person, distinguishing it from regular "synchronization," which is when you follow a beat from a non-person stimulus, like when you dance to a song. While it seems simple, the science behind this universal skill is steeped in complicated interactions within the brain as well as a history of conflicting models to explain it. This article will explain the most widely accepted cognitive model of synchronization, discuss the practical implications for social synchronization, and as introduce you to a field of study where social synchronization is used commonly: two-person neuroscience.

As you can see in the picture to the , social synchronization is needed to keep parades looking organized. It can also be implicated in any other organized movement such as dance routines, playing patty-cake with a child, and of course synchronized swimming.

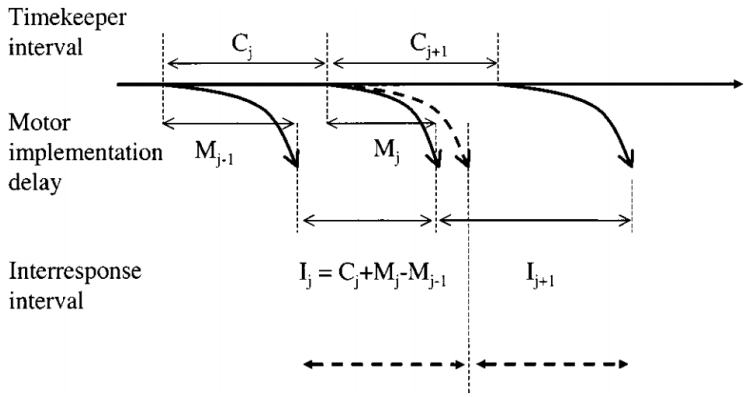
The current cognitive model

If you've ever heard of a pacemaker, the surgically implanted device that helps hearts beat regularly, you already know the importance of keeping time in the body. Other uses for timekeeping includes circadian rhythms, which help you wake up and sleep on a regular schedule. These are examples of endogenous, meaning within the body, timekeeping. Early research on synchronization assumed that each cell, including the neurons in the brain, had an endogenous timekeeper and that whichever collection of neurons had an especially robust ability to keep time, with whatever cellular mechanism that might turn out to be, would be responsible for estimating when the body should respond to a stimulus. However this avenue of research, as many often do, yielded to a more complicated notion: that there was a specialized collection of neurons that handled coordination (Wing, 2002). Now, you may have heard of the cerebellum as the part of the brain that, when exposed to intoxicating amounts of alcohol, makes you clumsy. There, specifically in the right lateral cerebellar cortex, is where the two-level timing model takes place.

The two-level timing model, developed by Alan Wing and A. B. Kristofferson, is a mathematical

Photo taken by Louis Bricese. Retrieved from United States Air Force Photo Gallery.

Figure 2 Wing-Kristofferson two-level timing model. Timekeeper intervals (*C*) are subject to motor implementation delays (*M*) in defining interresponse intervals (*I*). Average I is equal to the average *C*. However, variation in I reflects both C and M. In particular, variation in *M* results in negatively correlated *I* (tendency for short and long intervaals to alternate), as suggested by the dashed lines (Wing 2002).

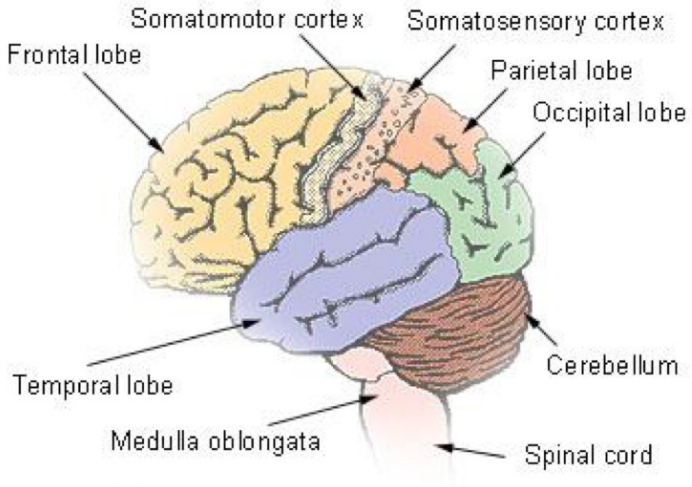


explanation for how the brain synchronizes. The two levels within the model are the "timekeeper interval" and the "motor implementation delay," which refer to the external signal to which you are trying to synchronize and the time at which you perform the synchronizing action (such as a clap or tap of the finger) respectively. Before you are synchronized with a tempo, be it from a metronome or someone else's cue, there is a temporal discrepancy between the signal and your response. The goal of synchronization is to reduce this discrepancy to zero. In order to do that, the right lateral cerebellar cortex must a) measure the length of time between signals (the timekeeper interval), b) measure the length of time between your responses (the motor implementation delay), and c) determine the difference between the two. When this is resolved by averaging multiple signals and responses, the cerebellum sends signals to the motor cortex in the parietal lobe to adjust your motor responses. Essentially, the right lateral cerebellar cortex is responsible for telling you when to clap, based on how off-beat you already are.

Biological correlates for synchronization

The right lateral cerebellar cortex does not act alone in the process of social synchronization. It must interact with the oculomotor system, involving inputs from the visual cortices in the occipital lobe and outputs to the motor cortices in the parietal lobe. Similarly, if the timekeeping stimulus is auditory, then connections with the auditory cortices in the temporal lobe are also used. Interestingly, there is evidence of a structural connection via white matter (i.e. myelinated axons of neurons, which send signals across the brain) between the right lateral cerebral cortex and the left inferior frontal gyrus (IFG) (Hodge et al., 2010). This second area is better known as Broca's area, discovered by French physician Paul Broca in 1861, and is commonly known to be involved in producing speech. However, some interesting newer research also implicates the area in the interpretation of social actions (Nishitani et al., 2005). Therefore, social synchronization may rely on the left inferior frontal gyrus to interpret signals from other people as appropriate for synchronization.

Let's apply this to a practical example of social synchronization. Imagine that you are sitting at a table when your friend begins tapping out a tune on the table, and the rest of your friends begin to sing along. Your visual system (the oculo- part of the oculomotor system) sends information in real



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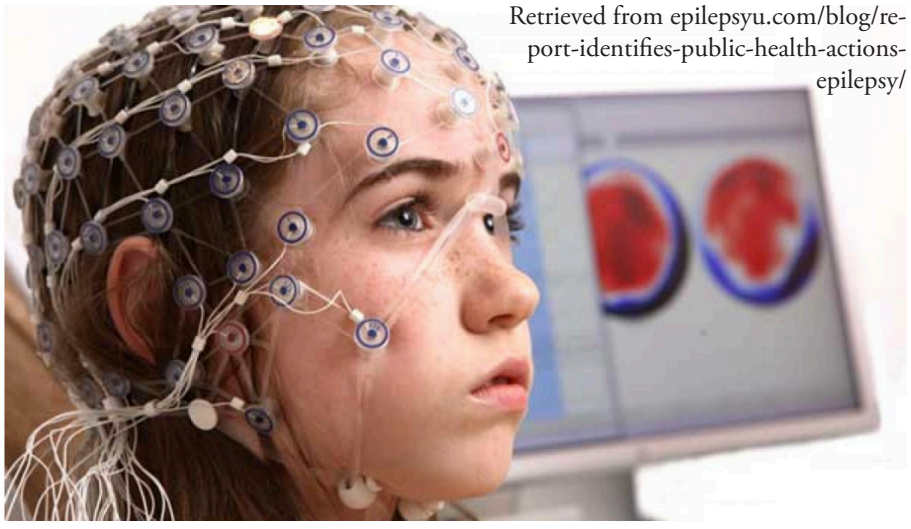
time to the inferior frontal gyrus and the right lateral cerebellar cortex at the same time. When the left IFG recognizes the tapping as musical, and not, say, a very emphatic addition to your friend's rant, then the right lateral cerebellar cortex can start synchronizing your hands as they begin to tap on the table as well. Your motor system (the -motor part of the oculomotor system) plans out how your arm and wrist and hand will move together in one smooth motion, but it is your cerebellum that tells you when to do it.

The left IFG is also known to have a high amount of mirror neurons, which help us to mimic other people's behavior. It is tempting to assume that social synchronization relies on the activation of the mirror neuron system, but in synchronization paradigms where voluntary movement is limited, motor neurons do not activate (Yun et al., 2012). They only activate during purposeful motor activity. Synchronization can happen on a very small scale with nonpurposive movements, so mirror neurons may help to understand complex motions, but may not be necessary for the synchronization process specifically.

The right lateral cerebellar cortex also handles hand-eye coordination, which, for example, helps you to catch an incoming football at just the right moment. Some research has shown that the ideal disparity between a signal (such as the sight of an oncoming football) and the performance of a behavioral response is 75 milliseconds (Miall & Reckess, 2002). When this temporal lag between the expectation of feedback and the actual sensory experience is unexpectedly long, the right lateral cerebellar cortex shows increased activation (Blakemore, 2001). The existence of a preference, or even an expectation, that must be compensated with extra activation when unfulfilled provides strong support for the localization of synchronization to the right lateral cerebellar cortex. By performing experiments that artificially manipulate the sensorimotor lag, synchronization can be studied as the right lateral cerebellar cortex actively regulates motor behavior.



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Practical Uses for Social Synchronization

Aside from the myriad of anecdotal opportunities to exercise your knowledge of the neurological underpinnings of social synchronization, research on interpersonal effectiveness has shown that social synchronization correlates with better teamwork and likeability (Yun et al., 2012). Not only do those who practice social synchronization later synchronize more quickly and more accurately (Yun et al., 2012), they also perform better on cooperative tasks with improved joint attention, which helps to problem-solve more efficiently (Szymanski et al., 2017).

The chameleon effect is an interpersonal phenomenon wherein people in dyads or a group will mimic each other's posture and small movements. According to Chartrand (1999), this behavior is an automatic process, much like synchronization. It is reasonable to hypothesize that the chameleon effect relies on the activation of the mirror neuron system in the left IFG which informs the synchronizing process that lies within the cerebellum in order to keep up with micro-expressions during a social interaction. Chartrand goes on to describe the perception-behavior link, which states that your perceptions of others' behavior will influence your own. This resembles the fundamental effect of social synchronization: another's cues guide your own motor activity, and the interaction between the two facilitate rapport. A well-fa-

cilitated rapport is useful in professional settings, but sometimes difficult to promote naturally. Because social synchronization can be practiced and improved, however, even a little effort could help you to literally get on the same wavelength as your co-workers.

Two-Person Neuroscience

Neuroscience has long been focused on the singular, individual brain. While some of the most compelling questions neuroscience asks are fundamentally interpersonal in nature, data collection is limited by both mechanical and financial cost. For example, an fMRI machine can only fit one person in it to measure brain activity at a time, and its maintenance costs are often prohibitively expensive for many research groups. A technique called hyperscanning is an innovative solution to this dilemma because it allows for two or more research participants to have data collected at the same time. Hyperscanning involves collecting electroencephalography (EEG) recordings through electrode caps (see image below) from two participants simultaneously while their data is time-locked (Liu & Pelowski, 2014). This allows researchers to measure interpersonal interactions directly, rather than make assumptions based on data taken sequentially. By locking two participants' data in time, phase synchronization can be measured.

Phase synchronization is when two people's EEG recordings, which are visually represented by waveforms, match up so that the crests and valleys of the waves occur at the same point in time (Liu & Pelowski, 2014). When phase synchronization occurs at the same node of an EEG cap, researchers can assume that the activity in the corresponding brain area (such as the left IFG) is similar across the two participants (Liu & Pelowski 2014). This means that the micro-expressions and spontaneous motor behaviors are not just due to random muscle contractions, but are the result of neurological processing derived from face-to-face interaction. The importance of this distinction is immense: synchronization can be described as having a dedicated neurological basis. If this is true, then it might be able to be studied in model animals or applied to more integrative theories than if it were considered emergent at rates resembling chance. Data, models, and theories about synchronization could have the potential to explain how language and music are developed prenatally and during critical learning years. Because phase synchrony is a marker of social synchronization in general, which is in turn a correlate of efficient interpersonal efficiency, the applications of hyperscanning can potentially be very direct in answering questions about the social behaviors of humans.

One promising model for synchronization in general, though not necessarily social synchronization, are birds like the cockatoo, who can be observed dancing to music with a strong beat (Patel et al., 2009). By studying their synchronization processes and occasionally their brains, posthumously, neuroscientists could come to conclusions that are difficult to make while studying the human brain, which is more complex. In fact, areas like the cerebellum cannot be accurately measured by EEG, as it is more folded than the cerebrum, which makes the electrical signals picked up by the EEG more scattered in direction. If the cerebellum is to be studied in humans, one of the more effective approaches is to use magnetoencephalography (MEG) which is similar to EEG but better able to detect signals from this convoluted area of the brain (Baillet, 2017).

Conclusions

Social synchronization may not be the most immediately critical area of study, but understanding how it works leads to not only satisfied curiosity, but contributes to a body of knowledge that can solve tomorrow's problems. As two-person neuroscience develops using measures of social synchronization, new questions are asked and new perspectives are taken on a field that is itself constantly emerging. By answering the frivolous questions, we approach the answers to more fundamental explorations on the field: how do we connect with one another?

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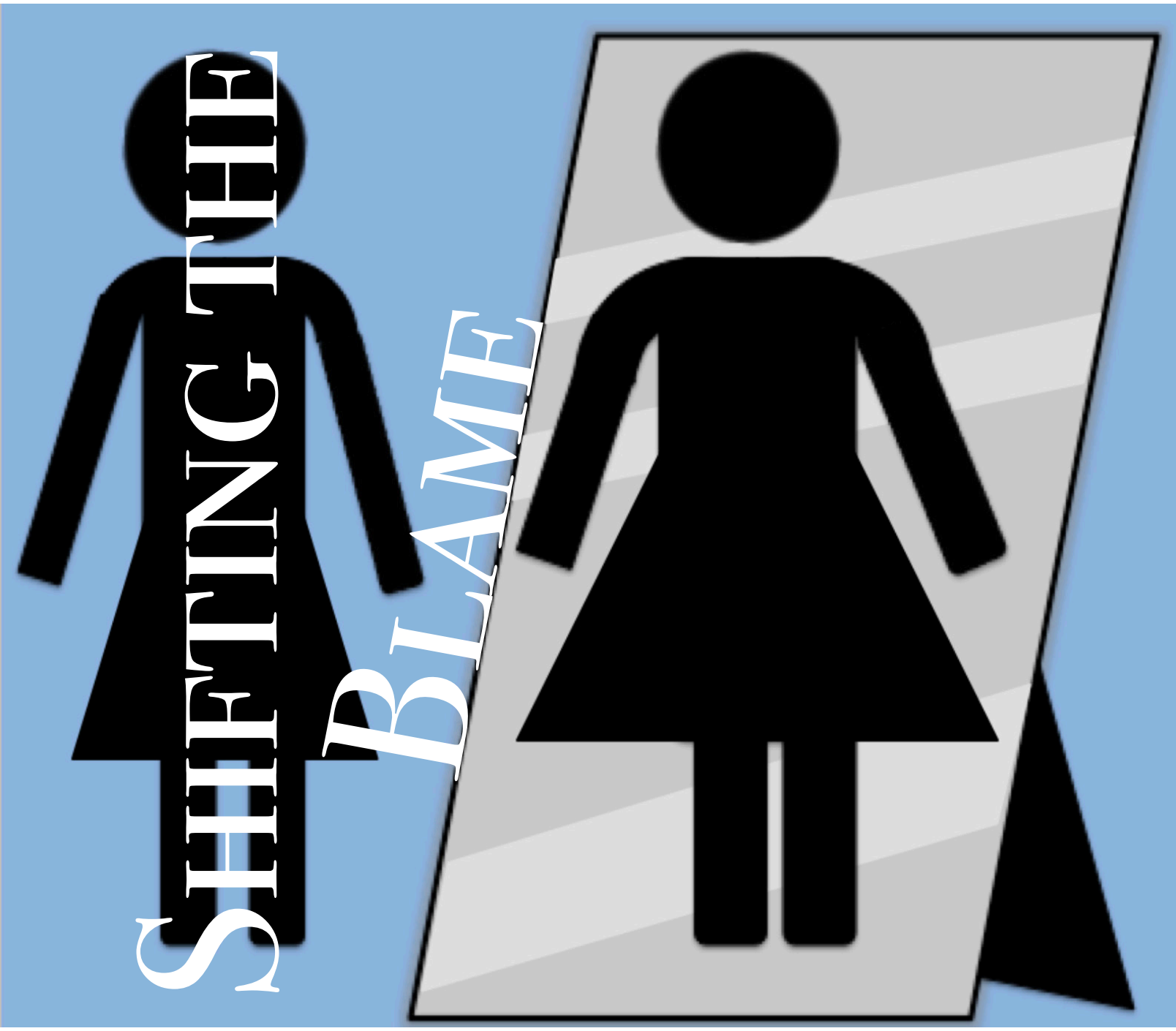


A CLOSER LOOK AT EATING DISORDERS

By **Kelsey Trulik**

My story begins at age 4…

I spent my entire childhood surrounded by weight stigma…

My eating disorder was unicorn in shape…

As a man and a person of color, I never had the space to be vulnerable…

My story with this battle begins with a lifelong fight against anxiety and depression…

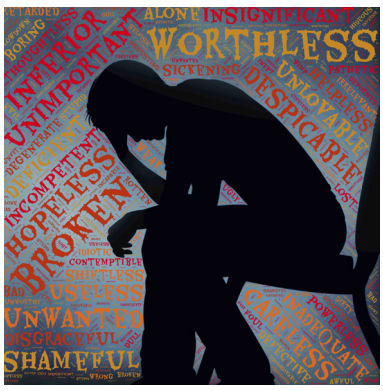
It has nothing to do with food…

I have more memories of my eating disorder than I do of my siblings and family and school…

It takes on a life of its own…

It just is…[1]

Every person battling or having battled an eating disorder has a story to tell, and every story is so different. These individuals had the courage to speak out and share their experiences with battling an eating disorder and the tough road to recovery. However, for many individuals, it's not as easy. While 3-5% of the population openly acknowledges their disorder with eating, many individuals go through life's motions without ever letting anyone know about the internal battle they face.[2]



"Depression, Voices, Self-criticism" by John Hain is licensed by CC0.

A Few Definitions [3]

Anorexia Nervosa (AN): Body weight that is less than 85% of normal weight for height and age, intense fear of fatness, disturbed appearance of one's body weight and shape. **Affects 0.5-3% of the world population**

Bulimia Nervosa (BN): Recurrent episodes of binge eating, compensatory behaviors (purging, exercising, and fasting) **Affects 1-3% of the world population**

Binge-Eating Disorder (BED): Regular binge eating episodes, absence of compensatory behaviors
Affects 2-4% of the world population

An eating disorder is not a something you can turn on and off. It's a lifelong fight, affecting many. It does not have a specific appearance, but rather affects people regardless of race, gender, and age. It removes the feeling of self-worth, respect, and love for its victims. It is common belief that familial practices, peer influence, hurtful words such as "chubby" and "fat," media, and constantly shifting societal pressures to physically "fit in" promote the development of eating disorders, but the root may go beyond this.

In a society where *fashion magazine models are a size zero*, movements like "pro-ana" and "thinspiration" exist, Photoshop and various other forms of digital technology manipulate "ideal" body imagery, smartphone applications track calories consumed and burned, and social media platforms consume the time and thoughts of children and young adults, the incidence of eating disorders has greatly increased. We are constantly bombarded by societal definitions of "beauty" and the "ideal" body through various public routes such as television, magazines, billboards, and other sources of media. And if one does not fit these physical standards, society, especially one's peers chastise them. As a result, media is often considered the root cause of eating disorders, but eating disorders are more complex than what media contributes to them. Yes, social and environmental factors influence the development of eating disorders, but the true complexities lie in the combination of social, psychological, and biological factors.

"Individuals developed eating disorders when our culture developed a standard of beauty that they couldn't obtain by being helathy When unnatural thinness became attractive, indiviudals did unnatrual things to be thin."

Culture has shifted perceptions of the body significantly over the

past few decades. These cultural shifts are reflected through various forms of media, which have introduced a new "ideal" body image for both men and women. Female beauty is defined as being thin and lean, and male beauty is defined as being muscular and strong.[4] What the public sees in media are "ideals" that are unattainable, and often unhealthy. In fact, recent studies reveal that 70% of models are under a healthy weight.[4]

Western media imagery is seen everywhere these days, and children and young adults are heavily influenced by it. The power of Western media imagery is often difficult to see, especially for people who grow up with it; however, the negative effects can clearly be seen later on in life in various aspects such as the development of eating disorders. Many young adults diagnosed with or recovering from an eating disorder reported initially changing their eating habits and the ways they viewed their bodies in order to look like a certain person—a character from their favorite TV show or a model on the cover of Vogue or Men's Health magazine.[4] The negative effects of Western media imagery can further be explored by Becker and his team.

Alarming Facts (as of 2016)[2]

- At least one person dies every 62 minutes as a direct result of an eating disorder.
- Eating disorders have the highest mortality rate of any mental illness.
- At least 30 million people suffer from an eating disorder in the US alone.
- 6% of transgender college students report having an eating disorder.

The Power of Western Media Imagery:

In 1995, a group of researchers (Becker and his team) traveled to small, remote province in Fiji. While the television had been invented 68 years prior to this year, this Fijian community had yet to be exposed to Western media imagery via television before. And similarly to the lack of televisions, the prevalence of eating disorders in this area was rare to none.[5] Becker and his team journeyed to this province at a critical time, as television was just being introduced into this community. The researchers took time to interview and survey the attitudes and behaviors of female adolescents in this province. Their results confirmed what they had expected from a traditional, Fijian community: robust women were glorified and a hearty diet was encouraged.[5] A desire to reshape one's body through exercise and diet was actually discouraged. Three years after the emergence of television, Becker and his team returned to this province. They reported a major shift in female adolescent's attitudes about their traditional, cultural diets and appearances.[5] In fact, the prevalence of weight loss significantly increased, and there was a greater focus on body image

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three years following the introduction of Western media imagery.[5] Above all, these Fijian adolescents reflected that peer pressure and changing societal body ideals played a large role in this shift in diet, behavior, and attitude.[5] Media and imagery is a very powerful tool that has become standard in our society, but the negative effects of it, as seen in this Fijian province, are undeniable.

Social Media is Everywhere:

Society regularly discusses how problematic social media can be; yet most of us still spend hours on our computers or smart phones

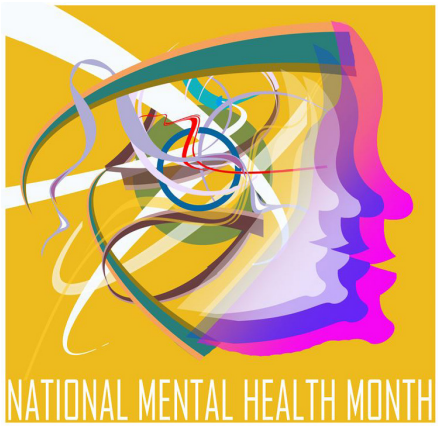
"Fiji, Flag, Fingerprint" by Kurious is licensed by CC0.

"Social Media Cubes" by Blogtrepreneur is licensed by CC BY 2.0.

scrolling through new Instagram or Facebook posts throughout the day. In fact, the average person spends six to seven hours a day viewing some sort of media.[4] While social media is a wonderful way to stay informed and spread vital information, it is also the perfect platform to compare ourselves to others. Numerous studies show the extent to which social media influences eating disorders. Increased time spent on social media has been shown to increase disordered eating behaviors such as engaging in appearance-based behaviors like comparing one's photos to their friends, or untagging oneself from "unflattering" photos.[6] But who are we comparing ourselves to? People post pictures on social media to show the best and skinniest versions of himself or herself, not the reality of what we all see or face. It shows fake perfection, not reality. Yet, it is this peer competition that feeds into our insecurities.[7] Constant changes in technology and the introduction and further advancement of social media has increased the risk of developing and eating disorder through the use of a constant space for people to compare themselves to others.

With a rise in media comes a rise in perceptions and blame. Pop culture sometimes suggests, or does not refute the pre-existing attitude, that eating disorders are a personal choice only influenced by media—that individuals with eating disorders are mentally weak and not strong enough to overcome their negative attitudes and behaviors towards eating and body image. These societal attitudes foster stigma and discrimination against individuals with eating disorders and create an environment in which individuals are afraid to get help out of fear of being attacked for their internal battle. As a result, many suffer in silence for years until it is too late.

While media does influence the risk of developing an eating disorder, it is not the only culprit. We often solely talk about the adverse effects of media, because it is readily visible and constantly in the limelight. However, there are many factors that influence eating disorders that persist beyond eyes-meet. Similar to how we say, "eating disorders do not have a look,"



"National Mental Health Month" by Jeff W. Gates was retrieved from https://media.defense.gov/2010/May/20/2000360787/-1/-1/0/100520-F-JZ025-987.JPG

neither do the factors that influence the development of them.

Eating disorders appear to run in families, suggesting that genetic factors may predispose certain individuals to eating disorders. Several twin and family studies have shown a link between eating disorders and genes, further promoting the idea that eating disorders

"An eating disorder is not just a mental illness."

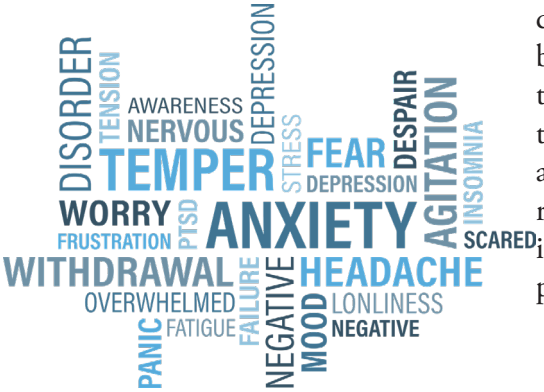
are hereditary. While behavioral, environmental, and familial practices greatly influence the development of eating disorders, genetics may provide an underpinning for this disorder. Certain careers such as wrestling and modeling create weight expectations, which may be the catalyst for individuals already genetically predisposed to an eating disorder. Likewise, stressful environments, and chaotic situations may drive some toward eating disorders who already have genetics predisposing them to anxiety and obsessive-compulsive disorder.

Individuals with eating disorders often display certain personality traits or mood disorders including anxiety, low reward reactivity, high punishment sensitivity, depression, and obsessive behaviors.[8] Many neural pathways play overlapping roles in these personality traits or mood disorders and eating disorders.9 Different brain areas and neural pathways are responsible for and activated in response to food intake, reward, and mood. Variations in activation and specific neurotransmitter levels may

correlate to how individuals with eating disorders approach food. Deficits or other changes from "normal" within specific neural pathways may further reflect upon attitudes and behaviors toward food: reward or punishment.[8]

Serotonin—the "Feel Good" Molecule:

Several neural pathways in the brain are linked to reward, emotion, motivation, body weight regulation, appetite, and impulse control, all of which contribute to thoughts and attitudes and play a role in symptoms associated with eating disorders.[8,10] Specifically, research shows that individuals with eating disorders have disturbances in the serotonergic and dopaminergic systems.[8] The serotonergic pathway is important for regulating appetite, mood, emotional behavior, and sleep.[11] Recent studies demonstrate that changes in serotonin (5-HT) levels and 5-HT receptor functionality affect different areas of the brain, causing changes in satiety, mood, and impulse control.[8] Ill or recovered individuals with eating disorders



"Anxiété Nuage De Mot" by Mary Pahlke is licensed by CC0.

"Appetite Beef Big" by Robert Owen-Wahl is licensed by CC0.

have an increased 5-HT1A binding and reduced 5-HT2A binding.[11] These receptors (5-HT1A and 5-HT2A) are responsible for serotonin uptake into postsynaptic neurons, which leads to further excitatory or inhibitory effects. These effects differ from normal when 5-HT receptor binding affinities vary, as seen in individuals with eating disorders. They have been shown to contribute to anxiety, depression, stress, impulsivity, and eating disorders.[8]

A polymorphism is a discrete genetic variation that results in several different types or forms of a single gene in an individual or a group of individuals.[9] While polymorphisms are quite common within populations, they may result in several changes that can drastically change function and behavior. Recent evidence suggests that a polymorphism of the serotonin transporter gene (5-HTT), a protein responsible for serotonin reuptake in presynaptic neurons, increases the risk of developing depression and an eating disorder.[9]

Dopamine—the "Reward" Molecule:

The dopaminergic pathway is another important regulatory neural pathway. Recent studies demonstrate that changes in dopamine (DA) levels and DA receptor function cause changes in the rewarding effects of food, motivation, and executive functions such as decision-making.[8] Ill or recovered individuals with eating disorders have increased DA D2 and D3 receptor binding affinities for dopamine.[8] These receptors are responsible for dopamine uptake into postsynaptic neurons. The increased binding affinity for dopamine may send dopamine centers in the body into overdrive, resulting in increased anxiety and compulsive behaviors as seen in individuals with eating disorders. Likewise, a polymorphism of the DA D2 receptor has shown to increase the susceptibility of developing an eating disorder.[12] Interestingly, research suggests that the DA D1 receptor plays a large role in food intake. Stimulating DA D1 receptors significantly increases food intake, while inhibiting these receptors greatly reduces food intake.[12] Can control over these neurons affect individuals hunger drive or subsequently, lack of hunger drive?

33-50% people with an-

"DNA RNA Gene" by Clker-Free-Vector-Images is licensed by CC0.

"An eating disorder is not a choice"

orexia and roughly half of people with bulimia have a comorbid mood disorder (ie. depression).[13] And roughly half of bulimic and anorexic patients have a comorbid anxiety disorder (ie. obsessive-compulsive disorder, social phobia).[13] These statistics are astonishing and show a strong connection between eating disorders and other mood or anxiety disorders, which are often also associated with disturbances in the neural pathways previously described. Yes, societal and environmental factors influence mood disorders and eating disorders, but strong evidence suggests that dysregulation of these neural pathways contributes to changes in personal reward, mood, body weight, impulsivity/compulsivity, and emotion, all of heavily influence disordered eating behaviors and attitudes.[8]

Genetic heritability accounts for 50-80% of the risk of developing an eating disorder and contributes to many of the neurological factors that affect eating disorders previously mentioned.[8] While people have been talking about the heritability of eating disorders for years, scientists had yet to correlate certain genetic mutations with an increased predisposition for eating disorders. This is, until recently. New evidence studying large families greatly affected by eating disorders show that family members with or recovered from an eating disorder all had a point mutation (single nucleotide change results in an entirely different amino acid14) in the ESRRA or HDAC4 gene.[14] Had each family member with an eating disorder been exposed to the same Western media imagery? From personal experience, I can tell you I do not watch the same shows or follow the same celebrities as my parents or grandparents. So, is this genetic mutation just a coincidence?

"Fork, Tape Measure, Diet, Nutrition" by minka2507 is licensed by CC0.

ESRRA and HDAC4 Association:

ESRRA (estrogen-related related receptor alpha) is a gene in the central nervous system that regulates metabolic processes for neuronal functioning.[16] A point mutation of ESRRA would reduce the number of receptors in the brain and reduce metabolic functioning. This has been shown to induce several behavioral deficits in mice that are symptomatic of eating disorders in humans: behavioral rigidity, social impairment, maintenance of body weight 15% below normal, and reduced response for a high-fat diet.[16] In another family, all members currently with or having a history with an eating disorder had a point mutation of the HDAC4 gene. HDAC4 (histone deacetylase 4) is a gene that represses transcription (the first step in DNA synthesis) and affects cell progression and development.[17] A point mutation of HDAC4 has been shown to induce similar behavioral deficits in mice symptomatic of eating disorders in humans and the behaviors seen in ESRRA-null mice. These two pathways, ESRRA and HDAC4, work in conjunction with each other, reducing mitochondrial function in the brain, which may increase the

"Eating disorders are like a gun that's formed by genetics, loaded by a culture and family ideals, and triggered by unbearable distress."

What is epigenetics?

A new and innovative field worth mentioning is epigenetics. Epigenetics is a field of study that looks at regulation and changes in gene function without changes in the DNA sequence. For example, it's hypothesized that the environment plays a large role in obesity as well as thinness. The rise in high-fat and carbohydrate dense diets may increase the number of fat related genes in individuals. On the other hand, genes that suppress appetite may be over expressed in an environment that promotes thinness. [15]

"Scale, Diet" by Vidmir Raic is licensed by CC0.

risk for developing eating disorders.[17] These new findings are the first to link specific genes to the development of eating disorders.

Eating disorders are a very complex disease, with contributions from social, environmental, neurological, and genetic factors. Often times, society blames the media, individuals, or their families for causing eating disorders. While environmental and social factors do contribute, genetics have been shown to predispose individuals to the development of eating disorders through mutations in neurological pathways (serotonergic and dopaminergic) and specific genes (ESRRA and HDAC4).

With these new findings, research is moving forward in a direction aimed at finding a way to boost or reduce certain neural pathways to prevent or reduce and relieve the effects of eating disorders. Currently, there are many drugs on the market to minimize anxiety, ADHD, OCD, depression, and other mental disorders often co-expressed in individuals with eating disorders. These drugs often times inhibit or facilitate reuptake of certain neurotransmitters to induce a reversal of effects. Antidepressants such as Norpramin and Prozac, anticonvulsants such as Topomax, and various other drugs have been utilized to treat eating disorders, namely bulimia nervosa and binge-eating disorders.[18,19] While these drugs may be useful in managing a mental disorder, taking them does not affect the initial development of eating disorders, nor contributes to recovery through a natural process. Likewise, a pill does not teach individuals how to form self-worth or love, or how to be less impacted by the media and other environmental and societal factors.

Through new research, we understand that the development of eating disorders is predominantly genetic related. While environmental factors such as media messages fuel the fire of eating disorders, genetics forms the base for the fire to ignite. Children and young adolescents are at the highest risk for developing eating disorders, because they are in a period of their lives when they are trying to figure out who they are as their bodies begin to change, and the environment and peer influence can greatly affect how they view themselves and their bodies. Eating disorders not only affect the individual, but also those close to them. And often times, individuals with eating disorders are looked upon as being weak, easily influenced by others, and having low self-esteem. Likewise, families may be attacked for causing the problem in the first place. Educating families and society in general about the gene-environment combination of eating disorders can replace many of the simplistic conceptualizations that exist surrounding eating disorders as being either wholly social or entirely biologically based disorders. An understanding of the layers of an eating disorder (environmental and genetic) may help to remove the "blame" we often like to put on certain factors or the individuals themselves.

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Deafness & Language

By **Yara Al-nouri**

According the World Federation of the Deaf, deafness - or auditory deprivation - is the third most common physical condition following arthritis and heart disease; as such, it presents an interesting case for studying human communication. As defined by the Oxford Medical Dictionary, deafness refers to total or partial hearing loss in one or both ears (2016). While deafness can be acquired through injury or trauma to the inner ear or through old age , it can also be a congenital condition. In the United States alone, an estimated two to three children out of every one thousand are born with profound hearing loss in one or both ears every year (Hearing Loss Association of America). For those born with hearing loss and those who lose their hearing before they learn to speak, their deafness could be categorized as prelingual deafness. Prelingual deafness poses a challenge for language and speech acquisition, given that auditory input is necessary for the development of both processes. Further, as Andrew Solomon writes, "the issue of deafness in most societies is one of linguistic exclusion" (2012:83). Deafness can be isolating for many because there is not so much a physical barrier between them and their social world, but an invisible one wherein communication is effectively cut off.

However, this is not to say that deaf individuals do not have any language ability. In fact, many deaf people learn to speak orally or use alternative forms of communication, such as American Sign Language (ASL). Additionally, the development of technologies, specifically cochlear implants, also simulate the experience of hearing for individuals with hearing loss; therefore enabling them to more effectively communicate with the hearing world. However, the debate surrounding cochlear implants is not so much about their efficacy, but rather the ethics of the implant. In this paper, I articulate the debates surrounding cochlear implants, and then move forward to an examination of the neuroscience underlying language acquisition for prelingually deaf individuals.

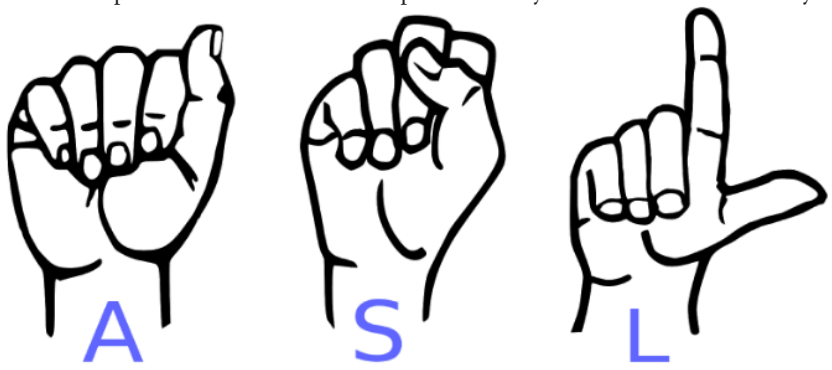
Big "D" versus Little "d"

In examining deafness as a topic, it is necessary to include a discussion about the debate between Deafness as a culture and deafness as a disability. The capitalization of "Deafness" refers to culture whereas the lowercase "deafness" indicates the pathological condition or impairment (Solomon 2012:50). While those in the medical sciences see deafness as a disability, there are many in the Deaf community who oppose this notion, opting instead to celebrate their difference as a cultural minority.

In fact, those who identify with Deafness as a cultural identity define their lived experiences as being enhanced by "Deaf gain", rather than being tarnished by hearing loss (Bauman and Murray 2010). As a concept, Deaf gain shifts the narrative of deafness from one of impairment and loss to a narrative of embracing and celebrating the benefits of being Deaf (Bauman and Murray 2010).

Part and parcel of Deaf gain and the Deaf community is the use of American Sign Language, or ASL, as a primary means of communication (see Figure 1). ASL is a type of language which utilizes physical gestures, as articulated through the hands, face, and body, to communicate (National Institute on Deafness and Other Communication Disorders). As such, it is a highly visual language; indicating that sensory information for the deaf is usually obtained through vision (Lane and Bahan 1998:298). It is a distinct language from English as it has its own grammar rules. For an estimated half million Americans, ASL is their primary language. Moreover, cultural and artistic endeavors have been created using ASL. In other words, ASL provides people in the Deaf world a sense of connection, community, and identity (Lane and Bahan 1998:297). Additionally, those in the Deaf community tend to condemn the use of cochlear implants as they see the device as a threat to their culture (Solomon 2012). In fact, some members of the Deaf community are so averse to cochlear implants that they argue that the implants are a form of "genocide" against the Deaf (Sparrow 2005:135). More specifically, cochlear implants represent a threat to the linguistic component of Deaf culture as cochlear implants are intended to boost spoken communication while discouraging the use of ASL (Ringo 2013).

Figure 1 Visual representation of ASL. "ASL spelled out" by Psihedelisto is licensed by CC0.



While the Deaf community exists, this does not mean that all deaf individuals choose to identify with the Deaf group. Many deaf individuals choose to identify as individuals with disabilities, and use English as their primary form of language (Lane and Bahan 1998:298). Additionally, many of those who identify with Deafness as culture are Deaf of Deaf, or Deaf children born to Deaf parents, meaning that they are often brought up within the Deaf community (Mitchell and Karchmer 2004). However, there are also deaf children born to hearing parents. According to the National Institute on Deafness and Other Communication Disorders, more than 90 percent of deaf children are born to hearing parents in the United States (2016). A large number of these deaf children learn to use spoken English through speech therapy and cochlear implants.

The commonalities between the two camps, however, extend beyond the condition of hearing loss. Because the society and world we live in is made for those who can hear, those who cannot hear will always "be at a disadvantage." As Andrew Solomon phrases it, the question moving forward is "whether people prefer to be marginal in a mainstream world, or mainstream in a marginal world, and many people quite understandably prefer the latter" (2012:107). In other words, those who "prefer to be marginal in a mainstream world" refers to those who see their deafness as a disability, and those who "prefer to be mainstream in a marginal world" refers to those who see Deafness as a culture. Yet the two are not mutually exclusive, and seeing your deafness as a disability does not necessarily encompass a sense of self-loathing. Solomon invites us to think more empathically about the ways that we interact with difference, to think deeply about the ways that we construct our society, and to ask ourselves: how welcoming is our world to the other?

A Brief History of America's Treatment of Deaf People

To understand the resistance of the Deaf community to advocate for and accept cochlear implants, we must first look at the history of marginalization of the deaf. Throughout history, and we see evidence of this even in Aristotle's writing, the perception of deaf people has always been derogatory; as assumptions about deafness, because of silence, were always associated with assumptions of stupidity (Solomon 2012:51)(Padden 2005:509). As such, one reason why the Deaf community so vehemently defends ASL is because ASL symbolizes a sort of liberation as it gives them a voice to be heard (Padden 2005: 509).

There is a history of the segregation and exclusion of deaf people from society. For instance, throughout American history, in every state, deaf children were institutionalized (Padden 2005: 508). While the late 1970s brought along a decrease in institutionalization as deaf children were integrated with hearing children in education, deaf people still face certain forms of discrimination and oppression to this day. One of the most revolutionary moments in American history is the creation of educational and academic institutions specifically for the deaf and hard of hearing. The first American school for the Deaf was founded in 1817. Springing from it was the continued proliferation of these types of Deaf schools throughout the nation, lasting until 1953 when the last deaf school was built (Padden 2005:509). These deaf schools segregated deaf children from hearing children, acting like boarding schools. They also influenced the demographics and locations of deaf communities in the United States, by reorganizing deaf people into certain geographies based on the location of deaf schools. While these schools separated deaf children from other children, they also brought together individuals who felt extremely isolated because of their deafness (Padden 2005:510). Deaf children were also able to learn sign language at these schools, which is of particular importance for those born to hearing parents (Padden 2005:511).

Advancements in modern technology, including cochlear implants, such as cell phones and digital means of communication have opened up the social worlds of the deaf and hard of hearing, decreasing the communicative divide between the two.

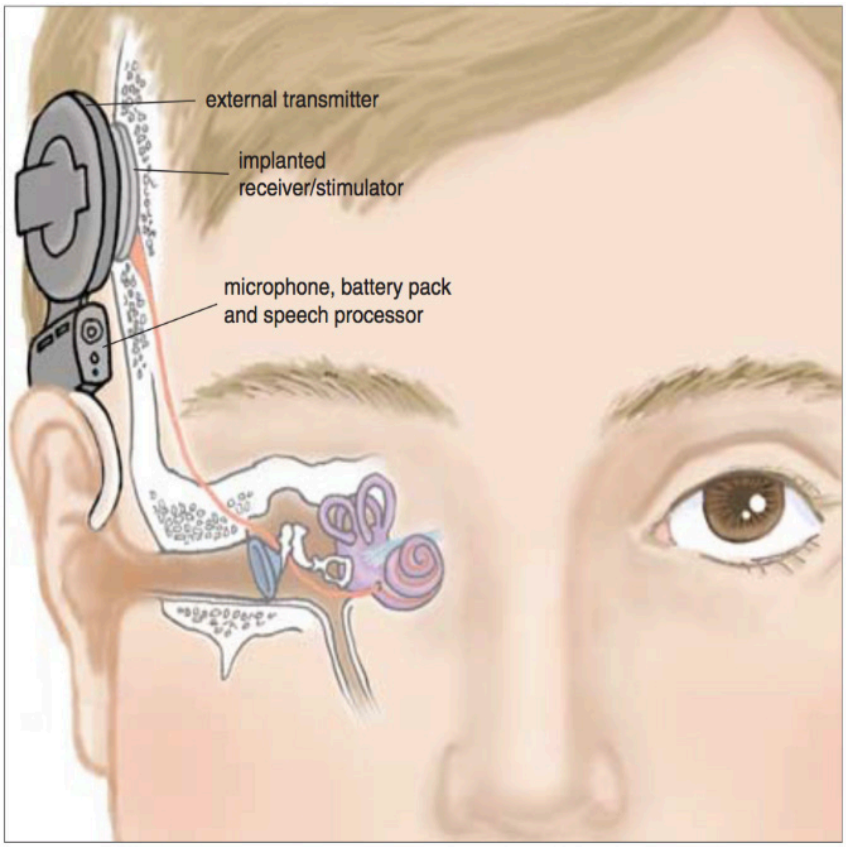


Figure 2 Visual Depiction of Cochlear Implant Mechanics. Taken from: Dorman, M.F. & Wilson, B.S. (2004). The Design and Function of Cochlear Implants. *American Scientist, 92,* 436-445.

Cochlear Implants

Cochlear implants are neural prosthetics that use electrodes to electrically stimulate the cochlea or inner ear: in turn providing the recipient with functional hearing or sound perception. The device is surgically implanted. The implant consists of external (i.e a microphone, speech processor, and transmitter) and internal (i.e. a receiver and electrodes) components

(see Figure 2). The internal and external components of the cochlear implant are able to communicate via radio frequencies. A microphone picks up sound signals from the external environment, sending them to the speech processor and transmitter, where these sound signals will then move to the receiver-stimulator, where they will be converted by the electrodes implanted at various points throughout the cochlea. Electrodes are placed at different points along the cochlea to code for different sound frequencies and produce a percept or stimuli that matches the location of the electrode; in other words, electrodes work by frequency-to-place representation. Because speech has many different frequencies, it is necessary to place the electrodes throughout the cochlea to electrically code speech. The more electrodes, and subsequently, the more channels, the closer the cochlear implant is able to get to detecting normal speech. The electrodes, then, electrically stimulate the auditory nerve endings, which send the information to the brain where it is then processed (Dorman and Wilson 2004)(Namasivayam 2004) (Macherey and Carlyon).

The first attempt at developing a neural prosthetic that would mimic audition was in 1957 in Paris, France, and ultimately, failed. In 1961, an American otologist, William House attempted to recreate the device, deciding to improve on the failures of the last attempt by stimulating five different points along the cochlea, as a way to make the implant more

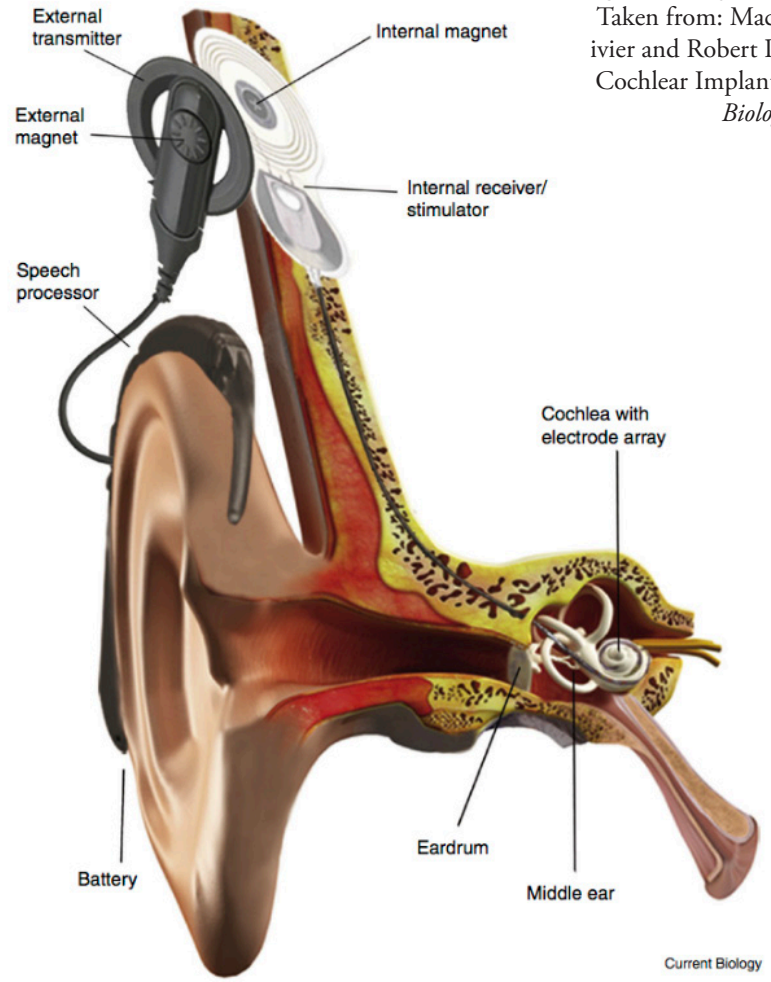


Figure 3 Diagram of the ear. Taken from: Macherey, Olivier and Robert P. Carlyon. Cochlear Implants. *Current Biology 24 (18)*

sensitive to different frequencies of speech. Again, this attempt failed (Blume 1999:1258). However, the 1970s brought along advancements in medical technology, allowing House and his cohorts to develop a more successful model of the device. As the technology of the implant improved, so did its global, professional recognition in the 1980s. The FDA approved the device in 1984, and six years after that, the FDA moved to approve minors for the implant in 1990 (Blume 1999:1258).

Given that cochlear implants essentially require an individual to learn how to hear with the device and that there is a critical period for language acquisition, it is typically recommended that prelingually deaf children receive the implant as early as possible. However, there is an ethical dilemma surrounding the surgical implantation of cochlear implants in children. There are three primary ethical debates about the issue. The first concerns the fact that children are unable to give informed consent, and that medical practitioners do not take into account the possible psychological and social effects of the surgery on children. The second concerns the culture clash between the Deaf community and the hearing world as they have different values regarding cochlear implants. The

third debate argues that policies that allow children to be implanted impedes on the rights of the Deaf community, and is an attempt to rid the world of deaf people (Lane and Bahan 1998).

Neurological Basis of Hearing

As a mechanical process, hearing requires the conversion of sound waves into neural impulses. As the sound waves move from the air, they are funneled into the eardrum or tympanic membrane by the outer ear. The sound waves then cause a vibration of the tympanic membrane, moving through the tiny bones of middle ear or ossicles. From the ossicles, the sound waves cause the movement of fluids contained inside the cochlea, bending the stereocilia and tiny hair cells lining the basilar membrane. It is at this point where the physical sound waves are converted into neural impulses as the auditory nerve is stimulated. Ultimately this auditory information lands itself in the auditory cortex, located in the temporal lobe.

Neurological Basis of Language

The traditional neurological bases for language are considered to be Broca's area, Wernicke's area, and the arcuate fasciculus which serves as a bridge between Broca's area and Wernicke's area (Fujii et al. 2016). Wernicke's area is responsible for language comprehension whereas Broca's area is responsible for speech production; both areas are located in the cerebral cortex. Language is processed through both the dorsal and ventral streams (Fujii et al. 2016). Additionally, spoken language is usually lateralized to the left hemisphere.

Deafness and Neuroscience

As acknowledge by Olulade et al., most extant neuroscience research on deafness has been conducted primarily on deaf individuals who are native signers, despite the fact that this sample is not representative of actual deaf populations. In fact, approximately 95% of deaf Americans use English as their primary language, and as such, it is necessary to turn researchers towards sampling methods that accurately reflect the deaf population (Olulade et al. 2014: 5613).

Much like spoken language, deaf native signers also exhibit lateralization of language processes to the left hemisphere as indicated by studies on unilateral stroke patients. Some studies, however, have shown that deaf native signers of ASL also exhibit activity in their right hemisphere (Campbell et al. 2007). These findings suggest that language processing "is not determined by the auditory input modality" (Campbell et al. 2007:5). In regards to specifically sign language production, studies have been able to corroborate that sign production is very much lateralized to the left hemisphere. Further, neuroimaging studies have consistently shown that left inferior frontal region activation for the production of sign language, and that Broca's area is consistently utilized in this process of sign production (Campbell et al 2007:13). Given this, we can infer that the production of sign language is similar to that of spoken language.

While prelingual deafness has potential for altering the development of some neurological processes of language, that does not exclude them the possibility of language acquisition nor necessarily mean that they will be hindered by their deafness.

Conclusion

In conclusion, the neuroscientific study of deafness is relevant to society because it has larger implications for the ways in which we think about disability, and the quality of life for deaf individuals. However, the neuroscientific study of deafness is enhanced by thinking about the nuances underlying deaf identities and Deaf culture. While neuroscience contributes necessary knowledge about the science of deafness, it can often tend towards a conception of deafness as a negative life experience. Deaf culture invites us to celebrate difference, and re-conceptualize what "normal" means when we think about the body and ability.

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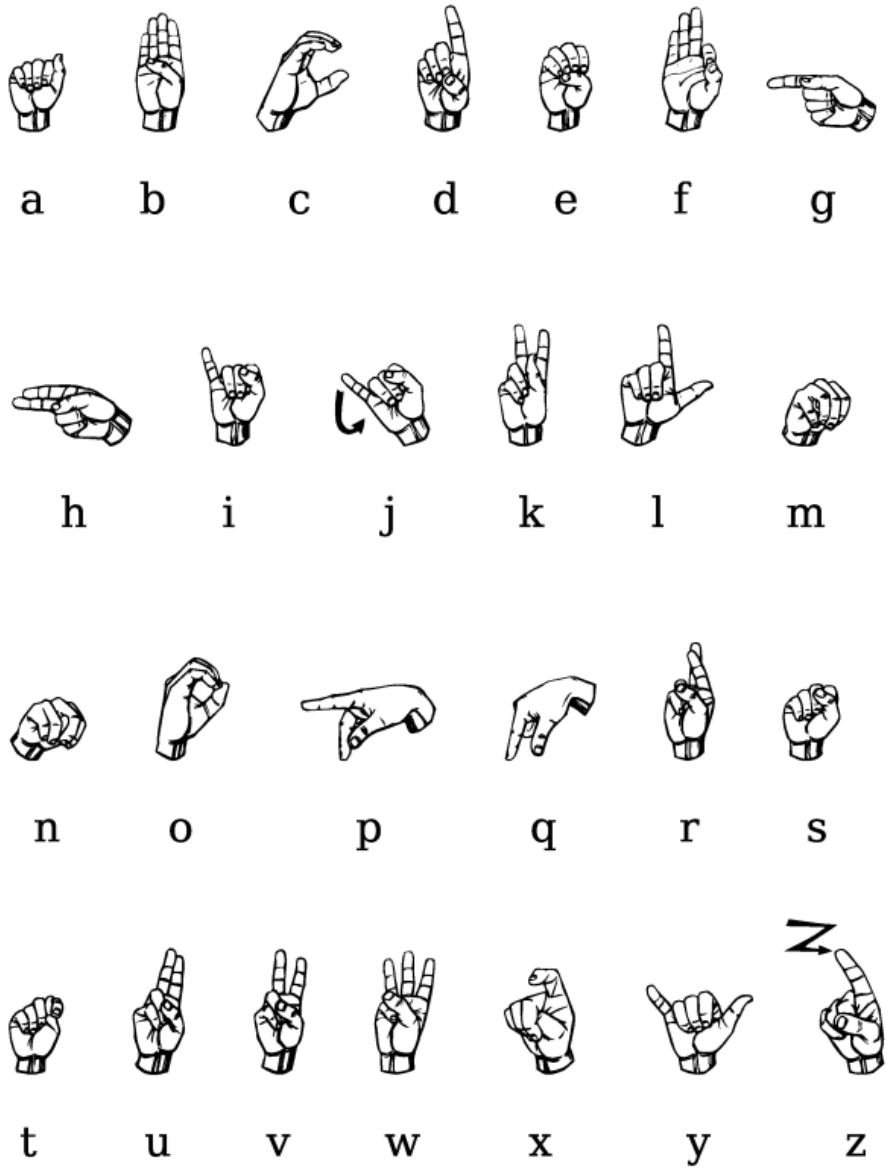

“American Sign Language Alphabet” laid out by Darren Stone is licensed by Public Domain.

New Body, Who Dis

Getting aHead

By **Dana Oakes**

Change is the only constant in life. The human body constantly transitions throughout life; whether through ageing, sickness, injury, or surgery, the body is never static. People's thoughts, opinions, ideas, and feelings – all elements of the mind - are also constantly changing. The body and brain are not two separate entities, but are inseparable. The biological, emotional, and mental changes from childhood to adulthood characterize our experience as humans. As bodies grow in the world, so too do the minds they shelter.

But what happens when a person's body is degenerating, paralyzed, or sick, while their mind is still active and capable? Drs. Sergio Canavero and Ren Xiaoping, along with their surgical team, believe that surgery has come far enough to help patients with failing bodies but active minds. Their solution? Head transplant surgery. This technology has great potential for helping the sickest among us, but with powerful technology also comes great ability to abuse that technology.

The Science

Head Transplant

Allo-head and body reconstruction (AHBR), cephalosomatic anastomosis (CSA), head transplant, body-to-head transplantation (BHT), are all different ways of referring to head transplants. But they all are attempting to take the healthy head and brain of one individual and put it on the healthy body of a brain-dead donor. The hope is that after recovery and therapy, a healthy individual comes out on the other end.

The technology to complete the first human head transplant has been a long time coming. Research into other types of transplants has been ongoing, including recent success in hand transplants, as well as the reconnection/regeneration of sensory neurons. Recent advances in neuroprotection, neural fusogen (agents that reconnect neurons after they have been cut), immunosuppression, and recovery therapy have lead Drs. Canavero and Ren to be optimistic that this surgery will work.

The first human head transplant surgery is scheduled for December 2017. Drs. Ren and Dr. Canavero will conduct it with a support staff through Harbin Medical University, in Harbin, China, and conducted on a Chinese national (because it is more likely for a body donor to become available).[10] The donor body will

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be a brain-dead organ donor, and the head donor will be a patient who suffers from some level of full body degenerative disease, and who is willingly participating in the surgery, with the promise of obtaining a new body. The identity of the body and head donors have not been released to the public.[4]

Feasibility

While this is an experimental surgery that has never been done on human subjects before, the expectations of Drs. Canavero and Ren's surgery is that it will be highly successful, and help the lives of patients suffering from tetraplegia (paralysis from the neck down), multiple organ failure, intractable cancer without brain metastases, progressive muscular dystrophies, or any number of genetic or metabolic disorders.

The operating theater on the day of transplant will be busy. Two surgical teams, each working in concert on either the donor head or the donor body, must perfectly time the surgical proceedings. The body donor and head donor will both be situated in upright sitting positions in order to maximize the access to the site during surgery. The HEAVEN protocol as laid out

by Dr. Canavero in his 2013 paper will build off the techniques discussed above in History. The procedure from White et al. (1971) will be used as guidance for the separation of the head from neck, hypothermia technique, as well as reconnection of the vascular system. The operation will open the area between C4-C6 vertebrae (this is the part of the neck about 4 fingers from the base of the scull and about 2 fingers above shoulder level), with the spinal cord and vascular system transected at the C5-C6 level. The Thyroid complex of the body will be kept intact, and the head's thyroid system left behind.[1] The Thyroid is responsible for hormonal regulation of many different parts of the body.

The GEMINI protocol will use a diamond blade to sever the spinal cord on both the body and head. This will make the cleanest cut possible; important for giving the PEG fusogen the best chance to fuse the two separate nervous systems together. In order to effectively work, the cords must be connected with fusogen no more than 2 minutes after spinal cord severance or the PEG will significantly decrease in efficiency.[1,5]

The surgeons must be fully prepared to work under extraordinarily tight time constraints, and be confident in their work. In order for this fast transfer to occur, all other aspects of the surgery will need to be prepped before the transfer, so that as soon as the spinal cord is severed the head can be seamlessly transferred to the body, the PEG fusogen applied, and the spinal cords aligned, all within a 2 minute window.

Throughout the surgery, the patient will be in a drug-induced coma, which will continue for three days after the surgery. As with all transplants, immunosuppressant agents will be used to prevent organ rejection. After the surgery there will be therapy to assist the patient regain motor movement with the help of spinal cord stimulation (SCS).

There is still work that needs to be done as far as smoothing out surgical challenges and practicing further. The time crunch mentioned under the spinal fusion, and the low rate of success with the SCS therapy are the two biggest barriers to this surgeries success. Further testing needs to occur before this surgery should be tested on a human.

1900 **Early 1900's** Head Transplant Surgery first conceptualized. Challenges: reconnecting blood vessels [7]

1910 **1908** Dr. Carrel (French) and Dr. Guthrie (American) successfully attached one dog's head to another's neck allowing for blood flow [7]

1920 **1912** Received the Nobel Prize in Physiology and Medicine for work on limb/organ transplantation[7]

1930 Dr. Demikov's two headed dogs[7] (Adapted from Lamba, Holsgrove & Broekman)

1940

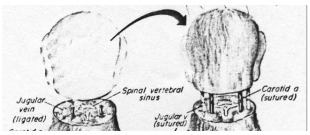
1950 **1953** Dr. Demikhov of the Soviet Union conducted the first coronary bypass surgery in dogs; the dogs survived 2 years post-surgery [7]

1954 First dog head transplant surgery; survived for 29 days with some motor movement and ability to lap up water. Challenges: immunosuppresion [7]

1960

1970 **1970** Robert White an American Neurosurgeon conducted the first total head transplant on monkeys. Challenges: High levels of immunosuppressant agents killed the monkeys prematurely [7]

1980



First total head transplant in a monkey (from White et al. 1971)[7]

1990 **1999** Immunosuppressant agents developed and can be delived in non-toxic doses

2000 **2006** First successful face graft: shows skin rejection will not occur using new immunosuppressants [7]

2012 Spinal Cord Stimulation therapy for regaining motor movement after spinal cord trauma [9]

2010 **2013** Dr. Canavero published the paper that outlined the proposed surgery HEAVEN and the protocol for spinal cord reconnection, GEMINI[1]

Nov 2017 the first head transplant practiced on a cadaver [4]

2020

Dec 2017 The first head transplant is scheduled to take place [10]

The Ethics

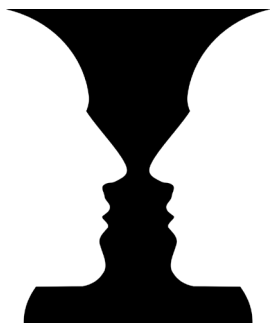
Who wakes up on the other side?

This surgery asks the fundamental question of what makes a person himself or herself. Is it their brain? Is it their body? Is it some interaction between the two? If the fairly significant amount of research that suggests that embodied cognition is correct is true,[14] there should be a totally new and independent person who comes out of the surgery. Embodied cognition is a

Surgical Challenges	Successful?	Progress to date	Further Issues
Blood flow and circulation	Yes	**1908** Carrel & Guthrie[7]: two-headed dog **1954** Demikhov[7]: two-headed dog **1965** White[7]: monkey head transplant **2016** Ren et *al.*[12]: two-headed mice	No further issues to address before the surgery
Immunosupression	Yes	**1950-60's** Development of azathioprine, 6-mercaptopurine, and corticosteroids[7] **1999** Immunosuppressants that are effective in preventing skin rejection without toxic events[7]	There is always room for improvement, but current immunosuppressants should work for this surgery.
Severed Spinal Cord	Yes	A diamond scalpel makes a clean cut through the spinal cord.[4] Human cadaver practice	The cleaner the cut, the cleaner the rest of the procedure will be.
Spinal cord fusion	Not Fully	**2016** Kim et *al.*[5]: PEG fusogen help with spinal cord reconnection Human cadaver practice	While this technology is very powerful, and has had success, it must be admistered within the **first 2 minutes** or the fusion will **not** occur, and the spinal cord will not reconnect.[1]
Neuroprotection	Yes	**2016** Ren et *al.*[12] **2017** Li et *al.*[8] - EEG monitoring shows hypothermia provides neuroprotection from ischemic events in a two-headed mouse experiment	Induced medical coma and localized hypothermia at in both the donor brain and the donor spinal cord will give the surgeons time, there the surgeons will still need to work fast.
Recovery of motor movement	Not Fully	**2012** Minassian et *al.*[9] - SCS a therapy that helps patients regain motor control **2016** Kim et *al.*[5] - the fusogen	SCS shows some promise, **but does not have a high rate of success.** The fusogen, again, need to be applied quickly in order to work.
Pain Control	Yes	**2007** Canavero & Bonicalzi[2] - Central Pain Syndrome understood and treatment found	It is still uncertain if this will be enough to treat all of the pain that will arise from the surgery.

theory of self that suggests that the mind – our cognition – arises from how our bodies, including the brain, interact in the physical world - that the brain is not the only part of the mind, but rather that the body also participates in the formation of self. This means that not only are you your brain, but you are also how your body interacts with the world.[14] Embodied cognition postulates that the brain and body are greater as a whole than as its parts, and that together they make up whom you are.[3]

The specific issue in head transplant surgery is whether the mind derives from the donor head or donor body, or from the interaction of the two? If the surgery is a success, when the patient wakes up we have no way of knowing who is waking up: is it the person whose brain was donated? or the person whose body was donated? Or is it someone new altogether? This person has the genetic material of the body donor, the memories of the brain, and a major surgery to recover from. This new person will at the very least be confused, will likely need to work through some basic metaphysical questions, and may suffer from serious psychological complications, including mood disorders, suicidal ideation/tendencies or psychosis.[3] It will be critical to the success of head transplant surgery that trained specialists be available to assist the patient in his or her psychological recovery, as much as in his or her physical recovery.



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Who has Reproductive Rights? If the patient survives and thrives, and wants to have a baby, what should happen?

The genetic material of this new person will be that of the donor body, which comes from a person who is brain dead. Does the donor body – or since he or she was brain dead – his or her family, have a say in the new person's reproductive behavior? In an attempt to salvage control over the genetic material that they share, in the absence of consent from the brain-dead body donor or his or her family, and no genetic material should be passed along through this new person.

Is this the best use of a Donor Body?

The waiting list for livers, hearts, lungs, pancreas, kidneys, and other organs for transplant is years long. Donor organs are hard to come by, and must be used as soon as possible. In the case of a head transplant, a donor body is valuable as a whole to possibly prolong one life, in an extremely high risk experiment. But it is significantly more valuable, and can potentially help more people, by being distributed to many people who could use a number of different organs.

Given current circumstances, including long organ wait lists, and the extremely experimental nature of head transplant surgery, donor bodies should be used to help alleviate the most suffering. This experimental surgery has not been proven to work - cadaver cases do not count[4] - and with an over $100 million price tag for the first attempt, this will be a costly endeavor, not only in expendable resources like money, but also in biological resources which could be distributed to numerous other persons in need.

What are Future Uses, Abuses, and Misuses?

There is always a risk that when a powerful technology is developed that – in addition to the great positive effects it may have – it also will be misused and abused. In the case of head transplant, when the technology is refined it might be used for a sex change, so a person can be the biological sex they identify as. This surgery could be used to change health outcomes, swapping a diseased body for a new one. Also, this surgery has the potential to change your body's age, artificially elongating life to far past what is considered normal today. This surgery has the potential to be a ticket to immortality.

So for a moment let's pretend like this surgery is already perfected. The kinks have been worked out as far as the technical side goes, and we will say that the head donor will be the person who comes out on the other side of the surgery, making the philosophical question of "self" void. For

the sake of this article, let's imagine that a wealthy middle aged to elderly man wishes to become young again. All he has to do is find a donor body, sign a waiver and prepare himself for the surgery to come.

The outcomes of the surgery will mean a higher quality of life - having a fit, young body again - and also will elongate the elder man's life. A younger body means the hormone levels and blood of a younger person. These different factors have age-protective effects on the body, and younger blood even has a neuroprotective effect on the brain. The thyroid complex will be that of the donor body. This means that the hormones that are released into the body, and eventually introduced into the new brain, are that of a younger man. Recent work looking at what causes age-related changes looks at two hormones, growth hormone (GH), and insulin-like growth factor-1 (IGF-1). GH and IGF-1 have important mechanisms for ageing, and restoring these hormones to aged animals restores cellular protein synthesis, lean body mass, immune function, skin thickness, and vertebral bone density. It can be assumed that in the aged head and brain this would help with recovering from the surgery, and also preservation of the aged head.[6]

For a long time blood was thought to be our life force. Now we know that blood is the transporter of nutrients around the body, without which we would not be alive, which while similar in meaning, has a different connotation from life force. But recent research showed that blood could take on an almost supernatural ability. The Villeda lab group showed that introducing the blood of younger mice could counteract cognitive decline in older mice. There was improvement in neurogenesis along with synaptic plasticity, which counteracts age related cognitive decline. Also introducing 'pro-youth' factors from young blood can help reverse age related impairments in the brain.[15] This shows that a new body, and therefore new blood, will actually improve the older brain of the head donor. This neuroprotection will allow for the head donor to have better health outcomes and be healthier all around, not just a stronger body but also a stronger brain as well. This isn't immortality in a classical sense, because eventually the brain will decay; however, this will be a method to push the boundary of what old age is.

Because this surgery holds so much promise for a variety of different populations, it makes body donors highly valuable. Sex change, health improvement, and age adjustment, all face the criticism mentioned above that by using this donor body for their own purposes, they take the donor body out of circulation for all other types of donorship. There is already a black market for donor organs, and if this surgery becomes viable the demand for whole donor bodies will only increase. I believe that there is a real opportunity for financially needy people to be taken advantage of

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for the economic benefit to their family. For instance, any of these 3 populations of head donors may have the means to pay a person to give up their body, for the economic gain of their family. While this is an extreme postulation, there are extreme situations that happen all over the world, and it would be naïve to turn a blind eye to this ethical concern for the possible corruption of the technology. However, we still have some time before we have to truly start worrying about full donor body markets. Perhaps before that occurs, we will put in place guidelines to help us only use this technology for diseases that have no other effective therapy or cure.

Is it worth it?

This is a risky surgery, not only because of high risk of patient death, but also because it could lead to a totally new, psychologically unstable person coming out on the other side. The resulting "new person" is an amalgamation of a brain and body that have given consent but the "new person" has not consented to the uncertainty of physical, mental and emotional

recovery. Since the surgery and technical tests give no certainty of ever regaining goal-directed movement, which is what most patients on the "brain" side are seeking, and since the "body" side has the most work to relearn rudimentary motor skills[9], there is a basic ethical dilemma facing the resulting new person, and the mind that controls it. And the psychological development and healing facing the patient is significant, with virtually no known guidance on how best to assist in this endeavor. Moreover, basic ethical questions, such as who should control reproductive rights, is this the best use of a donor body and its variety of useable organs, and how to avoid black markets from developing for use in head transplants, must be considered and thoughtful plans developed to deal with those issues. Doctors have a duty to their patients, and to their profession, to uphold the Hippocratic Oath. The Hippocratic Oath states that:

"I will apply, for the benefit of the sick, all measures [that] are required, avoiding those twin traps of overtreatment and therapeutic nihilism… Above all I must not play God…"[13]

Given the substantial open issues involved, perhaps it is time to step back and re-evaluate whether the world is ready for head transplant surgery.

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Understanding Blindsight as A Window to Consciousness

By **Danielle Wald**

Understanding Vision

From the Eyes

The process of vision begins in one of the most complex sensory organs: the eye. There are two main visual pathways that begin at the retina in the eye. The geniculostriate pathway begins when light that hits the retina and is transformed via a map of intercommunicating neurons, namely photoreceptors, horizontal cells, bipolar cells, amacrine cells, and ganglion cells. After exiting the eye, the optic nerve carries the information to the lateral geniculate nucleus (LGN), which then relays the signals towards the back of the brain, ultimately reaching the visual cortex (Figure 1).[1] In the second pathway, the tectopulvinar pathway, signals from the retina project to the superior colliculus. From this location, the projections continue to the pulvinar, where they then finally end in the extrastriate cortex.[2]

To the visual cortex

Once the input has reached the visual cortex, it is ready to begin its journey through more complex processing, resulting in higher order perception. The visual cortex may be broken down into a hierarchy of different mechanisms which work together to create the experience of sight. This projection starts with Area V1, which is also referred to as the striate cortex.[3] Area V1 is an important location for the conscious perception of vision.[4] After spending time in Area V1, visual information is forwarded to the extrastriate cortex, specifically Area V2 and Area V4, where it is further processed and then sent to regions of the brain to be analyzed (Figure 2).[1]

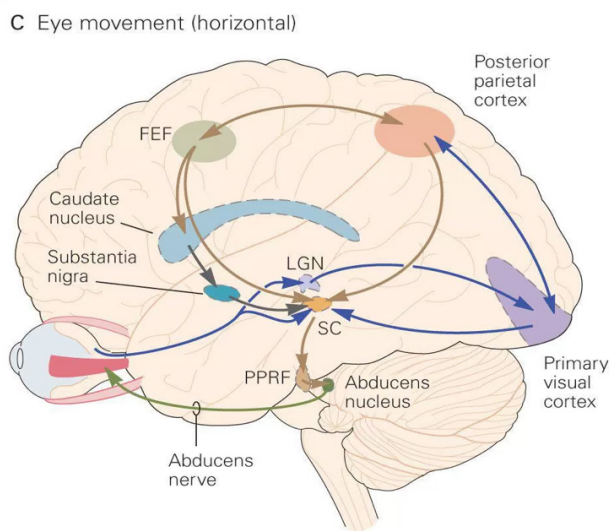


Figure 1 Visual information travels from the eye throughout the brain where its ultimate goal is the Primary Visual Cortex.[16]

When Something Goes Wrong

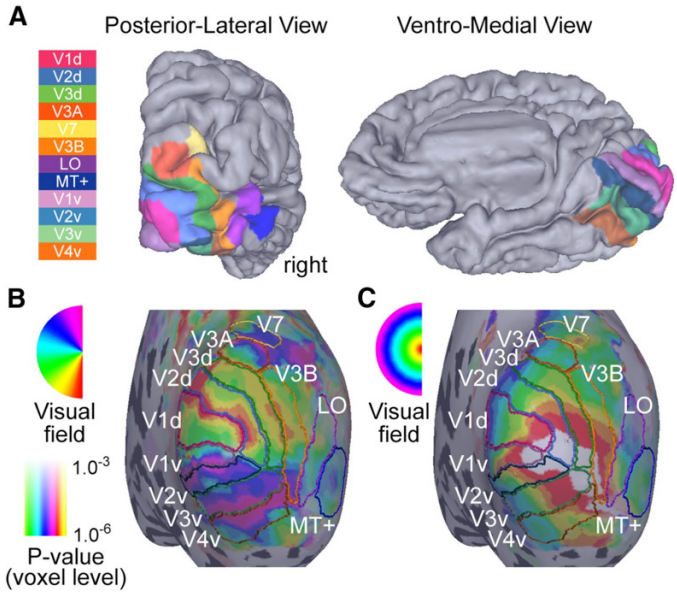
Cortical Blindness and Blindsight

Cortical Blindness results from a lesion to Area V1 of the visual cortex, causing the individual to experience a lack of awareness of visual input to the extent that they report either partial or complete blindness.[5,6] Despite feeling as if they have a complete visual deficit, these individuals still show behavioral signs of lower level visual processing, including motion detection.[7,8] This phenomenon most likely arises from the absence of functionality of the geniculostriate pathway, leaving the tectopulvinar pathway to operate as the sole pathway of visual perception (CitationA).

Distinction from Typical Blindness

Cortical Blindness differs from typical blindness in that typical blindness results from a fault of

Figure 2 Divisions of the Visual Cortex.[17]



sensation, a lesion to the eye, while the former is caused by a deficit of perception, damage to the visual cortex.[6]

Famous Case Studies

Patient DB

Arguably, the most famous and thoroughly investigated blindsight patient is Patient DB, who became cortically blind after the right hemisphere of his visual cortex was removed during surgery for the purpose of eliminating a benign tumor. Despite the unilateral removal of this area of the brain, DB has shown that he is able to discriminate between different objects despite his inability to consciously perceive them. Additionally, DB has demonstrated his ability to utilize binocular distance perception.[9]

Patient GY

Another well studied patient is Patient GY who, due to an injury, suffered a lesion to Area V1 in his left hemisphere. GY has the ability to detect movement. Additionally, this patient has provided significant neuroimaging evidence for the basis of vision; various PET scans have shown an absence of activation in the lesioned Area V1, demonstrating that GY's subconscious ability to perceive vision is, in fact, independent of Area V1.

Patient TN

Patient TN suffered a stroke causing a bilateral lesion to his striate cortex. As a result, TN experiences complete cortical blindness. Remarkably, when presented with a hallway cluttered with obstacles, TN is able to successfully navigate around these objects.[11]

Researching Blindsight

Contrast Sensitivity

There are various tests that researchers have created in order to better understand the various mechanisms that underlie blindsight. One of the most basic aspects of vision is contrast sensitivity, which refers to the ability to detect stimulus on a background when difference between the background and the stimulus continues to lessen. In patients with blindsight, this test is presented as a forced-choice paradigm.[12] The forced-choice model of research is essential for many tasks when working with blindsight patients, because most patients will report the inability to complete the task, due to their lack of conscious awareness of their visual field.

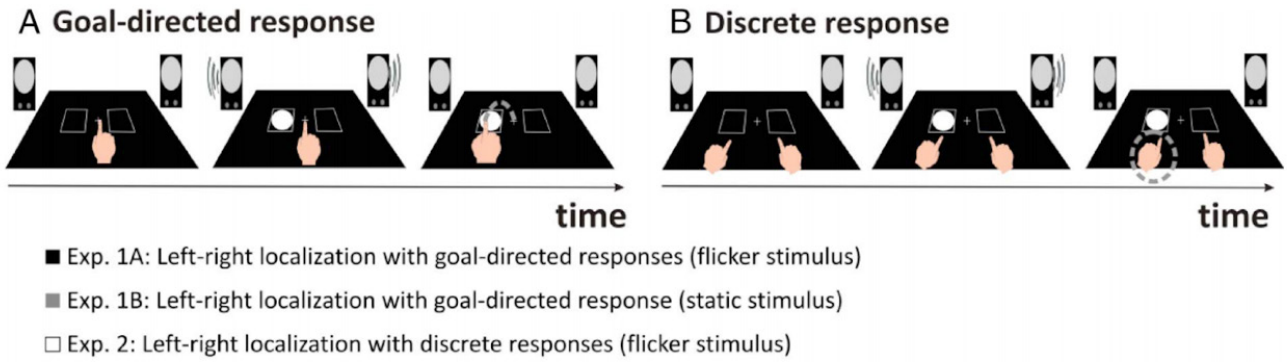
Goal-Directed vs. Discrete Response Localization

Some researchers believe that the interaction of the visual and motor cortices may play a role in blindsight patients' abilities to locate an object on a two-dimensional surface (i.e., a computer screen). This specific hypothesis was tested on the aforementioned Patient TN; the patient was tasked with locating an object on a screen in front of him. In part one of this task, the subject must lift his hand and point his finger to the object on the screen (a goal-directed response). In this part, the subject is exposed to both static and flickering stimuli. In part two of this task, the subject must simply lifting an index finger to signal the relative location of the object within their visual field (a discrete response); in this part, the subject is only exposed to a flickering stimulus (Figure 3). According to the results from Patient TN, the goal-directed response provides for greater accuracy in this population.[12]

Effect of Stimulus Size on Perception

In another forced-choice task, blindsight patients are presented

Figure 3 Goal-Directed Response vs Discrete Response Experiment.[11]



with stimuli of various sizes in order to determine whether the size of stimuli has an effect on their detection ability. In this task, patients are asked whether or not they see an object on a screen. Previous research in this area suggests that larger sized objects are easier to detect, but there is individual variability in ability to detect smaller objects.[13] This is to be expected of a typically sighted group, thus, it is possible that effect of stimulus size doesn't interact with blindsight any differently than it does with normal vision.

A Look at Consciousness

Perceiving visual stimulus below the threshold of consciousness

In examining the phenomenon of blindsight, a certain question arises: What is the benefit of having the ability to perceive vision below the threshold of consciousness? A potential answer to this lies in the fear response. This automatic mechanism is necessary to human survival, thus possessing a significant evolutionary benefit.[14] Like other animals, human experience of fear is essential in that it motivates avoidance of and escape from potentially dangerous stimuli.[15] Because it is beneficial to the individual that the fear response to be as quick as possible, the activation of ventral stream occurs quickly and automatically, bypassing the normal level of consciousness in humans.[14]

Because the automatic fear response is such a key part of our evolution, it is possible that the automatic nature of this mechanism is indicative of an evolutionary role of visual perception that lies below the threshold of consciousness.

Criticisms

Is Blindsight real?

One particular piece of literature has been cited many times for its significant arguments against the existence of the blindsight phenomenon. Campion et al. point out that it is possible that these blindsight patients are not exhibiting behavior that is significantly different from that of typically-sighted individuals.[15] The lack of demonstrated confidence in detection of stimulus by the blindsighted population can be compared to hesitance of a typically-sighted group when asked to report on stimuli near their visual threshold. Thus, this argument would support the idea that blindsight patients just have a visual deficit, altering the threshold in which they perceive visual stimulus.

The argument continues with a more obvious point: could the minimal spared areas of the striate cortex be picking up slack for their lesioned neighbors? This argument has the most strength in the cases of blindsight where damage is unilateral. In these cases, one hemisphere of the visual cortex is completely intact, and thus, could potentially be compensating for the absence of that region of the other hemisphere. Considering the sensory organ, itself, it is possible that the intact retina is, in fact, playing a more significant role than previously thought in perception of light.[15]

Campion et al. end their argument in reference to subjects who are not cortically blind throughout their entire visual field. They suggest that these individuals are simply using different methods to describe or perceive their visual experiences in seeing vs blind areas in the visual field.[15]

Reflection on Criticisms

While these criticisms contradict or ignore certain evidence, they are still significant to further research into blindsight and consciousness alike. It is important to remember that science is advanced by disagreement and questioning is an essential factor in furthering the understanding of our environment.

Future Research

The existence of a subconscious pathway of visual perception in humans that yields consistent behavioral results across studies inspires greater research into not only the nature or purpose of consciousness, but it also the drives the idea that there may be other neural mechanisms that lie just beyond our awareness.

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Let's Get Scent-I-Mental

By **David Perez**

Have you ever wonder how important your nose is? For some animals, sense of smell is the most important type of sense. Since a dog's sense of vision is awful, their sense of smell is incredible compared to humans. Dogs sense of smell is between 10,000 to 100,000 times more acute than humans.[13] An analogy to vision of this would be, "what you and I can see at a third of a mile, a dog could see more than 3,000 miles away and still see as well."[13] Even though our nose isn't as powerful as dogs, we need our nose to survive. Our is nose is responsible for more than picking up odors from the air.

People who have lost the ability to smell lose more than just being able to smell things. Nick Johnson, a person that lost his sense of smell, can remember the exact day he lost his sense of smell, it changed his life forever. He was playing hockey with his friends and he fell and hit that back of his head on the ice. He made a rapid recovery, but a couple days later he found himself trying a new beer with his friends. "Can you smell the hops in the beer?" and he couldn't "It's got this pale biscuit flavor" and he couldn't taste it. He then realized that his loss of smell hindered him from smelling and tasting. Dr. Rachel Hertz says that, "Sense of smell is essential to our humanity: emotionally, physically, sexually and socially". It's also clinically documented that acquiring anosmia often leads to anxiety and depression. Even knowing all this, people still ranking losing sense of smell at the bottom and people compare it to losing a big toe. Some people don't understand how important the nose truly is.

Our nose is also necessary for our safety. Our noses can detect smoke, spoiled food and toxic gases.[12] The nose is also responsible for other things like humidifying the air, shaping the sound of your voice, and even helps you find a mate.[12] The nose is also important for something indirectly. Everyone knows the smell of freshly baked chocolate chip cookie. For me, I always remember baking them with my grandma when I was a kid. That memory always makes me happy and smile. By being in a good mood, I made good decisions based on my feeling because I didn't want to lose my current mood. There also therapy sessions that people can do that can alter one's mood by just using odors. This line of succession shows that the nose can alter people moods and therefore could potential hinder their decision making through the memories that are evoked by odors.

Mechanism of Odor Detection

The exact mechanism behind odor detection is still rudimentary. Knowing the exact mechanism could unlock new ways people can alter their decision making. Odor molecules connecting to the olfactory receptors is the first step to odor detection. Olfactory receptors are responsible for the detection of compounds that have odor which gives us the sense of smell. The olfactory receptors are in the cilia synapses and the epithelium tissue of the human airway. The epithelium, a type of tissue that

"Woman Smelling Flowers" by Petr Kratochvil is licensed by CC0.

"Insect, fly, wing, macro, animal" is licensed by CC0.

lines the cavities and surfaces of blood vessels and organs, is highly permeable and therefore, highly sensitive to various odors molecules and even various pathogens.[1] The location of the olfactory is unique to humans. In insects, the olfactory receptors are located on the antenna. In fruit flies, adults have about 1200 olfactory receptors neurons (ORNs) on each antenna.[2]

In the epithelium tissue, each ORN expresses only a single type of receptor. So only one gene is expressed by each receptor.[4] According to the Human Genome Project, humans have about 400 genes that codes for olfactory receptors, the rest of the genes of are pseudogenes. Pseudogenes means that the genes are similar enough to the 400 genes, so that the olfactory receptors will express them.[5] So, each receptor has the capability to detect more than one odor. Even with the combining of genes, humans can distinguish hundreds of different smells. But other animals can smell more specific things than humans[13].

After the odor molecules binds to the receptor, the receptor will send electrical signals through the ethmoid bone and to the olfactory bulb.[15] The ethmoid bone separates the nasal cavity and the brain. The olfactory bulb is the area where those signals are analyzed and processed.[15] The olfactory bulb contains nerve tissues called glomeruli that are formed from branching ends of axons of the olfactory receptors and from dendritic branches of interneurons known as mitral cells.[6] So overall, the axons of all the receptor cells that produce a specific chemical or range of chemicals with similar structures converge on a single glomerulus, where they connect to similar mitral cells and the mitral cells transfer the signals to the brain.[6] This way, similar information from many receptors can be brought to the glomerulus together. The signals travel to different brains areas like the hypothalamus and the amygdala, which can result in bring up emotional memories. The human odor detection can discriminate between hundreds or even thousands of different odorant molecules. It is very important to discriminate these odors, especially for decision making because each odor could produce different memories.

Did you know?

Sperm cells also express odor receptors, which is thought to be how sperm can locate the eggs.[3]

Odors and Memories

Odors can evoke different types

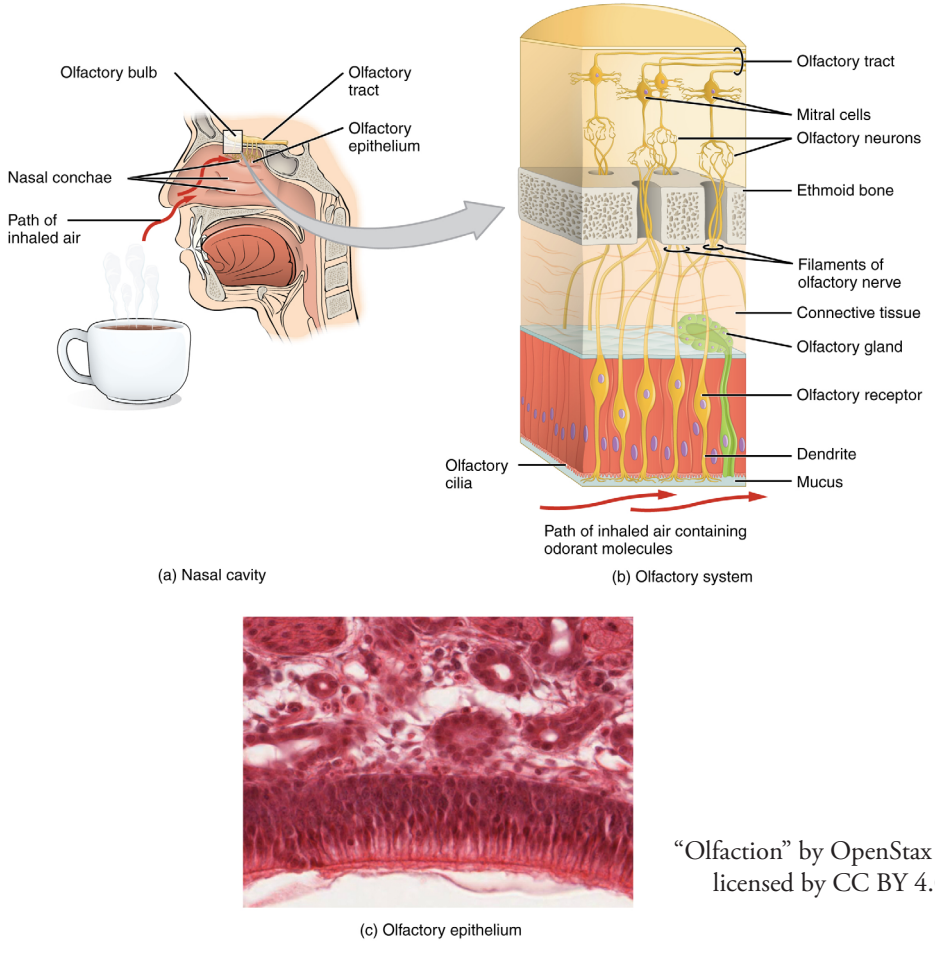

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Table I. Odor preparations presented to the subjects — Adapted from Herz & Cupchik 1992.[7]

Odor ref. no.	Odorant	Typical name[b]	[Conc]	Rank pleas.	Rank fam.
1	iso-amyl acetate	banana	1%	3	4
2	aldehyde AA triplal	grass	1%	6	7
3	peppermint oil natural	peppermint	10%	2	1
4	dimethyl disulphide	faeces	1%	14	10
5	amyl vinyl carbinol	mushroom	pure	18	20
6	violet leaf ABS	mildew	10%	12	18
7	jasmine	jasmine	pure	4	6
8	NK pine 003 relaxing	pine	10%	7	8
9	*n*-butyric acid[a]	rancid butter	1%	19	17
10	iso-valeric acid[a]	dirty socks	1%	20	15
11	eugenol	honey-vanilla	10%	9	11
12	clove Bud oil usp	clove	10%	8	5
13	beech-wood creosote	tar	25%	17	14
14	myrrh coeur	vinegar	10%	11	16
15	heliotropin	lotion	25%	5	9
16	coconut	coconut	10%	1	2
17	cumin oil	curry	10%	16	12
18	vetiver oil bourbon	rotting leaves	pure	13	13
19	clean fresh pine	'Vicks'	10%	10	3
20	birch tar rect	smoke	10%	15	19
Practice odor:	lemon oil	lemon	pure		

Rank pleas. = pleasantness rating rank score out of 20 odors; rank fam. = familiarity rating rank score out of 20 odors.
[a]Obtained from Sigma, St Louis, MO.
[b]Typical names supplied here do not represent the only possible 'correct' name for each odorant.

of memories in humans. The type of odor is very important for the type of memories that is evoked. Memories evoked by odors tend to be emotional, very clear, specific and comparatively old.[7] Odor-evoked memories are also thought of less and very emotional. This shows that the most familiar odors elicited the most memories. So, for example, Table 1 shows an experiment where Peppermint odor has the highest familiarity out of the other 20 odors and which increased the potency [7]. The ranking system isn't constant for everyone though. Even though coconut is ranked the most pleasant doesn't mean everyone in the word would enjoy coconut. There also is a difference between the sexes. The females tend to use more emotion descriptors in their memory description than did males which, produced clearer memories[7]. Odors can evoke memories, but can other cues also produce the same memories?

We use our five senses every single day; sight, hearing, touch, smell, and tasting. We need these senses to thrive through the day. Some people are missing at least one sense which could hinder their way of living. These senses actually work together, so if one sense is not working, then the other senses will take over and make up for the missing sense.[14] Although our senses are important not all of them are able to evoke memories. A study was done to see which senses produced the most vivid memories, vision, smell, and hearing. The results showed that memories evoked from odors are talked about and thought about less than when its evoked from the other cues.[8] Odors produce more pleasant and more intense emotions.[8] In sum, this study shows that odor can evoke emotional memories that are old. One reason why these memories are not talked about as much could be because these memories are emotional. These emotional memories could

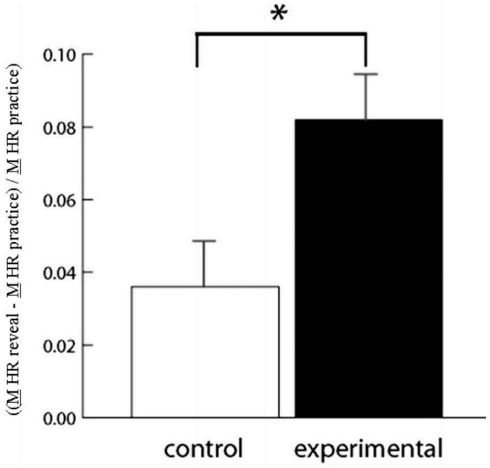
elicit a certain mood weather it would be happy or unhappy.

Another study was conducted to see what type of emotions would arise from different odors. The study used various odors, the odors were either pleasant or unpleasant. This test is interesting because people have different standards for what is pleasant and what is unpleasant. Some people might think a certain smell is pleasant when other people might think is unpleasant and vice versa. In the study, subjects that were given a pleasant odor produced happy memories and unpleasant odor produced un happy memories. The odors that were given to them was shown to affect the retrieval process rather than the rating process.[16] This shows that odors do evoke memories and not just how we rate them. These studies have shown that odor can evoke different memories for different people. Each person has different memories brought up from odors if they are familiar enough with them. The odors also produce an emotional memory that could eventually affect the person's mood and therefore their decision making.

Emotion and Decision Making

Once the odors recall a certain memory, the memory is going to evoke a certain emotional mood and then that certain mood is going to determine what decision you make.[17] Decision making is a very important thing for humans. Wayne Dyer, an American philosopher, once said that, "Our lives are the total of the choices we have made".[17] Every day we are faced with choices that we must make. Some decisions are minor, and we don't think twice about them. Some decisions are major, and we must spend a lot of time thinking about them. Even though those minor decisions aren't going to affect our lives immediately, those decisions could add up quickly and become something bigger. To make all these important decisions, we must be in the right type of mood which is how our emotions come into play. For example, a person who feel anxious about an outcome of a risky choice may choose a safer option rather than the risky option.[17] Emotions are an integral part of a person internal state and therefore has big influences on one's decision.[17] There are many theoretical approaches that link emotions and decision making. The agreed steps to decision-making are; Asses the available options, the selection of option based on value that has been associated with it, and the outcome associated with the decisions is evaluated and incorporated into existing knowledge.[18] Emotions come into play by modulating the assessment, selection, and the outcome evaluation of options. For example, A sad mood may result from an undesired outcome, but it can lead to an increased salience of negative attributes of options.18 The choices we make are also dependent on the type of option we are given, the degree of the affect associated with the option and the nature of the presentation of the option.[18] Based on this, emotions effect the value and weight computation of available options. Also, the choosing of options is based on the environment and the individuals internal state.[18] That means the emotions of the person making the decision can alter their decision making. Some disorders hinder the ability of decision making effectively.

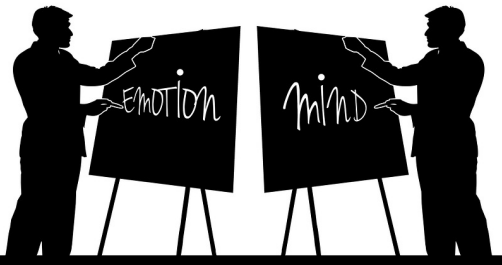
Adapted from Preston et al. 2007.[20]



Decision Making with Anxiety and Stress

All of us have been in those situations where we have an important exam coming up and you have cram as much as possible. Do you remember feeling stressed or having anxiety about the exam? Well stress has been seen to enhance memory formation, but stress also impairs memory retrieval and it impairs the ability to update mem-

"Man Presentation Feeling" by Gerd Altmann is licensed by CC0.



The Iowa Gambling Task[14]

- There are 4 decks of cards (A, B, C, and D).
- Participants choose a total of 100 cards, one at a time.
- Each time they choose a card, they get feedback about winning and/or loosing money.
- Participants did not know what each card would yield in advance, like a lottery.
- Participants started with a "loan" of $2,000 and were told to make a profit.
- Decks A & B always yielded $100. Decks C & D always yielded $50.
- For each chosen card, there is a 50% chance of having to pay a penalty. Decks A & B have a penalty of $250, whereas decks C & D have a $50 penalty.

ories in the light of new memory.[19] Stress could hinder one's ability to succeed on those exams. Stress can affect people's ability to make decisions. This research ran an IGT and during their test, the experimental group was told that they had to give a public speech right after. This made the people in the experimental group to stress out.[20] The people that were stressed were slower to learn the task meaning it took longer to shift toward advantageous decision making in the IGT.[20] So far in this magazine, I have shown that odors can recall certain memories, which then could elicit certain moods and those moods could alter your decision making. Maybe odors could be used to de-stress people since it has been shown to hinder people

Individuals with anxiety disorders have shown to increase bias towards threat-related content and intolerance of uncertainty. That would mean that the individuals with anxiety disorders will lean towards bad content than the good content. Which for the large negative consequences, individuals with anxiety make more sensitive and thus more aversive to the large negative consequences.[18] This could be a good thing and a bad thing. This could hurt individuals with when a highly negative outcome is the best value. This situation could pop up when people are deciding from two negative outcomes and they must decide the lesser of the worse. By being more aversive to options with large negative consequences, individuals with anxiety perform better in the Iowa Gambling Task (IGT).[18]

Overall, these studies have shown that different emotional states can hinder human's ability to make decisions which is a vital thing. Since decision making is a fundamental part of living, finding a way to control emotions arising during decision making is important. One form of therapy that has been shown to decrease stress and other mood using odors is aromatherapy.

Aromatherapy

Have you ever been anxious or stressed and wish there was an easy way to get rid of that? If only there was a simple way to fix that. Good thing there is aromatherapy to help that. Aromatherapy have been in use for therapeutic purposes for nearly 6,000 years.[21] Aromatherapy is the art and science of utilizing naturally extracted aromatic essences from plants to balance, harmonize and promote the health of body, mind and spirit.[9] Aromatherapy uses natural oils from flowers, barks, stems, leaves, roots, and other parts of the plant. This process has been shown to enhance an individual's innate healing process, stimulate brain functions and has been shown to decrease stress.[9,10] A study was conducted to examine the level of stress in nurses after aromatherapy using lavender oil. The results showed that the nurses stress symptoms dropped for three days and their stress dropped from 6.1 to 2.8 (a scale for job stress-related symptoms was used).[21] By decreasing stress, this allows nurses to make quicker and better decisions which will help immensely in their line of work. Aromatherapy has also been shown to affect moods in a positive way.

A study was done to see how alert and how well participants can do in computational tasks after a treatment of aromatherapy. The aromatherapy used two different oils that have been shown to produce two different outcomes. Lavender oils have been shown to relax individuals while Rosemary oil has been shown to

increase alertness.[22] The results of the study showed that lavender produced a less depressed mood therefore performed math computation faster and more accurately. The rosemary showed that the participants were more alert and showed faster math computations than lavender group but not more accurate.[22] This shows that even though the rosemary increases alertness and therefore increases awareness, the rosemary participants performed worse than the group that was more relaxed. This also shows that different odors can evoke different moods and therefore lead to different results.

Aromatherapy has also been shown to help patients with anxiety and depression. A study done by Louis and Kowalski 2002, measured the responses of 17 cancer hospice patients to humidified essential lavender oil aromatherapy. The results showed that there was a positive change in blood pressure, pain, anxiety, depression and sense of well-being when treated by lavender aromatherapy.[23] The study also showed that water humidification treatment caused a positive change.[23] The results showed that repeated lavender treatment sessions could increase beneficial effects. Interesting enough, the caregivers also experienced relaxation due to the calmer atmosphere and environment after the lavender treatment. This was not observed at the end of the water humidification treatment.[23] Aromatherapy, in general, has a lot of potential of being a valuable treatment of anxiety, depression and stress.

Odors are important for many things because odors can alter one's decision. and it isn't a huge secret either. The fragrance industry spends up to millions of dollars trying to figure out what type of scent would people like most. Looking at what type of memories arise from certain smells could help those fragrance company figure out the perfect scent. You might not know this but stores around the world are already taking advantage of your sense of smell. One store that takes advantage is Cinnabon. Cinnabon's cinnamon rolls has an infamous scent that can persuade customers to buy a cinnamon roll. Cinnabon knows that their smells can lure people into their store, so they use many tactics to do so. One thing Cinnabon does is that they purposely put their ovens near the front of the store.[24] That way the smell will linger out of the store and into the hallways of the mall. Kat Cole, the president of Cinnabon, told WSJ that sales dropped significantly when the ovens were moved to the back of the store.[24] They also buy the "weakest hood possible" that is legal for their ovens.[24] That way the smell can seep through the oven and linger through the halls. These are some of the ways Cinnabon uses their notorious smells. They know what the power of scent and they use it to their advantage. Cinnabon isn't the only company that uses smells, Nike showed that adding scents to their stores increased sales by 80 percent.[25] Many companies are already using odors to their advantage. It's time for us to use odors to our advantage. Odors have a lot of power and has to ability to help many individuals.

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Oxytocin & Vasopressin

HOW SOCIAL TIES ARE FORMED

By **Rachel Arens**

Humans are socially bound to one another in complex and fluid ways that are distinct from other mammals. The relationships formed and sustained between two *Homo sapiens* are unique among the animal kingdom and are a large part of why humans have been able to come so far. There is no argument when begged the question, "Which species is most developed?" or perhaps, "Which species is most powerful on Earth?" Humans clearly win out here, as they have the power to build and destroy. In just the past 200 years humans have completely changed the climate and the biological makeup of the Earth. They did this through innovation and elaborate collaboration with each other, in which their ability to form deep and meaningful social bonds was critical. For example, humans have changed the world with their extreme use of fossil fuels. To use these fossil fuels humans first needed to discover how to extract these fuels, and even before that humans needed a purpose for the fuels: machines. To develop a machine, a drug, or a new way of thinking requires a group of people working together towards that common goal. For many hundreds of years, humans have formed families and communities to reach these goals.

So why are humans able to form these social bonds that enable them to change the world? What is different about humans that makes them *special*? Scientists have found that two neuropeptides, oxytocin and vasopressin, may be a part of the answer. While other mammals have these neuropeptides, studies have shown that in humans these play a more significant role in social bonds than in these other animals. As neuropeptides, oxytocin and vasopressin both act as hormones and neurotransmitters. As hormones, they produce physiological effects including uterine contractions or water conservation. As neurotransmitters, their functions are widespread and not completely understood, but revolve around forming social bonds.

History

Starting in the 1800's, scientists began investigating extracts from the posterior pituitary gland. First, in 1906, Sir Henry Dale found that an extract facilitated uterine contractions in cats[1]. He named the molecule "oxytocin", because it means "quick birth" in Greek. As early as 1911, oxytocin was used to induce labor in women[1]. This practice is still used today, however, rather than giving women oxytocin extracted from other mammals, women are given a synthetic version called pitocin. Pitocin has gained popularity in recent years as many women schedule the birth of their child due to the inflexibility that often comes with being employed[2]. Popularity has also risen due to a shortage of hospital beds in large cities; this shortage pressures providers to get people in and out of the hospital as quickly as possible. Natural labor takes on average 8 hours, but with pitocin this time is cut down to only 6 hours[2]. Thus, women and providers can be aided by this synthetic form of oxytocin, reflected in the doubling of the frequency of labor induction between 1990 and 2012[2]. Oxytocin is often given the abbreviation OT in scientific literature.

In 1913, the antidiuretic component of the extract was discovered by Farini and Vongraven[1]. Because of its properties, it was originally named antidiuretic hormone (ADH). However, as the hormone has gained popularity in neuroscience research and literature, the name vasopressin has also been used, originating from the fact that it is a vasoconstrictor and a pressor agent. In 1954, Vincent du Vigneaud won the Nobel Prize in Chemistry for his organic synthesis of ADH and oxytocin[1]. Following this accomplishment, ADH was frequently used as a medication in the 1960's-1980's to

treat diabetes and gastrointestinal hemorrhage.

Physiology

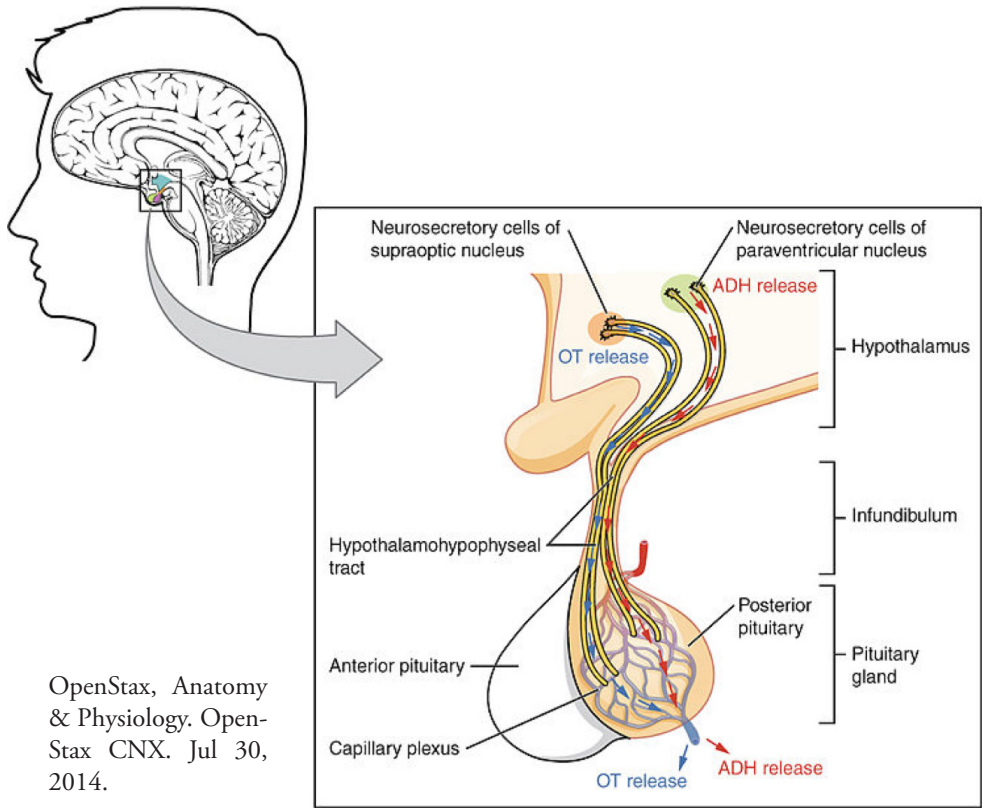
Oxytocin and vasopressin were both originally discovered and known for their roles as posterior pituitary hormones. As hormones, oxytocin and vasopressin are critical for multiple physiological processes. Understanding these processes is important to understanding how these neuropeptides affect the body holistically.

The role of oxytocin in general physiology is centered around reproduction. In relation to this fact, the highest concentration of oxytocin receptors is found in the magnocellular neurons of the hypothalamic paraventricular and supraoptic nuclei[3]. These nuclei are key in processes associated with reproduction, stress, growth, and metabolic rate. When a mammal encounters a stressful stimulus or a stimulus associated with reproduction (like suckling) oxytocin is released from the posterior pituitary into the bloodstream. In addition to these nuclei, oxytocin is secreted by multiple other tissues, including the uterus and testes, the placenta, and the heart[3]. As mentioned earlier, oxytocin is critical in the induction of labor through stimulation of the smooth uterine muscles. On a molecular basis, this happens through an up-regulation of oxytocin receptors in the myometrium and decidua, resulting in an increase in a steroid called PGF(2 alpha), which increases the body's sensitivity to oxytocin[3]. In males, oxytocin is important in the generation of spontaneous erections and ejaculation.

Based on the physiological processes in which oxytocin is involved, it is easy to imagine that oxytocin may also play a role in social bonding. Vasopressin's role is a little more elusive. Vasopressin is involved in many physiological processes, most of which have to do with the maintenance of body homeostasis, not reproduction. The two main sites of action for vasopressin are the kidneys and the blood vessels, where its primary function is to regulate the kidney's management of water[4]. This regulation happens when vasopressin binds to V2 receptors located in renal collecting ducts, increasing water permeability via a cAMP mechanism[4]. This process decreases the formation of urine while increasing blood volume. There are also V1 receptors, which are involved in vasoconstriction, the secondary physiological function of vasopressin. This process increases arterial pressure through a complicated combination of the IP3 signal transduction pathway and Rho-kinase pathway[4]. Release of vasopressin occurs through stimulation of stretch receptors within arterial walls and large veins, alerting the body to a decrease in arterial pressure often due to dehydration or hemorrhage[4]. These stretch receptors communicate with the medulla, which sends the message to the hypothalamus, which then relays to the posterior pituitary that vasopressin should be released.

Neural Anatomy

While oxytocin and vasopressin



OpenStax, Anatomy & Physiology. OpenStax CNX. Jul 30, 2014.

have many roles within the body, they also have roles in the brain. As stated above, the highest amount of oxytocin receptors is found in the magnocellular neurons of the hypothalamic paraventricular and supraoptic nuclei, which are heavily related to reproduction. However, there are also high concentrations of oxytocin receptors in the central amygdala[5]. Similarly, there are high concentrations of vasopressin receptors in the medial amygdala, another section of this brain structure[5].

The amygdala is a brain structure heavily associated with the processing of fear, anger, and emotion in general. Among the neuroscience community the amygdala is jokingly called "the teenager center" of the brain. Specifically, the central amygdala is the area that communicates with the hypothalamus, alerting the brain to stimuli that induce fear, anxiety, or other strong emotions. The hypothalamus then tells the posterior pituitary to release oxytocin and vasopressin.

How does the placement of oxytocin and vasopressin receptors in the amygdala affect behavior? Because the amygdala is associated with emotion and anxiety, the fact that there are so many receptors here is good evidence for these neuropeptides relating to these feelings. Interestingly, these two neuropeptides can have seemingly opposite effects, with oxytocin producing maternal care and positive social interactions while vasopressin produces aggression and anxiety. Although these neuropeptides may have different effects, on a cellular basis they both excite the brain regions with which they are associated. This circuit places the role of oxytocin and vasopressin in the realm of emotion, but exactly what type of emotion and what purpose does that serve?

Neurobiological Purpose

Through years of research, oxytocin and vasopressin have been found to be critical in pair bonding. The most obvious example of this is the bonding that occurs between a mother and her infant; during birth and breastfeeding there is an up-regulation of oxytocin receptors, thus an overall increase in sensitivity to the neuropeptide[3]. It has been found that while oxytocin is critical to the physiology of these processes, there is also a strong psychological component due to the upregulation of the receptors in the central amygdala and other brain regions. When women give birth, breastfeed, or even just hold their child, they receive a burst of oxytocin which bonds them to their infant.

The psychological side effects of this increase in sensitivity to oxytocin include an increase in maternal behavior, an increase in feeling close to someone, and a decrease in anxiety. A study found that when virgin rats were given an exogenous dose of oxytocin, they behaved maternally to pups that were not theirs and had no relation to them[6]. This is interesting because the rats did not go through any natural processes that elevate oxytocin levels (e.g., labor, milk production and let down), yet exogenous oxytocin was sufficient to induce maternal behavior including carrying the pups away from a dangerous stimulus. This same study looked at the effect exogenous vasopressin had on the maternal behavior of the virgin rats. Interestingly, the exogenous vasopressin did elicit maternal behavior towards the pups, but not as "complete" as the maternal behavior triggered by oxytocin[6].

Interestingly, these maternal bonds go both ways; the increase in oxytocin in females who give birth and who breastfeed is mirrored in their offspring. One study found that when young men were given an intranasal dose of oxytocin, they looked upon their childhood memories of their mother more fondly[7]. With exogenous oxytocin, these men were more likely to say that their mother was "exceptionally caring" than men without exogenous oxytocin. This was especially true for men that already felt close to their mothers; the oxytocin amplified the positive feelings that were already present[7]. This provides evidence that oxytocin is critical for the bonding between a mother and their child.

The ways in which oxytocin and vasopressin produce social bonds goes beyond the formation of mother-child relationships. Curiously, these neuropeptides facilitate the induction of many different human relationships. One study found that oxytocin increased participants' propensity to blindly trust others; for example, there was one participant that was more or less at the mercy of anoth-

er participant[8]. Individuals who were given a nasal dose of oxytocin were much more likely to trust the person who held all the power in the situation. There was no discussion between the two participants and they were complete strangers, so there was no reason for one participant to trust the other, but with oxytocin the participant trusted against logic. Thus, oxytocin helps build friendships and professional relationships in addition to familial ties, critical for the formation of the communities humans rely on.

With respect to familial ties, we've previously only talked about mother-child bonds. However, oxytocin, and to some extent vasopressin, have also been shown to be important in the formation and strength of relationships between spouses. In a study where they administered small blister wounds to spouses, they measured levels of oxytocin, vasopressin, and the rate of wound healing in relation to the relationship between the spouses[9]. Amazingly it was found that spouses that reported feeling closer to one another and had very positive relationships had the highest levels of oxytocin and vasopressin as well as the fastest rate of wound healing[9]. This demonstrates how complex and widespread the effects of oxytocin and vasopressin are in the relationships that humans form as well as how these neuropeptides are involved in a human's stress response.'

http://www.publicdomainpictures.net/view-image.php?image=234052&picture=mother-and-child

Evolutionary Significance of these Social Bonds

Let us return to the original question of why these neuropeptides are so important to humans. For the entirety of our existence, Homo sapiens have been very social creatures. The social nature of humans has evolved over time to increase the survival rates of humans.

Humans are known as "high K organisms" meaning that they only have a few offspring and they spend significant time and energy on these few offspring to ensure their success and survival. In humans, there is a long gestation period and a long period of dependence on the parents after birth. When humans are infants, they cannot even lift up their head without the help of a parent. This makes infants extremely vulnerable, why it has become so important for parents to be bonded with their children and to have an intrinsic desire to take care of their young.

During labor and then afterwards through breastfeeding, the infant and the mother spend a significant amount of time together, with the survival of the infant being completely dependent on how the mother cares for it. Additionally, it has been argued that humans are born prematurely so they can fit through the birth canal. This early birth makes human offspring especially vulnerable and the parental care of the offspring even more important. The chances of an offspring surviving to adulthood were much higher for humans if a parent was around to protect the offspring and teach it how to hunt, find shelter, etc. This dependence is one of the ways which oxytocin, and to some extent vasopressin, had the potential to evolve into a neuropeptide that has the power to form social bonds in addition to impacting physiological processes.

Beyond the mother-infant relationship, humans are incredibly social creatures. On a daily basis, neurotypical people work

closely with others to complete projects, come up with new ideas, cook dinner, and raise families. Humans have consistently formed communities and chosen to gather and work together rather than be on their own for thousands of years. Many other mammals also form cohorts or packs as this increases survival rates; if there are many animals, there is a high probability that many will escape a predator. There is strength in numbers. So then why have humans done this to a much greater extent than other mammals? Why is simply having a large cohort not sufficient, why do humans have these intense, deep social bonds?

Humans first started to stand out from the rest of the mammals when they started forming communities with gendered roles, hunting and gathering. Theoretically, each human could hunt or gather food on its own. However, humans developed a complex system where they depended on one another; the women gathered fruits and vegetables while the men hunted meat. All of this food was critical for survival at the time. From this original setup developed towns, cities, and countries.

Medical Uses of Oxytocin and Vasopressin

Because oxytocin and vasopressin are so important to the development of social bonds, many have hypothesized that an exogenous dose of these neuropeptides may be useful to those who have disorders that affect one's social interactions with others. Autism spectrum disorder (ASD) has gained the most attention in the field. Many researchers have investigated whether additional oxytocin or vasopressin can help people with ASD be less anxious in social situations and if it can help these individuals better interpret and understand others' emotions.

One of the greatest struggles individuals with ASD face in social interactions is the deficiency or lack in ability to recognize the emotion of others' faces. This poses a problem because someone may look sad or angry, but a person with ASD, unable to recognize that emotion, could say or do something that may make the other person feel worse. Luckily, the intuitions that scientists have had regarding these neuropeptides has been supported by research. Many studies have shown that children, adolescents, and adults with ASD have much more success and ease with understanding how other people feel and what their facial expression means when they have an exogenous dose of oxytocin[10,11]. Unfortunately, although a great deal of literature has supported the potentiality of oxytocin as a treatment for social deficiencies in people with ASD, it has not become a widespread medication. This may be due to insufficient research, the extremely short half-life of the drug, or potential side effects not discussed in these studies.

Another mental illness that has received attention from this field is Generalized Anxiety Disorder (GAD), especially people with social phobia. In this disorder, the amygdala, the brain structure discussed earlier, is hyperactive. This hyperactivity makes people feel fearful or anxious when there is no real danger. Because oxytocin helps decrease anxiety and facilitate the formation and maintenance of social bonds, researchers expected individuals given oxytocin to have a less hyperactive amygdala. As hypothesized, researchers have found that individuals suffering from GAD have lowered amounts of amygdala hyperactivity, and thus less anxiety, when administered oxytocin[12]. This makes oxytocin an interesting target for further research on potential clinical applications for these neuropeptides.

Oxytocin and vasopressin are two neuropeptides with a myriad of physiological and psychological purposes. They regulate many biological processes in humans, including the process of relationship formation. The ways in which humans interact with one another and form friendships, fall in love, and connect with their children are the central interests of many academic fields, including neuroscience. Further, understanding of the ways in which humans bond could help us form humans bonds where they are most needed: in the face of hate, discrimination, and war. These are terrible and common parts of the human narrative that occur because people are divided, but if we understand the neurobiological basis of the interactions that bond us, we may be able to form bridges between groups currently in opposition of one another. What will we learn about these neuropeptides next?

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Spinal Cord Injuries: The Life After

By **Woo Jeon**

How many times have you driven in a car? Or, how many times have you taken a hard fall? For most individuals, these events are not uncommon occurrences. Within a split second, a car crash or a bad fall can change an individual's life forever. Among the various consequences following an accident, one of the most catastrophic injuries are Spinal Cord Injuries (SCI). SCI are devastating conditions for two main reasons. First, SCI are usually sustained randomly or out of the blue. As seen in the example above, SCI can happen to anyone at any time doing normal daily activities. Second, the social exclusion that results from the inability to be physically and socially active can be a high barrier to overcome. For example, an individual with a SCI may not be able to go out to dinner with their friends as easily or that individual may feel as if they're a burden on others which can result in alienation. It is only with a functional and intact spinal cord that simple daily tasks such as brushing your teeth or taking a shower aren't viewed as strenuous activities. SCI are biologically complex and life-disrupting conditions that can affect an individual's life in various respects. There are many health consequences of SCI such as autonomic dysreflexia, a condition with a sudden onset of excessively high blood pressure, or pressure ulcers that can be prevented given the proper care. In addition to the health impact of SCI, this condition can affect many social aspects of an individual's life such as their occupational status, education, relationships with family/friends, marital status, and many more. These personal and social challenges are the barriers that individuals with SCI have to overcome in order to live a life that is of both high quality and good health. Due to the permanent nature of SCI, individuals with SCI experience a wide range of medical care such as surgery, intensive care, rehabilitation, etc., and can therefore reflect how well overall the health system works and what policies need to be addressed. As a result, it is crucial that interventions for SCI work to improve the survivability, and quality of life for individuals affected by this condition. Additionally, by looking at the main causes of SCI, preventative measures can be taken in order to reduce the risk of sustaining such injury.

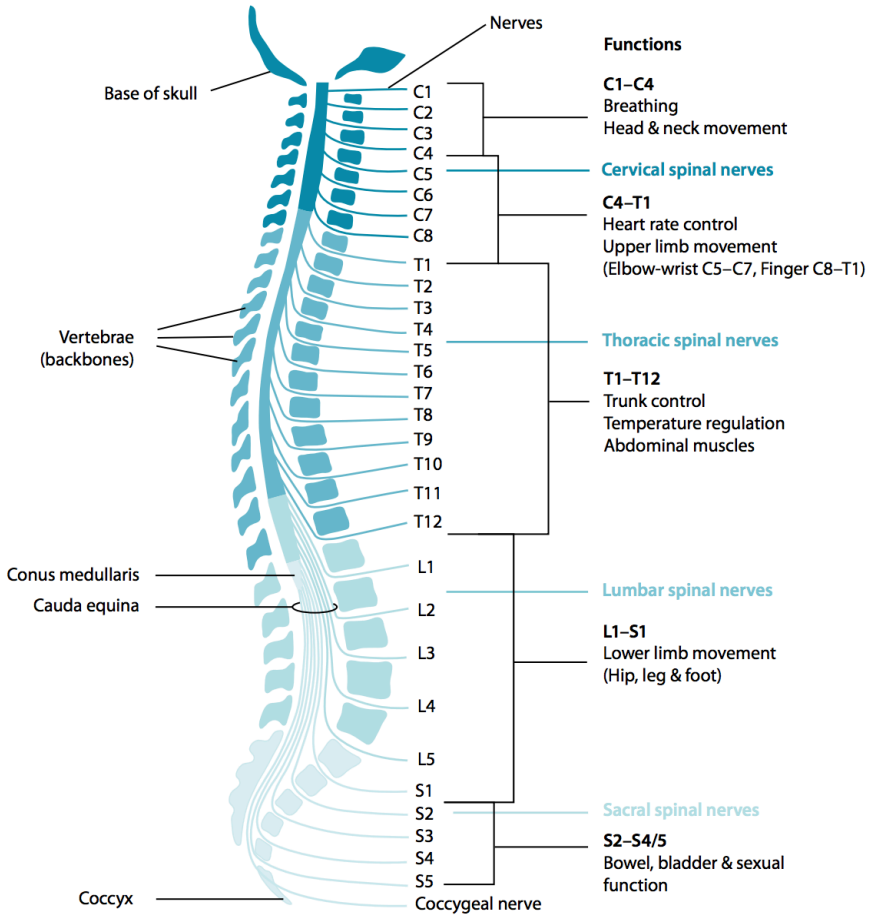
What is SCI?

It is important to understand the anatomy and biological consequences of SCI because the level of severity determines a large part, the resulting lifestyle experience The spinal cord is positioned within the spinal column, and extends down from the brain to the L1–L2 vertebral level, ending in the *conus medullaris*. The spinal cord consists of 31 spinal cord roots: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 1 coccygeal. Figure 1 represents well the organization of the spinal cord and the functions of each segment. The range of impairments induced by SCI is dependent on the location of the lesion along the spinal cord. The most severe cases are cervical SCI's which commonly cause sensory and motor loss in the arms, body, and legs, a condition called tetraplegia. Individuals with a lesion of C4 or higher may require a ventilator. Thoracic SCI's generally cause sensory and/or motor loss in the trunk and legs, a condition called paraplegia. Lumbar SCI's typically cause sensory and motor loss in the hips and legs. The extent and severity of sensory, motor and autonomic loss also depends on whether the lesion is "complete" or "incomplete"[1]. A complete SCI exhibits complete loss of sensory and motor function below the level of injury, and incomplete SCI's preserve some sensory and/or motor function below the level of injury. Regardless, both cases are no less serious and can still result in severe impairments.

A Global Picture on SCI

Quantifiable data in terms of the magnitude and cost of SCI are limited, and only a select few high-income countries have the means necessary to provide national statistics[1]. Therefore, the best available data on SCI can only

Figure 1 Spinal Cord organization and responsible functions[1].



provide a general epidemiological picture. However, this epidemiological picture of SCI is required in order to assess the socioeconomic impact of the condition. There are three main epidemiological indicators for SCI that can be quantified: prevalence rate, incidence rate, and etiology. These data are useful in determining primary and secondary prevention methods. Prevalence and incidence rates give insight to life after sustaining a SCI, and from this data, secondary prevention methods involving the proper management and care following the injury can be implemented. Etiology looks at the main causes of SCI which is useful for planning primary prevention methods which involves the removal of the initial causes.

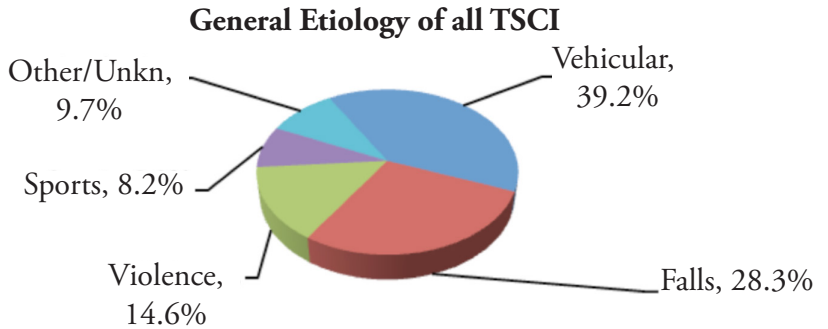
Types of SCI: There are two types of SCI; traumatic (TSCI) and non-traumatic (NTSCI). TSCI are most commonly a result of road traffic crashes, falls, and violence[1]. Whereas NTSCI result from communicable and non-communicable diseases such as tuberculosis and cancer, as well as nutritional deficiencies such as vitamin B12[1]. It is important to distinguish the two when looking at the epidemiological data because the approach in creating preventative methods can vary.

Prevalence of SCI

TSCI prevalence data show a range from 280 per million in Finland as high to 1298 per million in Canada[5,9]. The fivefold difference may not be an exact representation of the prevalence due to the various years the studies were performed. The studies also vary in methodologies which may have contributed to the variability of the data. Regardless, it still goes to show locations that need improvements in secondary prevention measures. NTSCI prevalence data from Canada and Australia show that ageing demographics may be the primary reason for increasing NTSCI prevalence[1].

Incidence of SCI

It is estimated that global SCI incidence is 40 to 80 new cases per million population per year, which means that 250,000 to 500,000 people become spinal cord injured[1]. In 2016, the United States, with a population size of 314 mil-



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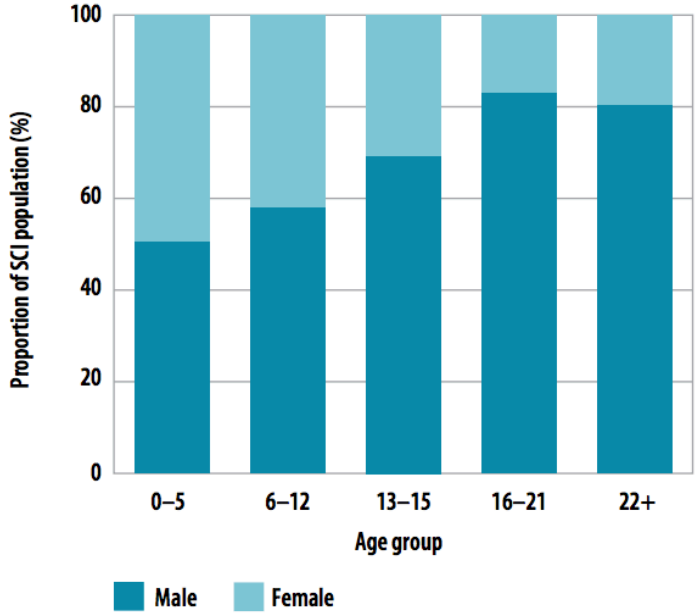


Figure 2
Distribution of TSCI by sex and age group. Source 1; Adapted from 34, 35

lion, had an annual SCI incidence of approximately 54 cases per million population, or approximately 17,000 new cases each year[5]. Although these numbers are low relative to other more common diseases and disorders, they still goes to show that SCI impacts a significant population. A few trends can be recognized from the TSCI country-level incidence data, and these trends can show which areas and what type of preventative measures need to be taken.

The incidence rate of TSCI is increasing, decreasing, stable depending on location. Studies from two Norwegian counties showed an increase in the incidence of TSCI between 1952 and 2001[3]. Developed countries such as the US, Finland, and Australia have noticed a decrease in incidence of TSCI[1]. Data from France showed the incidence rate of SCI to remain stable[6].

TSCI occurs much more frequently in males than in females. A study based in the US showed that males have a much higher rate of TSCI across all age groups especially from ages 16 to 21[7,8]. These results show that gender roles may play a role in the SCI incidence rate, where differences in alcohol consumption, driving behavior, and participation in high-risk sports that manifest after childhood may attribute to the fact that males more commonly sustain TSCI[1].

TSCI occurs mostly in young adults and the elderly. Data from a study in Canada revealed that two common age-associated peaks of TSCI occur in young adults (males 20-29; females 15-19) and in the elderly (males 70+; females 60+) (2), however, this increased incidence in the elderly has been a relatively recent development. Another study in Australia showed an overall increase from 4% to 12% in SCI incidence over a time period of 25 years[8].

There are far fewer studies on NTSCI incidence. However, a study in Australia revealed that NTSCI varies both by age and sex. This study found that NTSCI incidence to increase steadily with age[9]. This is mainly due to the increase in risk resulting from ill health with increasing age.

Etiology of TSCI & NTSCI

TSCI. As mentioned before, road traffic crashes are the leading cause of TSCI. As Figure 3 represents well, vehicle crashes account for 70% of TSCI in 3 African countries, 40% in South-East Asia, and 55% in the Western Pacific. Studies revealed that the common factor among these vehicle crash induced TSCI were the lack of and non-use of seatbelts which illustrates the importance of such safety measure[10,11].Falls are the second leading cause of TSCI. As represented in Figure 3, falls account for approximately 40% of all TSCI cases in the Eastern Mediterranean and South East Asia. Violence, including self-harm, makes up the third leading cause of TSCI, and constitutes approximately 14% of cases in the Americas, 12% in Africa, and 11% in the Eastern Mediterranean. Areas such as Afghanistan where violence is high due to the effects of war, a study found 60% of all TSCI cases being related to violence[12].

NTSCI. There are few reliable national data concerning the etiology of NTSCI. Limited data has found showing that in countries such as India, Peru, and Sweden, the leading cause of NTSCI are tuberculosis and other infectious diseases[13-15]. However, a compilation of studies suggests that the general leading causes of NTSCI are neo-

plastic tumors, degenerative conditions of the spinal column, and vascular/autoimmune disorders[1].

Prevention of Spinal Cord Injuries

SCI whether traumatic or non-traumatic, a large proportion of these injuries are preventable through primary and secondary prevention methods. Primary prevention involves steps to remove the initial cause of SCI before the problem arises. Secondary prevention involves proper management and care for individuals with SCI following the injury.

Primary Prevention Methods

The Safe Systems Approach

Road traffic crashes being the leading cause of TSCI, reducing the incidence of such events is a significant element in preventing TSCI. The adoption of a safe systems approach to road traffic crash prevention is crucial in reducing these types of cases. This approach recognizes that a properly managed system of vehicles, people, and roads reduces injuries resulting from crashes[16]. A successful implementation of road safety action requires effective advocacy, broad-based community acceptance, multisectoral intragovernmental cooperation, and the cooperation of industry and nongovernmental organizations such as automobile associations, the medical profession, and road safety advocacy groups[16].

Falls

Although the act of falling or an item falling is an uncontrolled random event, there are steps that could be taken to prevent such outcomes. These methods include the elimination of clutter, loose carpets, and uneven floor surfaces, and the provision of good lighting, hand rails, and appropriate level seats, toilets, and beds[17].

Violence

Sub-Sarahan Africa has the highest reported proportion of violence-related TSCI in the world making up approximately 38% of all cases[18]. As expected, there's evidence that jurisdictions with restrictive firearms legislation and lower firearms ownership tend to have lower levels of gun violence which includes bans, licensing, age requirements, and background checks[1]. Additionally, strategies other than those aimed at reducing access to guns and knives, such as developing safer relationships among children, reducing availability of alcohol which is a risk factor of violence, promoting gender equality to prevent violence against women, and a change in cultural and social norms that support violence can be implemented to reduce violence-related TSCI[1].

Secondary Prevention Methods

Secondary prevention methods involve everything after the event of a SCI which includes two things: management of the secondary conditions, and improvements in policies surrounding the health system for individuals with SCI.

Secondary Conditions and Rehabilitation Needs

Individuals with SCI are at risk for a variety of secondary conditions which can be a major cause

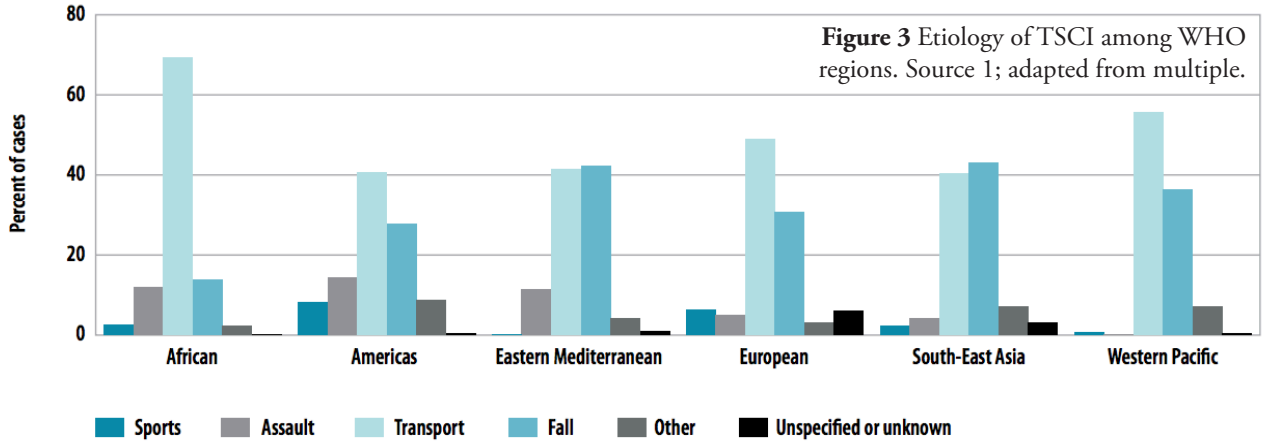
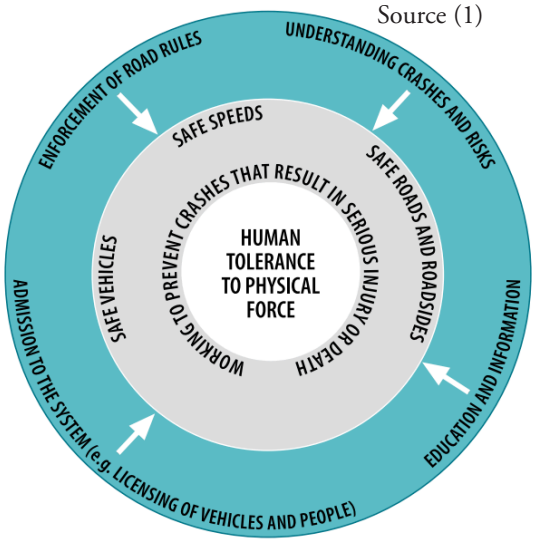


Figure 3 Etiology of TSCI among WHO regions. Source 1; adapted from multiple.

Source (1)



of morbidity and mortality[1]. Some of the major secondary conditions include autonomic dysreflexia, deep vein thrombosis (DVT), sublesional osteoporosis, chronic pain, and pressure ulcers.

Autonomic dysreflexia is a condition characterized by a sudden increase in blood pressure, and this condition is most commonly found in individuals with SCI at or above the T6 level[19]. If left untreated, it may cause serious consequences such as strokes, seizures, and death. Awareness of the necessary treatment procedures following autonomic dysreflexia by caregivers is crucial.

Deep Vein Thrombosis (DVT) is a high risk secondary condition of SCI and is characterized by a blood clot in a deep vein. DVT can lead to pulmonary embolism and death. Anticoagulant medication as well as wearing compression stockings have been proven to help with DVT[22].

Sublesional Osteoporosis results from the immediate loss of bone mass following SCI. Osteoporosis poses a risk for easy bone fractures from simple activities such as transfers[1]. Interventions such as bisphosphonates in junction with vitamin D and /or calcium have had efficacy in improving osteoporosis[23].

Chronic Pain can significantly impact quality of life for individuals with SCI. A significant number of individuals with SCI experience neuropathic pain characterized as burning, stabbing, and aching[20]. Musculoskeletal pain from overuse is also a common experience among individuals with SCI. Thus, pain management can be approached with medication, exercise, massage, acupuncture, psychotherapy, meditation, and relaxation[24].

Pressure Ulcers, which results from impairments in sensation and mobility, poses another high risk secondary condition for SCI affected individuals. Preventing pressure ulcers is the most important aspect of care for individuals with SCI, and can be done through regular skin checks, pressure-relieving methods, and adequate bowel/bladder care[21].

Health System Strengthening

Appropriate legislation, policies, and strategies ensure individuals with SCI to have adequate access to health care and rehabilitation centers, which ultimately result in a higher quality of life[1]. However, this is much easier said than done. Areas in a health care system that need constant improvement include delivery service, human resources, health technologies, and financial support.

Delivery Service

Adequate availability, accessibility, and acceptability of health care services for individuals with SCI is vital in maintaining a healthy lifestyle following SCI. Therefore, it is important to ensure appropriate access to all necessary specialized services in order for effective continuation of treatment for individuals with SCI following discharge from the hospital setting[1]. Additionally, caregivers and family members need to be well informed of the post-hospital medical care available according to their specific needs.

Human Resources

Individuals with SCI require access to a wide range of specialized service personnel such as medical doctors, nurses, paramedics, psychologists, therapists, and many others. It is crucial to promote access to specialist trai ning programs in order to produce more suitably trained personnel so that individuals with SCI have adequate access to these resources[1].

Health Technologies

Health technologies such as assistive technology and wheelchairs are essential for safe and effective prevention, diagnosis, treatment, and rehabilitation for individuals with SCI[1]. Studies have found that access to these technologies, which improve quality of life, can be limited due to eligibility issues. Other factors such as input, sustainability, appropriateness, and impact of these technologies also need

to fit into a given environment[25]. Therefore, it is important to establish transparent and fair eligibility guidelines to enable people with SCI with access to assistive technology, and identify cost-effective models for the provision of assistive technology[1].

Financial Support

Individuals with SCI require ongoing medical care and rehabilitation from the time of injury, and therefore both the initial and ongoing costs associated with SCI is significant[26]. As a result, there needs to be sufficient funding for specialized services in order to ensure access to comprehensive and affordable health insurance to individuals with SCI.

Conclusion

Clearly, it is evident that SCI's can cause significant changes to the quality of an individual's life. Does this mean that individuals should treat each day as if they were going to sustain such a devastating injury, and not participate in their daily activities? Absolutely not. But SCI's are serious conditions where primary and secondary prevention methods work not only to treat and improve the lives of individuals affected by a SCI, but by reducing the risk in the first place. Hopefully, with a better implementation of these methods, the risk and rate of SCI's will significantly reduce.

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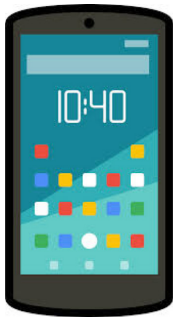
MINDFULNESS FOR THE MASSES

By **Emma Klug**

Nearly two thirds of Americans are smartphone users.[1] As of 2015, 64% of Americans owned smartphones, and it is reasonable to suspect that this proportion has only grown within the past 2 years. As we are spending more and more time interacting with these devices, scientists are beginning to ask how this technology is affecting our brains, bodies, and behavior. This inquiry is highly warranted, as it has been reported that we check our smartphones about 85 times each day, accumulating to a total of five hours.[2] These numbers might seem shocking, and recently, a number of studies have reported the negative effects of smartphone use on our wellbeing, particularly regarding attention and mood regulation.

Media multi-tasking describes a person's consumption of more than one item or stream of content at the same time. For example, switching back and forth from writing an email to responding to a text, all while scrolling through your Facebook feed. Historically, evidence has indicated humans are poor multi-taskers.[3] This prompted researchers at Stanford University to question how our simultaneous use of numerous applications on our smartphones affects our cognition. They found that media multitasking places new demands on our cognitive processing, specifically our allocation of attention.[4]

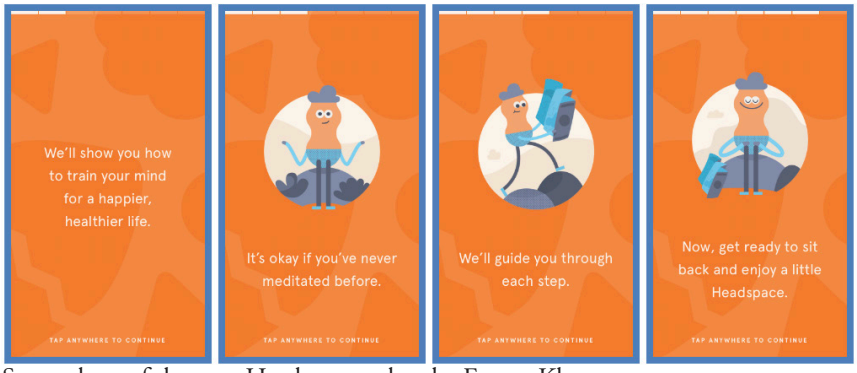
Consistent with the notion that we are not predisposed to multitasking, participants classified as "heavy" media multi-taskers performed consistently worse across three measures of attention compared to "light" media multi-taskers[4]. Unsurprisingly, heavy media multi-taskers were less capable of filtering out irrelevant information or thoughts.[4] What is perhaps most troubling about these results is that they suggest the effects of our media consumption persist even after we lock our screens.



"Smartphone" by OpenClipart-Vectors is licensed by CC0.

Not only has smartphone usage placed unwelcome strains on our cognitive load, but a growing body of evidence suggests it may also negatively effect our wellbeing. Older generations of smartphone users have reported feeling "happy" and "productive" when engaging with their devices1. However, younger smartphone users seem to experience a wider range of emotions, also reporting feelings such as "distracted" and "angry".[1]

In line with this, a 2014 study of more than 300 universi-



Screenshots of the app, Headspace, taken by Emma Klug.

ty students revealed higher smart phone usage was correlated with increased depression, anxiety, poor sleep quality, and daytime dysfunction.[5] Further analyses demonstrated that high levels of depression, anxiety, and younger age were predictive factors of smartphone overuse, demonstrating the vulnerable position of young smartphone users who grow increasingly more dependent on their devices.[5]

The rise and spread of smartphone technology has been accompanied by the rise of the field known as mobile health. While smartphone use has been associated negative health outcomes, the mobile health field recognizes the incredible staying power of this technology. Therefore, it aims to take advantage of the overwhelming presence of smartphones in people's lives in order to deliver effective healthcare interventions. Specifically, in its Mental Health Action Plan 2013-2020, the World Health Organization recommended "the promotion of self-care, for instance, through the use of electronic and mobile health technologies".[6] Ironically, while accumulating evidence suggests smartphone usage wages war on our cognitive systems, they may also provide an easy and effective opportunity to get some piece of mind.

Mindfulness: A Brief History

Mindfulness is famously described by scientist and educator Jon Kabat-Zinn as a way of paying attention on purpose.[7] It is a state

"Stethoscope Medical Health" by StockSnap is licensed by CC0.

of being aware of what is taking place in the present moment, in an accepting, compassionate, and nonjudgmental manner.[8] Simply put, mindfulness is pretty straight forward– when your mind is fully attending to whatever you're doing, seeing, or experiencing, you're being mindful. Many have developed this way of approaching the world through years of meditation training. Lucky for us, the foundations of mindfulness are now available on the app store.

The most downloaded mindfulness app is Headspace.[8] The creator of the app, a former Buddhist monk, describes the app as a "gym membership for your brain".[8] Headspace consists of daily, guided meditations, teaching beginners the fundamentals of mindfulness-based meditation practices. Users begin with the "take 10" program, practicing mindfulness meditation just 10 minutes daily, for 10 days. Users build on this practice for an additional 20 days until they have completed the foundations course, at which point they are given access to advanced content related to health, relationships, and performance.

Mindfulness meditation dates back to over 2,500 years ago to the Buddhist vipassana meditation techniques practiced by Gautama the Buddha, himself. In the mid-20th century, mindfulness practices began to evolve into key components of secular psychological interventions, due their ability to reduce stress and improve emotional wellbeing. Currently, mindfulness-based programs have proven successful in treating a number of disorders, including anxiety, depression, post-traumatic stress disorder, and addiction.[9-11] Further studies also support the use mindfulness practice in improving the wellbeing of nonclinical populations.[12]

Advocates of mindfulness interventions boast it has the ability to improve one's self-control, capacity to deal with stress, regulation of emotions, and concentration.[9] But does this bite-sized Buddhism have the power to counteract the deleterious effects of smartphone overuse? As mindfulness has gained popularity over the past 2 decades, researchers have set out to answer this question.

Your Brain & Mindfulness

Much of the research surrounding the efficacy of mindfulness train-

"Meditation Yoga" by Clker-Free-Vector-Images is licensed by CC0.

ing looks to define existing differences in experienced mindfulness meditators compared to inexperienced individuals. For example, studies show that mindfulness meditators with years of experience perform better on laboratory tasks probing attentional processing compared to non-practicing control subjects.[13] Specifically, participants experienced in mindfulness were significantly better at directing and re-directing their attention, most likely a result of years of practice in efficiently engaging and disengaging from stimuli in their environment.

Interestingly, differences in attentional processing can be observed even after just brief mindfulness training.[14] Research shows that after just five, 20-minute meditation sessions, novice mindfulness meditators exhibit improvements in measures of executive attention, or our ability to resolve conflict between discrepant incoming information, detect errors, and plan responses.[14,15] Not only did participants display marked improvements in attentional processing, they reported decreased feelings of depression, fatigue, anxiety, and anger, and increased feelings of vigor, all previously reported benefits of mindfulness.[14]

The brief mindfulness training also affected the way participants' bodies responded to stress. Cortisol is a hormone released in response to stress, and acts as a common laboratory measure for tracking how we respond to stressful situations. To induce stress, participants in this study were challenged with mental math task. Those who had received the five-session crash-course in mindfulness meditation displayed lowered salivary cortisol levels after the math test compared to participants who had completed the same amount of time practicing standard relaxation techniques.[14] These results indicate that the mindfulness intervention promoted regulation of the participants' physical response to stress.

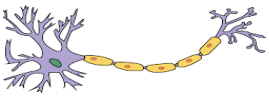
From attentional processing to hormonal regulation, changes in our bodies and behavior are precipitates of changes in our brain. Synaptic plasticity refers to the capacity of neural activity generated by an experience to modify the strength of neural circuits.[16] This, in turn, modifies our subsequent thoughts, feelings, and behaviors. In other words, when we change our habits, our brain is happy to change with us. Therefore, structural and functional adaptations are made in the brain as a result of mindfulness practice, resulting in improved attention and mood, and reduced stress.

Tang's group at the Dalian University of Technology in China, along with collaborators at the University of Oregon, have conducted comprehensive research on the capacity of mindfulness meditation to change the structure and function of our brains. Indeed, they have strong evidence that mindfulness training leads to changes in our brain's white matter, or myelin, specifically in areas known to regulate attention and emotion.[17]

The anterior cingulate cortex (ACC) has connections to both the "cognitive" pre-frontal cortex and the "emotional" limbic system.[18] The ACC is a part of a circuit involved in a form of attention that serves to regulate both cognitive and emotional processing.[19] Tang and colleagues report that mindfulness training was able to strengthen the connectivity in this region, either through prompting increases in myelin-

What is Myelin?

Myelin is a highly specialized membrane that wraps around axons, the long thin projections that extend from the main body of the neuron. Myelin acts as an electric insulator, increasing the velocity of signals being transmitted from the neuron cell body to its target. Myelination of axons occurs differently in the central and peripheral nervous systems. Specialized cells in the central nervous system called oligodendrocytes reach out and wrap sections of multiple axons. In the peripheral nervous system, a different specialized cell known as a Schwann cell, individually wraps around a single axonal segment. Myelin is essential for proper nervous system function, as exhibited by the debilitating effects of demyelinating diseases such as multiple sclerosis.



ation, or the reorganization of existing myelin tracts.

Our brain is composed of gray matter in addition to white matter. Gray matter is the darker tissue in the central nervous system, consisting primarily of neuronal cell bodies and their branching dendrites. Regional differences in gray matter are generally assumed to arise due to repeated activation of the region.[20] This makes sense as differences in gray matter have been associated with performance abilities and the acquisition of new skills, suggesting that increased gray matter corresponds to improved functioning in that particular brain region.[21]

Dr. Britta Hölzel's group at Harvard Medical School identified increases in gray matter density in multiple brain regions associated with some of the generally accepted benefits of meditation.[21] For example, the temporoparietal junction has been suggested as a crucial structure for the conscious experience of one's self. Furthermore, the posterior cingulate cortex, not far from the anterior cingulate cortex mentioned previously, is associated with assessing the relevance or significance of a stimulus for oneself. Taken together, Hölzel suggests that mindfulness practices increase gray matter density in these regions as a result of repeated activation during the meditative process.[20]

Your Body & Mindfulness

Beyond changes in our brain, mindfulness interventions have induced measurable changes in our physiological functioning, especially in response to stress. Mindfulness-Based Stress Reduction is a standardized 8-week training program that includes mindfulness education and practice.[22] This practice has proven efficacious in reducing blood pressure in response to stressful situations.[22] Furthermore, participants in this same study reported lower levels of perceived stress and negative mood after the intervention, complementing previous research that mindfulness meditation also improves our overall wellbeing.[12]

Researchers have attempted to measure these differences in physiological responses to stress in a number of ways. Rosenkranz's group at the University of Wisconsin-Madison demonstrated that individuals experienced in mindfulness meditation displayed significantly reduced cortisol levels in response to a laboratory stress challenge compared to a group of inexperienced participants.[23] To further probe just how all-encompassing the effect of mindfulness practice is on physiological responses, the researchers measured a skin response to capsaicin, the active component of chili peppers known to trigger inflammatory responses in any tissue with which it comes in contact. Remarkably, they observed that experienced meditators displayed a less severe inflammatory skin response compared to inexperienced individuals.

Despite this research, it remains unclear how mindfulness meditation reduces our physiological response to stress. One possible explanation could be that through extensive practice, experienced mindfulness meditators have learned a controlled, diminished stress response. This diminished response would be characterized by reduced activation of inflammatory compounds that are normally triggered when we find ourselves in stressful situations.[23] Control of physiological responses at this level suggests that the effects of mindfulness meditation may extend into processes regulating how our DNA is interpreted and expressed.

Your DNA & Mindfulness

Epigenetics was first described by Conrad Waddington in 1942 as, "the branch of biology which studies the causal interactions between genes and their products, which brings the phenotype into being".[24] Since Waddington, the field of epigenetics has evolved, and there are several existing definitions. For our purposes, epigenetics can be seen as how our environment impacts our DNA. Specific biochemical changes are made to our DNA that influence how it is read and transcribed, resulting in the unique expression of genes without changing the actual DNA. With this knowledge, researchers have questioned if mindfulness meditation can induce changes in our epigenome.

Evidence from the lab of Rosenkranz's Barcelonian counterparts demonstrated that after a day of intense mindfulness practice, experienced meditators exhibited lower levels of key epi-

genetic modifiers compared to a group of untrained participants.[25] More specifically, these modifiers are proteins known to be key regulators of inflammatory pathways. In light of this, researchers also examined whether or not meditators would exhibit reduced expression of known pro-inflammatory genes. Indeed, they found meditators exhibited reduced expression of two pivotal genes that regulate inflammatory processes, supporting the notion that after years of mindfulness meditation, these participants' bodies had learned how to better regulate responses to stress.[25]

Further interested in how mindfulness could be affecting stress-induced inflammation, researchers measured participant's levels of the stress hormone cortisol after performance of a laboratory task shown to induce psychosocial stress. Interestingly, they reported that lower levels of the aforementioned DNA-modifying proteins were correlated with faster recovery of resting cortisol levels. Taken together, these findings suggest that a day of intense mindfulness practice triggers an anti-inflammatory response in experienced meditators that is not observed in inexperienced control subjects.[25]

Epigenetic Modifications

DNA methylation is a process in which methyl groups are added to DNA molecules, changing the activity of a segment of DNA without changing its sequence. DNA methylation is critical to normal development, and plays a role in silencing repetitive DNA sequences in organisms from fungi to humans, inactivation of the X chromosome in female mammals, and mammalian imprinting. Irregular methylation has been implicated in many human cancers.[28]

"DNA White Male 3D" by Peggy und Marco Lackmann-Anke is licensed by CC0.

In our chromosomes, DNA is tightly wound around histones. The addition of chemical groups to histone proteins alters this structure, making our DNA available for transcription, and therefore, expression. Further, these modifications often recruit the transcriptional machinery to specific segments of the DNA.[28]

Mobile Mindfulness

The benefits of mindfulness meditation have been widely documented. Not only do meditators self-report feelings of increased attentional capabilities and elevated mood, but a great body of evidence shows that this practice holds the power to change our bodies in addition to our mind. The rise of mobile health offers a unique opportunity to deliver these positive interventions to a wider population by increasing access and reducing time commitments. However, the majority of studies reporting the benefits of mindfulness have utilized in-person delivery methods. Therefore, the question remains whether or not the many apps on your mobile device are capable of delivering a mindfulness practice with the same efficacy.

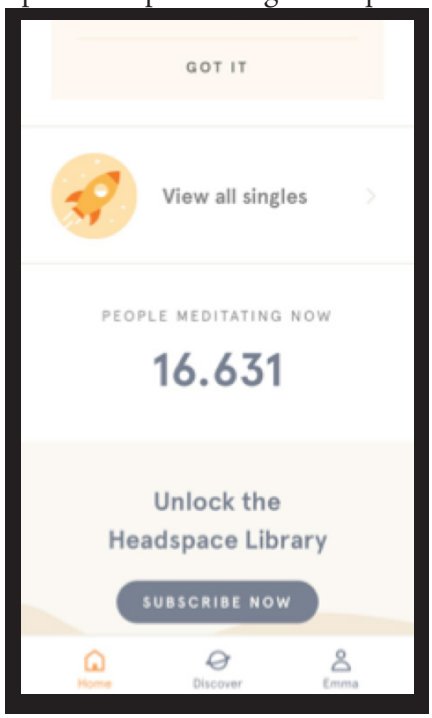
Researchers have begun to investigate whether these applications will provide the same beneficial results as in-person methodology. Bennike's group, based in Denmark, asked whether or not mindfulness training via the Headspace app could improve laboratory measures of cognitive performance as well as reduce mind wandering.[26] After 4 weeks of training with Headspace, researchers reported decreased mind wandering, measured by better performance on a laboratory measure of sustained attention.

Results of participants using the Headspace app were compared to those using another app, Luminosity, for the same period of time. Luminosity is a "brain training" app, reported to show improvements in a number of cognitive abilities including memory, attention flexibility, and problem solving. This comparison allows us to make direct conclusions about the beneficial effects of mindfulness practice *specifically*, in contrast to another app that claims similar cognitive improvements.

Other researchers have investigated if the positive effects on mood seen after traditional mindfulness meditation are still visible with use of the Headspace app. Howell's group at the University of East London recruited active "happiness" seekers to par-

ticipate in the Headspace "take 10" program. Researchers investigated positive affect by measuring participant's satisfaction with life, positive and negative affect, as well as depression. In line with previous research, they saw significant improvements in positive affect and depression levels in Headspace users compared to control participants who had interacted with a neutral app. These results led researchers to suggest that smartphones are an effective method of delivering mindfulness interventions that make people significantly happier.[27]

Currently, Headspace is the only app to be utilized in randomized control trials. However, scientific evaluation of more apps is beginning to take place. Researchers well-practiced in mindfulness, as well as professionals who had delivered it as a part of their psychological practice, developed an expert rating scale quantifying the features of high-quality mindfulness apps.[29] High quality apps share features with many of your favorites— quality graphics, and simple and easy to use interfaces. Additionally, these apps require mindfulness education and a soothing voice for guided practice to earn high expert ratings.



Screenshot of the app, Headspace, taken by Emma Klug.

Most importantly, high quality apps need to provide an "app community" — a social network allowing users to identify mutual meditators and share experiences. While mobile health technology is highly accessible, versatile, and cost-effective, its most powerful feature may be the opportunity to engage with an active community of users. A supportive app community provides a forum to share and discuss accomplishments and challenges of daily practice.

There is no current evidence indicating sharing user status on other social platforms, or engaging with an app community increases the effectiveness of app-based interventions. However, developments over the past decade have demonstrated the power of social networks— like Twitter, Facebook, or Instagram— to guide and change our behavior. If similar networks can be built to encourage healthy habits, like mindfulness, we may see welcomed increases in the wellbeing of the smartphone society. So, download one these mindfulness apps now, and spend a fraction of the five hours you'll spend on your phone today feeling mindful.

Top 5 Mindfulness Apps to Download Now:

1. Headspace
2. Smiling Mind
3. iMindfulness
4. Mindfulness Daily
5. Buddhify 2

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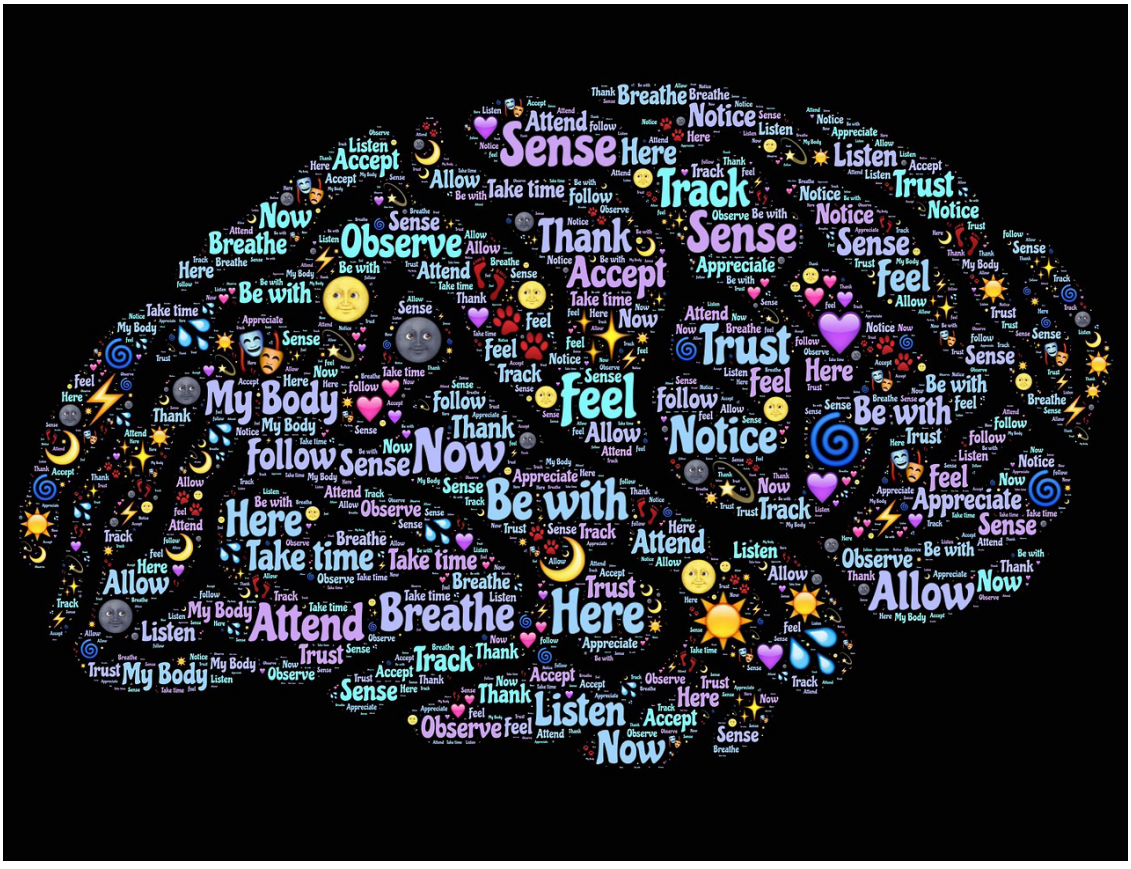


Pixabay. 2015. https://pixabay.com/en/brain-mind-mindfulness-conscious-998994/

The Genetics of Being a Lightweight: Tipsy Genes

By **Jessica Khrakovski**

It is a standing tradition that every annual Thanksgiving dinner commences with each legally aged member of my family giving a toast to something they are thankful for. Once this ceremony is finished, so is every glass of wine. It is also a standing tradition for my Aunt Rebecca to be visibly and positively tipsy after only two toasts.

Why is it that some people, like my Aunt Rebecca, are unable to hold their liquor and seem intoxicated after merely sniffing alcohol, while others seem to be unaffected by multiple servings? What is it that earns someone the label of a lightweight drinker?

The designation as a "lightweight" is typically earned by those who feel the psychological, physical, and emotional effects of low doses. The lightweight drinker likely gets intoxicated at a disproportionately rapid rate. The lightweight drinker is someone who is more likely to get sick from alcohol or someone who generally is incapable of holding their liquor. Needless to say—my Aunt Rebecca is a lightweight drinker. It is likely that you have encountered multiple lightweight drinkers, and perhaps you even are one!

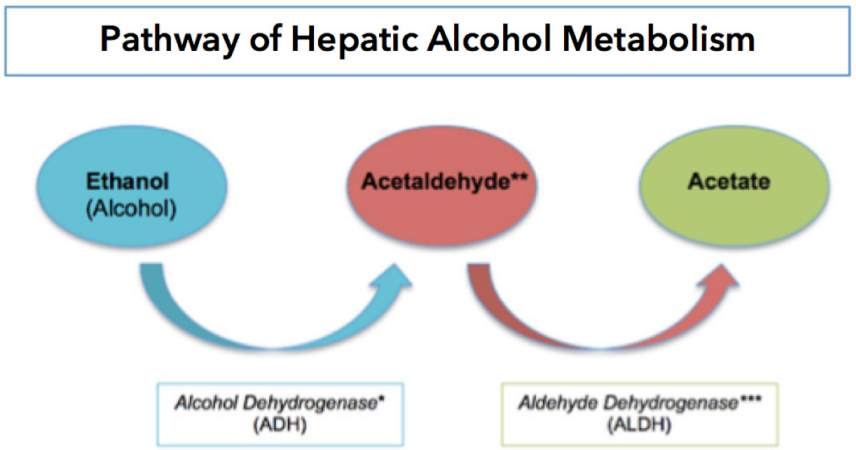
For convenience and ease, the behavioral response to alcohol use is generally discussed with respect to the blood alcohol content (BAC).[1,2] Though there is minimal consensus on standardization, it is a commonly used tool for estimating the concentration of alcohol in the blood and the expected behavioral effects resulting from a certain number of drinks.

Beyond purely the number of drinks consumed, there are numerous physiological and molecular factors that affect BAC, and consequently the level of response to alcohol. Thus, genetic factors are largely responsible for individual reactions to ethanol consumption and could dictate why someone is, or is not, a lightweight.

Why do females get drunker than males?

Sexual Dimorphism of Muscle and Blood Content It is well established that equal quantities of alcohol consumed in the same time frame will disproportionately affect females when compared to males.[1,2] This phenomenon is partially attributable to the fact that males, on average, are larger than fe-

Figure 1 "Pathway of Hepatic Alcohol Metabolism" was created by Jessica Khrakovski.



males. However, after accounting for differences in size, it is evident that differing alcohol distribution rates result from sexually dimorphic muscle mass and blood volume, both of which are disproportionately greater in males than in females.[3,4] Conversely, females have higher subcutaneous fat content and smaller liquid compartments for the dissolving and distribution of alcohol.[4,5]

Ethanol, the active ingredient in drinking alcohol, is both water and lipid-soluble and travels though the blood to disperse into tissue for processing.[3,6] Because muscle tissue is highly vascularized, with more extensive blood vessel connectively than fat, alcohol is more rapidly distributed throughout the male body. In females, alcohol remains concentrated within fat because it is unable to disperse through the blood as rapidly.[7] The accumulation of alcohol within fatty tissue prolongs its duration in the body, leading females to maintain higher BACs for longer.[2]

Enzyme Concentrations Not only does the rate of alcohol distribution contribute to the maintenance of higher BACs in females, but also the rates of alcohol processing and metabolism. The majority of alcohol metabolism occurs through hepatic enzymes in the liver, where ethanol is converted into other molecules for excretion and clearance from the system.[2,8,9,10] The process begins with the breakdown of ethanol into a metabolite called acetaldehyde (Fig 1.). This conversion is catalyzed by alcohol dehydrogenase (ADH), the enzyme in metabolism that is directly responsible for decreasing BAC.[10,11,12] Acetaldehyde, a compound even more toxic than ethanol that can produce unpleasant and even detrimental effects, is then transformed into acetate by aldehyde dehydrogenase (ALDH).[13,14]

Though the primary metabolic pathway for alcohol is conserved in the livers of both males and females, the contribution of gastric first-pass metabolism is not.[2,13] Males contain ADH not only in their livers, but also in their stomachs, where alcohol can be broken down as soon as it enters the body. Thus, prior to hepatic ethanol metabolism, up to 30% of alcohol consumed by a male will be converted into acetaldehyde in the stomach, allowing for a substantially lower amount of ethanol to circulate through the bloodstream and absorb into tissue.[7,10,12,14] On the other hand, females have nearly negligible amounts of ADH in their stomachs, such that their BACs are virtually unaltered until alcohol reaches the liver for hepatic metabolism.[2,9]

By nature of design, females are less efficient than males at spreading alcohol throughout their systems, and consequently at metabolizing alcohol in preparation for excretion, resulting in higher BACs and more behavioral symptoms. Nonetheless, the sexual dimorphisms of alcohol processing are insufficient to explain what exactly it is that makes someone a lightweight. Although my Aunt Rebecca is female and all of these factors undoubtedly contribute to her inability to process alcohol well, sexual dimorphism fails to account for lightweight males. What else could account for the unleveled playing field regarding alcohol consumption?

The Lightweight Traits

Hepatic Enzymes

Enzymes *catalyze*, or speed up, various reactions in the body. Hepatic enzymes, found in the *liver*, metabolize and break down compounds like ethanol so that they can be excreted from the body.

Aldehyde Dehydrogenase (ALDH)

Within the pathway of hepatic ethanol metabolism, aldehyde dehydrogenase (ALDH) is the enzyme that catalyzes the conversion of acetaldehyde to acetate.[10] Though ALDH does little to reduce BAC, it is essential in clearing the body of acetaldehyde, a compound that is markedly more toxic than ethanol itself.[13, 14] The accumulation of acetaldehyde within the body during metabolism leads to perceived hangover effects such as headache, nausea, dizziness, and hypnotic sedation.[8,15]

Generally, ALDH is more efficient than enzymes that oxidize ethanol into acetaldehyde, such as ADH, and works concurrently to clear acetaldehyde faster than it is produced.[7] Thus, within most individuals, the toxic, hangover symptoms of residual acetaldehyde are apparent after a night of heavy drinking, during which the metabolism system is oversaturated and ALDH cannot outpace acetaldehyde production.[7,10,15]

In some instances, consuming even the smallest amount of alcohol has the same effect as flooding the entire system. Individuals in which this phenomenon occurs possess an allele, or a gene variant, called ALDH2*2, which encodes a dysfunctional version of the ALDH enzyme.[15,16] ALDH2*2 delays the clearance of acetaldehyde so drastically that the accumulation of acetaldehyde manifests as immediate sickness in response to alcohol.[16]

While it is estimated that nearly 50% of individuals of Eastern Asian descent possess the ALDH2*2 allele, the variant is almost nonexistent in those of African and European descent.[10,16] Thus, the alcohol flush reaction and reddening of the face that is common in ALDH2*2 individuals has been colloquially termed "Asian flush." Additionally, markedly lower rates of alcoholism in Asian populations are thought to be attributable to the high numbers of ALDH deficiency acting as a protective mechanism. The ALDH2*2 enzyme produces a similar response to ethanol as does Antabuse (Disulfiram), a drug used to treat alcoholism that interferes with functional ALDH. The inhibition of ALDH causes toxic acetaldehyde sickness that should prevent consumption in alcohol abusers.[15,16]

Since alcohol flush due to the ALDH2*2 allele induces sickness and toxic effects, there must be another tipsy gene that accounts for different sensitivity to alcohol.

Cytochrome p450 2e1 (CYP2E1)

Though the majority of alcohol within the body is metabolized by ADH in the liver, a small but significant portion is metabolized in the brain within the microsomal ethanol oxidizing system (MEOS). The MEOS normally accounts for up to 10% of ethanol oxidation to acetaldehyde in the body, but it increases activity to ameliorate oversaturation of the hepatic pathway when BAC is elevated.[14,17,18] Cytochrome p450 2e1 (CPY2E1) is the brain enzyme that helps breakdown ethanol into acetaldehyde through an unstable intermediate called a gem-diol.[17,19]

In a similar vein to ALDH, there are multiple genetic variants of the CYP2E1 enzyme, some of which are linked to behavior. Alleles that increase CYP2E1 The Microsomal Ethanol Oxidizing System (MEOS) (MEOS) expression, such as the CYP2E1*5B allele that specifically increases gene transcription, are associated with a heightened level of response to alcohol.[20] Elevated levels of CYP2E1 not only produce greater concentrations of toxic acetaldehyde, but also generate high amounts of unpaired electrons as a result of oxidation. These free radicals form reactive oxidative species (ROS) that cause oxidative stress, inflammation, and cellular damage in the brain and interfere with cell pro-

Did you know?

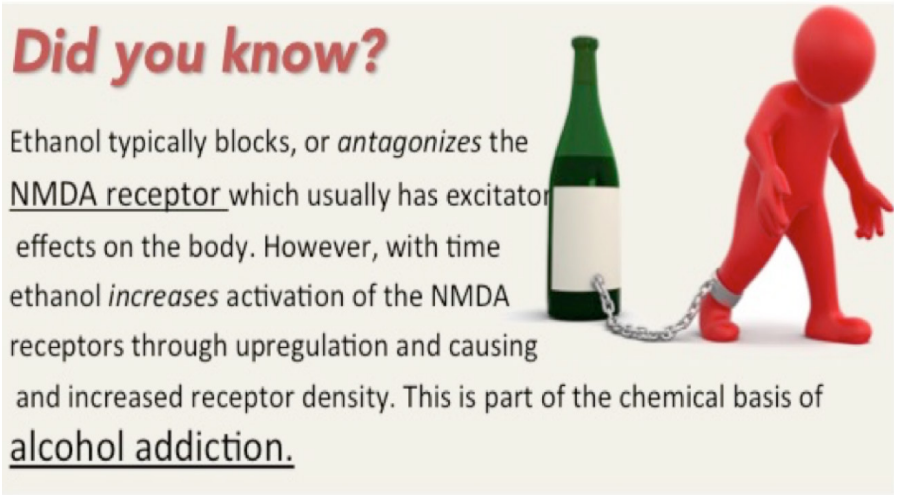
Recent studies have shown that extract from the Oriental Raisin Tree (HDE), *Hovenia dulcis*, is a promising treatment for alleviating symptoms of increased acetaldehyde in ALDH2 individuals such as nausea, dizziness, headaches, and weakness.

cesses.[19,20] The oxidative stress that results from high levels of CYP2E1 increases ethanol sensitivity and the prevalence of sedative/hypnotic effects of alcohol.[20,21] Counterintuitively, high levels of the CYP2E1 enzyme marginally lower BAC, but result in unprecedented alcohol sensitivity due to oxidative stress. It is estimated that 10-20% of the population is affected by this tipsy gene![20]

The tipsy genes work to increase behavioral sensitivity to alcohol, but there are also factors that shift the response to alcohol in the opposite direction.

Does drinking more eventually turn you into a "heavyweight?"

The human body, in particular the brain, is an ever-adapting, plastic organism that adjusts its connectivity and functions to accommodate for changes in alcohol intake. In other words—it learns.[12] Theoretically, a female who heavily uses alcohol might process and metabolize alcohol faster than an equally sized male who rarely imbibes. It is essential to note that chronic use of alcohol will eventually have detrimental consequences on one's health, not the least of which include addiction, liver disease and cirrhosis, and heart disease, [22,23] and that the body cannot be trained to combat these effects. However, the body of a cautious, occasional, social drinker will develop ways in which to more efficiently respond to alcohol and build tolerance.



Tolerance A brain can undergo pharmacodynamic changes in response to alcohol, in which the receptors that ethanol binds to, such as the GABA A receptor, are affected.

The GABA A receptor is responsible for the anxiolytic and sedative-hypnotic effects of alcohol.[23] With time, the receptors could either become desensitized to alcohol or decrease in density of these receptors to become downregulated.[24] Thus, ethanol levels that were once sufficient to activate the receptors would no longer produce effects of the same magnitude, leading the drinker to consume more.

Alternatively, concentrations of metabolizing enzymes that breakdown alcohol, particularly ADH, could elevate with time to account for increased alcohol in the system.[24,25] This pharmacokinetic tolerance results in increased metabolic activity that allows for faster alcohol processing, lowers BAC at an elevated rate, and produces a sort of behavioral tolerance to higher doses of alcohol.

Risk of Addiction Although tolerance might seem like a positive thing for those are not genetically endowed with the means to process or metabolize alcohol efficiently, the development of tolerance is a risk factor for addiction. As tolerance increases and the body becomes more efficient at processing higher concentrations of alcohol, previously effective doses become

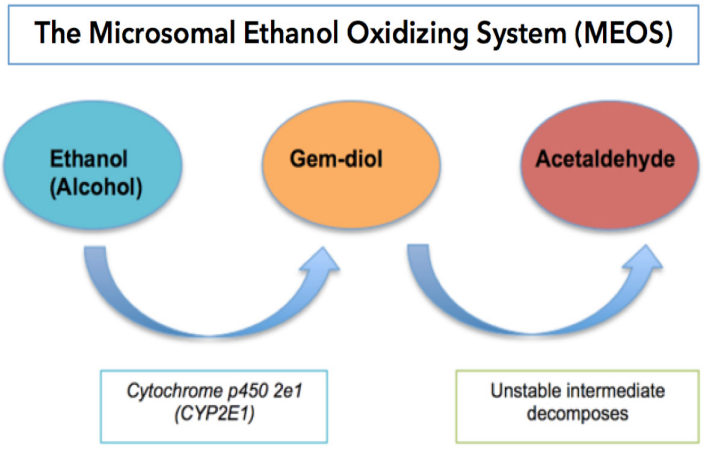


Figure 2 Created by Jessica Khrakovski.

insufficient to provide the desired sensations. Consequently, increasingly higher doses of alcohol are required to achieve effects.

Overview and Recap

While BAC charts may be useful in estimating one's blood-alcohol concentration, there are underlying genetic mechanisms that might explain why my Aunt Rebecca cannot be classified with such a table. Beyond the amount consumed, sexual dimorphism and differing enzyme concentrations result in gendered differences in alcohol processing that affect BAC and behavioral and physiological sensitivity to alcohol.

Further, tipsy genes result in deviation from behavior predicted at certain BACs. Though it is unknown exactly how prevalent the ALDH2*2 and CYP2E1*5B alleles are within the population, further research is critical in understanding the vast effects than alcohol can have on an individual. The creation of BAC tables that link expected behavioral effects to the amount of alcohol consumed is not a trivial task. It is still unknown what percentage of the population is affected by tipsy genes and shows disproportionate behavioral effects to seemingly small amounts of alcohol. This could have implications for reform regarding the legal driving BAC of 0.08 in the United States,[26] at which Aunt Rebecca surely would be incapable of safely driving.

While the development of tolerance through increased consumption trains the body to process more alcohol, it is also linked with a higher risk for alcohol dependence and addiction. Perhaps the lightweight trait is not the most desirable, but it does provide inherent protection against alcoholism. I do not know for sure if Aunt Rebecca has the tipsy gene,

NUMBER OF DRINKS	BLOOD ALCOHOL CONCENTRATION (BAC)	TYPICAL EFFECTS	ANTICIPATED EFFECTS ON DRIVING
1-2	0.02%	❖ Some loss of judgment ❖ Relaxation ❖ Slight body warmth ❖ Altered mood	❖ Decline in visual functions (rapid tracking of a moving target) ❖ Decline in multitasking ability-divided attention
2-3	0.05%	❖ Exaggerated behavior ❖ Loss of small muscles control (i.e. focusing eyes) ❖ Impaired judgment ❖ Usually good feeling ❖ Lowered alertness ❖ Release of inhibition	❖ Reduced coordination ❖ Reduced ability to track moving objects ❖ Difficulty steering ❖ Reduced response to emergency driving situations
3-4	0.08% *	❖ Poor muscle coordination (i.e. balance, speech, vision, reaction time, hearing) ❖ Harder to detect danger ❖ Impaired judgment, self-control, reasoning, memory	❖ Concentration ❖ Short-term memory loss ❖ Speed control ❖ Reduced information processing capability (i.e. signal detection) ❖ Impaired perception
4-5	0.10%	❖ Clear deterioration of reaction time and control ❖ Slurred speech, poor coordination, and slowed thinking	❖ Reduced ability to maintain lane position and brake appropriately
5-7	0.15%	❖ Impaired muscle control ❖ Vomiting or blackouts may occur ❖ Major loss of balance	❖ Substantial impairment in vehicle control, attention to driving task, and in visual/ auditory processing

but I definitely do not anticipate her ever developing a tolerance!

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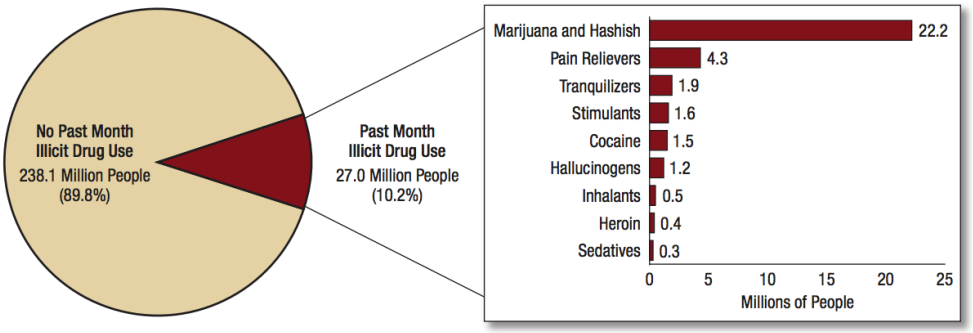
BATTLE OF THE SEXES: DOES SEX MATTER IN CANNABIS USE?

By **Toneisha Stubbs**

Cannabis is a widely used illicit drug in the US with the 2016 National Survey of Drug Use and Health (NSDUH) reporting that an estimated 24.0 million Americans aged 12 or older are current users of cannabis (Figure 1)[1]. Delta-9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis, is reported to decrease anxiety, induce a "high", produce perceptual changes, and impair both psychomotor and cognitive performance, including working memory[2]. Overall, these effects are subjective and vary from user to user. Cannabis and its chemical components have also been shown to possibly have medical uses ranging from the treatment of eating disorders to chronic pain[3]. In 1996, California became the first state to legalize the use of cannabis for medical purposes and, since then, medical cannabis has been legalized in 28 states including The District of Columbia[4]. Recreational cannabis use has also been legalized in 8 of those states as well as DC (Figure 2)[4]. While studies show that men use cannabis more frequently than women[5], a growing number of women report cannabis use for medical purposes[6]. This increase makes it important to look at possible sex differences in the effects of cannabis as well as its proposed therapeutic uses.

Many studies states that females are more sensitive to the subjective effects of cannabis and are more prone to THC withdrawal symptoms (Figure 3)[3]. While no one answer has been given to why this may be, researchers have come up with three possible reasons why females may be differently affected by cannabis use. In this paper I set out to talk about the differences seen in research and, hopefully, help us reach a conclusion to if sex matters in cannabis use. While there is not extensive human research done on sex differences in cannabinoid effects, we will examine data from experimental and

Figure 1 Substance Abuse and Mental Health Services Administration. (2017).Retrieved from https://www.samhsa.gov/data/



survey based human studies, as well animal studies.

Sex Differences in the Endocannabinoid System?

When THC and the other chemical components of cannabis enter the body, they interact with the endocannabinoid system. The endocannabinoid system is comprised of two receptors, endogenous cannabinoids and their metabolite enzymes. The two receptors in the system are the CB1 and the CB2 receptor, the CB1 is primarily found in the brain and the CB2 receptor is found in the peripheral nervous system. There are two common endogenous cannabinoids and they are anandamide and 2-arachidonoylglycerol (2-AG) which are metabolized by fatty acid amide hydrolase (or FAAH for short) and monoacylglycerol (or MAGL for short) respectively[7].

According to research[7] differences in this system occur early in the development of rats as it has been found that rats younger than 21 days show a huge increase in CB1 receptor density followed by a decrease in density during late adolescence. Another sex difference in this system is that peak levels of CB1 receptors are reached earlier in female rats than male rats[7]. Later in life this system is greatly affected by the hormonal cycle, which we will discuss later. Sex differences in the endocannabinoid system have yet to be identified in humans. Based on the research reviewed for this paper the endocannabinoid system is the foundation for the sex differences observed by researchers. It is within this system that researcher has identified three possible mechanism behind why sex may be a factor in cannabis use. Those three mechanisms are the hormonal cycle, pharmacodynamic factors, and pharmacokinetic factors. As you will see the examples I've already mentioned fit into these mechanisms. Through my research on this topic I have identified two other factors that may also relate to the factor of sex and those are body fat percentage and age.

Is it the hormonal cycle?

When sex differences are observed in any study, the first culprit to be pointed out is the hormonal cycle of females. To study the relationship between the hormonal cycle and cannabinoid effects researchers typically ovariectomize the female rats, meaning they remove their ovaries and/or administer hormones such as estradiol and progesterone to females. One such study was done by a lab out of Washington State University. They found that the administration of these hormones could alter the effects of THC in females including antinociception (the ability to block pain) and alter CB receptor density and affinity in certain areas of the brain[8]. Other studies looking at the role hormones might play in sex dif-

Figure 2 By Toneisha Stubbs

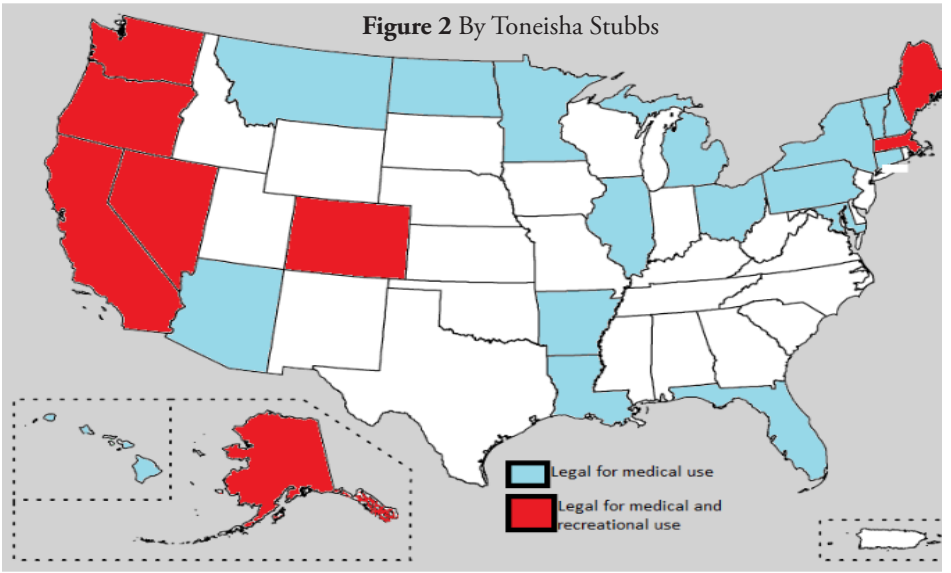
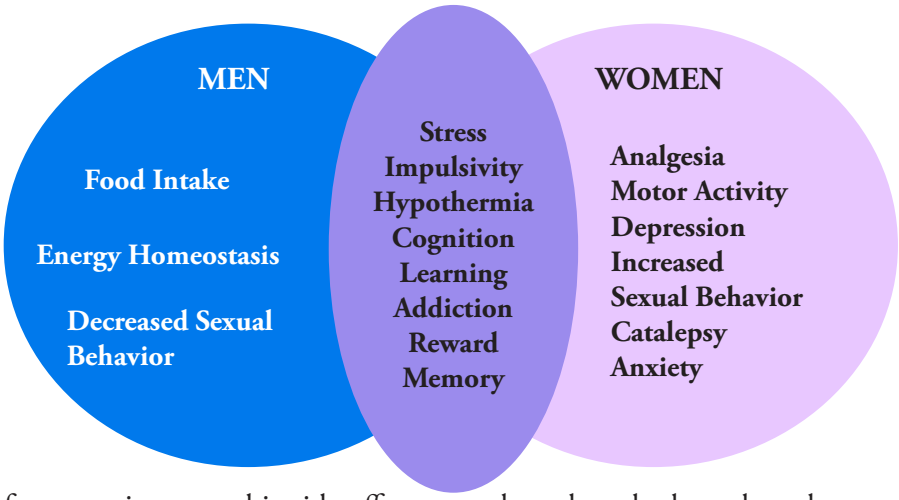


Figure 3 Adapted from Lynch & Ware (2015)



ferences in cannabinoid effects found that female rats with their ovaries removed, were more like males in cannabinoid self-administration. In humans there is also evidence that hormones may influence the endocannabinoid system, with endocannabinoid tone being shown to vary across the human menstrual cycle[21]. Plasma levels of the natural cannabinoids, such as anandamide, are observed during ovulation and positively associated with estradiol, luteinizing hormone, and follicle stimulating hormone[9]. However, not many studies have examined the effect of the menstrual cycle on cannabis use or effects. In summary what this data tells us is that the hormonal cycle of females may be responsible for differences in the effects of cannabis. To relate this idea to a larger picture in terms of the potential increase in the use of medical cannabis, it may be important for medical professionals to consider this factor, particularly when treating women. While this may seem like enough to determine that sex should be a factor considered in cannabis use, we'll also take a look at the other proposed mechanism and see what the results tell us.

Is it pharmacokinetic factors?

Pharmacokinetic factors include differences in the metabolism, distribution, and absorption of THC Animal studies have identified the possibility that cannabinoids are metabolized to active and inactive metabolites differently in males vs females. With females preferentially metabolizing THC to its highly active metabolite, 11-OH-THC and males to multiple compounds[10]. In males, the formation of 11-OH-THC from THC depends on the CYP2C11 isozyme whereas, in females, it is the CYP2C6 isozyme[10]. Differences in the distribution and absorption of THC have also been found, as Wiley, et al., (2014) reported that after repeated THC administration, the concentration of 11-OH-THC (main active metabolite) was higher in the brains of female adult and adolescent rats than that of males[11]. It was also shown that even when blood levels were equal, females have higher brain levels of THC[11]. It is safe to assume that if the metabolites are reaching the brain faster, then females are also feeling the effects faster. In humans given an oral dose of THC, women had significantly greater Cmax, meaning higher maximum plasma concentration of THC was observed[12]. The same study also found that females had a shorter tmax, meaning it took less time for females to reach peak concertation of THC and greater AUC (area under the curve), which means females experience exposure to the drug longer than males[12]. These findings relate to the THC metabolite 11-OH-THC and indicated a difference in elimination of the metabolite. While this study does not measure the metabolites like that in the animal studies, it still shows that THC is reaching higher levels in females and is doing so relatively quickly. Taken together these results appear to show that females produce more of the active metabolites of THC and those metabolites seem to reach the brains of females faster and stay in the body longer. It is probably safe to assume that females could be feeling the effects of THC faster and for longer durations than males. Thus, we may have another point in favor of sex being a factor in cannabis use.

Is it pharmacodynamic factors?

The third mechanisms that is believed to play a role in the sex differences observed are pharmacodynamic factors that affect the way the drug acts on the body. Phar-

macodynamic factors include differences in receptor density and/or affinity. Animal studies have indicated sex differences in CB1 receptor density in several areas of the brain including the mesencephalon, striatum, limbic forebrain and pituitary, with males showing greater density and/or affinity than females (Figure 4)[10]. CB1 receptor density has also been shown to fluctuate across the estrous cycle in female rats particularly in the hypothalamus and anterior pituitary (Figure 4)[10]. Although no consistent sex differences in cannabinoid receptors have been found in humans, one study did report that CB1 receptor protein expression in leukocytes was reported to be greater in women than men[13]. Other studies using human subjects have found greater CB1 receptor density in men than women in the cortico-striato-thalamic circuit (Figure 5)[14]. Together, these results show that males have a higher density of CB1 receptors in certain brain areas than females, which goes against the fact that females feel more of the effects of cannabinoids than males. While in the other two factors we've discussed so far, the hormonal cycle and pharmacokinetic factors, we have relativity consistent results in the sex differences, the results for the pharmacodynamic factors go back and forth, at least in humans. Despite the lack of inconsistent data, the influence of sex and the hormonal cycle on CB1 density and affinity is an important factor to be looked at when it comes to the use of THC as a medical treatment as well as in its recreational use.

Other Factor that Intersect with Sex

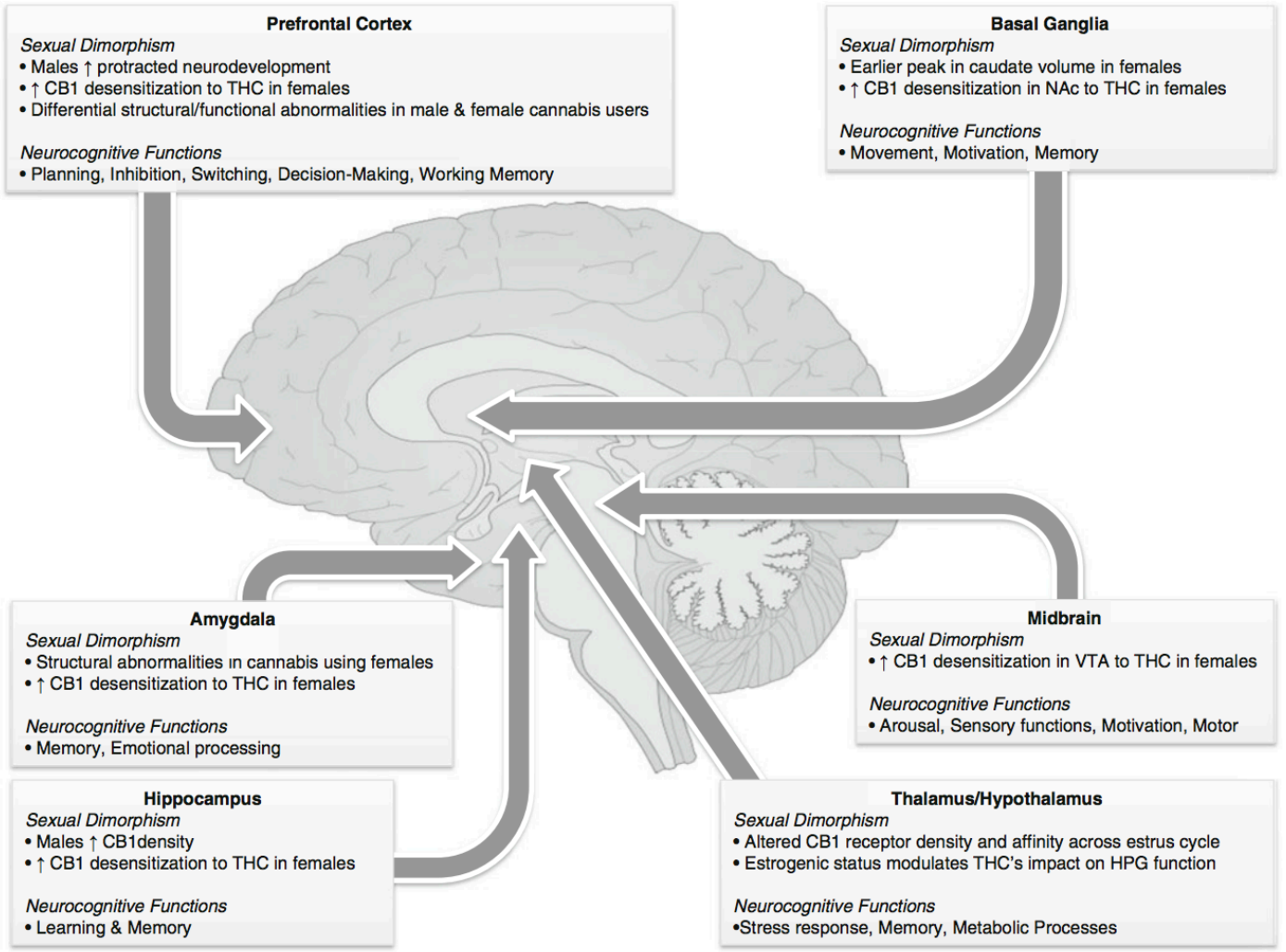


Figure 4 Crane, N. A., Schuster, R. M., Fusar-Poli, P., & Gonzalez, R. (2012). Effects of Cannabis on Neurocognitive Functioning: Recent Advances, Neurodevelopmental Influences, and Sex Differences. Neuropsychology Review,23(2), 117-137. doi:10.1007/s11065-012-9222-1

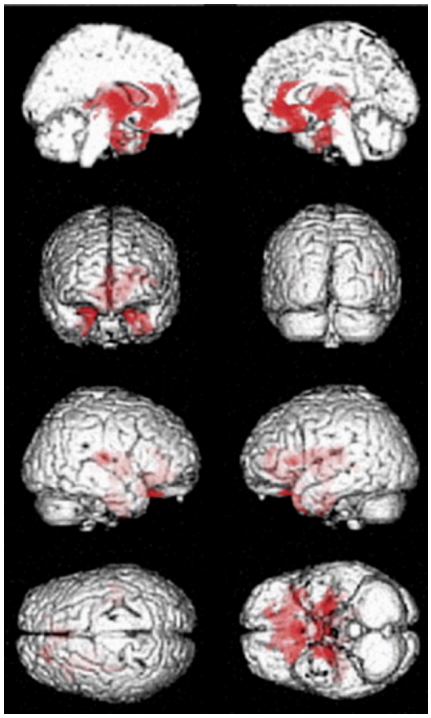
Despite the extensive research done on the three factors discussed so far, there are some other factors that don't fit into the categories of PD, PK or hormones but also play a role in creating the sexual dimorphisms in cannabis effects. One such factor is fat deposition. Cannabinoids are lipophilic, meaning it is found in high concentrations in fat tissue[15]. This factor is interesting in that human females tend to have higher percentage of body fat than males, whereas animal studies have shown the opposite in rodents, with males having a higher percentage of body fat[15]. These contradictory results make it difficult to fully translate preclinical animal studies to human studies as we would expect to see opposite results with regard to this factor. Another factor to consider is age. On a societal level males tend to start drug use, in this case cannabis, at younger ages than females. This earlier onset of use can lead to long term issues being seen in higher rates in males than females. With respect to age it was also found that CB1 receptor binding increases with age, especially in the memory, limbic, and motor circuits[14]. This could indicate that older cannabis users are affected more than younger users and if we connect this to the point about females starting drug use at older ages, it further indicates a greater effect among women. While there is not much human research that also examined these factors, the studies (both humans and animal) that have provided a good look at what can possibly be observed in clinical studies.

Spotlight on Human Studies: Sex differences in potential therapeutic effects

While human research looking at sex differences in the effects of cannabinoids is far less extensive than that done in animals, it is still important to look at what has been found. Before we dive into the therapeutic effects, let's discuss some of the overall trends in cannabis use. A survey of over 2,000 cannabis users revealed that men reported using cannabis more often and in higher amounts than women. Men were also more likely to report using joints/blunts while women reported using pipes or oral administration more often[6]. In terms of side effects, men were more likely than women to report increased appetite and improved memory while high. Women, on the other hand, reported side effects such as loss of appetite[6]. These results are from one survey collected from a population in Washington state and, while it is not safe to generalize these results to all cannabis users they offer a quick glimpse into what cannabis users might be experiencing and how those experiences differ between the sexes.

Cannabis and its chemical components are believed to provide several medical benefits for medical issues such as chronic pain, chemotherapy induced nausea, anxiety, PTSD, neurological disorders and several other health conditions[21]. It is important to note that some of these conditions have more research support behind

Figure 5 Taken from Fattore & Fratta (2010).



them than others. Clinical trials such as those conducted by Lynch and Ware[16] coupled with the reported use of cannabis to reduce chronic pain[6] provide support for the pain relieving effects of cannabis. A 2008 study also suggested that cannabinoids may be helpful for women suffering from chronic pain[3]. However, in another study among daily cannabis smokers it appeared that women were not more sensitive to the pain relieving effects of cannabis. In looking at the effects of cannabis on chemotherapy-induced nausea one study found that based on self-reported measures of appetite women showed greater improvements in appetite after an oral dose of THC but no sex differences were observed in ratings of nausea or other measures[17]. From this data it seems that while sex differences have been observed in some of the proposed therapeutic effects

of cannabis, they have not been consistent. Due to these inconsistencies, more data is needed before it is fully determined if sex should be a factor considered in cannabis use, medical or recreational.

But It's Not All Good

While we can talk about the potential good associated with the medical use of cannabis, we must also discuss the negative side of it use. One thing that has been suggested is that women may be more sensitive than men to adverse effects such as dizziness induced by cannabis exposure[18]. Chronic cannabis users have reported intense bouts of vomiting and stomach distress, which are symptoms collectively known as cannabinoid hyperemesis syndrome (CHS) and, when reported, this condition is more likely diagnosed in men than in women[3]. With these adverse effects we must also talk about the development of tolerance and dependence to cannabis, which are both risks associated with its use. The development of both conditions can lead to an increase in cannabis/THC use, which is an important issue to consider on both the medical and recreational sides of things. It has already been shown that men have higher rates of chronic use[6] as well as longer episodes of cannabis use disorder (CUD) a condition associated with the continued use of cannabis despite health distress[19]. A study that looked at abuse-related subjective effects showed that while males and females did not appear to be differently sensitive to stimulus effects of oral THC, women were more sensitive to the lowest does tested by the study and reported higher ratings related to abuse liability[20]. An earlier study looking at the effects of smoked cannabis reported that even though men and women did not differ in ratings of "intoxication", females were more sensitive to the subjective effects as they related to abuse liability which includes ratings of liking the drug, and willingness to take the drug again[21]. Sex differences have also been explored in the craving for cannabis, which serves as a measure of addiction severity. One study found that there was no difference between men and women in their ratings for craving[3], indicating that there was no difference in chances of reinstating drug use. However, another study found that women had significant decreases in compulsivity after oral THC treatment compared to men[22], which can indicate higher chance of reinstating drug use. Studies looking at withdrawal effects have also found differences in the withdrawal effects reported by men and women. Men are more likely report effects such as cannabis craving and sleep disruptions than women, while women are more likely to report nausea, irritability and anxiety[3]. Unlike the biological underpinning that affects the three mechanisms discussed earlier in the paper the sex differences in the effects in this section are influenced by societal structures that affect "acceptable" drug use in certain groups or hinder the willingness to report health issues to name a few.

Gender Influences on Cannabis Use

With all the possible biological mechanisms, the role of age and weight, the differences in reported effects, use, and adverse side effects being considered, we must briefly discuss how social factors can affect results, particularly self-reported data. One finding from the Washington survey not mentioned earlier was that men were more likely to report recreational use than women, with women being more likely to report medical use [6]. While we may like to think we've moved past gender norms it is possible that women still feel societal pressures creating the idea that drug use among women is not acceptable and are therefore, likely to report recreational use. This might change as legalization of cannabis use spreads and as social change continues but is at the moment still heavily influenced by cultural/familial norms. When it comes to self-reporting adverse effects, gender norms can cause a lack of confidence in men reporting their withdrawal symptoms or other health issues caused by their cannabis use, such as pain. If men are less likely to report these issues because of how they think it would be perceived, then this could skew results in the area. Just when we thought we had enough confounding factors to deal with, the changing and variable gender-based social expectations surrounding cannabis use adds another.

So, what does any of this mean? Should sex be considered a factor?

If we expect states around the country to follow the lead of the states that have already legalized the use of medical and recreational cannabis, it is important that we understand not only the effects of the drug but also the factors that lead to those effects. One of those factor is biological sex, and while it may come with other confounding variables, it should be a major factor considered when medical cannabis is prescribed to patients and even in it recreational use. Cannabis is a difficult drug to study due to the differences in legality across the country and the terms of legality in states where it is legal (such as being legal for medical use but not recreational, or legal for both) but an important drug to continue to look at. As mentioned throughout the paper more concrete identification of sex differences in the effects of medical cannabis could have clinical implications. However, finding these sex differences are not the final piece to the puzzle. Once these differences are identified and shown to be significant, it then needs to be determined exactly how treatment and dosing will change to accommodate for them. For example, if large sex differences are found in the potency and efficacy of medical cannabis, this could indicate the need to increase drug dose/concentration, which can lead to problems such as tolerance and dependence. It will be important for clinicians to find the balance between doses that are effective enough to overcome possible sex differences and doses that produce tolerance and dependence. So, with all this being said, if asked if sex should be a factor considered in cannabis use, my answer would be yes, and as research related to cannabis and its chemical components continues, I hope that sex is incorporated into both preclinical and clinical studies.

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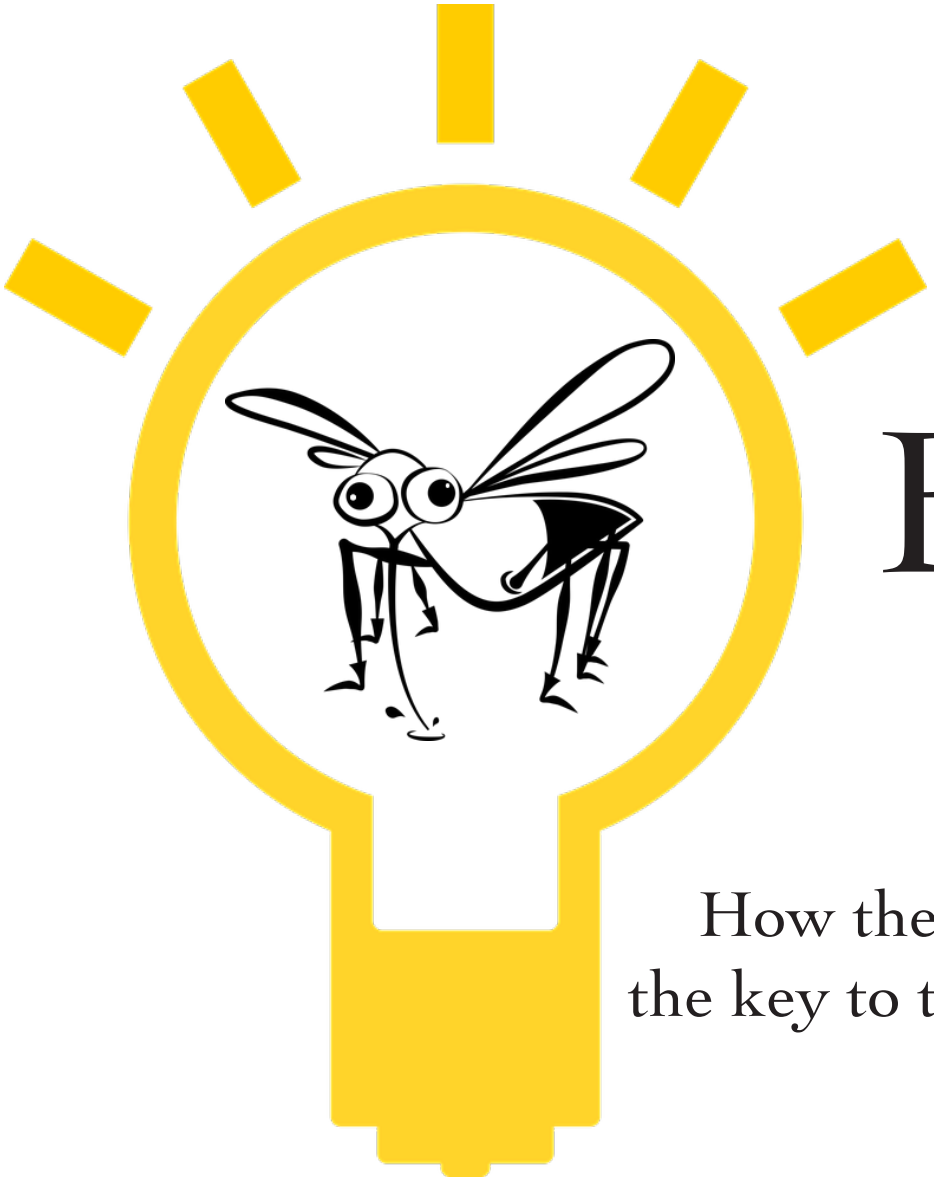


Eureka Zika!

How the feared virus may be the key to treating Gliobastoma

By **Samantha Palicz**

With the recent surge of women in Central and South America giving birth to babies with abnormally small heads, the Zika virus has become a popular topic of discussion in the media. The Center for Disease Control has issued travel warnings for pregnant women and those of childbearing age regarding traveling to countries where Zika is prevalent.[1,2] The virus is a mosquito-borne infection that is spread either from the bite of a mosquito or passed sexually from one partner to another.[1] For most, the infection goes either unnoticed or results in mild flu-like symptoms.[1] It is how the virus spreads from mother to fetus during pregnancy that is concerning. But even though the fears of pregnant women are justifiable, this virus may be the key to unlocking a treatment for Glioblastoma, a form of brain cancer.

Zika and Pregnancy: A terrifying tale

When a mother is infected with Zika during pregnancy, it can cause deleterious effects on the fetus throughout development. Among these are birth defects and problems including miscarriages, stillbirths, and extreme degrees of microcephaly.[1] Of these, the most common and simultaneously severe birth defect is microcephaly. Microcephaly can be simply defined as an abnormally small brain that is indicative of incomplete brain formation.[1,2,3] Physically, microcephaly is characterized by a reduction in head circumference. Behaviorally, microcephaly results in motor, visual, hearing and cognitive impairments.[3]

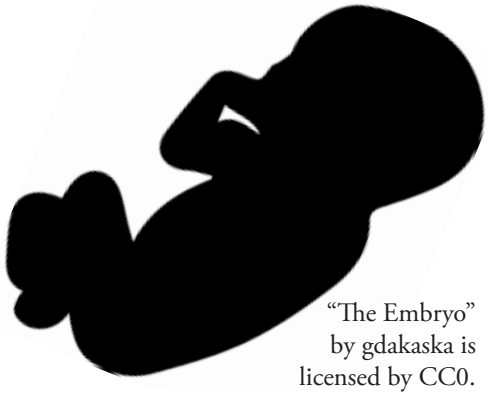
The transmission of the virus from mother to child during

Did You Know?

The Zika virus has been identified in and carried by mosquitoes in Miami, Florida now.[1]

pregnancy results in these drastic fetal brain abnormalities because the virus can cross the mother's blood to the developing fetal brain.[4] It remains unknown how the virus is capable of this, but it appears that the Zika virus then only attacks undifferentiated and still developing fetal brain cells that would otherwise be growing into brain cells with specific functions.[5] It is these undifferentiated brain cells that grow and form the brain. The presence of the virus in the brain is associated with both a decrease in the production of and death of the fetal undifferentiated brain cells resulting in a smaller and underdeveloped brain.

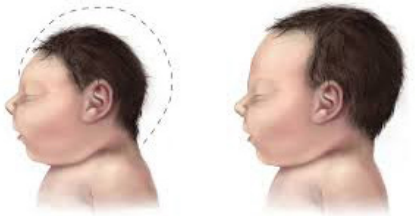
Recent reports from the Brazilian Ministry of Health suggest that the number of cases of microcephaly in newborns has increased by a factor of about 20 with the presence of Zika.[3] A research team followed the case of a 25-year-old pregnant woman who was infected with Zika during her first trimester. The researchers wanted to look into the passing of the virus from mother to fetus, as well as, the effects of the virus on the developing fetus.[3] At 32 weeks, fetal brain imaging showed evidence of brain abnormalities that were indicative of severe microcephaly.[3] The pregnancy was terminated at this point and further studies were run.[3] The results were shocking. It was found that the fetus was only in the fifth percentile for body weight and the head size was in the first percentile.[3] Furthermore, the placenta weight was only in the third percentile and the whole brain weight was four standard deviations below average.[3] They also found that the Zika virus was local to just the brain and not found in any other organs. This is a very important finding as it demonstrates that Zika only infects and attacks brain cells.



"The Embryo" by gdakaska is licensed by CC0.

In a similar study, another pregnant woman who contracted Zika early in pregnancy was followed by researcher and they found similar and equally upsetting.[5] Between weeks 16 and 20 of pregnancy, the fetal head circumference decreased from the 47th percentile to the 24th percentile and at 20 weeks, substantial brain abnormalities were observed.[5] The fetus did not survive pregnancy and postmortem analysis revealed severe microcephaly and high levels of the Zika virus present both in the placenta and in the brain tissue.[5] However, an important finding was obtained from this devastating case; the virus only caused cell death in the undifferentiated fetal brain cells and not in developed brain cells.[5] This was apparent as no microscopic abnormalities were found in the eyes, spinal cord, spinal nerves, or in the well-differentiated neurons of brain areas such as the basal ganglia and limbic.[5]

"Microcephaly" by CDC is licensed by Public Domain.



Why Zika is causing so much trouble now

The Zika virus was first initially isolated in 1947 in Uganda so why is it just now causing so much trouble?[3,5] From sequencing the genome of Zika virus samples isolated from infected people and fetuses, researchers discovered that a single change in a sequence of the viral DNA that codes for a structural protein of the virus seems to have occurred in 2013.[6] It has been proposed that this one mutation is responsible for why the virus now has the ability to aggressively attack fetal brain cells resulting in the observed developmental abnormalities such as microcephaly.[6] Studies involving mice, each with a differently mutated strain of the Zika virus, demonstrated that this

Did You Know?

Since 2013, there have been just over 4000 cases of babies born with Zika related to microcephaly.[1]

"Gene Editing" by Julie McMurry is licensed by CC0.

one specific mutation causes the most damage. This new, modern strain of the Zika virus kills more fetal brain cells than the ancestral, or older, strain.[6]

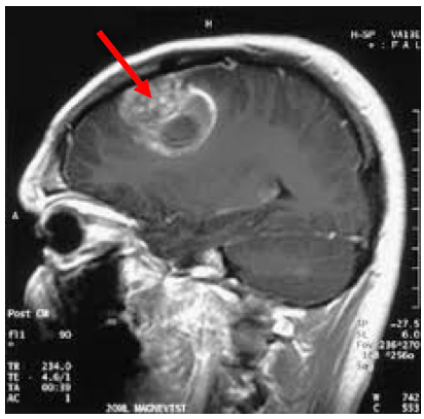
A fear for some, but a blessing for others

While the modern Zika virus has calamitous effects on the developing brains of fetuses, in the near future, this feared virus may be an effective treatment for glioblastoma, a deadly brain cancer. A research group from Washington University School of Medicine in St. Louis and the University of California San Diego School of Medicine has shown that the Zika virus kills brain cancer stem cells.[7] This is incredible as these stem cells are the most resistant to the current treatments provided for glioblastoma.

Glioblastoma are brain tumors that arise from cells in the brain called astrocytes, which are supportive, star-shaped cells found in the brain.[8] Glioblastoma are considered especially dangerous because they grow quickly.[8] The fast growth of these tumors results in symptoms that are the direct result of increased pressure on the brain.[8] Some of these symptoms include headaches, dizziness and sudden changes in vision.[8] Despite the current treatment of surgery, chemotherapy, and radiation, glioblastoma remain lethal with an average survival rate of fewer than two years.[9]

Every year, about 12,000 people are diagnosed with glioblastoma in the United States and it is the most common form of brain cancer.[7] The standard treatment is aggressive with surgery, followed by chemotherapy and radiation. Yet, most tumors recur within six months and less than ten percent of patients diagnosed will live to five years post their diagnosis.[8] The cancer is so aggressive in its growth because the glioblastoma stem cells survive the current treatments offered and continue to divide, thus producing new tumor cells to replace the ones being killed during treatment.[8]

Unlike other cancers, glioblastoma do not spread to other parts of the body.[9] In fact, in most patients, the tumors continue to grow from their original locations, even after the majority of the tumor has been surgically removed.[9] This is because glioblastoma have root-like projections that contain glioblastoma neural stem cells from which the tumor grows.[8] The projections of glioblastoma take root and this makes them very hard to remove. Surgeons are especially cautious when they are removing tumors in brain regions that control important functions such as vision, language, and coordination.[8,9] Since glioblastoma have this unique trait of not spreading and regrow from their roots, researchers have begun to investigate using viruses as a way to attack theses cancerous roots.[4,9]



"Glioblastoma" by Christaras A is licensed by CC BY 2.5.

Did You Know?

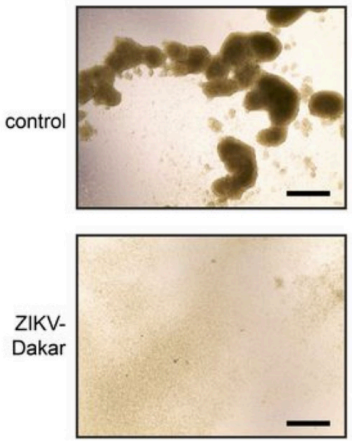
Gliobastoma is the same brain cancer that took the lives of Ted Kennedy and Gary Carter, and is the cancer that Senator John McCain was recently diagnosed with.

The effects of the Zika virus on fetal brain cells versus developed brain cells has led researchers to think of the Zika virus as a potential treatment method for glioblastoma.[9] This may be possible because the virus has shown to differentially attack only fetal brain cells, such as neural stem cells. These types of cells also happen to be the cells found in the root projections of the glioblastoma tumors.

There are many similarities between glioblastoma neural stem cells and the brain cells in a developing fetal brain.[9,10] Glioblastoma stem cells resemble fetal neural stem cells both in their neurological origins and ability to grow and create new cells.[8] One of the only differences between the two is that neural stem cells

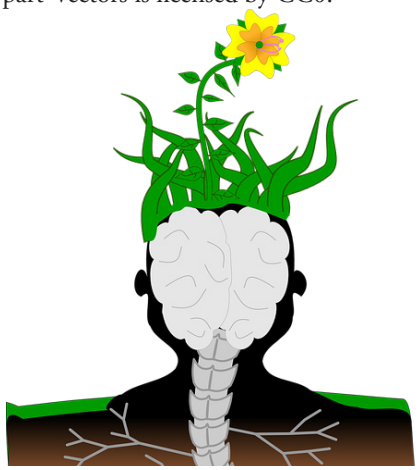
and fetal brain cells stop growing in response to environmental cues within the brain once they have developed, whereas glioblastoma stem cells do not respond to these cues to stop growing.[10] It was the similarities between fetal brain cells and glioblastoma stem cells that led Dr. Zhe Zhu to consider the potential use of the Zika virus to target and destroy the tumor-specific stem cells of glioblastoma.[10]

In lab studies, when Zika was added to dishes containing human glioblastoma stem cell cultures, the virus completely infected and killed the glioblastoma cells and no regrowth was observed.[9] When speaking about their results, Jeremy Rich, M.S., stated that, "Zika very specifically killed brain tumor stem cells with little effect on differentiated tumor cells and adult neural cells."[10] Furthermore, mice models with glioblastoma tumors survived much longer and at greater rates when injected with a mouse-specific strain of Zika.[9] These results suggest that Zika can preferentially target the glioblastoma stem cells that drive tumor growth. Since traditional treatment for glioblastoma fails to eliminate the stem cells, the



Adapted from Zhu et al. (2017)

"Planta Cérebro Coluna" by OpenClipart-Vectors is licensed by CC0.



tumors continue to regrow. By introducing Zika into the treatment plan, the virus would help combat this problem as it would attack just the glioblastoma stem cells in the roots of the tumor.

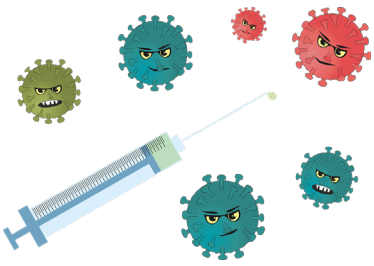
So, overall, how does this work? When combined with the current treatment methods, Zika literally gets to the root of the problem. When introduced to a tumor, Zika spreads through the tumor, infecting and killing the tumor stem cells. Then a combination of radiation, chemotherapy, and surgery could be used to kill the bulk of the tumor. Imagine that your yard is full of dandelions. Sure you can temporarily get rid of them by mowing or plucking them, but that is a temporary fix. This is the same problem when treating glioblastoma. Sure we can remove the bulk of the weed, or in this case the tumor, but if the roots are left, the weed will grow back. That is where Zika comes in. Like a weed spray or a patient gardener, Zika gets down and kills at the roots to prevent any regrowth.

What does this all mean?

Now that early studies have shown that Zika specifically targets only neural stem cells and has no effect on differentiated brain cells, where to next? First, more research needs to be done before this becomes a feasible treatment option because we cannot just inject people with the modern and active Zika virus as it is now. Researchers are already looking into bioengineering the virus to be more safe, while still being as effective.[10,11] They are looking to introduce additional mutations to prevent the infection from spreading after being therapeutically introduced. Excitedly, one of the researchers stated that "Once we add a few more changes, I think it's going to be impossible for the virus to overcome them and cause disease."[7] Additionally, the researchers are cautious as it is possible that the virus may behave differently than has been observed when introduced to an active glioblastoma in a person.[11] It is also still unknown how long the virus remains active once in the body.

Bioengineering: Making good out of the bad

While this idea of using Zika, a feared and dangerous virus, to treat brain cancer seems revolutionary, researchers have actually



"Influenza Flu" by Sabine Kroschel is licensed by CC0.

Adapted from "Botox Moving Into the Medicine Cabinet by Lee Health, licensed by CC0.

been bioengineering treatments out of deadly viruses and toxins for quite some time. For example, back in the 18th century, Edward Jenner used cowpox to protect humans against smallpox.[12] Fast Forward to the 1960s, and "vaccinating" was supported and campaigned for by the World Health Organization and this resulted in the elimination of smallpox.[12] The success of vaccines has also led to a drastic decrease in the occurrence of polio and measles and are also proving to be helpful in preventing hepatitis B and human papilloma virus induced cancers.[12] Recently, the measles virus has also been bioengineered and may have an ability to specifically target a known marker for tumor-initiating cells in glioma, colon and hepatocellular cancer as evidenced by success in mouse tumor models.[13]

In addition to the use of viruses to fight cancers, over the years, a neurotoxin has become a popularly used substance to treat a variety of disorders. Botulinum toxin is the neurotoxin that is responsible for botulism.[14] The toxin works by interfering with the release of a neurotransmitter, acetylcholine, that is responsible for muscle function.[15] The toxin blocks the release of acetylcholine, thus resulting in a form of paralysis.[16] Botulinum toxin is one of the most poisonous biological substances known, but bioengineers and researchers have found a way to harness the power of this toxin and turn it into a "miracle poison."[16] Botulinum toxin, or more commonly referred to now as Botox, is now widely used to treat a variety of medical conditions including problems with muscle spasticity, migraines, hyperhidrosis, and even for cosmetic purposes to reduce the effects of aging on appearance.[16]

Botox has shown to be beneficial and even life-changing for people who suffer from cerebral palsy.[17] Children with cerebral palsy often suffer from spastic, or rigidly tense, muscles.[17] Despite early interventions with physical therapy and bracing, these tense muscles can lead to permanent deformities in the legs and feet and thus will negatively impact an individual's ability to walk normally or at all.[17] This is where controlled injections of Botulinum Toxin Type A work as a therapeutic treatment. The toxin works by reducing the rigidity of the muscle and the muscle tone by disrupting the release of the acetylcholine that is causing the muscle contractions. With muscles that over contract and do not release, the toxin is a blessing. Botox injections into the leg muscles allow the muscles to relax just enough to allow for the development of proper walking habits during physical therapy, strengthening of surrounding support muscles, and improved balance.[17] Together, this all leads to an overall improved quality of life.

"Cerebral palsy" by National Institutes of Health is licensed by CC BY-NC 2.0.

Did You Know?

Since 2000, Botox-A injections have been the #1 medical procedure in the United States.[18]

Botox has also become a method of treating severe migraines. As with treating muscle rigidity in patients with cerebral palsy, botulinum toxin-A has shown to reduce pain associated with muscle spasms that can lead to migraines.[15] Controlled injections of Botox-A into the forehead are effective in reducing migraine frequency, severity, and associated vomiting as it reduces muscle contractions believed to be causal, at least in part, to migraines.[15] Studies, like the one done by Dr. Stephen Silberstein, have also shown that the toxin may be inhibiting the pain pathway as well.[15] Additionally, the effects seem to last for up to 3 months at a time and with limited side effects at proper dosage levels.[15]

As if helping kids with cerebral palsy and lessening the intensity of migraines were not enough, Botox-A has also been clinically proven to help those

with hyperhidrosis (overactive sweat glands).[14] In addition to relaxing spastic muscles, Botox-A also inhibits sweat gland activity.[14] The inhibitory action of Botox-A extends beyond muscles and includes inhibition of other nerve fibers such as those in sweat glands. Hyperhidrosis commonly results in the overproduction of sweat on the hands, and/or forehead, and/or underarms.[14] Botox-A has shown to be an effective method at temporarily reducing the amount of sweat produced when other medical treatments fail. It is a more feasible and less dramatic option for many than having their sweat glands surgically removed as some level of perspiration is still necessary to cool the body and prevent friction irritation.[14] Controlled injections of Botox-A are effective for many at reducing sweating when injected into the hands, forehead and/or underarms.[14] A clinical study demonstrated that Botox-A was successful in reducing sweating with no reported side effects and can last anywhere between 6 and 11 months depending on the injection site.[14]

The future with Zika

The history and success of the clinical use of biologically engineered viruses and toxins as treatments speak for itself. These once feared viruses and toxins have improved and continue to improve the lives of people of all ages, backgrounds, and economic status worldwide. It appears now, that the Zika virus is next up to save lives, rather than destroy them. With continued studying, the power of the Zika virus may help cure brain cancer.

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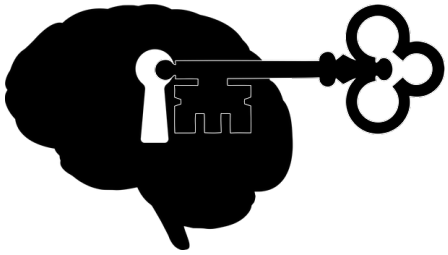

Viruses and toxins exist in our environment and all function in specific ways with specific targets. By further studying what we biologically fear, not only can we treat these infections more effectively, but we can also use these viruses and toxins to treat other illnesses. It is feasible to believe that within the next decade, the Zika virus could be adding years to lives by attacking and destroying cancerous tumor stem cells.

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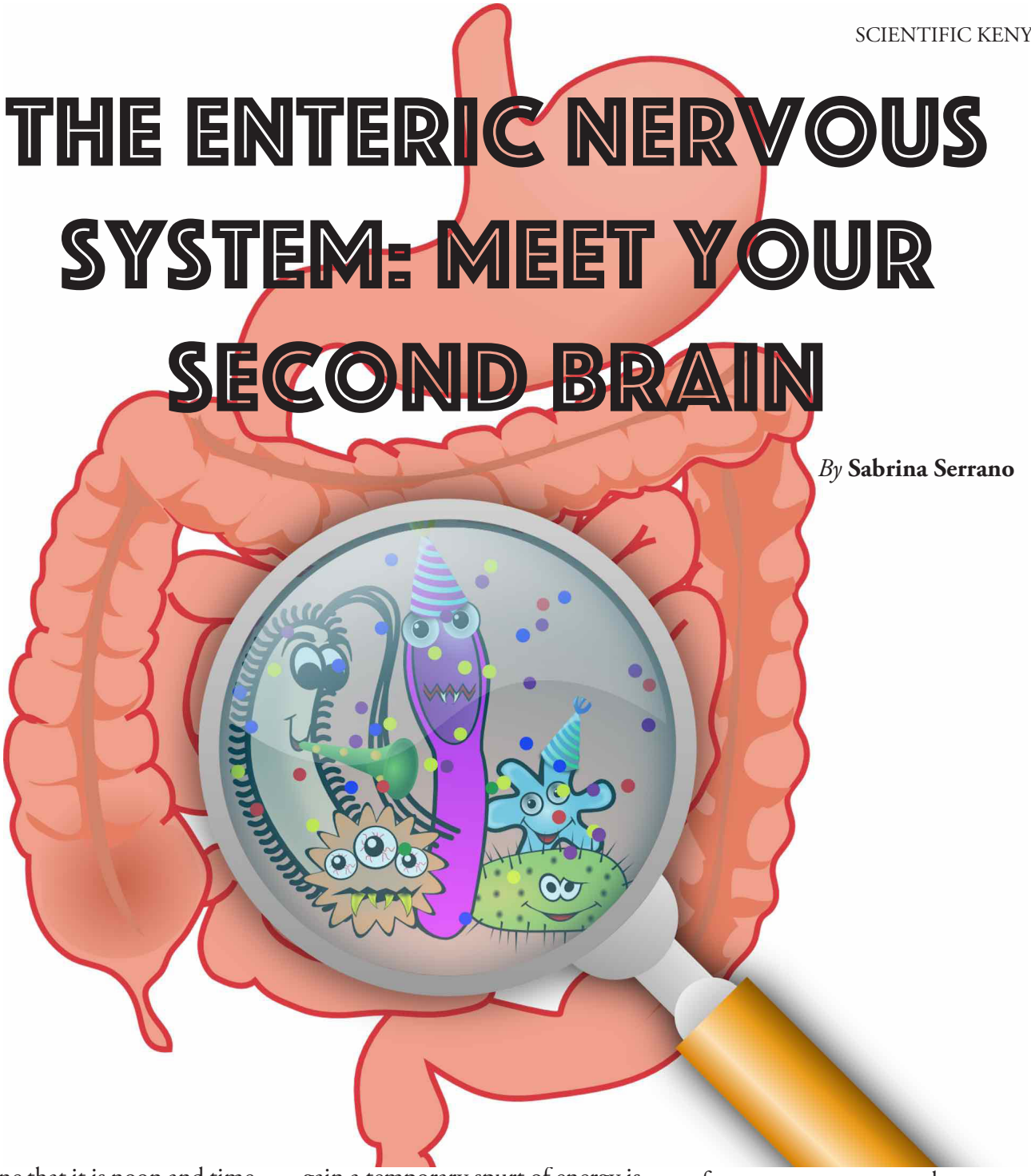
THE ENTERIC NERVOUS SYSTEM: MEET YOUR SECOND BRAIN

By **Sabrina Serrano**



Imagine that it is noon and time for your lunch break. You decide on eating something you can buy quickly and easily, like Taco Bell. After a few hours, you notice that you are groggy, maybe even sleepy, and are having a hard time concentrating on work. You also find yourself feeling more stressed out than usual, Maybe it's because you're not being efficient enough. The only way you can gain a temporary spurt of energy is through a highly caffeinated drink like coffee. You're probably wondering... *why is this happening? Did I get enough sleep last night?* There is a good chance that your symptoms of fatigue, stress, and inattentiveness could be due to processes other than those occurring in your head.

The Enteric Nervous System (ENS) is an autonomous part of our nervous system that many people are unaware of. An autonomous part of your nervous system that many people don't know , is the enteric nervous system, or the ENS. The ENS has important implications to complex cognitive behaviors, such as stress and anxiety. The ENS is made up of all of the neurons that activate your digestive gut.[1] Most of the func-

Did You Know?

Your ENS, located in the digestive gut, has hundreds of millions of neurons, or nerve cells. This is about 1/200 of the amount that your brain has and about 5X as much as your spinal cord![14]

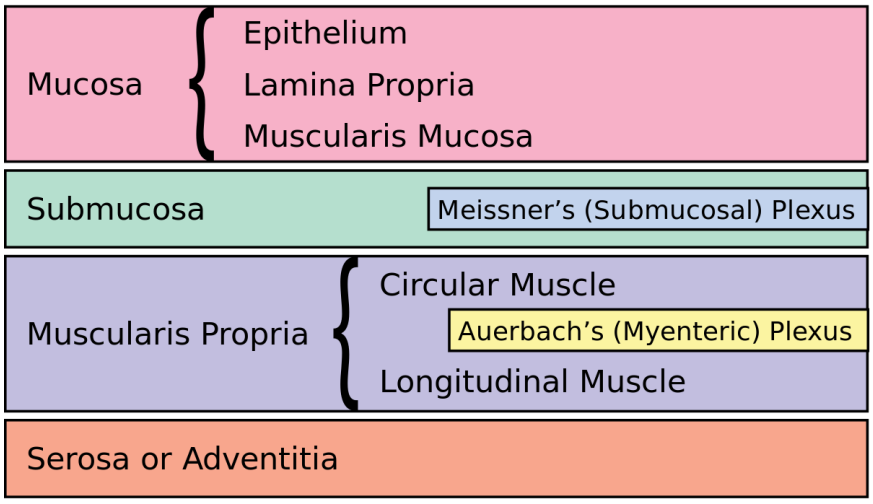
tions of your digestive system, including breakdown, movement, and discharge of food, is completed through the activation of your ENS.[1] This part of your body is more important than many people realize: studies have shown that the neurons in the ENS are highly influenced by your gut's bacterial composition and nutrient composition.[7] The ENS acts as a mediator between your central nervous system (CNS) and the digestive gut. That means any alteration of the ENS will heavily affect both the digestive gut and the CNS, both crucial for bodily functioning. Therefore, in the context of digestive pathology, even minor pathologies like the "2pm energy slump," it is important to understand the functioning and impact of the ENS as well as its interaction with the digestive gut.

What makes up the ENS?

The location of the ENS exhibits its importance in gut function. The ENS is hugely important for the activation of basic bodily functions such as movement through the intestines, proper absorption of water/electrolytes, and regulation of local blood flow.[4] The human ENS is located in your gastrointestinal (GI) tract. The human GI tract is made up of four layers: the mucosa, the submucosa, the muscularis externa, and the adventitia/serosa.[3] The ENS is located within 2 layers of the GI tract, forming two different plexi: the myenteric plexi and the submucosal plexi.

The myenteric plexus, located between the inner and outer and muscle layers of the GI tract's muscularis externa, is responsible for muscular functioning. The other plexus, the submucosal, located in the submucosa, regulates the mucosal functions.[2]

General Organization of the Gastrointestinal Tract



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"Stomach pain" by CDC is licensed by Public Domain.

Why is this important?

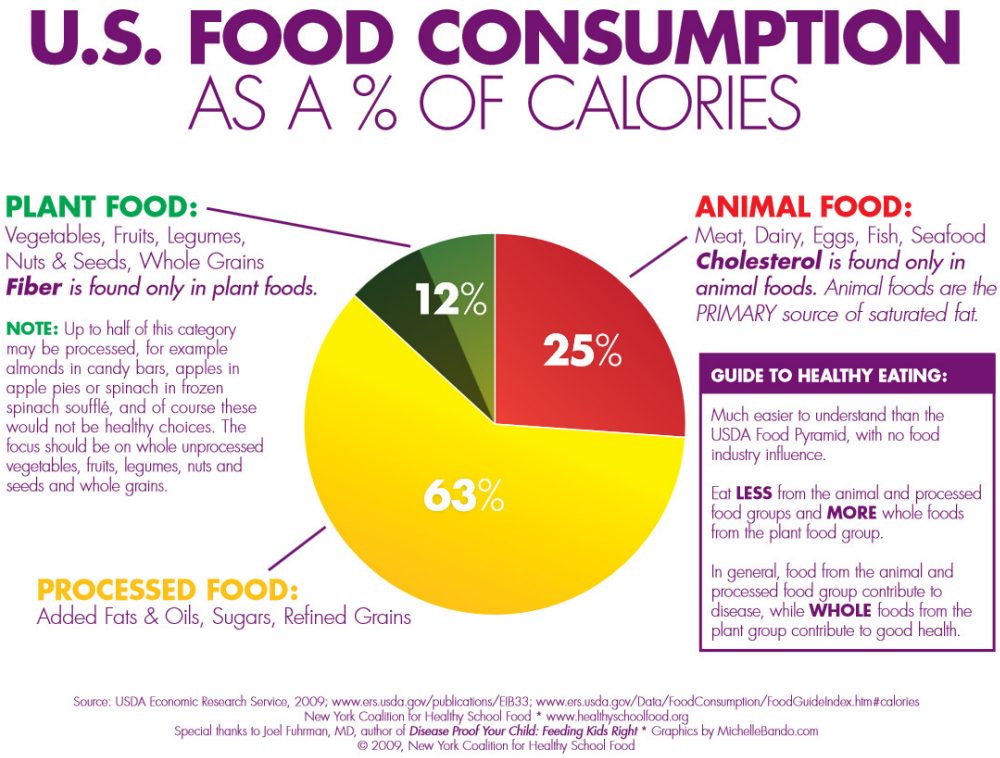
Nowadays, there are many disorders in which the ENS function is abnormal, called enteric neuropathies.[4] These enteric neuropathies are much more familiar with the common person's ear than you think. One of them is Irritable Bowel Syndrome (IBS). IBS shows symptoms such as abnormal bloating and the feeling that your food moves too quickly or too slowly through your digestive system, causing unexpected changes in your bowel movements.[15] Public health researchers have estimated a 11.2% global prevalence of IBS, or about 836,000,000 people! Another major ENS neuropathy is diabetic gastroparesis, which is a disorder that slows or stops the movement of food from the stomach to the small intestine. Diabetes itself affects about ~10% of the global population, with the symptom gastroparesis affecting approximately 5-12% of the diabetic population.[6] Most major enteric neuropathies are the result of improper communication between

neurons in the ENS. This results in subsequent dysfunction of the digestive system, which is manifested through symptoms like bloating, nausea, diarrhea, chronic pain, and sensitivity to foods.[6] These neuropathies are also highly correlated with having high rates of depression, anxiety, and abnormal bacterial infections.[15] However, not all symptoms of dysfunction of the ENS are necessarily linked to having severe digestive system disorder like IBS. Having symptoms such as stress, anxiety, or even inattention, could also be the result of certain interactions occurring within the ENS. With such a high prevalence of people having these symptoms, with varying severity, it is important to understand the different factors playing into proper ENS regulation. Comprehension of these factors will allow us to pinpoint possible mechanisms that play into enteric disorders and symptoms.

Food and the ENS

Have you ever heard the idiom, "You are what you eat?" This serves as a realistic interpretation of the way in which your ENS is affected by food. The kind of food we eat has been shown to have correlations with, not only the functioning of our digestive system, but also higher-order cognitive abilities, like memory functioning.

The Western Diet, which consists of highly refined/processed foods with high sugar, fat, and salt content, is a common diet that makes up approximately 63% of the US's food consumption.[16]



Studies have pinpointed significant correlations between the development of enteric neuropathy symptoms and the consumption of Western-like diets. One particular study conducted by Ohland et al., tried to understand how memory functioning and weight gain correlated with a Western diet. Ohland fed mice lacking the IL-10 gene, a gene that predisposes them to digestive illness. They found that the mice fed a Western diet, lacking the IL-10 gene, had decreased memory functioning, specifically working and special memory, only after a few weeks.[7] They also found increased anxiety behavior and weight gain in mice fed a Western diet.[7] Mice fed the Western diet also had higher rates of Proteobacteria, which is the major phyla of bacteria that include pathogens such as salmonella and *E. coli*, suggesting growth of "bad" bacterial infection.[7] This goes to show that genetic predisposition to enteric neuropathies, in combination with a Western-influenced diet, has the ability to negatively affect memory function. On top of that, a diet high in fat and sugar can increase symptoms like anxiety and weight gain.

Another study investigated memory function and bacterial composition within high-fat (42% fat), high-sucrose (66% sucrose), and normal diets in mice. After only two weeks of weaning on the high-sucrose diet, mice had greater difficulty with cognitive flexibility, or the mental ability to switch between thinking about two different concepts, and to think about multiple concepts simultaneously.[8] They also found that the mice had difficulty with their working memory.[8] They also found that, when comparing the high-fat and

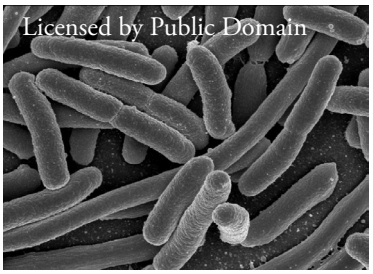
high-sugar fed mice to the normal diet fed mice, mice had greater percentages of the bacteria *Clostridiales* and lower percentages of the bacteria *Bacteroidales*.[8] The high presence of both of these bacteria types were also correlated with poorer performance on cognitive flexibility tasks.[8] Even though the exact function of both of these strains of bacteria is not precisely known, this study goes to show that the even the most specific types and amount of bacteria in the gut is very important for proper functioning.

Both of these studies indicate that high-sugar and high-fat diets, which are likely the diet composition of whatever food you are going to buy at fast-food chain restaurants like Taco Bell, can have a notable impact on your gut bacteria. Manipulation of your gut bacteria has been shown to be linked to higher-order cognitive function, like long and short-term memory as well as anxiety, making it vital to understand how food affects the bacteria in your gut. Even though none of the mice in these two studies were diagnosed with a specific enteric neuropathy like IBS, it is important to note that there are correlations with Western diets and cognitive functioning that begin to closely resemble the symptoms of enteric neuropathies.

Gut Microbiome and the ENS

We have seen firsthand how diet composition, specifically one filled with high-sugar and high-fat, results in changes in higher-order memory function, with possible correlations to bacterial composition. Now let's see specifically the direct interaction between the gut bacteria and the enteric neurons.

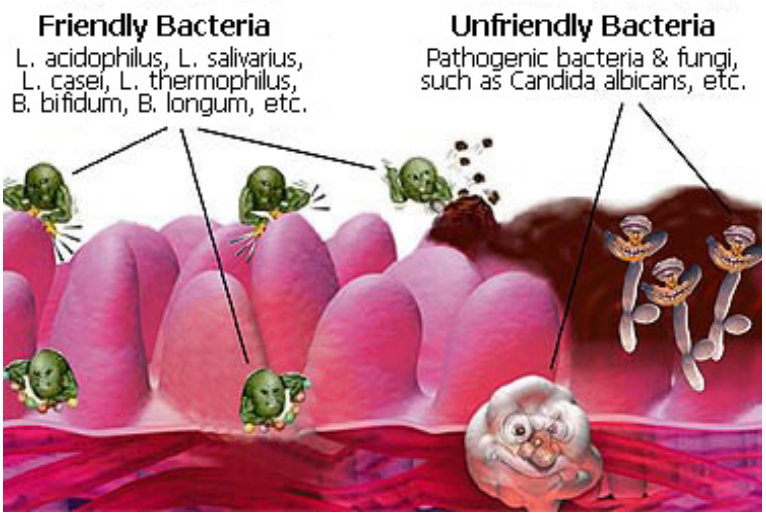
A 2014 study revealed that the presence of normal bacteria in your gut is important for the formation of proper nerve density and formation in the ENS.[10] They found that mice raised in a bacteria-free environment had decreased number of enteric neuron cell bodies in their small intestine.[10] Bacteria-free mice also showed decreased small intestinal movement compared to mice raised in normal bacterial conditions, confirming that gut bacteria is important for normal digestive functionality. This is especially applicable to neo-natal care unit babies that are frequently given antibiotics and raised in specific hygienic environments that may be inhibited from normal exposure to microogranisms.[12] These babies may exhibit similar symptoms to that of the bacteria-free mice who were found to have ENS developmental defects.



Normal development of the ENS is also needed for proper maintenance of bacterial equilibrium. Another study that looked at zebrafish lacking the gene, sox10, which mimics the complete absence of a functional ENS, found that the zebrafish had some specific bacterial strains exhibiting overgrowth and others showing undergrowth.[12] This further suggests that bacteria are involved in some of kind of intestinal homeostasis that is disrupted with lack of regulation by the ENS.

What Can Probiotics Do?

As mentioned earlier, gut bacteria and the ENS have an important interdependence, and if disrupted, can significantly disrupt digestive functionality. What is a way we can heal this dysfunction? Multiple studies have looked at the effects of probiotics on dysfunction



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of the gut and enteric nervous system. It has been found that certain probiotic therapies have the ability to restore some or all normal digestive functions. However, some studies have also found that probiotics work more significantly depending on your state of health. In a study discussed previously, it was found that the probiotic treatment with *L. helveticus* significantly reduced gut inflammation, corticosterone levels, and number of Proteobacteria in the IL-10 gene deficient mice on the Western diet.[7] However, this probiotic treatment increased brain stress levels in WT mice fed the Western diet, indicating that probiotic treatment will differ in effect depending on both the genotype and diet of the host.[7] Another study looked at a probiotic combination L. helveticus and B. longum effects on stressed mice, also revealing reduced corticosterone levels.[13] The probiotic treated group also showed restoration of central neuronal activation and neurogenesis.[13] This is especially important because chronic stress often reduces the activation of the hypothalamus, a part of your brain important for memory and learning. They also observed decreased corticosterone levels in the HPA axis, which is heavily involved in your body's "fight or flight" response.[13]

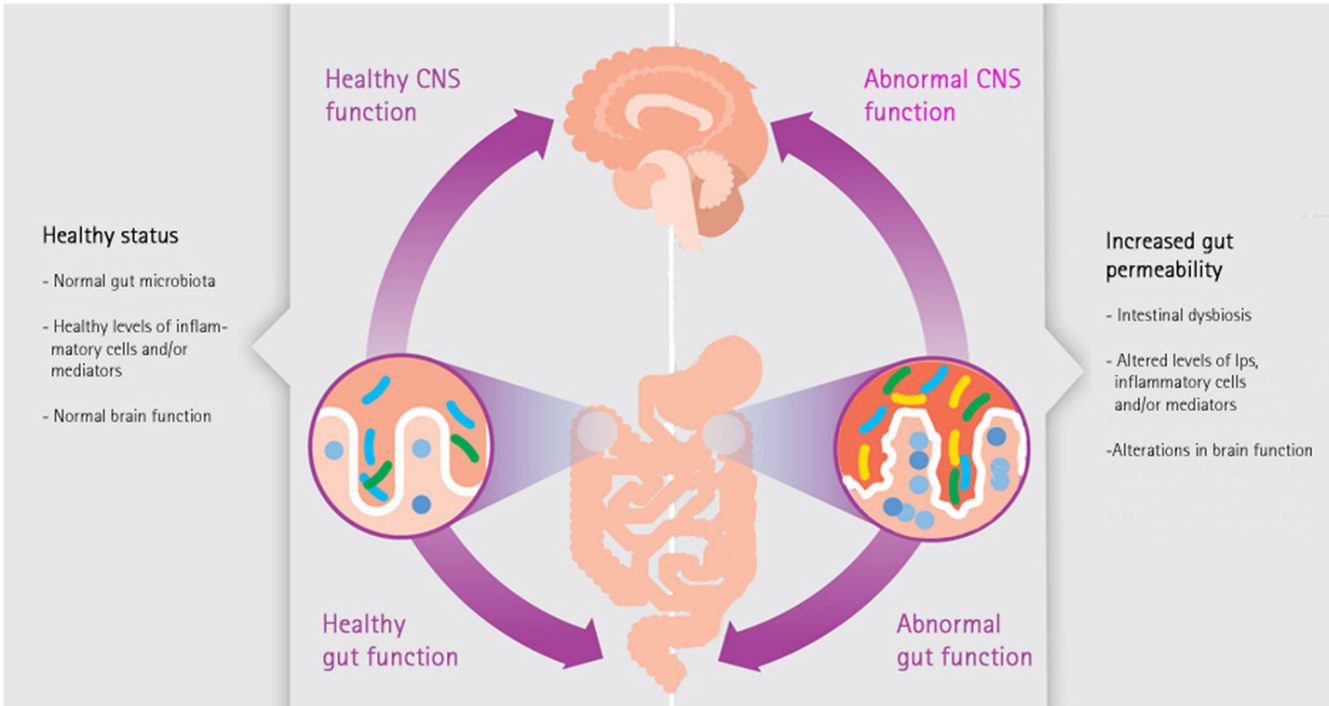
Therefore, probiotic treatment, specifically through the combination of the strains B. longum and *L. helveticus*, can help restore normal levels of stress required for proper behavioral functioning.[13]

Probiotic treatment therefore has the potential to ameliorate the negative symptoms caused by both diet and environmental stress. This is likely due to probiotics' ability to restore normal gut bacteria populations that subsequently allow for proper innervation of the ENS. This restoration of normal innervation of the ENS suggests that restoration of normal digestive functioning is directly a result of gut bacteria influence.

Conclusion

Given the large influence of both diet and the gut microbiome on the ENS, it is important to understand the ENS in the context of understanding animal and human behavior as a whole. Research has shown that the ENS is an important regulator of not only digestive but physical and psychological behavior.

There are numerous pathologies, as previously discussed, that occur because of some abnormal interaction between gut bacteria and the ENS. These pathologies, although the direct cause not



completely understood, should be more researched in a holistic context, where the emotional behavior, gut physiology, and lifestyle of person are taken into account. Given the small amount of common knowledge of the ENS throughout societies, it is a field that needs a lot more understanding of in the context of larger neuropathology and neurobiology fields.

Further study of the ENS has potential to be incredibly important for human health. For these reasons, the general public needs to be better educated on its existence and maintenance. Additionally, the significance of a healthy diet on not just your physiological health but also your mental health needs to be stressed.

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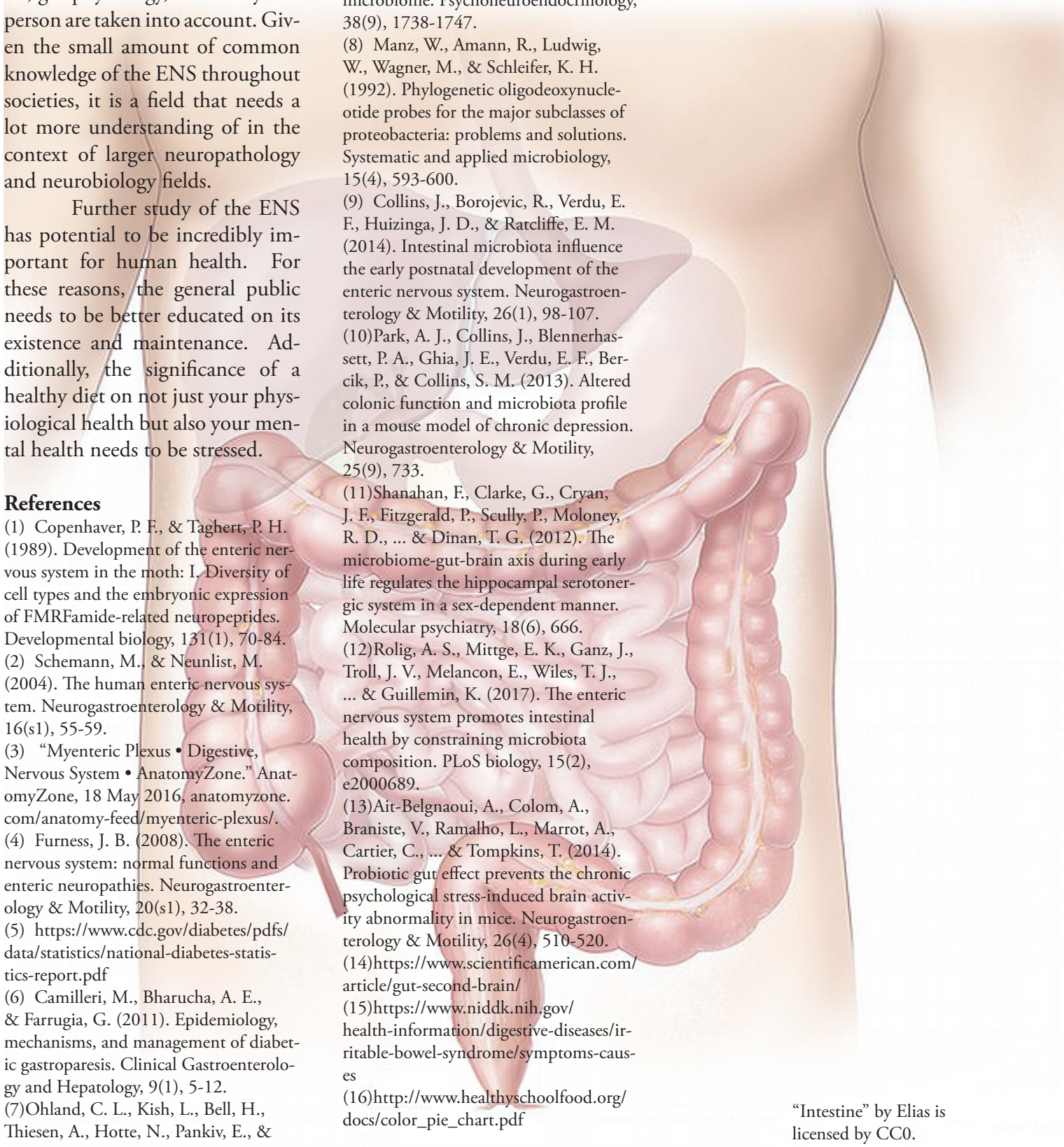

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THE GOOD, THE BAD, AND THE CORTISOL

By **Christina Ennis**

Think about the last time you felt stressed. Did your heart beat faster? Did your stomach tie into knots? Maybe your hands went cold, or possibly started shaking? The brain is in control of all of these physiological changes, and is actually trying to help you survive what it interprets as a potentially life-threatening situation. It's commonly thought of as the fight-or-flight response; either your body prepares to run away from the problem or readies itself to stay and tackle the threat.

The pathway in charge of this response is known as the hypothalamic-pituitary-adrenal axis, or the HPA axis for short (see Figure 1). It is so important for survival that it has been conserved by evolution, appearing in some form in even the earliest of vertebrate species (Denver, 2009). The HPA axis consists of a complicated series of steps that begin in the hypothalamus, where a specific group of cells secrete corticotropin-releasing hormone. This hormone is then able to travel through the brain to reach the pituitary, which is the pea-sized gland sitting just behind the bridge of the nose. Once the corticotropin-releasing hormone interacts with this gland, it stimulates the release of adrenocorticotropic hormone. Because of the location of the pituitary, adrenocorticotropic hormone is able to be transported throughout the body until it eventually finds cells on the adrenal cortex with which it can interact. This hormone works to stimulate the production of the steroid hormone cortisol. Once cortisol enters the bloodstream, it has significant effects all over the body.

The Many Roles of Cortisol

Cortisol greatly impacts both metabolism and digestion. Specifically, it is associated with glucose, the sugar that converts into every cell's energy supply known as adenosine triphosphate. Cortisol, by influencing gene transcription, stimulates gluconeogenesis, which is the process of forming glucose from precursors other than carbohydrates, during periods of fasting (Khani & Tayek, 2001). This response allows the liver to use glucose that the peripheral tissue does not need and converts it into liver glycogen, thus preparing the body should it encounter a food shortage and starvation (Barcellos et al., 2010). In addition, cortisol plays an important, though indirect, role in both liver and muscle glycogenolysis, which is the breakdown of glycogen once the body needs to use its stored glucose (Barcellos et al., 2010; Coderre et al., 1991). Cortisol is able to do this by influencing and interacting with glucagon, the hormone that regulates the usage of glucose (Lecavalier et al., 1990). Because of the many interactions between cortisol and glucose, researchers believed and have, ultimately, demonstrated that HPA axis activity is enhanced in many patients with diabetes (Chiodini et al., 2015).

Besides affecting glucose processes, cortisol influences electrolyte balance. Cortisol is a diuretic, preventing cells from losing

Did You Know?

Some scientists believe that cortisol's original purpose may have been sodium transport. They have found that freshwater fish use a cortisol-based system to bring sodium in, whereas saltwater fish use it to expel extra salt (Laurent & Perry, 1990; Maetz et al., 1967).

sodium as well as promotes potassium excretion, thus helping to regulate bodily pH (Knight et al., 1955). Maintaining a pH between 6.0 and 7.5 is important because of the negative consequences of having too much acid, known as metabolic acidosis, or bicarbonate, known as alkalosis, in the blood, which range from muscle twitches to lung collapse (Arruda & Kurtzman, 1977).

Cortisol also affects the immune system. It prevents the release of substances that cause inflammation, such as IL-12, interferon, IFN-gamma, and TNF-alpha, by antigen-presenting cells and Th1 cells, while also upregulating anti-inflammatory substances, such as IL-4, IL-10, and IL-13, by Th2 cells (Elenkov, 2004; Franchimont, 2004). Because of these effects, cortisol is often used to treat conditions such as rheumatoid arthritis, vasculitis, lupus, and allergies, as well as skin problems like rashes and eczema (Vane & Botting, 1987).

Circadian rhythm is also greatly impacted by cortisol. Normal cortisol secretion, meaning when it is not induced by the activation of the HPA axis, undergoes diurnal variation: the levels peak around 8:00am and bottom out around midnight (Chung et al., 2011). This pattern contrasts that of melatonin secretion, with melatonin being the hormone responsible for regulating sleepiness and wakefulness. In the morning, melatonin levels are low, and eventually rise at night once the brain's pineal gland is activated by the hypothalamus (Monteleone et al., 1992). Researchers have found that cortisol and melatonin actually work to counteract each other, with a high concentration of one inhibiting the activity of the other (Monteleone et al., 1992; Zisapel et al., 2005).

Finally, cortisol works to inhibit the further production of itself in a negative feedback loop (see Figure 2). The presence of high concentrations of the hormone within the bloodstream inhibit the release of both more corticotropin-releasing hormone and more adrenocorticotropic hormone (Gold et al., 2002; Wood & Rudolph, 1983). There are similar points of negative feedback along the HPA axis, namely how high concentrations of adrenocorticotropic hormone prevents the secretion of additional corticotropin-releasing hormone (Abelson et al., 2007; Yehuda et al., 2006). These loops exist because of the dangers associated with high levels of cortisol, and actively work to ensure that these levels are not reached.

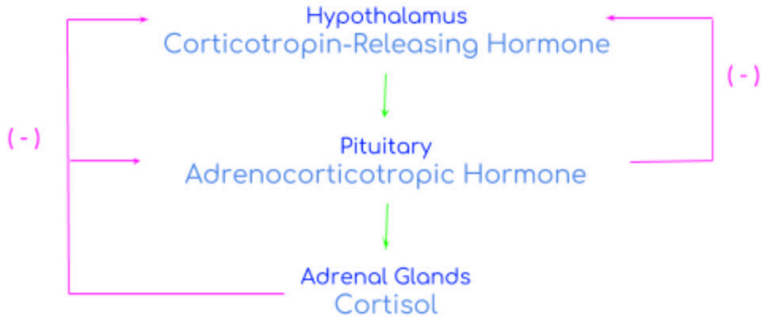

Figure 2 Here, you can see the many negative feedback loops (pictured in pink) involved in the HPA axis. Created by Christina Ennis.

Stress and Development

Researchers have found that prenatal stress can influence HPA axis regulation after birth and later in life. In animal experiments, exposure to prenatal stress causes a hyperreactivity of the HPA axis. Prenatally stressed rats, for example, have higher basal levels of corticosterone, their version of cortisol, as well as abnormal circadian rhythms (Koehl et al., 1999). They also require a longer period of time after the presence of a stressor for their hormone levels to return to their baseline. Other studies have demonstrated that prenatally stressed animals have high blood glucose levels, as well as have fewer glucocorticoid receptors in some areas of the brain (Weinstock et al., 1992). Switching over to human studies, there is growing evidence that prenatal stress impacts HPA axis regulation. Children that were stressed prenatally have been shown exhibit abnormal cortisol rhythms (Glover et al., 2010; Gutteling et al., 2005). Additionally, prolonged maternal stress is associated with mild impairments of intellectual activity and language development in their children, and is linked to disorders such as attention deficit hyperactivity disorder, schizophrenia, anxiety, and depression (Weinstock, 2008).

However, the effect of early

life stress on HPA axis functioning is less understood. Differing levels of stress seem to have opposing effects later in life: exposure to mild or moderate stressors early in life enhance HPA regulation whereas early-life exposure to extreme or prolonged stress can induce hyperreactivity of the HPA axis and thus contributes to a lifelong vulnerability to stress (Flinn et al., 2011; Liu et al., 1997). Several mechanisms have been proposed to explain these conflicting impacts of stress. Some believe that there is a critical period of development in which the levels of stress hormones within the bloodstream permanently calibrate the functioning of the HPA axis (Champagne et al., 2003; Macrì & Würbel, 2006). Others, however, hypothesize that such effects are mediated by maternal care, either through inducing epigenetic changes or promoting a sense of calmness in the offspring (Champagne et al., 2003; de Kloet et al., 2005; Schechter et al., 2015). Whatever the cause, prolonged early life stress is thought to sensitize the HPA axis, thus resulting in the hypersecretion of the various hormones involved in the pathway. This aspect of sensitization is supported by the findings that adulthood victims of childhood abuse have increased concentrations of adrenocorticotropic hormone and corticotropin-releasing hormone after exposure to a psychosocially stressful event (Heim et al., 2001).

Did You Know?

Yoga and meditation have proved to be effective techniques in reducing stress and regulating HPA axis stimulation. It also triggers alpha brain wave activity, which is thought to promote relaxation and creativity while minimizing depression (Kamei et al., 2000).

Hyperactivity of the HPA Axis

You may be wondering why non-life-threatening events, such as a meeting with a boss or a final exam, are able to trigger the activation of the HPA axis, and thus the production of cortisol, in some people. In the face of periods of severe stress during adulthood, such as those caused by negative work or family relationships or combat exposure for example, the dynamics of the HPA axis change (Stephens & Wand, 2012). Specifically, chronic stress triggers a shift in the normal diurnal release of cortisol as well as in the stress-induced levels of this hormone (Juster et al., 2011; McEwen, 2007; Stephens & Wand, 2012). In short, this means that chronic stress increases the baseline levels of cortisol in the body while also increasing the sensitivity of the HPA axis, resulting in its activation during times where typically it would and should not be. It is here, when the HPA axis is inappropriately or persistently activated, where problems start to arise.

Clearly, the hyperactivity of the HPA axis has a role in anxiety disorders. Anxiety disorders, including generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, and social phobias, are the most common psychiatric illnesses, affecting up to 33.7% of the population (Bandelow & Michaelis, 2015). Often, these maladies are treated with drugs such as selective serotonin-reuptake inhibitors and benzodiazepines, which work by altering the levels of neurotransmitters able to interact with brain cells. However, researchers have identified a secondary action of these drugs: they correct HPA axis hypersensitivity (Lenze et al., 2011; Lopez et al., 1990). These findings are significant because the process of directly assessing HPA axis functioning is difficult and complex. Since this pathway is activated during stress, measuring cortisol levels in the bloodstream after exposure to various triggers would be too specific to each individual since not everyone has the same reaction to the same stimuli, if not cruel to all of the participants of the study. Therefore, the ability to study HPA axis dysfunctioning in patients with anxiety disorders through their treatment plans is optimal.

In addition, the HPA axis has been shown to dysfunction during psychotic episodes. One model of psychosis posits that predisposing biological factors make some individuals more sensitive to stress, and thus more vulnerable to developing psychosis after stressful events (Mondelli et al.,

Did You Know?

Caffeine stimulates the release of cortisol. However, if you consume moderate levels of caffeine, meaning 300 mg, or three cups of brewed coffee, daily, then cortisol secretion is less than if you do not (Lovallo et al., 2008).

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2010). Following this assumption, first-episode psychosis patients display HPA axis hyperactivity and high basal levels of cortisol, acting as both a causal and exacerbating factor of their clinical symptoms as well as cognitive impairments (Gallagher et al., 2007; Herz et al., 1985; Lammers et al., 1995; Sachar et al., 1970; Tandon et al., 1991). However, some theorize that this hyperactivity contributes to the pathogenesis of psychotic disorders by increasing brain dopaminergic activity (Mondelli et al., 2010; Walker & Diforio, 1997). This idea is supported by the fact that antipsychotic drugs, in addition to regulating dopamine levels, have a secondary function of lowering HPA axis activity (Cohrs et al., 2006; Lammers et al., 1995; Mondelli et al., 2010).

HPA dysregulation has been identified in many other mental health disorders. In particular, depression has been extensively studied as cortisol has a multifaceted role in its symptomatology. In over half of the cases of major depression, the diurnal rhythms of this hormone is disturbed and the negative feedback loops that prevent its accumulation are nonfunctional (Burke et al., 2005; Herbert, 2012). Additionally, patients with major depression have been shown to have significantly higher levels of cortisol than in those with either panic disorder and schizophrenia (Yehuda et al., 1993). It is thought that cortisol contributes to major depression by altering the volume and metabolism of various brain regions, including the prefrontal cortex, the amygdala, and the hippocampus (Gold et al., 2002). Interestingly, cortisol has been shown to activate the genetic basis of major depression in the same way as environment events amplify the risk of this disorder, with its influence beginning prenatally but continuing into adulthood (Herbert, 2012).

However, there is a disease in which cortisol hypersecretion is present without a hypersensitivity of the HPA axis: Cushing's syndrome. This disease, though rare since it affects on average only one person per million per year, can have devastating effects on the health of those affected by it (Sharma et al., 2015). Cushing's syndrome is usually caused by a tumor somewhere along the HPA axis, such as on the pituitary or adrenal glands, or is induced by high levels of exogenous glucocorticoid exposure, as is the case in some patients with autoimmune disorders. The treatment options for this disease are limited, with surgeries resulting in complete remission in 60% of cases (Sharma et al., 2015).

Hypoactivity of the HPA Axis

At this point, you may be thinking that cortisol is a dangerous hormone, and that less of it would lead to a healthier and happier life. However, this is not always the case. There is a life-threatening disease, known as adrenal insufficiency or Addison's disease, in which the adrenal glands do not function properly, resulting in the body producing too little cortisol. Affecting only 100 people per million, it impairs quality of life by causing problems with circadian rhythm, weight loss, low blood pressure and sugar, as well as triggering stomach issues (Bensing et al., 2016).

Just as in hyperactivity, there are also disorders in which the HPA axis is abnormally inactive. Perhaps the most common of these is chronic fatigue syndrome, as it affects nearly 5% of the population (Johnston et al., 2013). Researchers have demonstrated that the HPA axis in patients with this disease have low basal evening levels of cortisol, yet high basal evening levels of adrenocorticotropic hormone, and even hypothesize that the disease is in fact caused by problems in this pathway (Demitrack et al., 1991).

The Bottom Line

Clearly, the HPA axis has a signif-

icant impact on multiple aspects of both physiological and mental health. Though cortisol gets a bad reputation, with multiple vitamin and drug companies claiming that it is at the root of any issue you may encounter, this is not true. It is only in the presence of chronically high or low levels of this stress hormone where such problems arise. However, that does not mean to say that stressful periods are in isolation healthy. While they are necessary for both motivation and even survival, times of stress can result in discomfort and ultimately lead to the development of various disorders, including anxiety and depression. So, the next time you notice that you're feeling stressed, take into account the processes going on within your body and the damage you may be causing if you let stressors affect you too much.

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HUGS VS. DRUGS

How zebrafish and the science of social attachment can help us understand America's opioid epidemic

By **Eduardo Vargas**

Setting The Stage

The United States has a problem with drugs — specifically a $78.5 billion opioid drug problem. Legally available only by a physician's prescription, many synthetic opioids such as oxycodone (Percocet) and hydrocodone (Vicodin) are used to mitigate moderate to severe pain, and in 2015 they were prescribed to around 38% of American adults.[1] Just last year, one in eight patients were shown to misuse prescription opioids, and of approximately one million opioid overdoses, 64,000 resulted in death.[2] A study by the University of Pittsburgh in October 2017 identified how different demographic subsets of the population are affected by the opioid crisis (Fig. 1). These sub epidemic statistics show that there is a soaring death toll caused by fentanyl. These studies also report that contrary to the popular media narrative of the average overdose victim being middle-aged, rural, and white, fentanyl and heroin victims are actually younger, urban, and more racially diverse.[3] Additionally, it has been reported that most victims are not chronic pain patients themselves but friends or family of patients that obtain pills, with some reports of people taking veterinarian-prescribed medicine from their pets.[4]

To tackle this massive epidemic, over the last couple of years the FDA has supported new proactive solutions to drug addiction aimed at preventing abuse of prescribed opioid analgesics to reduce the impact of drug abuse on American individuals and families. Among these initiatives is the push for more widespread use of non-opioid painkillers, prioritizing the development of "additional alternative medications that alleviate pain but do not have the addictive properties of opioids".[5] Although the problem has been clearly identified, both the impact on health and the economic fallout are increasing the need for comprehensive approaches to addiction treatment, and scientists are racing to find the multi-billion dollar solution. To understand the behaviors of addiction in humans, many drug studies on animal models have begun to show promise for understanding the underlying mechanisms of addictive behavior,

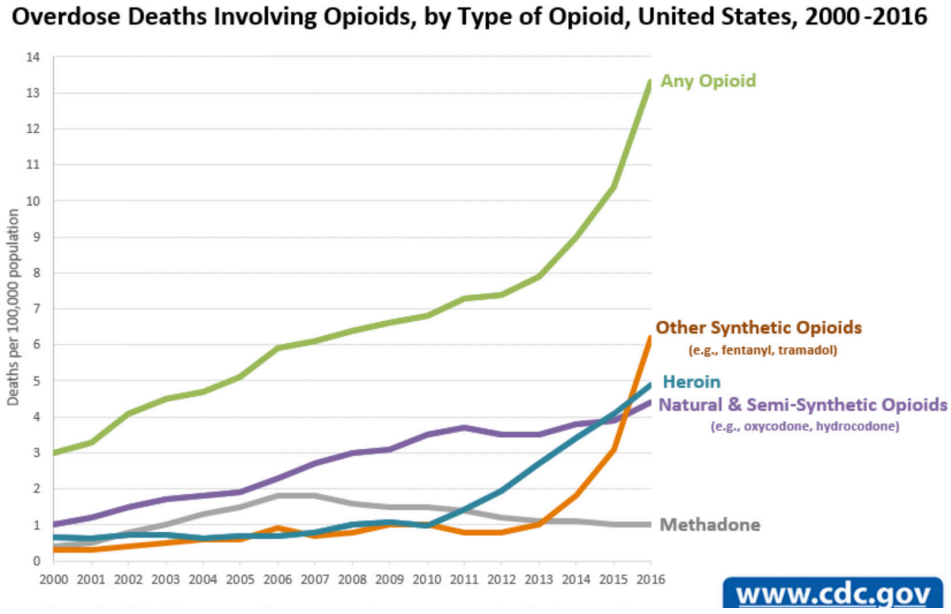


Figure 1 Data collected by the CDC displaying death rates by overdose of different opioid types. Not pictured is data from 2016-17, which shows that deaths from other synthetic opioids such as fentanyl have far surpassed prescription-based overdose.[2]

and zebrafish provide interesting opportunities for this kind of research.

The Case for Zebrafish

Neuropharmacologic research of drugs often relies on animals to model the behaviors induced by the drugs in question, and zebrafish (*Danio rerio*) happen to be good behavioral models. Sometimes referred to as the 'new lab mouse,' zebrafish are relatively easy to raise in large quantities, can be modified genetically, and have neural mechanisms that respond to drugs in similar ways as human mechanisms (Fig. 2). With a 70% similarity in their genome to humans, zebrafish brains conserve the dopaminergic and glutamatergic projections involved in reward pathways found in humans, and display the same μ-opioid receptors that interact with the synthetic opioid drugs such as hydrocodone.[6] More than just having the same cellular and molecular underpinnings, zebrafish are also capable of displaying behavioral hallmarks of addiction to drugs. Among these hallmarks of addiction are differences in various swimming behaviors and social group behaviors.

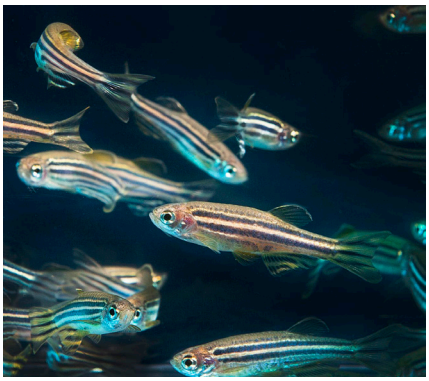
Figure 2 The zebrafish (Danio rerio) is a type of tropical freshwater minnow, averages around 4 cm in length, and has lateral stripes of pigmentation. Their genome has been fully sequenced, making them ideal for genetic studies and manipulation. Image taken by NICHD, licensed by CC BY 2.0.

The best evidence to support zebrafish as relevant addiction models was found in August 2017 at the University of Utah by researchers who developed an opioid self-administration assay using zebrafish.[7] First, the zebrafish were trained to swim over one of two active squares in their tank to trigger a food reward. Paired with a light cue, the trigger was activated by camera that detected the zebrafish swimming above the correct square. The zebrafish could not randomly swim over the active platform, since a computer would calculate whether the zebrafish were swimming above the platform more than a pre-programmed threshold. Once the zebrafish were trained to use this trigger mechanism, the researchers tested whether they would do the same if the trigger released an opioid drug instead of food. Their results showed that the zebrafish would consistently swim over the drug active platform, even when the zebrafish were given obstacles to the task. For example, the researchers attempted to keep the fish from activating the platform by placing it at an uncomfortably shallow level in the tank, but the fish still swam over it to receive the drug. They performed another test in which the fish would have to progressively activate the camera an increasing number of times, and the fish were still more likely to continue to trigger the platform until the drug was released. The researchers, Dr. Gabriel Bossé & Dr. Randall T. Peterson, claim that this is indicative of drug-seeking behaviors, especially given that the zebrafish were displaying characteristics that resemble addiction. The zebrafish had to actively perform a specific behavior to secure the drug, and after long term exposure they would show heightened anxiety as measured by a reduction in exploratory behavior.

To ensure that their findings were a direct result of the drug, the researchers also tested whether the same behaviors were observed when the zebrafish were treated separately with naloxone (an opioid drug antagonist), and NMDA and dopamine receptor antagonists which would effectively stop the reward pathways. Their findings were consistent with what was expected, and in all three cases the treatment effectively removed the zebrafish's preference to activate the drug-releasing platform.

In the final part of the study, zebrafish had been pre-exposed to hydrocodone and were essentially made addicted to it. The behavior of this treatment group was tested against a naive group that had not been exposed to any kind of drug, but was trained to use the triggering mechanism. The dependent variable measured was each group of zebrafish's social cohesion, or shoaling (Fig. 3). Like many other fish, zebrafish are known to form shoals in the wild for various benefits, such as procuring food in new environments. Shoaling has been identified as a potential social behavior in zebrafish, so the researchers

Figure 3 Forming shoals provides zebrafish with many fitness advantages, including safety from predation, exploration of novel environments, and recovery of food. "Zebra Fish" by Oregon State University is licensed by CC BY-SA 2.0.



sought to compare how the behavior changed when groups were affected by opioid exposure.[8] By measuring the space in between each fish with computer tracking, they found that the zebrafish that had been preconditioned with hydrocodone but were no longer exposed to it displayed more anxious behavior and a closer, tighter shoaling group indicative of withdrawal. By contrast, the group that wasn't exposed to hydrocodone in the long term formed a looser shoaling group, and displayed generally more exploratory behavior.

The findings of this study provide strong evidence for zebrafish as a bona fide model for studying drug addiction. But as concrete as the evidence is for zebrafish to experience addiction and withdrawal to opioids, how much of this information can inform our understanding of drug-seeking behavior in humans?

How Opioid Addiction Works

The neural mechanisms of addiction are well studied, especially the pharmacokinetics of drugs of abuse involving the dopaminergic projections in the brain. An opioid analgesic drug such as oxycodone will act on the three kinds of opioid receptors in both the peripheral and central nervous system: the mu-, delta-, and kappa- opioid receptors. These receptors already naturally interact with endorphins secreted as an endogenous form of pain relief — these are the same neurotransmitters responsible for the oft cited 'runner's high' — and they function by blocking the sensation of pain by reducing a neuron's excitability, preventing it from firing an action potential.[9]

Opioid drugs act on the same exact neuron receptors, and have slightly different mechanisms of action depending on where in the synapse they act. Binding to the pre-synaptic opioid receptor of dopaminergic neurons increases the release of dopamine in the synapse. As it activates the next neuron in the dopaminergic reward pathway, it is experienced as a pleasurable, euphoric sensation. When the opioid binds to post-synaptic opioid receptor, it

Figure 4 Acetaminophen/oxycodone pills, a combination of and opioid and non-opioid, commonly pr scribed for pain relief. Image by Michelle Tribe, licensed by CC BY 2.0.

antagonizes several different receptors and prevents them from receiving neurotransmitters, meaning that when acting on neurons and interneurons responsible for nociception, it will reduce the sensation of pain.[9] This is where the drug's medicinal properties come from.

To repeat this high, opioid users will need to continually take higher and higher drug doses, which is due to the plasticity of neurons. Over a long period of sustained drug intake, the increasing amounts of dopamine present in the synapse causes the neurons to increase the number of auto-receptors to compensate for the excess neurotransmitter. The increase in auto-receptors means that dopamine is more likely to be taken back up into the cell, so it will be removed form the synapse at a normal rate, thus diminishing the euphoric feeling. This change in receptors available is the pharmacodynamic basis of tolerance (Fig. 5). The user may then compensate for this change by increasing their intake, further increasing their pharmacodynamic tolerance to the drug and, if enough of the drug is available, becoming dependent on it to the point of addiction. The spiral of addiction is continued because the user is avoiding the adverse effects of withdrawal, and continuing to seek the reward associated with the drug intake experienced in the earlier stages of drug abuse.

Although we understand how tolerance and addiction go hand in hand at the molecular, cellular level, and behavioral level, not

as much attention has been given to the environment surrounding the person suffering from opioid addiction. As the more widely accepted behavioral model of alcoholism suggests, when looking at addiction treatments we should not only look at biological and genetic mechanisms that facilitate addiction, we should also take into account the interactions between the individual's behavior, their biology, and their environment. One potential gap that remains to be filled in the opioid crisis is an understanding of the relationship between addiction and social attachment, and zebrafish may help us study the extent to which addiction is a product of biology and the extent to which it is a product of a person's social environment. Since previous research has already established the hallmarks of the zebrafish's social and addictive behavior, there is opportunity to use these animal models to test out different interactions between the social environment and the chronic effects of drugs.

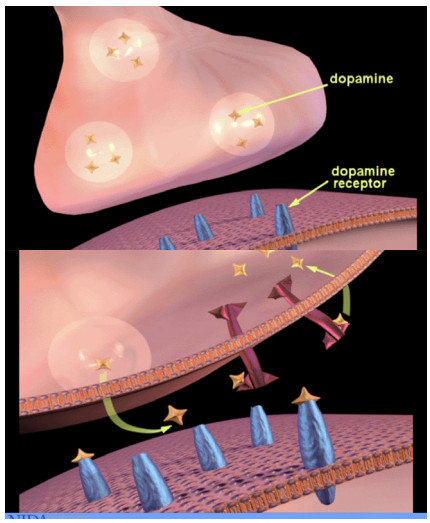


Figure 5 Pharmacodynamic tolerance occurs when a neuron compensates for the effects of a drug by increasing or decreasing the number of receptors available for the neurotransmitters involved. Here, dopamine receptors are increasing in response to the increased amount of dopamine available in the synapse. Image by National Institute on Drug Abuse, licensed by Public Domain.

Addiction as a Form of Social Attachment

We can take a look at this exact interaction by looking at how social attachment and oxytocin can protect against addiction and stress. Oxytocin is a type of neuropeptide and hormone that, while implicated in many brain activities, is paramount to successful pair-bonding, such as a mother-child bond, or lifelong monogamous pair-bonding in voles.[10] In these social interactions heavily involved in reproductive success, oxytocin receptors become up-regulated as oxytocin availability increases.[11] Oxytocin has also been implicated in learning and memory, which has led some researchers to explore how it affects the "learning and memory processes involved in the mechanism by which the addictive drug maintains control over behavior".[12] While relatively little is known about the direct mechanisms through which it could affect addiction, research on oxytocin has found that it does have a measurable effect on addiction. One review of the literature found that, regarding oxytocin, "in general, when the social interactions occur outside of the drug-taking context, positive, prosocial interactions are protective against drug abuse-related behaviors, whereas social stressors facilitate these behaviors".[12] In other words, the presence of oxytocin can indicate a social reward that can, to some extent, mitigate or even suppress the reward of a drug-induced high.

Researchers at VU University Amsterdam further explored the affiliative aspect of oxytocin, and examine further evidence for its palliative effects on addiction processes. As it is heavily involved in the formation of social bonds, oxytocin specifically "is thought to increase interpersonal trust, to reduce stress responses, and to increase resilience, while protecting against drug addiction and negative health effects of stress".[13] Their research centers on the theory that when people or other social beings forge close and supportive social relationships, they shift from novelty-and reward-seeking behaviors to an appreciation of familiarity.[13] The researchers attribute this shift to the ventral and dorsal corticostriatal systems of the brain. The corticostriatal pathway is a reward circuit in the brain in which the striatum receives the dopaminergic and glutamatergic signals mentioned previously. According to the researchers, the positive and euphoric rewards produced by novel experiences corresponds to heightened dopaminergic activity in the ventral striatum pathway, and it occurs when new social bonds are being formed. The dorsal striatum pathway becomes involved when the novelty seeking behavior begins to shift from impulsivity to compulsivity.[13] These pathways can also apply to when an individual is exposed to rewarding drug effects. At first, rec-

reational use of a drug falls in line with the novelty-seeking behavior supported by the ventral pathway, but over time, as the user begins to seek out the drug out of compulsion to escape effects of withdrawal, their attachment to the drug is maintained by the dorsal pathway. These explanations of the behavioral underpinnings of addiction suggest that a lack of social attachment can increase sensitivity to drug addiction.

In mice studies, individuals experiencing various forms of stress were more likely to become addicted to drugs.[12] It is easy to imagine how this can apply to humans as well. We are familiar with the narrative of individuals dealing with economic hardship or social isolation finding it easier to fall into the downward spiral of addiction. Thinking of these behaviors in terms of brain pathways can give us a more nuanced picture of how an individual's social bonds and environment can have an impact on addictive behavior. We can begin to change our understanding of addiction as a strictly biological disease to include a model of addiction as a form of social attachment. If the presence of oxytocin stemming from strong pro-social bonds protects from stress and addiction, then what does this mean for how we approach addiction treatments moving forward?

The Future of Addiction Treatment

The biosocial understanding of how opioid addiction functions can have profound implications for how we approach addiction treatments. In fact, the authors of the study from Amsterdam University urge other scientists to apply their findings to animal models of addiction. The zebrafish model could be a useful organism to use for this type of research. As the self-administration assay showed, they can display hallmarks of social, addiction, and withdrawal behaviors, so they may prove useful in for exploring how social attachment and cohesion play a role in addiction. They could even help scientists come up with novel, holistic solutions to treating addiction.

The rise in opioid overdose victims has already pushed physicians to research new treatments for addiction. Cannabis, for example, is gaining popularity as a treatment since it helps victims come off of their opioids without experiencing the debilitating effects of withdrawal. In some cases, other drugs such as weaker opioid derivatives have been used for a similar purpose, but with less promising results. What might treatment look like if we can take a more interdisciplinary approach to treating a person's addiction? It's possible for the answer to be hidden in zebrafish, or another viable animal model. While the solutions remain varied and elusive, the concrete reality is one: the opioid crisis is one of our generations biggest unforeseen problems, and it will require concerted contributions from many fields before we start seeing positive results of a similar magnitude.

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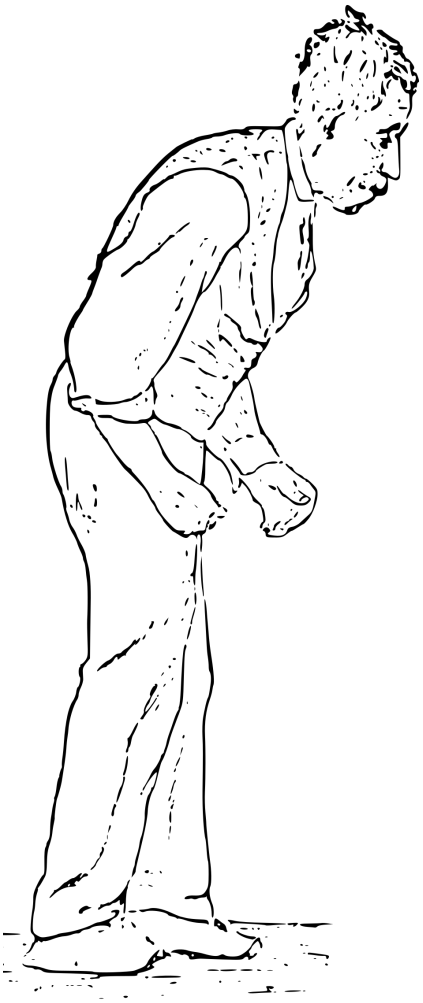
TIRED TREMORS

Parkinson's and Sleep Disturbances

By **Julia Wilson**



We have all experienced the pain of a sleepless night, and thus we can all understand the consequences it has on our cognitive, emotional, and physical abilities. Sleep is, after all, a vital physiological function, and most of us feel deleterious effects if we get about 2-3 fewer hours of sleep than normal.

Now imagine if your sleep was restless and disturbed for years at a time; not only would this disrupt your daily routine, but it would begin to chip away at your physical and emotional well-being.

Many Parkinson's patients experience such a struggle. Parkinson's is a chronic disease characterized by neurodegeneration, which is premature deterioration and death of neurons. Dopaminergic neurons, which produce the neurotransmitter dopamine and are most notably involved in producing motor movements and controlling mood, are the primary cellular victims of this process of neurodegeneration[1]. Over time, neural degradation in Parkinson's produces symptoms such as tremors, gait and posture abnormalities, depression—and sleep disruptions (see Figure 1). The underlying cause of the disorder is still unclear, which presents a challenge for research on and treatment of symptoms[1]. Nonetheless, examining the etiology of symptoms such as sleep disorders in Parkinson's is an important task. Not only would clinical populations such as Parkinson's patients benefit from such an investigation, but it would also provide us with a more comprehensive view of how sleep works, which is another murky scientific subject. Thus, information from this research could be used to develop treatments and interventions for sleep disorders, but it could also be applied to non-clinical populations. Everyone sleeps—or at least everyone should.

What is sleep and how does it work?

Before we discuss the neural and biological underpinnings of sleep disruption in a clinical population, it is important to understand what typical and atypical sleep look like. *Why* we need sleep is still a question shrouded in mystery. Insufficient sleep can cause problems with the immune system, irritability, impairment in cognitive processes such as memory, etc.[2].

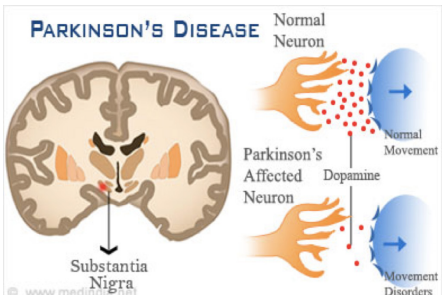


Figure 1 Cartoon depicting reduced dopamine in the substantia nigra and in a close-up of the synapses, leading to movement disorders.[16]

However, there is not a definitive etiology of these effects. In other words, sleep is clearly necessary for normal, healthy functioning, but we are not sure exactly why that is the case.

Brain regions involved in sleep. Sleeping and waking is regulated by the reticular activating system (RAS) in the brainstem, and other sleep-regulating areas of the brain, such as the thalamus, hypothalamus, spinal cord, hippocampus, and suprachiasmatic nucleus. Cells in the suprachiasmatic nucleus regulate melatonin release, which is a chemical that makes us feel sleepy[2]. Anyone who has ever experienced jetlag can attest to the fact that melatonin is an important chemical, and when its cycle of release is thrown off (by travel or other factors, such as disease), our day-to-day functioning is impaired.

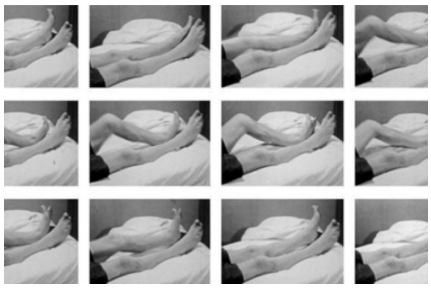
Circadian rhythms. In addition to these brain regions that regulate sleep, we also have internal "clocks" that regulate organ function, body temperature, and secretion of hormones over a 24-hour period[2]. These are known as our circadian rhythms. These circadian rhythms encompass both our waking states and our sleep cycles.

Stages of sleep. In a typical person, sleep cycles through five stages. There are four stages of non-rapid eye movement (NREM) sleep and one stage of rapid eye movement (REM) sleep. NREM sleep encompasses both light and deep sleep throughout the four phases. REM sleep is when brain activity and eye movements spike as we dream, but our muscles are paralyzed to avoid movement. When we go to sleep, we first enter stage 1 of NREM sleep, in which we are easily awoken. Stages 1 and 2 of NREM sleep are light sleep, lasting about 10-25 minutes each, whereas stages 3 and 4 are slow-wave (deep) sleep. Stages 3 and 4 last about 20–40 minutes in the first sleep cycle of the night. REM sleep generally occurs for the first time about 90 minutes after falling asleep. The lengths of NREM and REM sleep change as we age, as we spend less time in slow-wave sleep and REM sleep[2]. In many sleep disorders, the sleep cycles are severely disrupted. For example, in chronic insomnia, patients are generally unable to fall asleep or stay asleep, leading to a complete disruption in the normal cycle of NREM/REM sleep. In REM sleep behavior disorder, a common sleep disruption in Parkinson's, the stages of sleep "blend" into each other. For example, REM sleep is characterized by muscle paralysis, but this pattern breaks down in REM sleep behavior disorder, leading patients to "act out" their dreams[3]. This can lead to severe injuries. Thus, many sleep disorders are characterized by disruption in sleep stages and circadian rhythms. These atypical patterns of sleep, and sleep disorders, are more common in certain clinical populations such as Parkinson's.

Parkinson's and Sleep

Our knowledge of sleep and the atypical patterns that appear in Parkinson's beg the question, "What exactly is Parkinson's Disease? And how is sleep so closely linked to it?"

Figure 2 An example of a single periodic leg movement in the lower left limb in a periodic leg movement disorder patient.[17]



As explained previously, Parkinson's is a neurodegenerative disease primarily afflicting dopaminergic neurons. This neurodegeneration could be linked to sleep in myriad ways. For example, it is possible that degeneration of dopamine neurons reduces excitatory connections and causes functional abnormalities in brain regions regulating sleep and wakefulness, such as the brainstem. There may also be other pathological changes, such as cellular and genetic abnormalities, associated with Parkinson's that contribute to sleep disruptions. The most common sleep disruptions in Parkinson's patients are REM sleep behavior disorder, periodic leg movement disorder, and excessive daytime sleepiness and, therefore, these disorders will be the focus of our inquiry. REM sleep behavior disorder is the loss of muscle paralysis during REM sleep. Periodic leg movement disorder (Fig. 2) is repeated movement of upper and lower limbs during sleep, and excessive daytime sleepiness is abnormally high levels of exhaustion during the day.

Many studies have at-

tempted to answer the question of how sleep is linked to a primarily motor-related disease. Several of these links appear to be secondary or indirect relationships; before we delve deep into the neural and genetic underpinnings of sleep disruption in Parkinson's, we will first discuss a few surface-level links.

Dopamine Medication. There appears to be an unfortunate link between dopamine-increasing medications and sleep disorders. One recent study found that shorter time between the last dopamine dose a patient takes, and higher doses within a few hours of bedtime, were associated with worse sleep quality. Higher dopaminergic medication doses were also associated with lower mean percentage time in REM sleep. Thus, dopaminergic medications might reduce quality of sleep, particularly REM sleep, thereby possibly contributing to REM sleep behavior disorder in Parkinson's patients[4]. Given the prevalence of REM sleep behavior disorders in Parkinson's patients, this is a critical finding. However, it raises the question, does dopaminergic medication *intensify* existing REM sleep disruptions, or does it *cause* the disruptions themselves? This is a critical distinction, as sleep disruptions must be treated at the root; if dopaminergic medications are not the root of the issue, but merely an exacerbating factor to existing disturbances, adjusting dopamine doses will not completely resolve the problem. However, this is an important finding because it provides a manner in which medical policy can help Parkinson's patients. For example, prescribing physicians could recommend reduced dopamine doses at night or a course of medication that is only taken in the morning.

Age. Age is another seemingly secondary, but nonetheless important, connection to sleep disruptions in Parkinson's. Younger Parkinson's patients are found to have sleep patterns that are not significantly different than healthy age-matched controls, but older Parkinson's patients have fairly disrupted sleep (insomnia, reduced average sleep per night, and higher rates of excessive daytime sleepiness)[5]. In addition, frequency of REM sleep behavior disorder is higher and slow-wave sleep is reduced in older Parkinson's patients[6]. These results indicate that age may play an important role in the progression of sleep disturbances in Parkinson's. We are quite certain that sleep changes—and sleep quality reductions—occur naturally as part of the aging process. Unfortunately, the natural process of aging cannot be effectively halted or reversed (though we all wish it could!). This is bad news in terms of addressing possible contributors to sleep disorders, particularly in clinical populations that already suffer from other physiological stresses. However, it is important to note that the rates of sleep disturbances in Parkinson's are indisputably higher than in healthy elderly populations—so age is likely not the only factor contributing to this phenomenon. So, what then? If age and dopamine medications are not the roots of sleep disturbances in Parkinson's, perhaps we can find the answer within the etiology of the disease itself.

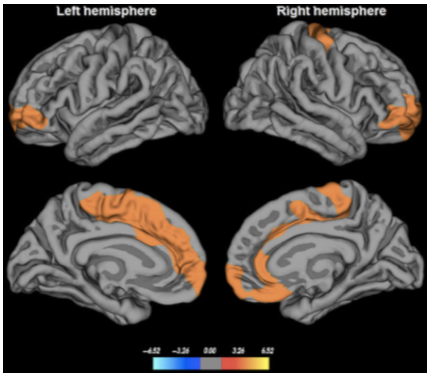


Figure 3 Orange regions indicate irregular regions of gray matter in REM sleep behavior disorder, demonstrating severe abnormalities.[7]

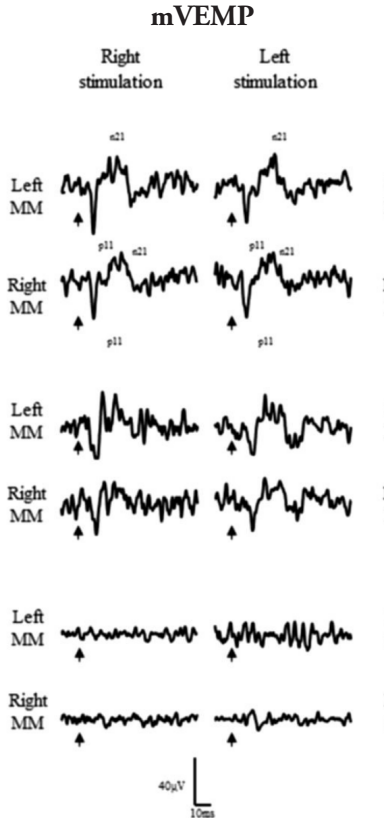
Structural contributions to sleep disorders in Parkinson's

Dopamine and age might exacerbate symptoms of sleep disorders in Parkinson's, but a more pertinent focus is from where the symptoms are actually arising—meaning that we must explore the biological mechanisms of the disease.

First, structural issues may play more of a role than we originally believed in producing sleep quality changes in Parkinson's. Recently, researchers have found severe thinning, volume reduction, and shape abnormalities in gray matter, particularly in the motor cortico-subcortical loop, in REM sleep behavior disorder patients (see Figure 3). Impaired motor function correlated with these abnormalities in the motor cortico-subcortical network[7].

While this was not a study of Parkinson's patients, it provides interesting preliminary evidence for a relationship between gray

Figure 4 Examples of control, early Parkinson's disease, and late-stage Parkinson's disease mVEMPs (from top to bottom). Arrows point to the event-related spikes in electrical activity, and responses differ significantly from control to late-stage Parkinson's.[8]



matter degradation, motor abnormalities, and sleep disorders. The nature of this relationship is not yet clear, but a study on the gray matter of Parkinson's patients would contribute to our understanding of it. Additionally, this relationship between sleep disorders and gray matter degradation in motor areas points to a potentially harmful feedback loop for Parkinson's patients; if Parkinson's Disease increases risk of sleep disorders, and sleep disorders are associated with degraded motor regions of the brain, sleep disorders could diminish Parkinson's patients' already-deteriorating motor abilities.

Another intriguing structural contributor to sleep disorders in Parkinson's is the brainstem. There is evidence that vestibular-evoked myogenic potentials (VEMPs), which are spikes in electrical activity in response to stimulation of vestibular receptors in the brainstem, demonstrate functional abnormalities in both early and late Parkinson's compared to healthy controls. Masseter VEMPs (those involved in the motor control of the masseter muscle in the face) in particular are more abnormal in late-stage Parkinson's than in the early-stage (see Figure 4).

This indicates progressive degeneration of brainstem structures throughout Parkinson's. Importantly, the number of altered VEMPs and the total level of VEMP alteration is found to be associated with incidence of REM sleep behavior disorders[8]. Thus, REM sleep behavior disorder may be related to brainstem abnormalities, arising out of multifaceted degradation of brainstem structures. Therefore, sleep disturbances in Parkinson's may be partly due to an association between sleep abnormalities and brainstem degradation. The precise mechanism of this association is not fully clear, but preliminary evidence does suggest that structural changes—such as gray matter and brainstem degradation—may underlie sleep disorders in Parkinson's.

Cellular and genetic contributions to sleep disorders in Parkinson's

In addition to pathological structural changes associated with sleep disorders, there may also be cellular and genetic abnormalities underlying sleep disturbances in Parkinson's, providing us with a new micro-focused lens through which to explore the foundations of both typical and atypical sleep patterns. In monkey models, dopamine deficiencies alone appear to be enough to produce sleep quality changes, including decreased REM sleep[9]. However, human research has found evidence for cholinergic deficiencies contributing to sleep disturbances in Parkinson's. For example, there is evidence for up to a 40% reduction in cholinergic neurons in the pedunculopontine nucleus in the brainstem of Parkinson's patients (see Figure 5), and this reduction may contribute significantly to sleep behavior disorders[10]. Thus, cellular mechanisms are clearly disrupted in Parkinson's, and this disruption likely contributes to sleep disturbances in a complex, multi-faceted way.

Hypocretin. In addition

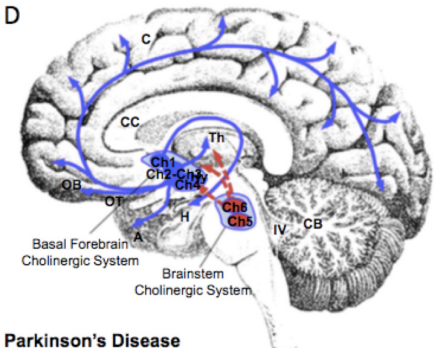


Figure 5 Red pathways indicate cholinergic pathways that may be disrupted in Parkinson's. Both originate in the pedunculopontine nucleus of the brainstem and project to midbrain structures, some of which are heavily involved in sleep (e.g., the hypothalamus).[10]

to dopamine and acetylcholine, hypocretin (sometimes known as orexin) may also contribute to sleep disturbances. Hypocretin cells are implicated in the maintenance of sleep-wake cycles. Parkinson's disease is associated with lower levels of hypocretin, and there is preliminary evidence that hypocretin progressively deteriorates throughout the course of the disease[11]. However, there is some contradictory evidence in this field, as other studies have found that hypocretin levels do not differ between Parkinson's patients and healthy controls[12]. Thus, cellular research is inconclusive, but potentially points to multiple origins of sleep disruptions in Parkinson's. It is possible that dopamine and acetylcholine both play a role in sleep disruptions, but perhaps underlie different sleep disorders (e.g., dopamine may underlie REM sleep behavior disorder while acetylcholine contributes to excessive daytime sleepiness). Hypocretin's role is still uncertain, but it is possible that it is only involved in sleep disorders relating to sleep-wake cycles (such as frequent nighttime wakings), given its role in maintaining sleeping and waking patterns. More specific research elucidating the type of sleep disruption associated with cellular abnormalities would be helpful in addressing these ambiguities. Nonetheless, there are clearly forms of cellular disruption contributing to sleep disturbances in Parkinson's.

Circadian rhythm genes. In addition to neural abnormalities, there is also evidence that genetic and circadian rhythm disruptions may underlie sleep disturbances in Parkinson's. In MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, an injected toxin used to create a model of Parkinson's disease) mouse studies, MPTP-treated mice showed behavioral markers of sleep disturbances and demonstrate associated decreased amplitude in circadian rhythm-related oscillations of gene expression[13]. In other words, the molecular "switch" that dictates when circadian rhythm-related genes turn "on" (are expressed) and turn "off" (are silenced, not producing proteins) is disrupted in MPTP mice. This molecular disruption is associated with behavioral markers of sleep disorders. Thus, disruption of the molecular circadian clock in Parkinson's may contribute to sleep disturbances, and the mechanism of that disruption may be through gene expression.

This evidence from mouse models has recently been replicated in human research as well. In blood measurements of circadian rhythm-related protein expression and cortisol levels in Parkinson's patients, early Parkinson's Disease has been found to be associated with sleep disturbances. These disturbances include increased sleep latency (meaning it took longer for patients to fall asleep) and reduced REM sleep. These data mirror the findings from the mouse studies, demonstrating strong cross-species evidence for genetic underpinnings of sleep disruptions in Parkinson's. In humans, these genetic disturbances included abnormalities in regulating hormones, such as reductions in melatonin, and reduction in expression of circadian rhythm-related proteins[14]. Thus, there is strong evidence for a molecular and genetic component of sleep disruptions in Parkinson's. Future research may need to focus upon exploring genetic and molecular therapies for Parkinson's patients to improve sleep disruptions.

Application of findings

There is not yet conclusive evidence for the basis of sleep disorders in Parkinson's. Speculation surrounds structural, neural, and genetic underpinnings, but research has pointed to an extremely complex association between sleep disturbances and biological bases. While research must continue in order to elucidate a more precise etiology of sleep disruptions in Parkinson's, clinical and treatment-based steps should be taken in the meantime to ameliorate the quality of life of Parkinson's patients. Findings from neural research could be applied to clinical use; for example, prescription protocol for dopamine medications could include a recommendation for lower doses at night due to dopamine's potential interference with normal sleep cycles. Perhaps physicians could also recommend courses of over-the-counter melatonin tablets for Parkinson's patients who have trouble sleeping, as regular melatonin boosts at night would likely improve symptoms of excessive daytime sleepiness. In addition, we could address the potential role of hypocretin cells in producing sleep disturbances in

Parkinson's through gene and stem cell therapies. New treatments are currently in development for hypocretin-deficient narcolepsy, such as introducing hypocretin-producing cells into the brains of patients using stem cells[15]. Perhaps these new treatments could be used in Parkinson's patients as well, as this would both clarify whether hypocretin contributes to sleep disturbances in Parkinson's and potentially improve sleep quality of these patients. Finally, Parkinson's patients may benefit from government-funded courses in sleep hygiene. If, for example, sleep disturbances in Parkinson's arise from circadian rhythm irregularities, these issues could be ameliorated (though admittedly not fully treated or resolved) through careful maintenance of good sleep habits. This would include going to bed and waking up at approximately the same time each day, keeping rooms dark and quiet, and not eating or drinking for an hour or so before bed. These environmental cues are associated with improved regularity of sleep cycles, and it may benefit Parkinson's patients in early stages of the disease.

Sleep deprivation is a phenomenon that we can all understand. A clinical population, already suffering from other neural and physiological stressors, cannot afford to lose sleep. The physiological toll that sleeplessness takes on us becomes more and more costly if other internal systems are already not functioning correctly. Thus, sleep disorders in Parkinson's are a pressing issue that faces our scientific community today; understanding the link will not only remarkably improve the quality of life and outlook of Parkinson's patients, but also it will inform our understanding of normal sleep and how disrupted sleep may arise in clinical settings.

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Nothing tastes as good as SKINNY feels

Unmasking the Neurobiological Basis of Anorexia

By **Louise Yang**

Food is an unquestionable need for basic human survival. It is also present at most social events and celebrations due to the central role it plays in bringing people together. Yet for some people, every single meal and every single bite is a struggle. This isolating and life-threatening condition is anorexia nervosa (AN), a chronic illness characterized by excessively decreased caloric intake, disturbed body image, and an intense fear of weight gain (Park et al. 2014). It is a debilitating and heartbreaking disease not just for the patient but for friends and family who must watch their loved one physically waste away before their very own eyes. The lack of proper food intake caused by anorexia deprives the body of essential proteins and nutrients that give way to a domino effect of health issues (Figure 1). This puzzling, treatment-resistant disease has long been thought of as Western culture-bound syndrome driven by toxic societal pressures to diet and be as skinny as possible. *How can it be that in countries with such abundance women are driven to starving themselves? Why are some people more susceptible to this disease? Is it their fault?*

The interplay between environment and genetics is essential for understanding the prevention and development of anorexia. In addition, discovering the neurobiological changes made by this disease are essential for treatment and grasping why recovery is so difficult. There is no clear recovery plan for anorexia and current treatments, such as psychotherapeutic or pharmacological ones that target abnormal serotonin systems, have proven inadequate (Fitzpatrick & Lock, 2011). Researchers are shedding light on the abnormal brain circuitry displayed in anorexic patients in hopes of discovering novel pharmaceuticals and better-targeted treatment methods for this currently incurable disease.

History of Anorexia

Despite its reputation as a modern disorder, the first medical report of anorexia was made in 1689 by London physician Richard Morton.

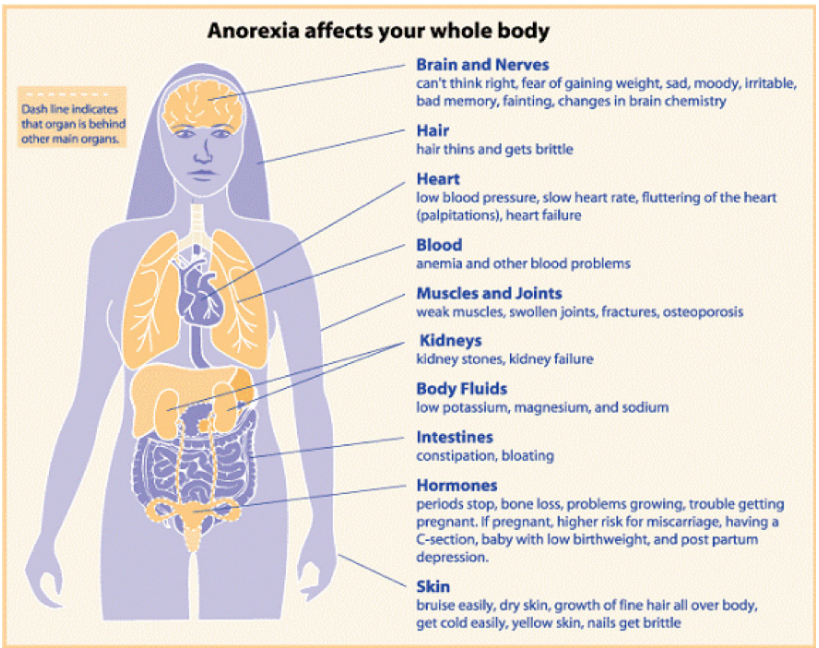
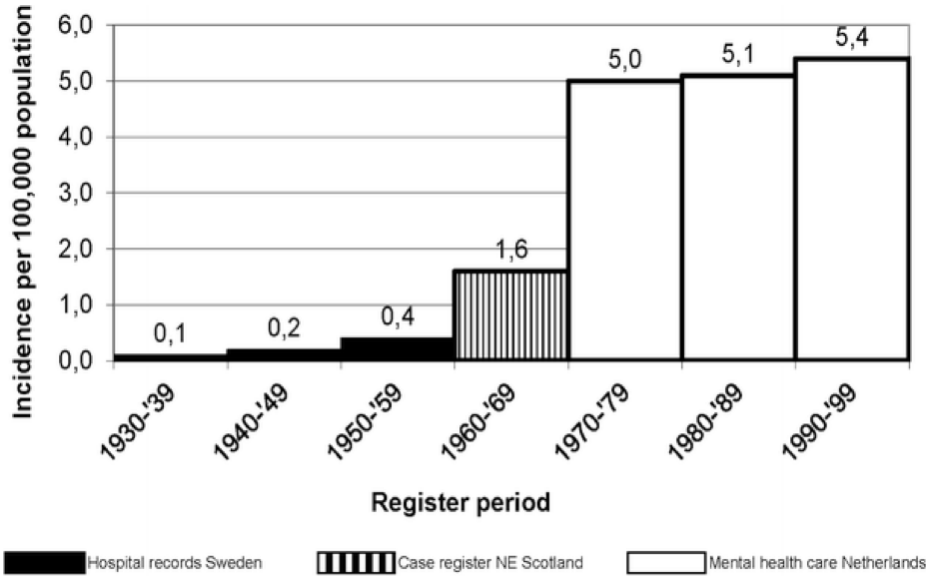


Figure 1 Diagram of the physical effects of Anorexia Nervosa. http://www.myedin.org/understanding-anorexia.html

Figure 2 Meta-analysis of yearly incidences of AN cases in northern Europe. (Makino, 2004)



However, even up to the 1970s, cases of anorexia were seen as clinical oddities that doctors rarely saw, let alone knew how to treat (Arnold, 2016). While rates of anorexia had been steadily climbing since the 1950s (Figure 2), it was not until the death of singer Karen Carpenter in 1983 that anorexia hit mainstream awareness. The young singer's death from anorexia-induced organ failure led to sensationalization of the disease as the media speculated on why teenage girls were suddenly "dying to be thin." Psychologists blamed the cause of the disease on a troubled home life and pushy parents, coupled with unrealistic standards of beauty propagated by the media and supermodels. Anorexia was seen as a willful choice made by selfish young teenage girls who simply had to choose to get better (Arnold, 2016). The answer to anorexia is simply to eat, right? Unfortunately, this backward approach was often recommended to those who suffer anorexia, to no avail. However, growing evidence of the genetic and neurobiological basis behind this debilitating disease have begun dismantling these dangerous preconceptions and brought about a new understanding of the cause and possible treatment of this currently incurable disease.

Who is affected?

Anorexia affects around 1% of the population, with 95% of anorexics being females. The average age of onset is between 14 to 19 years (Hudson et al., 2007). In addition, anorexia has the highest mortality rate among all psychiatric illnesses with one in five deaths being caused by suicide. Patients with AN show high comorbidity with mood disorders such as depression (35-50%), and around half have comorbid anxiety disorders including social phobias and obsessive-compulsiveness (Ulfvebrand et al., 2015). Anorexia is considered a chronic illness because even though weight restoration is manageable, relapse is a prevalent issue (Zanadian et al., 2007). For example, patients discharged from the hospital will slowly but surely return to their old unhealthy eating habits and continue the cycle of hospitalization.

A study found the following five personality traits increased the risk of developing an eating disorder: perfectionism, inflexibility, rule following, excessive doubt and caution, and a drive for order and symmetry (Anderluh et al., 2003). Patients with anorexia also have trouble zooming out and seeing the big picture and, instead, get stuck on the little details, which can cause difficulties with decision making. In addition, patients with anorexia show difficulty mentally switching from one task to another (Arnold, 2016). This strangely similar cluster of characteristics shared by patients with anorexia hints at the underlying biological factors behind this disease because, in addition to predating disease, these traits often persist after recovery.

Is Anorexia a Western Disorder?

Anorexia has long been thought of as a western issue that primarily affects white women. Since the late 20th century there have been many reports of eating disorders in Western countries, and few cases had been seen in non-western countries other than Japan. However, a study in 2004 found that while the prevalence of anorexia in non-western countries is lower than in western countries, it has

been slowly increasing. Population and patient-based estimates of AN in non-western countries ranged from .002% to 0.7% and was associated with an increase in abnormal eating attitudes (Makino, 2004). This is, perhaps, an effect of globalization and the spread of Western beauty ideals through the media. For example, before the 1990s there had only ever been one reported case of anorexia on the island of Fiji. However, after the introduction of television to the island in the mid-1990s, there was a sudden influx of cases. In addition, in Japan the increase in anorexia between 1985 and 1992 paralleled modernization. It is argued that anorexia is more prevalent during times of cultural change and confusion for immigrants and individuals who are part of rapidly developing countries (Pke et al., 2015). Even with this rise in anorexia, the numbers still remain relatively low in comparison to the general population. Therefore, the question must be asked, why are some people more vulnerable to developing the disease than others? Most people are exposed daily to unhealthy beauty ideals, yet never spiral into illness.

The Genetics Behind Developing AN

While many people diet and express sentiments to lose weight, only a small percentage actually develop an eating disorder. This is due to the highly genetic component of anorexia. Genetic heritability accounts for approximately 50 to 80% of the risk of developing anorexia, while also contributing to the neurobiological factors that underlie the disease (Kaye et al., 2009).

A recent transgenic mouse model demonstrates the interplay of genetics, biology, and sociocultural variables that contribute to the onset of anorexia. Researchers transgenically created mice with the BDNF gene, which is a gene that has been associated with anorexia in humans. Adolescent mice with the BDNF gene variant placed under environmental stressors of social stress and on a

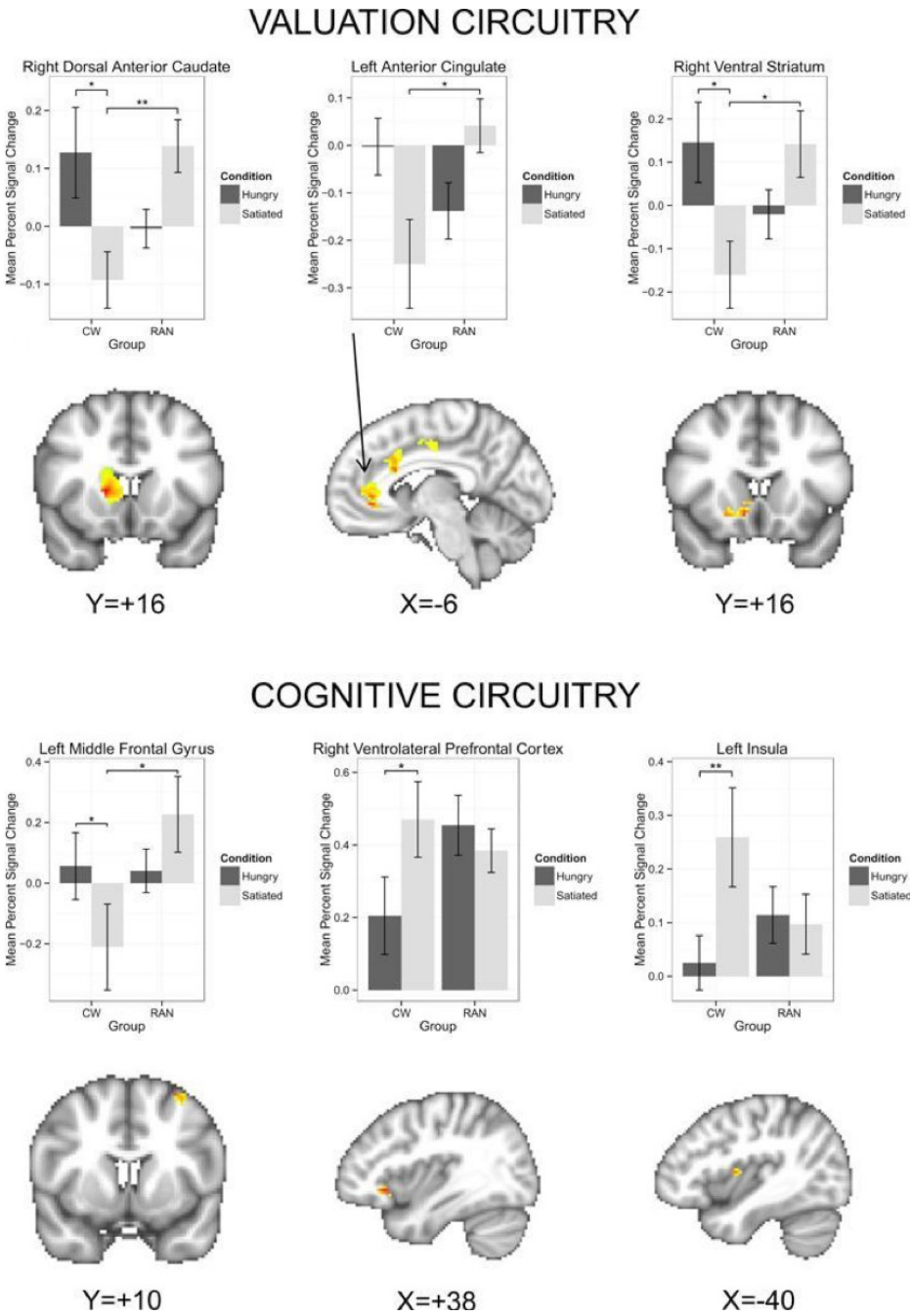


Figure 3 fMRI of the activation of the reward versus the cognitive circuitry of patients with AN versus controls when hungry versus satiated. (Wierenga et al. 2015)

calorie-restricted diet were much more likely than controls to begin avoiding food (Madra & Zeltser, 2016). This change was not seen in adult mice, and was also not induced when mice were subjected to only one stressor and not the other. This demonstrates that having an at-risk genotype in itself is not sufficient for developing anorexia-like behavior, but that disease development is the combination of stress, dieting, and age that work together with a genetic predisposition. This can help explain the increase in rates of anorexia in non-western countries due to the introduction of unhealthy socio-cultural standards of weight loss and beauty which then triggers disease development in youths who are already genetically susceptible. Researchers hope to use this new mouse model to study the change and disruptions in neuronal circuits that cause the metabolic, neuroendocrine, and behavioral disease symptoms (Madra & Zeltser, 2016). This leads to the question, what are the neuronal disruptions in AN?

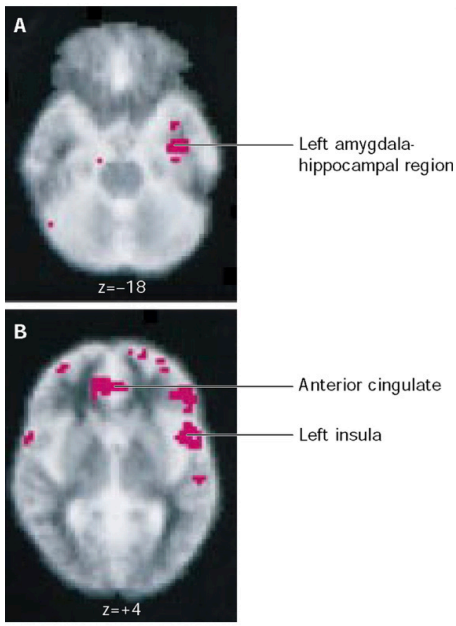


Figure 4 fMRI of increased activity in the left amygdala-hippocampal region, anterior cingulate, and left insula in the anorexic group (Ellison et al., 1998).

Dysregulation of the Reward System in AN

Many of us resolve to avoid fatty foods and unhealthy desserts, yet our self-control often vanishes when tempted by a piece of cake after a long day. This normal behavior makes sense considering the role of hunger as our body's cue to seek out and approach food. In addition, hunger actually increases the intensity of food rewards, and this enhanced sensitivity to reward is a motivational cue to eat, mediated through increased activation of reward salience circuitry in the ventral striatum, dorsal caudate, anterior cingulate cortex (Wierenga et al. 2015). How are patients with anorexia able to ignore these urges? Unlike healthy controls, who show an increased activation of reward circuitry when hungry, patients with remitted AN do not show this increased activation, lessening their sensitivity to the motivational drive of hunger (Figure 3).

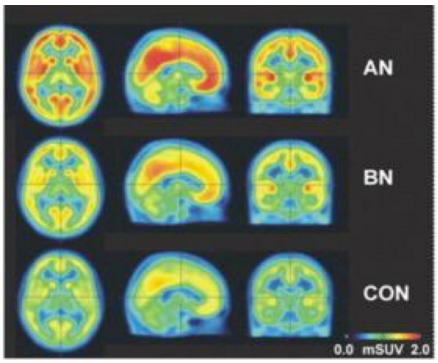
Furthermore, patients with remitted AN showed increased activation in the ventrolateral prefrontal cortex (Figure 3). This increased activity in cognitive control circuitry perhaps allows them to better resist the temptations of food. This can, perhaps, explain the puzzling question of how individuals with AN are able to restrict food intake (Wierenga et al. 2015). In addition, these differences in activation might possibly occur before the development of the disorder, demonstrating the strong biological factors that predispose certain individuals to developing AN. Frank (2013) proposed a model of structural and functional alterations in the insula and frontal cortex, areas that contribute to both reward and anxiety processing, that can occur prior to AN development along with additional changes in these circuits from malnutrition that can further hinder recovery by promoting illness behavior and relapse (Frank, 2013).

The neurotransmitter dopamine plays a vital role in regulating the reward system, and alterations in mesolimbic dopamine levels have been shown in activity-based anorexia mouse models (Avena & Bocarsly, 2012). Although current dopamine-targeting drug treatments have proven ineffective in treating the disease, there is promising research into atypical antipsychotics that may modulate the irregular dopamine systems seen in anorexia (McKnight & Park, 2010).

Abnormal Amygdala Activation

Patients with AN often display an abnormal preoccupation with food-related items, in addition to a fear of eating high calories items. Functional magnetic resonance imaging (fMRI) was used to study the response of patients with AN when they imagined drinking high versus low calorie

Figure 5 AN patients display elevated global CB1R expression in both cortical and subcortical regions (Monteleon et al., 2005).



food. Increased activation in the limbic and paralimbic network was associated with high calorie foods, suggesting a conditioned fear to high calorie foods (Figure 4). In addition, abnormal activity in the limbic and paralimbic areas has been associated with depressive and obsessive-compulsive symptoms, perhaps further contributing to the prevalence of these traits in patients with AN (Ellison et al., 1998). Even after weight restoration, patients recovering from AN continue to choose low calorie food over more nutrient dense, higher calorie food that would help them maintain a healthy body weight (Berridge, 2003). This calorie fear highlights how a better understanding of the neurobiological changes caused by AN can help the development of better-targeted strategies to improve existing treatment plans.

Anorexia is also frequently characterized by a preoccupation with body size and body dysmorphia, an obsessive focus on a perceived flaw in appearance. Concerned parents might look at their daughter and see an alarmingly skinny body with protruding bones, yet the girl herself would perceive her body as fat. fMRI was used to study changes in the brain when patients with AN and controls were stimulated with digital pictures of their own body image. In patients with AN, stimulation with their own body image caused activation in the right amygdala, the right gyrus fusiformis, and the brainstem region (Seeger, 2002). Studies have linked activation of the right amygdala to aversive, anxiety-producing stimulus. Understanding this activation of the "fear network" in response to one's own body can be used to help explain why, during mirror confrontation therapy, patients with AN display fear and avoidance when looking at their own body, especially during weight gain (Smeets, 1999). This knowledge can then possibly be used during recovery to learn how to combat this conditioned fear of one's own body.

A Potential New Treatment Site- the Endocannabinoid System

The endocannabinoid system is a new and relatively understudied potential treatment site for anorexia due to increased information about the critical role it plays in body homeostasis. CB1-receptors (CB1R) are densely located in key brain regions involved in appetite, food intake, and energy expenditure (Marco et al., 2012). Studies have shown a deregulation of the endocannabinoid system in anorexia. For example, fMRI research has demonstrated that AN patients display elevated global CB1R expression in both cortical and subcortical regions that is believed to be a long-term compensation mechanism for hypofunctioning of the endocannabinoid system (Figure 5) (Monteleon et al., 2005). Meanwhile, cannabinoids have been shown to be a safe and effective tool for treating anorexia associated with weight loss in patients with AIDS through activation of CB1 receptors ex-

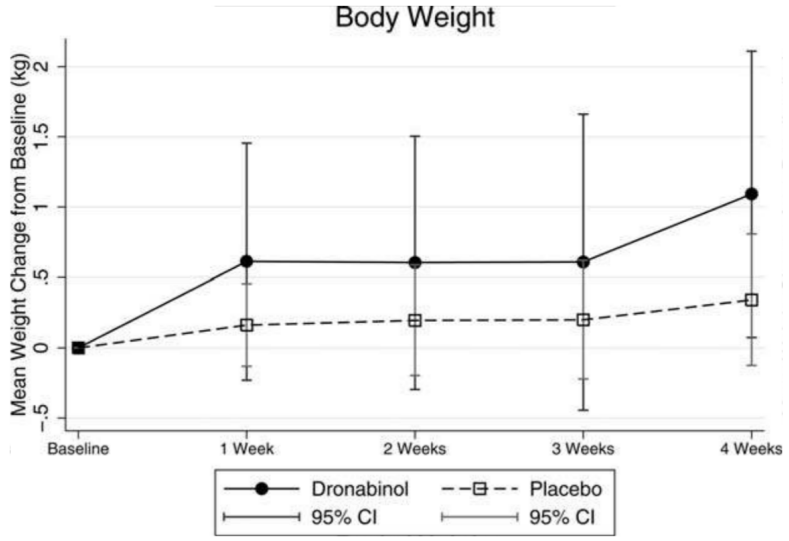


Figure 6 Dronabinol induced increase in weight gain of AN patients (Andries, 2013)

pressed in brain regions such as the hypothalamus and mesocorticolimbic system that are involved in energy modulation by promoting food intake and reinforcing the hedonic value of food (Gross, 1983).

Women with severe and long-lasting anorexia (AN) were treated with dronabinol, a synthetic cannabinoid agonist, to study its effects on body weight and eating disorder related psychopathological personality traits (Andries, 2013). Participants gained a significantly greater amount of weight during dronabinol treatment than during placebo treatment with no change in leptin levels. Dronabinol was believed to facilitate weight gain through an anabolic mechanism (Figure 6) (Andries, 2013). This result was supported by a study on the effects of CB1R agonist tetrahydrocannabinol (THC) on activity-based anorexia (ABA) modeling rats. ABA is the most widely used rodent model used to study the underlying changes in neural circuits behind anorexia. It models two key symptoms of anorexia: reduction in food intake and increase in exercise. Rats that experience food restriction while having unrestricted access to running wheel time exhibit hyperactivity by voluntarily spending more time on the running wheel than those with unrestricted access to food. These ABA also exhibit paradoxical reductions in food intake which leads to weight loss and even death without experimenter intervention. THC treatment was able to induce maintenance of a healthy weight in ABA modeling rats due to a decrease in energy expenditure through decreased thermogenesis (Verty et al., 2011). Studying the effects of THC on the endocannabinoid system is one step closer to a promising novel pharmacological treatment for anorexia.

Early detection and Prevention

Early detection is vital for treating AN because the longer the duration of the disease, the greater the harmful effects on the body, and the greater the changes in neural circuits. A fMRI study showed that even when recovered from anorexia, subjects showed irreversible grey matter volume deficits (Katzman et al., 1997).

Policies can be made to improve school-based health curricula starting at a younger age, with content aimed at preventing eating disorders. In a longitudinal study, adolescents who engaged in dieting and unhealthy weight-control behaviors had higher rates of obesity and eating disorders five years later. Dieting is a stressor that can trigger the development of illness, and parents and schools should create prevention programs that shift away from drastic weight-control measures such as dieting in favor of measures to implement long-term healthful eating and physical activity behaviors (Neumark et al., 2006). In addition, there needs to be better and increased training of educators and health providers with respect to identifying eating disorders.

Last of all, advertising and social media policies should be created to counter the negative self-image promoted by unrealistic and unhealthy body ideals on television, print, and social media. For example, several social media sites have paved the way by creating anti-anorexia promoting policies that have had varying levels of success. It is suggested that the media can actually be a positive influence on young, impressionable women through presenting a greater variety of body shapes and discouragement of dieting.

Conclusion

Overall, the etiology of anorexia is unknown, and much can be learned from studying the neurobiological basis of the disease. Not only can current treatment plans be altered to better fit the needs of patients in recovery, but promising new pharmacological drugs may also better target the abnormal neural circuitry in AN. Furthermore, understanding the interplay of genetics and environment in the development and maintenance of this disorder can help patients feel less guilty and isolated when battling this terrible disease.

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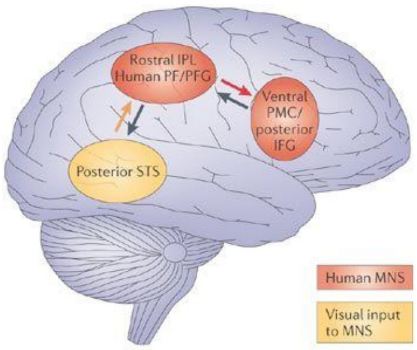
Mental Health in Young Adults with Autism Spectrum Disorders

By **Nikki Scheman**

The rate of psychiatric disorders in young adults with Autism Spectrum Disorders (ASD) is extremely high.[1] But, even though mental illness can be more common for people on the autism spectrum than the general population, the mental health of individuals with ASD is often overlooked. Co-occurring mental illness can come in the form of depression, ADHD, bipolar disorder, and others. One of the most common disorders co-occurring with ASD is anxiety disorder.[1] In fact, individuals with ASD experience anxiety at rates exceeding both the general population and other neurodevelopmental disorders.[2] The common co-occurrence of anxiety in ASD has been confirmed in over forty studies before 2014.[3] Managing multiple conditions can make the transition into young adulthood especially difficult for youth with ASD. Being able to recognize comorbid, or co-occurring, psychiatric disorders may identify targets for specific intervention that could reduce overall impairment and improve quality of life. Recognizing that the symptoms of mental illnesses, like anxiety, could look different in those with ASD than in those without could help individualize care for youth on the spectrum.[4] When these needs are not met, there is a social cost.

Autism advocate and co-founder of Autism Goggles, a website dedicated to expressing the experience of being autistic, Daniel Share-Strom, talks about the anxieties that come from living on the spectrum. Not surprisingly, difficulties in communication can contribute to the layers of anxiety individuals on the spectrum experience on a daily basis. In a blog post to his site, he writes that "the feeling of living on edge… of waiting to mess up… can cause tremendous anxiety."[5] Parents and teachers would benefit youth with ASD if they increased awareness, acceptance, and knowledge about

Figure 1 Imitation/Mirror Neuron Circuit. This includes the rostral inferior parietal lobule (IPL) and inferior parietal cortex (PFG) as well as the posterior inferior frontal gyrus (IFG).[25]



autism spectrum disorders and the common anxieties and mental health disorders that can often co-occur. This can lead to better strategies for support and reduce misunderstanding of youth with ASD both at home and in the classroom. This has the potential to help children with ASD become less anxious and more likely to be open to learning about how to improve their communication skills.

What are Autism Spectrum Disorders?

Autism spectrum disorders are increasingly common, with 1 in 48 children affected.[6] They are characterized by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as persistent deficits in social interactions and communication as well as restricted, repetitive patterns of behavior, interests, or activities.[7] Early indications of ASD include deficits in social skills such as mentalizing and face processing. Specifically, a lack of interest in the human face and voice and a preference for inanimate objects is an indication of ASD.[8]

Individuals with ASD sometimes struggle to connect with others in typical ways. Specifically, the ability to think about another person's perspective is essential for meaningful connections. Studies show that there may be atypical development of the neural circuitry that underlies mentalizing and self-appraisal.[9] Mentalizing is this ability to understand that others have different desires and perspectives than one's own. There is evidence for a whole system of the brain that co-activates to the actions, intentions, and emotions of the self and others. This system, called the mirror neuron system (MNS), is comprised of regions in the inferior frontal gyrus (IFG) and inferior parietal lobule (IPL) that are active during the perception and execution of actions (Figure 1).[9] In a study done by Dapretto et al., children with autism and controls both imitate facial expressions showing basic emotions. The children with ASD showed less MNS activation that healthy controls, and the extent of activation in the MNS was correlated with the severity of their autism symptoms.[10]

Children with ASD also show deficits in face processing that are due to issues in skills like eye gaze, face identification, and emotional recognition. Much of how we gather social information is from looking at other people's eyes. Individuals with ASD show significant impairment in gaze fixation to the eyes and erratic gaze patterns (Figure 2).[11] It is possible that the difficulty remembering faces that individuals with ASD also experience is because of this eye-gaze deficit. Dysfunction of the fusiform face area (FFA) also leads to this difficulty in people with ASD (Figure 3).[9] Individuals with ASD also focus on other features of the face besides emotional expressions, like accessories, suggesting that there is a difference in the salience in emotional expressions. Studies have shown dysfunction in the amygdala, a somewhat almond shaped structure that is a key part of the emotional circuit, in response to emotional faces.[12]

Emotions and the Amygdala

We know dysfunction has been

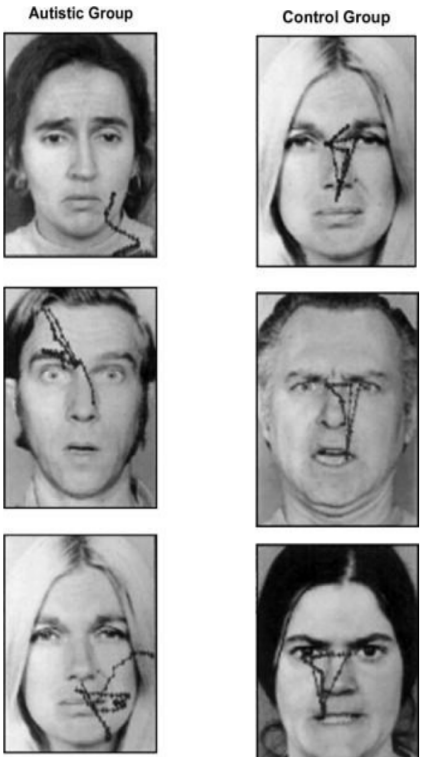
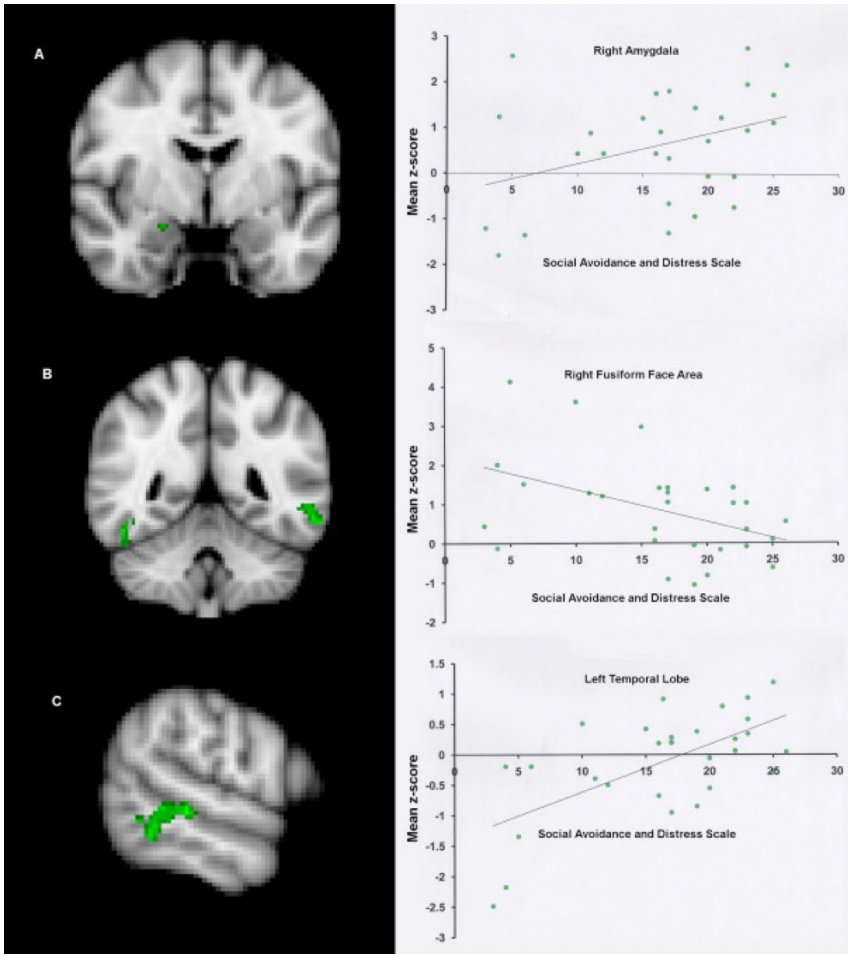


Figure 2 Abnormal eye-gaze patterns in patients with ASD. Eye gaze of ASD group shown on the left, and a control group with a typical inverted triangle pattern of visual gaze on the right.[11]

Figure 3 Results from an fMRI study presenting participants with either fearful or angry faces. In the ASD group, there was decreased fusiform face area and increased amygdala activation in as anxiety levels increased.[9]



shown in the amygdala of patients with ASD, but what is the amygdala and what role does it play in emotion? The amygdala is a collection of nuclei at the front end of the hippocampus that receives sensory input in a highly processed form from all types of senses (Figure 4).[13] While many types of input go to the amygdala, the most common emotion (but not the only emotion) following amygdala activation, is fear.[13] There are three main regions of the amygdala: the basolateral nuclei, centromedial nuclei and the peripheral nuclei. The basolateral group in particular has been implicated in both decision-making and social perception.[14] In fact, in one study, researchers looked at the role of the primate amygdala in decision-making with respect to others. Chang et al. found that the basolateral amygdala neuron activation seemed to mirror the value of the reward both to themselves and to a recipient primate. Their findings support the idea that the amygdala, specifically the basolateral region, is a critical area for regulating social decisions.[14]

However, the amygdala is associated with more than reward and decision-making. Interestingly, the function of the amygdala in emotional processing can be associated with anxiety, too. The main hormone associated with stress and anxiety is called cortisol. More cortisol is released from the adrenal glands in stressful situations. Researchers looked at the effect of cortisol levels on the connectivity of the amygdala to other face regions during emotional face perception. More cortisol was correlated with increased connectivity of the amygdala with many different parts of the brain, including the cerebellum. This connectivity has also been reported in anxiety disorder patients.[15]

A Brief Look at Anxiety Disorders

Before talking about the struggle that individuals with ASD face when they experience comorbid psychiatric disorders, particularly anxiety disorders, a brief description of the latter is required. Anxiety disorders are characterized by maladaptive anxiety symptoms that cause distress and impair function.[16] Many brain regions appear to be involved in the recognition and regulation of negative emotional stimuli and response to these stimuli. The principal neural circuits thought to be related to anxiety are presented in Figure 5.[17] While many structures seem to be

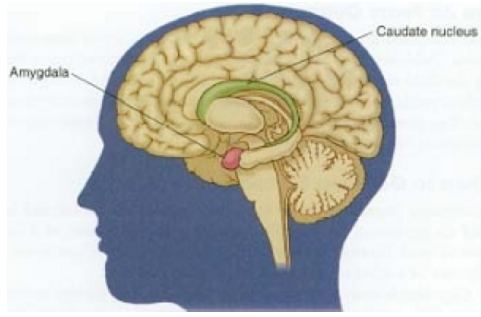
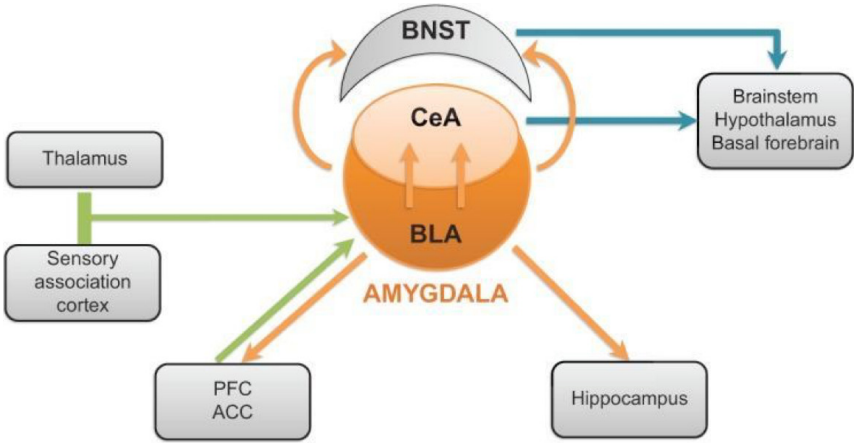


Figure 4 Location of the amygdala in the brain attached to the hippocampus.

Figure 5 Main neural circuits associated with anxiety. This includes the thalamus, prefrontal cortex (PFC), anterior cingulate cortex (ACC), hippocampus, hypothalamus, brainstem, and the basolateral (BLA) and central (CeA) nuclei of the amygdala.



critical for the regulation of negative emotion in anxiety, the amygdala, in particular, appears to play a crucial role.[17]

Researchers have shown that patients with anxiety disorders exhibit hyperactivation of the amygdala in response to faces than controls.[17] The basolateral nucleus of the amygdala receives information on potentially negative emotional stimuli from both the senses and the thalamus, the relay station for sensory input. This, in turn, activates the central nucleus of the amygdala, its main output pathway (Figure 6). Projections from the central nucleus send information to the hypothalamus and brainstem via inhibitory GABAergic neurons. GABA is a neurotransmitter that silences signals between neurons. Its levels may be linked to these feelings of anxiety and also to anxiety disorders.

The Amygdala in ASD and Anxiety

While it has been shown that the amygdala is hyperactive in individuals with anxiety disorders, evidence of amygdala abnormality in ASD is conflicting. Some studies have found that the amygdala is hypoactive and fails to process social stimuli as meaningful (Figure 7), while others say that the amygdala is hyperactive. In those cases, the avoidance of social stimuli seen in patients with ASD could be the result of an aversive over-arousal.[18] The abundance of inconsistent findings in the published literature on ASD may reflect differences between study populations regarding age, level of symptom severity within ASD groups, and not accounting for underlying anxiety level in the study groups.[19] Many studies have investigated the relationship between anxiety and ASD and the effect of their co-occurrence on the amygdala, since the rate of comorbidity is so high.

When looking at the relationship between self-reported anxiety and fMRI activation to emotional faces, Kleinhans et al. found that ASD individuals with higher anxiety showed increased amygdala activation (Figure 3).[9] They had participants look at angry or fearful faces and match the emotions seen to a target face. Interestingly, the area of the brain associated with face processing, the fusiform face area, was less activated the more anxious an individual rated themselves. This would suggest that more anxious participants avoided the face area entirely to avoid the negative feelings of anxiety. On the other hand, low-anxiety ASD groups have been shown to have decreased amygdala activity compared to controls.[20] So, maybe all the conflicting data on amygdala activity in people with ASD comes down to their anxiety levels. If this is the case, researchers and doctors could predict the level of social impairment that an individual with ASD might face. One study looked at the relationship between social impairments and amygdala habituation, the diminishing of a response to a stimulus after repeated exposure. They found that in the ASD group,

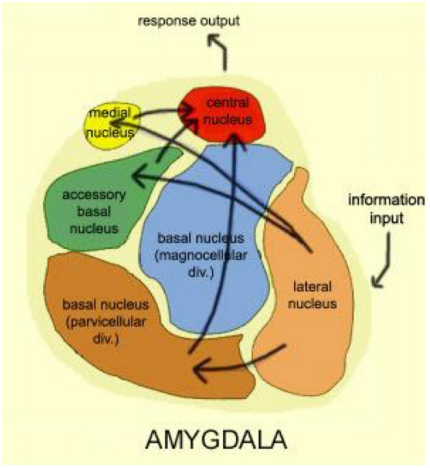
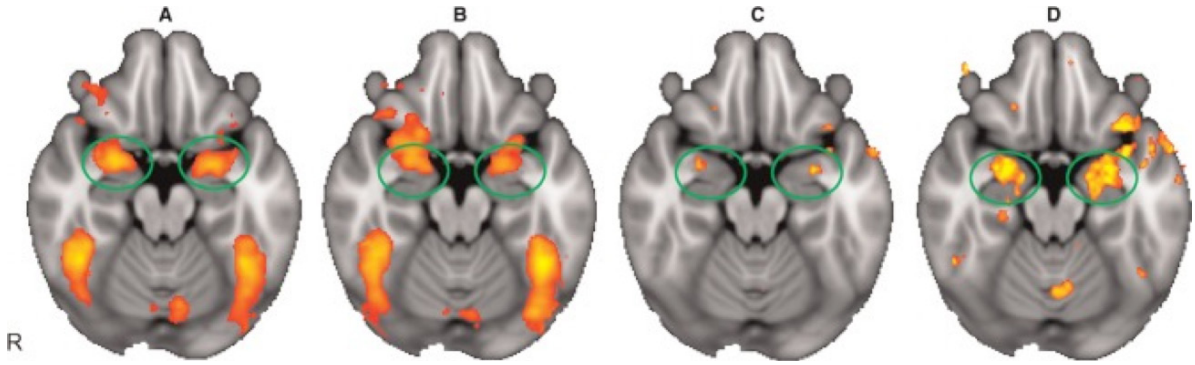


Figure 6 Different nuclei of the amygdala. This primary three nuclei are the lateral nucleus that receives input, the basal nucleus and the central nucleus that sends output information to other brain regions.

Figure 7 Decreased amygdala activation in ASD individuals with low anxiety. Amygdala activation is circled in green. (A) Control group only. (B) ASD group only. (C) Control vs a low-anxiety ASD group, measured by the SCARED total score. (D) Controls vs ASD patients with low anxiety, measured by the SCARED Separation Anxiety Score.[20]



lower amygdala habituation was associated with more severe social impairments.[9] This supports the idea that social impairment can be predicted in the lab, but evidence on the effects of anxiety could provide insight into how to target interventions to help with the increased ASD symptom severity that results.

Co-occurrence of ASD and Anxiety

Anxiety interventions would be especially important for individuals with ASD because children with anxiety disorders actually experience increased ASD-like traits.[2] In a parent rating of ASD severity, the children with the highest levels of anxiety were rated the highest for ASD symptoms as well.[2] However, the challenge comes in recognizing this anxiety, because youth with ASD express it in ways both similar and dissimilar to DSM definitions.[21] There is also the presence of unusual fears, worries, compulsive behaviors, etc., that appear to be associated with ASD-related traits that may be a distinct manifestation of anxiety symptoms and the increased risk of anxiety disorders. This provides an avenue for future research, but in the meantime requires more awareness from parents and teachers of youth with ASD in order to best provide support.

Challenges of ASD During Adolescence

While it is evident that co-occurring anxiety makes already existing ASD symptoms worse and provides added challenges, plenty of challenges exist already. The neural underpinnings discussed earlier, as well as other factors, have far reaching impacts on the daily lives of youth with ASD. These differences in brain function can manifest themselves in many different ways. To get a sense of what the daily challenges are for people with ASD, a blog post from the writers of Autism Goggles describes what individuals with ASD wish the people in their lives knew about their experience. Most of their focus was on communication. Despite this being the case, research has shown that social involvement with peers improves the behavioral skills essential for everyday life in people with ASD. However, making these social connections is tricky for a number of reasons.

To start, individuals with ASD can have trouble coming up with the words they want to say in a timely manner during interactions, despite having large vocabularies.[5] This can lead to deficits in their social interactions with people who do not understand why this occurs. It can also be hard for people with ASD to understand the main point of a request or reading topic, but they don't always know that they have misunderstood.[5] When others point out the error, it can cause shock and embarrassment. This was a common theme: the embarrassment that comes from mistakes that were completely unintentional. It can be very anxiety producing when you unexpectedly get negative feedback for your actions without always knowing why. However, individuals with ASD can also have a hard time finding the words to de-

fend themselves when they believe someone is angry or disappointed with them. Because of this, selectively going silent can be a coping method. In fact, it is not uncommon for children with ASD to be very quiet or even not speak at all in the school setting. Awareness of this is essential for teachers to be able to provide the right kind of support for their children on the spectrum.

Awareness from teachers, family, and society is not always the reality, though. Regardless of a diagnosis on the autism spectrum, adolescence is, in general, a time of increased demands on our youth. For example, adolescents are expected to begin following multistep directions, keep their school materials organized, begin to socialize outside of their families, and gain independence. However, studies show that the cognitive abilities of youth with ASD might not be improving fast enough during adolescence to keep up with these increased demands.[22] The gap between expectations and the abilities of adolescents with ASD widens over time. In particular, working memory (the ability to hold a memory for a short amount of time for processing), imitation, and organization become increasingly problematic over time.[22] Data in this area emphasizes the need for continuing intervention and support throughout later adolescence, when typically school and clinical resources become less available.

ASD and Mental Illness: Broader Impacts

Individuals with ASD experience challenges during adolescence that make life even harder than it already is during this time of growth and development. At the same time, the rate of comorbid mental health issues, like anxiety, is high. Environmental factors seem to play a major role in this. Daniel Share-Strom, from Autism Goggles, believes that "people with autism aren't immediately born anxious or with depression," but that "the world is fundamentally not built for us, and people are always judging and trying to change you, whether they have the best intentions or not."[5] Because of these added challenges, providing support and resources for young adults with ASD is extremely important.

However, many children with ASD are not getting the mental health services they need. Compared to children with other disabilities or mental illnesses, children with ASD have more unmet healthcare needs and more difficulty accessing mental health services.[6] Although inadequacies in mental health services affect many Americans, the problem is more severe for individuals and families affected by ASD. At least 15% of children with ASD who needed mental health services did not have access.[23] This is especially problematic when mental illness brings its own challenges and also exacerbates the already present challenges associated with ASD. Consequently, improving access to quality mental health services and other health care is necessary. However, this will require both insurance reform and improved training in medical school and healthcare systems.

Mental illness can inadvertently go untreated if it is believed to be just another characteristic of ASD. But it is, in fact, a misconception that some symptoms cannot be from other mental health disorders. In reality, mental health symptoms can still be treated or helped in individuals with ASD. This can come in the form of both medication, which can improve mood and reduce impulsivity and Cognitive Behavioral Therapy. This therapy involves changing the young adults' patterns of behaving and thinking by making them aware of why their patterns are not productive.

In addition, further training on working with youth with ASD should be required for teachers. This would help teachers to provide the kind of in-class environment that would support rather than add to the already existing anxieties and struggles that people with ASD face on a daily basis. However, training should focus on both ASD symptoms as well as signs of co-occurring mental illness. This way, the people who need extra help can get the support they should be receiving for mental illness disorders such as depression, anxiety disorders, ADHD, and others.

The occurrence of autism spectrum disorders has only grown over the years. Now, approximately 1 in 48 children are diagnosed with ASD.[6] This is an incredibly high statistic that is continuing to

rise. Within this population, the prevalence of co-occurring anxiety disorders and other mental illnesses is widespread but also widely overlooked. Parents, teachers, and communities all need to be more aware of the specific challenges individuals with ASD face, and the possibility for other mental health issues that could be occurring at the same time. But, while awareness is a great step, that awareness must turn to both acceptance and changes in the way teachers and health practitioners are trained with regard to people with ASD in order to really improve their quality of life.

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Mushroom For Improvement:

The Case for Psilocybin-Assisted Therapy

By **Harry Justus**

"I had a clear mind, it lifted the fog of depression. I could see my life, like a light in the tunnel."
"I was lucid and alert, the depression had evaporated. It puts your head above the fog."[1]

These are quotes from individuals who underwent a decidedly unconventional treatment for their depression: psychedelic-assisted psychotherapy. Psychotherapy itself is a commonly-used treatment for depression, with about 45% of Americans diagnosed with major depression receiving psychotherapy as a primary treatment method.[2] However, the traditional combination of psychotherapy and antidepressant medication does not work for everyone, and certain patients have depression that does not respond to these forms of treatment. This is referred to as treatment-resistant depression, which for this article will be defined as a consistent, professionally-diagnosed score of 17 or higher on the Hamilton Depression Rating Scale (indicating at least moderate-to-severe depression), and at least two failed attempts at treating their depression with antidepressant medications during the current period of depression.[1] This article aims to discuss the ways in which psychedelics affect the brain, the potential ways in which psychedelics could be implemented as an aid in psychotherapy, reasons why this is a potentially beneficial research area, and finally some potential future steps toward a better understanding of the ways in which psychedelics could be a valuable tool for the treatment of some mental health disorders.

Wait— what's a psychedelic?

Throughout history, humans have used naturally-occurring chemical compounds in a number of capacities, whether spiritual, therapeutic, or otherwise.[3] Psychedelics (meaning soul-revealing, from the Greek words psyche— soul and

deloun — to reveal) are a somewhat loosely-defined category of consciousness-altering chemicals which includes lysergic acid diethylamide (LSD, pictured above) psilocybin, which is the active-ingredient in so-called "magic mushrooms," (pictured below) and others.[4] Psychedelics are chemically

similar to the neurotransmitter serotonin, and have a strong effect on serotonin-2A receptors. In other words, that means that these chemicals affect various parts of the brain in order to produce profound shifts in our sensory perceptions and in the ways we think.[5] However, in the past it was difficult to research these chemicals much beyond their subjective psychological effects— little was known about the effects of psychedelics on the brain itself, only the behavioral effects that could be observed in people or animals to whom these compounds were administered.[4] By the mid-1960s, there had been a large number of studies that showed a great deal of potential for using psychedelics as a therapeutic intervention for mental health issues ranging from depression to addiction, and even end-of-life anxiety.[5] These older studies, while not up to the same rigorous standards as modern ones, provided a foundation of promising data upon which the modern renaissance of psychedelic research is based. Psychedelic research in the United States was stalled when psychedelics, increasingly associated with the counterculture movements of the 1950s and 1960s, were stigmatized and eventually made illegal under the Controlled Substances Act of 1970. The Controlled Substances Act designated LSD and psilocybin as Schedule I substances, which means that, according to the law, they have no accepted medical use and a high potential for addiction.[6]

In the past twenty years or so, there has been a revitalization of research into the psychotherapeutic potential of psychedelics. This is due in large part to more advanced technology and techniques that allow us to see with increasing clarity how exactly psychedelics affect our minds. For example, many studies are now using mod-

A brief history of psychedelics in the 20th Century:[4]

1943 *Albert Hofmann first discovers the conciousness-altering effects of LSD*

1947 *Werner Stoll publishes first paper on these effects*

1950 *First English-language paper on LSD published*

1956 *Term "psychedelic" first coined*

1957 *Term "magic mushrooms" first coined*

1958 *Hofmann discovers the presence of psilocybin as the main psychedelic chemical in "magic mushrooms."*

1965 *Sandoz, then the main manufacturer of psychedelic chemicals for research in the US, stops synthesizing LSD and psilocybin.*

1966 *Use of and research on psychedelics in the US begins to be suppressed.*

1970 *US President Richard Nixon signs the Controlled Substances Act into law, which designates LSD and psilocybin as Schedule I substances. This marks the end of research into psychedelics in the US for the foreseeable future.*

Some Other Controlled Substances:[6]

Schedule 1 (High risk of abuse and addiction, no accepted medical uses): *Heroin, Cannabis (marijuana), peyote, MDMA (Ecstasy).*

Schedule II (High risk of abuse, some accepted medical uses): *Vicodin, Methamphetamine, Adderall, Ritalin, fentanyl, cocaine.*

Schedule III (Lower potential for addiction than Schedule II, but still potentially harmful): *Ketamine, anabolic steroids, testosterone.*

Schedule IV (Lower potential for addiction than schedule III): *Xanax, Ativan, Ambien, Valium, Tramadol.*

ern brain imaging technologies to see in real-time which parts of the brain are being activated when someone is under the influence of a psychedelic chemical.[8,9] This has allowed for an entire new era of research that can begin to match the intense subjective effects of psychedelics with the regions of the brain that they appear to affect in order to better understand exactly

For clarification purposes in the rest of this article, unless otherwise indicated, the term psychedelic will be used to refer to both LSD and psilocybin, as these have been the psychedelic compounds that have received the most attention for research. However, this article is primarily about psilocybin and the case for further research into its use as a therapeutic tool to help people with treatment-resistant depression.

The aim of this article is not to push for total legalization of psychedelics. Far from it in fact— these are chemicals that have a powerful effect on the brain, and thus should not be taken lightly. Rather, this article aims to encourage a reevaluation of the current scheduling of psilocybin such that it could be researched further as a potentially revolutionary tool for helping individuals with treatment-resistant depression.

What could psilocybin-assisted psychotherapy look like?

Studies have been done to determine the most effective ways in which psilocybin would be integrated into a psychotherapeutic setting. The most common procedures involve two acute doses of psilocybin at two separate testing times, usually about a week apart. Here is a timeline of a potential treatment plan, compiled from recent studies whose results show promise for the efficacy of psilocybin-assisted psychotherapy:[1, 6 10]

Before the First Dose

1 **Participants undergo a battery of screenings in order to determine mental and physical fitness for the study.**

The Dosing Sessions

9:00am *Participants arrive at the testing facility and are tested for alcohol, marijuana, and other drugs. This is followed by a quick psychological testing session to ensure that there are no major deviations from the previously-gathered scores. Following successful completion of these tests, participants are then brought into the therapy room, where they are familiarized with the dosing environment and meet with the psychiatrists who will be supporting them before, during, and after the dosing sessions.*

Every half hour until 4:30pm *Participants' blood pressure and heart rate are taken; psychiatrists make note of the apparent intensity of the participant's experience. Psychiatrists also perform check-ins with the participant to determine the current subjective experience of the psilocybin— usually simply asking how they are feeling.*

2

Participants meet with the psychiatrists running the study and undergo a brain scan using an fMRI (functional magnetic resonance imaging), which will provide baseline levels of brain activity to which post-psilocybin brain activity can be compared.

3

Participants undergo a lengthy preparation session with their assigned psychiatrist. This includes a long conversation with the psychiatrist wherein the participant is encouraged to speak candidly about their life experiences, including their own thoughts on how and why their depression originated. Additionally, patients are exposed to some of the parts of the psilocybin-assisted psychotherapy session in order to familiarize themselves with the procedure, such as listening to selections of specially-chosen music with eye shades on.

Throughout the dosing sessions: *Supervising psychiatrists do not direct the participant, instead allowing them to direct their own session, giving them the freedom to immerse themselves in the experience without self-consciousness or inhibition.*

10:30am *Patients receive their dose of psilocybin. In the first session, they are given a low dose of 10 milligrams (mg) of psilocybin, which is meant to both familiarize the patient with the subjective effects of psilocybin and also to assess how well the patient can tolerate the effects of the psilocybin. The second session is the same, but the dosage of psilocybin is increased to 25mg.*

Approx. 11:30am *Subjective effects of psilocybin begin to manifest in the participants.*

Approx. 12:30-1:30pm *Participants experience peak psychedelic effects of psilocybin.*

After the Dosing Sessions

6-7 hours post-dosing session *Participants fill out a test that measures their subjective experience of an altered state of consciousness.*

One day post-25mg dose *Participants are invited back to the testing facility to take the same battery of tests that they underwent before the first dosing session, including an fMRI brain scan. Participants are given the opportunity to debrief their experience with the assisting psychiatrists.*

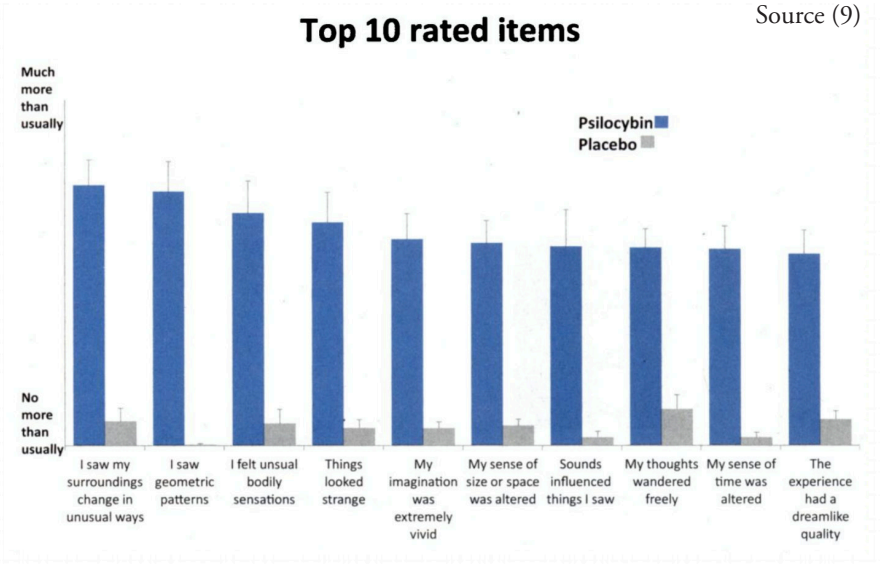
One, two, three, and five weeks; three months post-25mg dose *Participants take a follow-up test that determines their current level of depressive symptoms in order to determine the extent to which (if any) the psilocybin-assisted therapy has affected their mental health.*

how and why these effects manifest.

The Case for Psilocybin-Assisted Psychotherapy

How does it work?

As previously mentioned, psilocybin (and psychedelics in general) have a very strong effect on serotonin receptors in the brain. Serotonin is involved in vision, hearing, and a variety of other cognitive processes, meaning that psychedelics (as serotonin-like chemicals) have pronounced effects on these particular processes. To highlight this, brain-imaging studies found that LSD and psilocybin have a significant effect on brain activity in regions that are associated with vision, hearing, and organized thought. For a graphical representation of these changes in perception, see the above figure from Carhart-Harris and colleagues[9], which provides a comparison of the changes in perception and thought between individuals who had taken psilocybin compared to a non-drug placebo. Clearly, psilocybin facilitates profound changes in the way people experience the world around them. It has been proposed that this is one of the main mechanisms by which psychedelics could help with treatment-resistant depression— many patients with treatment-resistant depression note that they often get stuck in negative, circular thought patterns. That is, they become bogged down in depressive thoughts and cannot break free of them. Since psilocybin so totally alters the perception of thoughts



Source (9)

and feelings, researchers think that it can help the depressed patients to break out of these oppressive thought patterns and help them see the world in a new way.[1] To quote one participant from a psilocybin-assisted psychotherapy study,

> *"my mind works differently [now]. I ruminate much less, and my thoughts feel ordered, contextualized. Rumination was like thoughts out of context, out of time; now my thoughts feel like they make sense, with context and logical flow."*[1]

Another study evaluated a group of mentally healthy individuals who were given varying doses of psilocybin, from a very low dose (almost negligible) to a higher dose that is around the same as the dose that would be given in the second session of therapy as laid out above.[11] These participants were then asked to complete a series of tasks that measured, among other things, the experience of an altered state of consciousness. The researchers found that there were several shifts in the participants' perception of their consciousness, notably in the feeling of "oceanic boundlessness," which indicates a feeling of being connected to everything around oneself— as though they were one with the world around them.[11] This corroborates the subjective accounts of the psilocybin experience in another study, which notes a major shift in its participants' attitudes from feelings of disconnection with the world around them to feeling more connected to themselves, their emotions, and the world around them.[1] Another way in which it has been proposed that psychedelics in general change brain function to combat depression is through increasing what is called cortical entropy. Essentially, cortical entropy is an increase in random activity in the brain, allowing for communication between brain regions that are normally not associated.[12] Increased cortical entropy has been linked with the personality trait of openness to experience, which is

in line with the idea that psychedelics may help combat depression by aiding the individual in acquiring a new interpretation of the world around them and their own thoughts.[1,12]

Hold on, is this even safe?

Remember, this article is not written in support of recreational psychedelic use. The aim of this article is to provide support for the stance that psychedelics have the potential to be an effective tool in treating depression. Research has shown that psychedelics are actually quite safe physically, as they do not build tolerance easily and doses that could cause any lasting physiological harms are substantially higher than any dose that would be administered in a clinical setting.[11] Psychedelics also have not been shown to cause mutations in cells, which are a precursor for many negative health outcomes.[13] Moreover, psychedelics have less of a permanent effect than MDMA (which has been considered for treating some psychiatric disorders) on the brain's ability to use the serotonin that it produces naturally, which means that psychedelics may be less harmful for use in the long-term than other proposed drug therapies.[14] One study of a large sample of the US population found that people who had used psychedelics at some point in their lives experienced lower rates of psychological distress and suicidal behavior.[15] It is, however, important to note that psilocybin and other psychedelics can have some potential adverse effects. In fact, psychedelics have been used in some studies to model psychotic states; hence the importance of screening out patients in danger of having a psychotic episode as a result of their use.[16] One study found that some patients experience fleeting anxiety while undergoing the psychedelic experience.[11] That said, research shows that as long as the participants are adequately screened, prepared, and taken care of during the treatment sessions, none of these negative effects last beyond the dosing sessions. Moreover, it appears that the physical effects of psychedelics do not cause any lasting physical health issues in well-prepared users.[11] Additionally, in the unanimous opinion of the twenty participants in one study, the psilocybin-assisted treatment was preferable to any previous form of therapy for their depression.

Moving Forward

Current Limitations

Psychedelics are still not well-understood compared to other drugs, and have received an unsavory image in many countries due to their legal status and portrayals in popular media as being used mainly by less-than-reputable individuals. As such, there are many misconceptions about psychedelics that must be dispelled if they are to be legalized and publicly accepted for research in the US (or anywhere else in the world). The key to this will be education about these chemicals. It is important to note that any proposed psychedelic-assisted therapies do not call for simply handing the patient a powerful mind-altering substance and simply hoping for the best; remember, the patients are monitored closely and work with highly-trained mental health professionals at every step of the process, especially during the period where the patient is experiencing the acute physiological and psychological effects of these substances.[1]

Possible Future Steps

The first institutional step towards the implementation of psychedelic-assisted therapies is lifting restrictions that keep these chemicals from being researched in a way that could produce more powerful results than previous studies. The current group of studies, while important and vital to the furthering of this research area, all have very small sample sizes— usually fewer than twenty people, and often fewer than ten. Recent studies indicate that psychedelics (at the very least LSD and psilocybin) are safe to administer in well-controlled clinical environments, which for now are the only environments in which these studies should be taking place to begin with. Additionally, psychedelics have been considered for use as a way to better understand the neurological bases of other mental illnesses like schizophrenia, as some of the effects of psychedelics (such as hallucinations) are similar to those observed in patients with these illnesses.[17] In the future, with more data and less limiting laws on research, psilocybin-assisted therapies have the potential to be used in a variety

of clinical settings. These include therapies to treat end-of-life anxiety, alcohol and tobacco addiction, and obsessive-compulsive disorder, among others.[18,19] Additionally, new studies are beginning to look at other illegal or highly restricted substances like MDMA (ecstasy) and ketamine for use in treating depression, post-traumatic stress disorder, addiction, and others.[20, 21]

In sum, I believe the most important point to take away from this article is that psychedelics (especially psilocybin) are worth researching, because they could provide new and effective ways to treat otherwise treatment-resistant mental health disorders. They have already shown a great deal of promise— if psychedelics could be the way for a chronically-depressed person to finally get above that fog of incessant rumination and despair, then they are absolutely worth researching.

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Tasting the Rainbow:

Perception, Hallucination, Act of God, or Just Plain Crazy?

By **Olivia DePalo**

Sight. Hearing. Taste. Smell. Touch. Everything that we know and understand about the world is perceived through our senses. We rely on them every minute of the day and trust without question that our perceptions are accurate and tell us truths about reality. But what does it mean when individuals report hearing colors, tasting sounds, or smelling music? Are they crazy? Do these experiences represent some kind of divine intellect? Or is it possible that various brain mechanisms are leading to these experiences? *Synesthesia* is the experience in which the stimulation of one sensory or cognitive stream reliably leads to an automatic and involuntary stimulation of an unrelated cognitive stream. The experience of synesthesia has been recorded by individuals in various ways throughout the course of history. It has been reported that as many as 4.3% of the population has some form of these experiences. However, the ways in which the phenomenon of synesthesia has been perceived throughout history is extremely variable and can tell us a lot about the inherent nature of this phenomenon.

Brief History of Synesthesia

The book of Exodus in the Bible includes a passage in which the people who gathered with Moses on Mount Sinai *hear* visions and *see* the voice of God. Rather than being diagnosed with a medical condition or being called crazy, Moses was praised and believed to be a messenger sent from God because of the experience that the people on Mount Sinai were able to have through him.

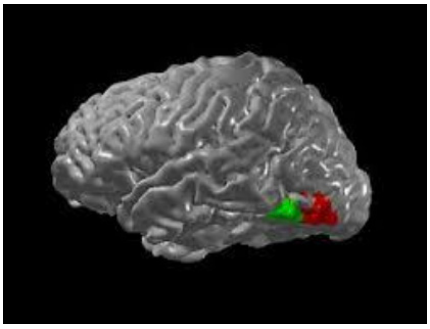
Hildegard Von Bingen, a Christian Visionary of the 11th century, was believed to receive messages from God through the five senses: sight, hearing, taste, smell, and touch. Throughout her recording of these visions, she extensively uses the term "veriditas" (translated as "greenness") which she uses to describe the lusciousness and fertility of the divine nature of God.

Around the time of classical philosophers such as Plato and Aristotle was when synesthesia moved away from its association with mystical or spiritual intervention from God and became solidified as an established sensory phenomenon. In his *On Sense and The Sensible*, Aristotle writes that the harmony of colors is equivalent to the harmony of sounds and went on to relate specific light and sound frequencies (Aristotle, 350 B.C).

By the 20th century, synesthesia begins to make more of an appearance in literature as a romantic ideal: Nabokov writes, "If I had some paints handy, I would mix burnt sienna and sepia for you as to match the color of a 'ch' sound..and you would appreciate my radiant 's' if I could pour into your cupped hands some of those luminous sapphires that I touched as a child." (Nabokov, 1935). In this case, it seems that the purpose of the author's choice to incorporate these synesthetic experiences was not to imply any type of mysticism of the narrator but simply to celebrate this experience as something beautiful to be appreciated.

Most recently, the experience of synesthesia in literature has been depicted as a symbol of health and balance. In her novel *A Mango Shaped Space*, Wendy Mass presents a young teenager named Mia who's synesthesia disappears when her beloved cat dies but returns once she has grieved and worked through the trauma of the experience (Brown 2010). It's clear that the perception of individuals who experience the phenomenon of cross activation of the senses has been extremely variable throughout the course of history. But as synesthesia became more normalized in our society, researchers became more and more invested in looking into the scientific pathways and brain mechanisms underlying the phenomenon, which

Figure 1 Visual Word Form area is located directly adjacent to V4 color area. Green = graphemes, Red= colors.



led to its medicalization.

Proposed Neurological Mechanisms of Synesthesia

Because the experience of synesthesia includes so many different subtypes and relies on individual experiences, a cohesive, working-theory of the neurological mechanisms of synesthesia has not yet been developed. However, Dr. V.S. Ramachandran, a leader in the field of synesthesia research, has come up with three main hypotheses as to the neurological underpinnings of synesthesia that have been widely recognized by the scientific community.

Local Cross-Activation Model

The first of these theories is the local cross-activation model (Ramachandran, 2005). This theory is largely based off of grapheme-color synesthesia, which is a form of synesthesia where individuals associate specific graphemes with specific colors. Dr. Ramachandran was interested in the fact that the "Visual Word Form Area" (the area of your brain that recognizes written graphemes) is anatomically adjacent to the "V4 color area" (the main region of your brain that recognizes colors) (Figure 1). Because this synesthesia is the most commonly reported subtype and because these brain regions also happen to be right next to each other, Dr. Ramachandran postulated that this form of synesthesia may be due to cross-activation of these two brain regions that are normally unconnected in non-synesthetic individuals. This theory built off of previous studies about "phantom-limb sensation", the experience in which an individual is still able to feel sensation and pain in a limb that has previously been amputated. These studies demonstrated that phantom-limb sensation derives from a cortical reorganization of brain connections and this model uses this same explanation of cross-activation in order to explain the sensory experiences of synesthesia. This theory also takes into account the fact that as brains develop, connections are cut or "pruned" over time. This makes sense with the cross-activation model because synesthesia is much more common amongst young children and decreases over time. This theory also hypothesizes that the cross-activation of brain areas involved in synesthesia is due to a failure of pruning of these connections over the course of development.

Disinhibited Feedback Model

The next theory of synesthesia that Dr. Ramachandran proposes is the "long-range, disinhibited feedback model". This model proposes that there may be a specific "sensory nexus" within the brain that is typically inhibiting connections between various senses in non-synesthetic individuals. This model hypothesizes that in synesthetes, people with synesthesia, this sensory nexus might be dis-inhibited (meaning connections between brain-regions would be enhanced!) The specific region of the brain that Dr. Ramachandran proposes might be this sensory nexus is called the "temporo-parietal-occipital junction" (figure 2). One piece of evidence for this theory is the fact that non-synesthetic individuals under the influence of psychedelics often report having synesthesia-like experiences. This suggests a sensory nexus by indicating that a specific brain area could be involved in all types of synesthesia. Another piece of evidence for the long-range disinhibited feedback model comes from the case study of a patient who developed a type of blindness at age 40 due to a condition called retinitis pigmentosa (Armel, 1999). While the patient was non-synesthetic before the onset of the disease, after 2 years of blindness he reported that tactile stimuli invoked the experience of

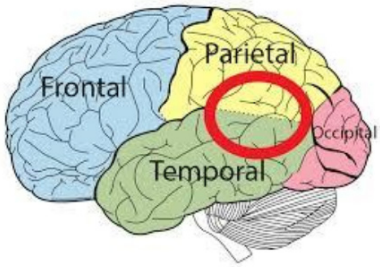
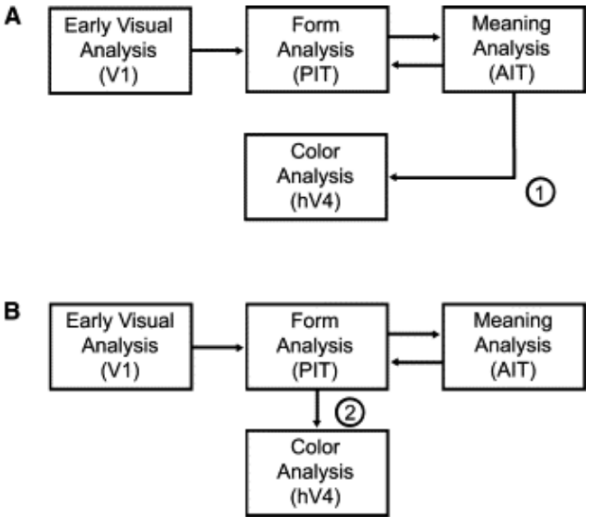


Figure 2 The temporo-parietal-occipital junction is proposed to be a "sensory nexus" that inhibits connections between senses in non-synesthetic individuals. (Image: TheBrainWashBlog)

Figure 3 Re-entrant processing model. Not only does the form of a word influence its color, but the meaning of word can also influence its color in synesthetic individials . (Smilek, 2002)



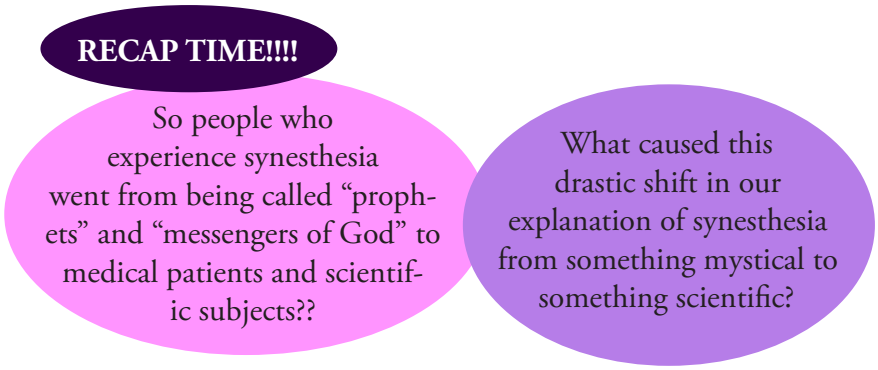
seeing visual movement. What's more is that these synesthetic experiences were enhanced if he placed his hand directly in front of his face which once again indicates that some type of multisensory structure could be involved in the neural mechanism underlying synesthesia.

Re-Entrant Model

The third hypothesis as to the neural mechanisms of synesthesia is somewhat of a combination of the local cross-activation model and the long-range disinhibited feedback model (Smilek, 2002). This model is referred to as the "re-entrant" model and suggests that sensory information transmitted in grapheme-color synesthesia flows not only from the visual word form area to the color area but also from the color area back to the visual word form area. This hypothesis is largely based on the fact that the meaning of the word can often affect its color for synesthetes but also that the shape of a word can have influence on its color.

While each of the proposed theories as to the neurological mechanisms underlying synesthesia seems to make sense for various subtypes, there is not one unifying theory that explains all facets of synesthesia. Because each of the senses are processed by different areas of the brain, it is quite possible that different brain mechanisms are responsible for different subtypes of synesthesia. Another piece of evidence for the idea that different brain mechanisms might be responsible for different facets of synesthesia is the fact that the subjective experience of this phenomenon differs even within the same type of synesthesia. For example, in grapheme- color synesthesia, there are thought to be two different sub-groups of synesthetes : projector and associators synesthetes (Dixon, 2004). Associator synesthetes experience their synesthesia as an association between a color and a grapheme. They don't see letters any differently than anyone else but just inherently know that the letter n is purple for example. Projector synesthetes, however, physically project the color of each letter onto the page and visual areas of the brain light up accordingly.

There are also many ways in which the outside environment can influence the experience of synesthesia. For example, a case study done in 2008 examined the synesthetic experiences of a grapheme-color synesthete (Dixon, 2008). They first had her record the colors that she associated with each letter of the alphabet and then had her do this same thing 21 days later in order to show that her perceptions were consistent over time, which is typically considered a criteria of synesthesia. They then compared these colors to a set of refrigerator magnets that she had as a child and found some remarkable similarities indicating that sensory experiences and memories that you have as a child can significantly effect your synesthesia throughout your life. Another study found that music-color synesthesia is mediated by emotion (Palmer, 2013). In this study, participants chose colors most similar to those seen when listening to specific classical pieces such as Bach, Mozart and Brahms. The general trend was that faster music in a major key produced colors that were brighter, lighter and yellower while slower, minor music produced colors that were desaturated, darker and bluer. This demonstrates that emotions can



significantly impact the experience of music-color synesthesia and suggests that other types of synesthesia may also be mediated by emotion.

Medicalization

The Medical Dictionary describes "medicalization" as the process by which life problems become articulated as health or mental health conditions. Around the 1950's, the notion of illness as a deviant behavior began to develop and with it came the categorization of illness in the form of medicalization. One reason for the medicalization of mental illness is that it is a way to give social membership to "deviant" individuals who would otherwise be alienated from society. Rogers and Pilgrim state, "To maintain our credibility in a social group, there has to be a consensus about what our senses detect around us. In most contexts, if a person sees or hears something that others do not, then their credibility, and therefore, their social group membership, is jeopardized." (Rodgers and Pilgrim, 2014) People bond with each other over the fact that they experience the world in the same way. When it is clear that someone experiences things in a different way, they are quickly isolated from society. However, the attempt to define synesthesia as a medical condition is an attempt to group synesthetes together and give them an explanation for their experiences. These scientific explanations tend to calm people down, whether or not they are proven to be the definitive cause of the experience.

The medicalization of mental disorders and of synesthesia in particular also results from our Western desire to rationalize and categorize the world. In *The Order of Things*, sociologist Michael Foucault coins the term "heterotopia", which he describes as those nuanced instances in which things have more than one meaning simultaneously and therefore cannot be explicitly defined or distilled into a singular explanation. He says, "Heterotopias are disturbing, probably because they secretly undermine language, because they make it impossible to name this and that, because they shatter or tangle common names, because they destroy 'syntax' in advance, and not only the syntax with which we construct sentences but also that less apparent syntax which causes words and things (next to and also opposite one another) to 'hold together'" (Foucault, 1966). Stated more simply, we theorize and categorize the world in order to avoid these heterotopias and get closer to a place where the world is completely understood, where there is no ambiguity. The fact that a small portion of the population seemed to be having synesthetic experiences without any type of explanation other than that it was the "will of God" must have become increasingly distressing. The medicalization of synesthesia makes sense according to Foucault's idea of categorization in order to avoid the ambiguous nature of these experiences and group these people together by providing a scientific explanation for what they were experiencing.

So what do you think about synesthetic experiences?? Act of God? Neurological diagnosis? Should time and money be put into researching the neurological mechanisms underlying this phenomenon?

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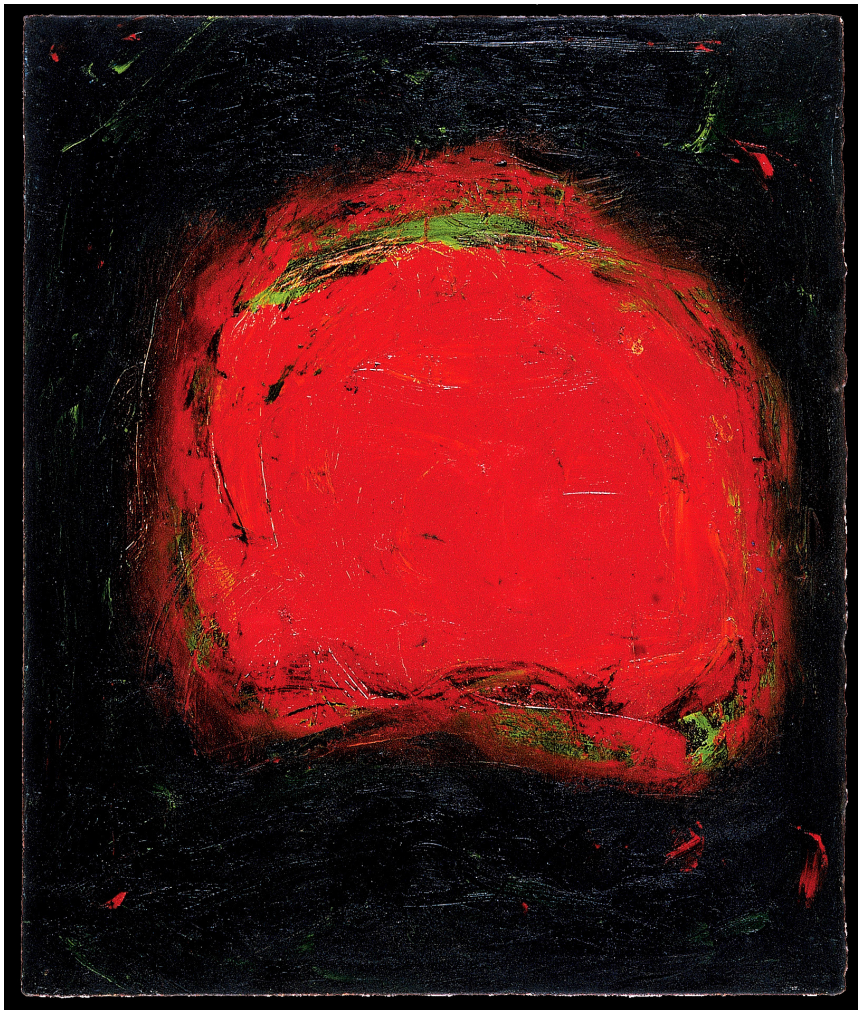


Vision by Carol Steen (An artist who experiences multiple forms of synesthesia); Oil on Paper; 15 x 12-3/4 inches; 1996

How to Read: A *Written* Guide

By **Ben Tauber**

"Dylan, like many other dyslexic children, went to great lengths to disguise his challenges. He employed his excellent oral vocabulary, sophisticated humor and emotional intelligence to keep us all distracted from the thing that privately shamed and haunted him: Dylan thought he was stupid." Kyle Redford, a teacher and a mother of a dyslexic son, retells her son's experience with dyslexia. "Too many educators still whisper the word, too few students get identified early, and many don't get identified at all... Dylan had to wait until fourth grade to learn to read." Lack of awareness around dyslexia is confounded by the many questions science still has about dyslexia.

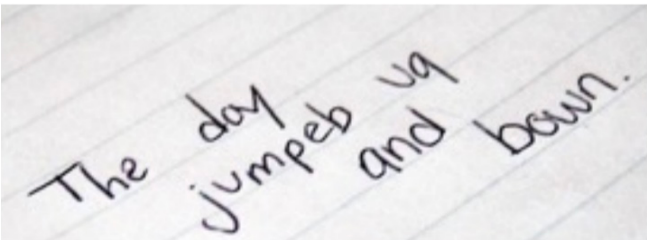
It is common for people to associate dyslexia with flipping letters such as "b" and "d" and poor spelling. Although not all people with dyslexia have the same experiences, some common behavioral characteristics are poor spelling, poor reading speed, and poor reading accuracy. Given the dynamics of a classroom these factors can compound and cause other issues. Students who struggle with reading and are required to do so in front of a group will become experts in evading this uncomfortable situation. Deirdre Griffin, a registered educational psychologist, writes "Some respond by 'acting out' or becoming upset about going to school or completing homework, others choose to give up – deciding it's better to not bother than to try and fail, while others opt to become the class clown." Aside from reading and writing, Griffin describes many other tasks that may be especially difficult for those with dyslexia. These include: poor planning, organization, and difficulty remembering dates including the current one. All of these factors can have deleterious effects on a student's self-esteem. To understand how differences in reading abilities arise, it is important to understand how humans' ability to read evolved in the first place.

The human brain has evolved to recognize faces because there is an evolutionary benefit to recognizing friend and foe quickly. Similarly, color vision was selected for as this gave us advantages such as determining the quality of food. These energetically expensive systems evolved due to the immense evolutionary pressure to be efficient at these behaviors. Many of our ancestors, stretching deep into the vertebrates, share these abilities. This demonstrates how far back in time these traits developed. The time scale for the evolution of these traits is on the order of hundreds of thousands of years. Our ability to read, on the other hand has only been around for approximately 5,400 years, as this is when the first written language formed. There are *color-vision* and *face recognition* regions to the brain because evolution has selected for it. However, there has not been time nor significant evolutionary pressure to create a *reading center* of the brain. Yet, as evidenced by your understanding of this text so far, many people have little difficulty reading. How can we accomplish such a feat if we did not evolve to have a reading center in our brains?

Stanislas Dehaene, a French neuroscientist working at *Institut national de la santé et de la recherche médicale* and a professor at the College of Paris, proposed the theory of neural recycling. "We can learn to read because we have a region which we inherit from evolution," Dehaene says; "[this region's] function is sufficiently close to reading and we can recycle [it] for this function." An area in the left posterior temporal lobe is highly tuned to respond to detailed images such as faces, objects, lines, and shapes. Dehaene proposes "We recycle areas that have to do with object recognition, shape recognition because our brain did not evolve for reading." This area of the brain has been termed the visual word form area. Multiple studies give strong evidence that this area is the site of grapheme interpretation and was recycled from other responsibilities. A

study compared the activity of the visual word form area in Israeli and American participants. When the known language was shown to the participants, functional MRI showed increased activity. However, when Hebrew was shown to the American participants and vice versa no increase in activity was noted. This indicates that the visual word form area is especially tuned to respond to letters we are familiar with. Evidence that the visual word form area evolved for purposes other than reading comes from an interesting observation. When first learning to write, children will often write their letters in a mirrored fashion, as depicted in Figure 1. It is unlikely that children have seen mirrored letters or that anyone is teaching children to write mirrored letters. Dehaene proposes it is likely that mirrored writing is a remnant from the visual word form area's previous responsibility as a face and object recognition center. When you see a picture and the mirror image of that picture, your eyes receive completely different sets of data. However, your brain is able to determine that the content is the same. This phenomenon is known as symmetry generalization and is very useful for objects and faces. However, letters require more specificity so this generalization must be unlearned, demonstrating neural recycling. Given the evidence for neural recycling and brain imaging, the visual word form area has been shown to be key in grapheme analysis. Grapheme analysis is one large component to the comprehension of the written word however; a word must be represented phonologically in the brain as well. This phonological representation occurs in Wernicke's area.

Figure 1 It is common for all children to write letters backwards. This may be evidence of neural recycling and not necessarily dyslexia. Image Courtesy of understood.org.



In 1993 Monica Strauss Hough, a researcher at East Carolina University, detailed the experience of Patient R.C.

"R.C. was a sixty six-year-old female who suffered to left hemisphere strokes verified by CT scan and neurological examination. After the first stroke, the CT revealed a lesion involving the posterior portion of the first temporal gyrus."

R.C. had her stroke in Wernicke's area resulting in death of the brain tissue and loss of function of that brain region. Her deficits included many phonological abnormalities including: inability to complete animal naming, inability to read, and poor auditory comprehension. This and earlier case studies lead researchers to hypothesis that Wernicke's area is heavily involved with phonological processing. In August of 2017, Kamel El Salek et al. used functional magnetic resonance imaging to look at participants' brains when completing reading tasks. Their aim was to more accurately and consistently identify Wernicke's area for brain mapping prior to brain surgery. El Salek writes "As a reading comprehension task, [incomplete sentences for which participants had to fill in a blank] can activate areas in the posterior temporal cortex that pertain to language processing." This technique allows for the highly precise identification of a brain structure needed for surgery. The authors reported that this specific type of reading test more precisely and consistently activated Wernicke's area as compared to word generation from a single letter prompt or word generation from a category prompt. Salek proposes the success of this test, as compared to the other tests, is due to participants simultaneously reading and semantically representing phonemes. Semantic representation of phonemes or phonological representation is the ability to cognitive relate the sound combinations that comprise a word. This experiment provides further evidence for the phonological importance of Wernicke's area.

Given the need for proper phonological representation in reading it was previously thought that this was the area in which dyslexic people struggled. French cognitive scientist Frank Ramus describes his work with this theory: " [we] initiated a series of ex-

periments tapping the phonological deficit in dyslexia and, against our expectations, none of them was consistent with the hypothesis of degraded representations. It also appeared that to us that the published literature was not as supportive as it seemed." Ramus and others proposed a new theory for dyslexia. Instead of an issue with the representation of phonemes, they proposed dyslexia is caused by an inefficiency with accessing these phonological representations. Although seemingly a subtle difference between the representation of phonemes its self and the access of the representation of phonemes it implies a completely different anatomical structure. Boets et al. (2013) published important findings in support of this theory. Boets showed pseudo-words to neuro-typical and dyslexic participants during MRI testing. Phonologic similarities of letters in pseudo-words and the degree of activation for specific brain areas was analyzed. To the surprise of the researchers, no difference in phonological representation was observed between dyslexic and neuro-typical participants. This became a large detractor of the prevailing theory that dyslexia is due to poor phonological representation. While studies have shown that phonological representation is not a source of dyslexia, poor access theory has received more support. Further support for the poor access theory, known as the connectivity theory of dyslexia, came with Boets' next experiment. As part of this study Boets et al. conducted functional connectivity analysis. This group looked at the relative residual signal intensity across 13 anatomical structures active during reading tests. They found that dyslexic participants had weaker connectivity in the area of Wernicke's area. Further evidence for the connectivity theory of dyslexia came with structural analysis of the collection of nerve fibers stretching from the visual word form area and Wernicke's area onto the frontal cortex in dyslexic populations. This tract of fibers is called the arcuate fasciculus. Jason Yeatman and his colleagues demonstrated that the arcuate fasiculus has structural differences in dyslexic people that contribute to inefficiency. This inefficiency is thought to be the base for the connectivity issue that causes poor access to phonological representation in dyslexic brains. Fortunately, the brain is highly plastic which allows it to be taught and grow. This means that although people with dyslexia will always have certain difficulties with reading and writing, it is possible for them to practice and improve these skills with proper education.

In our educational system there are two primary methodologies: the Whole Word approach and a phonics based approach. As the name would imply the Whole Word approach to reading education relies on gaining meaning from the entire word. This is in contrast to the phonics approach which breaks up a word into parts to ascertain its meaning.

The phonics based system, sometimes referred to as the sub-lexical approach, emphases decoding of words. Decoding involves breaking a word up into individual sounds. The word "food" would be broken down to the "f" sound, double "oo" sound, and "d" sound. The smallest part of a word that makes a single sound is referred to as a grapheme and the sound is a phoneme. Students can either be taught the connections between phonemes and graphemes explicitly or embedded in text. Explicit education often involves flash cards or other memory aid devices to help students' learning. Embedded instruction has students read as a group and as exam-

"Dislexia," licensed by CC0.

ples of complex phoneme-grapheme pairings present themselves in the text the teacher discusses them. A method that uses a combination of these two variations is the Orton-Gilligham method. Dr. Samuel Orton and others invented Orton-Gilligham or OG in the 1920s. In addition to a large phonics component OG relies heavily on multi-sensory education. In addition to seeing and hearing the phoneme, students would write out phonemes in sand, shaving cream, or on carpet remnants. Students may take shots with a foam ball on an indoor basketball hoop while reciting grapheme-phoneme combinations. This type of education is best practice for those with learning differences (LD) such as dyslexia or attention difficulties.

The Whole Word approach relies on the assumption that children acquire reading skills at the word level, rather than from individual letters. David Ingram, a researcher at Arizona State University, wrote, "First, children acquire words, not individual consonants and vowels, and show little awareness of segments...children are word-oriented, not segment-oriented." These assumptions stem from a philosophical theory that a whole is more than the sum of its parts. In the classroom this approach includes sight memorization techniques, reading aloud in a group, and prioritizing finding texts that interest the student. Especially in English language education, where a large percentage of words cannot be decoded using phonics given the lack of phonetic spelling, sight word memorization becomes necessary.

Although there is overlap between the two methodologies, the emphasis is different. Phonics relies on decoding of words where as the Whole Word approach relies on gaining meaning from a word as a whole. The Whole Word approach often supplements phonics which has become the predominate method of education in The United States of America. There is support in the literature for the benefits of phonics over the Whole Word reading method. Melissa Schmidgall, a researcher at The Ohio State University, and her team conducted a comparative analysis of several Whole Word reading protocols and a phonics based protocol. They found that there was no difference in efficiency or efficacy between Whole Word reading methods. They students cumulative word-reading performance was better when phonics instruction was used. It is important to note that this study was completed on neuro-typical students.

Just as brain structure affects learning, learning changes the structure of the brain. Michel Thiebaut de Schotten, a researcher at King's College, conducted a study that looked at the microstructure of illiterate people, literate people, and people who had learned to read as adults (ex-illiterate). The results of the study demonstrated structural difference between illiterate and literate people. The micro structural differences this team noted may be due to the diameter of the neuron's axon, the density of the axons in the arcuate fascicles, or the quality of the myelination or insulating covering. The compelling component of the study was that the results from ex-illiterate and literate participants were indistinguishable. This Demonstrates that learning changes the way the brain is structured at the cellular level. In 2014 Alicia Che, a researcher at the University of Connecticut, conducted a genetics study that looked these micro-structural components. The gene DCDC2 has been linked to dyslexia and is believed to causes differences in receptor density and cortical development. Specifically Che found that neurons in a mouse model with this dyslexia genetic variation had reduced temporal precision in action potentials firing. As the timing of action potentials is key to neuronal communication, such a finding may further support the connectivity theory of dyslexia. Several other genes have been linked to dyslexia as well. The relation between these genes, epigenetics, and environmental factors in the cause of dyslexia is still under investigation.

Reading is a highly complicated behavior that requires the seamless integration of many cognitive functions. Using advanced brain imaging, scientists have started to unravel the mystery of how humans who did not evolve to read gained such a remarkable function. Through this research a neural explanation for dyslexia has started to come to light. Having this neural base bolsters the idea that dyslexic people are not merely stupid or lazy, but in fact have cognitive differences. Changes in ped-

agogy have produced great results not only for students with learning difference such as dyslexia but for students in general. Redford explains this progress. "Dylan came of age during an educational renaissance. Over the last two decades, educators have learned that there are effective interventions for learning problems like dyslexia that used to merely carry scary names. We have also learned that dyslexia can be identified early, and there are effective evidence-based reading methods to ensure that children with dyslexia CAN learn to read." Despite the difficulties dyslexia causes, many people with dyslexia learn to successfully navigate their difference and achieve in their own ways.

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