Spatial Navigation and the Memory Network

The Drugs and Mechanisms of General Anesthesia

Resolving the Line Between Genius and Insanity
The Mind and Brain Society (MBS) was founded in the fall of 2008 in concert with BU’s new Undergraduate Program in Neuroscience. The group aims to create a network for undergraduate students who wish to take an active role in current issues and research. MBS serves as a hub for not only Neuroscience majors, but all students interested in Psychology, Biology, Philosophy, Computer Science, etc. Our goal is to support an eager multidisciplinary undergraduate community with the conversations and resources fundamental to Neuroscience today.

Throughout the academic year, MBS hosts events spotlighting many different facets of Neuroscience. We hold discussion sessions during which we informally discuss a topic of interest over coffee; previous topics include “The Neuroscience of Religion” and “NeuroEthics.” The group also hosts research presentations by BU professors and screenings of thought-provoking films containing neuroscience motifs.
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“When we speak of nature it is wrong to forget that we are ourselves a part of nature.” -Henri Matisse

Students of neuroscience decide to join the field for a myriad of reasons- not the least of which includes a sentiment of vanity. “My brain is amazing and I want to know how it works.” At the beginning, many walk around fascinated, suddenly more in tune with how we know and experience what we do- spouting off “Did you know’s…” to unsuspecting friends and family. As study continues, we learn of tinier molecules, more complex proteins, and the most finely tuned processes. The scale becomes smaller and several steps removed from our consciousness. It is easy to consider these inner-workings as only controlled experiments under careful watch in a lab, but if we can keep in mind that such precise orchestrations occur naturally within us, the whole thing becomes even more astounding.

Welcome to the second year of The Nerve’s infancy. Once again, we are thrilled to present an issue with breadth across the field of neuroscience while spotlighting a few of our favorite topics from the last six months. We’d like to extend our deepest thanks to The Nerve staff and writers and Boston University faculty for pushing us into our second volume.

As you read each article, be a little self-centered. Consider the way your wiring affects your daily life. Consider the amount of electricity running through you. Consider each molecule taking its course through your brain, moving in such synchrony to make your very reading this possible! It’s a lot to think about, but the exquisitely intricate nature of the system is what makes it so extraordinary.

This and other issues of The Nerve would not have been possible without the generous help of Paul Lipton, Howard Eichenbaum, Lindsey Clarkson, Denise Parisi, Zachary Bos, and Jarret Frank.

- Grigori Guitchounts and Kimberly LeVine
Editors-In-Chief
Pain management is an important branch of medicine, especially in fields that consider long-term pain-related diseases such as cancer or arthritis. People experience pain as a result of nerve impulses traveling through the spinal cord to the central nervous system in response to noxious stimuli. As the pain signal travels to the brain, it can be modulated in a number of different ways by intervening nerve fibers that cause an inhibitory effect, thus reducing pain. This interference can be experienced in the common instinct rub a wound: our body’s touch receptors connect to pain signal fibers in the upward pain pathway to the brain and slow the noxious signal’s travel by inducing various neuronal interactions. Other ways to modulate pain incorporate the use of analgesic drugs, most commonly opiates, such as morphine for acute pain, or lighter analgesics such as acetaminophen (Tylenol) and salicylic acid (Aspirin). Both act within the brain itself through molecular interactions to modulate pain in a top down fashion through neurotransmitter systems.

Neurotransmitters are a crucial piece of the puzzle in the neuroscience underlying pain. Current research is elucidating the mechanisms of anandamide, a mysterious neurotransmitter that acts on the much-researched cannabinoid CB1 and CB2 receptor as well as the vaniloid receptors. We do not know much about anandamide, but its levels spike in response to pain or inflammation and these receptors bind the neurotransmitter, creating an analgesic affect. In a recent Nature Neuroscience study, researchers elucidated a mechanism of anandamide in the peripheral nervous system (PNS) and its action on cannabinoid receptors. The team created an inhibitor of fatty acid amide hydrolase (FAAH), a compound that degrades anandamide under normal circumstances. The inhibitor, dubbed URB937, was designed to remain only in the peripheral nervous system and suppress FAAH activity, thus increasing anandamide levels in the periphery. As a result, behavioral responses to peripheral nerve pain and inflammation were reduced and neuronal activation in pain processing was suppressed in rodent models in response to increased anandamide binding at CB1 receptors.

Experiments subjected rodent models to neuropathic and inflammatory pain to test the efficacy of URB937 as an analgesic. For neuropathic pain, sciatic nerve injury was induced and the compound was immediately administered. Results showed decreased sensitivity to pain and daily administration of the drug showed consistent results. Chemically induced inflammatory swelling in the rodents was combated with URB937 with equally effective results. Spinal pain perception was also investigated by measuring levels of the protein Fos, whose levels are elevated in response to neuronal activity in the spinal cord and thus in response to pain. URB937 was able to attenuate Fos levels in regions of the neck and dorsal horn of the spinal cord, implying that the traveling pain signal was suppressed before it was able to reach the brain itself.

The suggestion of this research is that increased anandamide levels in the periphery and CB1 receptors can effectively attenuate pain signals to the CNS. Since URB937 was designed to remain exclusively outside the CNS, this research establishes the existence of a previously unexplored connection between the peripheral endocannabinoid system and pain perception. Given their results, the researchers hypothesize that peripheral anandamide acts as a diffuse paracrine signal to modulate pain stimuli as they arrive in damaged tissues. This implies that pain stimulates anandamide production and CB1 receptors are present in abundance in peripheral nerve endings and throughout tissues and organs. These results open new doors to pain therapy that can
ADHD is a disorder known to almost everyone; it has established a prevalence in our school systems and the media. The Center for Disease Control highlights that 3-7 percent of school-aged children suffer from ADHD. In the United Kingdom, where this particular study was done, it is reported that around one in 50 children is affected by the disorder. But even with such high prevalence and awareness about ADHD, the causes of the disease have escaped the scientific and medical community. Recent research from Cardiff University offers potential ground and stigma breaking information, shedding some light on this elusive disorder.

Children diagnosed with ADHD are restless, impulsive and distractible, and often experience dramatic learning difficulties. The causes of ADHD are largely unknown. The general population, as well as a portion of the scientific community, has believed that it is likely attributed to poor parenting and a sugar rich diet, but this study presents the first evidence that ADHD is instead a genetic neurodevelopmental disorder.

The study conducted at Cardiff University analyzed the genomes of 366 children with ADHD and 1047 controls. These children with ADHD were aged 5-17 years who were diagnosed with ADHD or hyperkinetic disorder, but not schizophrenia or autism. The researchers genotyped single nucleotide polymorphisms (SNP:DNA sequence variation in which a single nucleotide differs from the appropriate base pairing) for both groups, looking for and comparing copy number variants (CNVs) in their genomes.

CNVs occur when one of the two copies of a gene is missing or when there are too many copies. Their findings showed that 57 large, rare CNVs were identified in the ADHD population, in contrast to the 78 CNVs that were found in the much larger control population. This data shows that these rare CNVs were almost twice as likely to occur in children with ADHD (14%) compared to controls (7%), including a rate of CNVs that was particularly high in ADHD subjects with intellectual disability.

This data is the first of its kind to suggest a genetic basis to this disorder. The researchers also highlight that the rare CNVs identified occur in genomes in the brain that are known to correlate with susceptibility to ADHD.

— Frank DeVita


**Rare CNVs in the ADHD Genome**

exploit the cannabinoid system to effectively attenuate pain without the highly undesirable side effects produced by classical opioid pain therapy.
to autism and schizophrenia. One of these particular regions was identified on chromosome 16, which has been found crucial in the development of the brain and is affected in various major psychiatric and developmental disorders.

The suggestion supported by this research is that ADHD is not based on social elements or poor parenting, but instead a direct genetic fault. This CNV data paired with the fact that ADHD is known to be highly heritable, points the scientific and therapeutic approach to this condition in a whole new direction.

— Jennifer Richardson


Neuroprotection by Caffeine

For any student of Neuroscience, the neurotransmitter dopamine immediately brings to mind the pathways of "reward signaling." However, this neurotransmitter also plays a critical role in regulating movement. Parkinson's disease (PD), which injures dopaminergic neurons, unleashes a devastating effect on body control. In PD, the damaged nerve cells fire rapidly, losing all control over dopamine and causing involuntary muscle movements or tremors. Other effects of the disease include rigidity, slowness, or loss of coordination. A study conducted this year by Massachusetts General Hospital and Harvard Medical School revealed that caffeine and its metabolites, the parts left when it's broken down, may provide some neuroprotective properties that resist the damaging effects of Parkinson's disease.

Epidemiological studies have demonstrated a link between caffeine consumption and PD. In this particular study, the MPTP model of PD focuses on the effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in causing the devastating disease. The effects of caffeine on countering the actions of MPTP revealed insight into its effect against PD as a whole. Metabolites of caffeine as they appear in the human body when it is being broken down were administered to rodents so that the effects could be as similar to humans as possible. Over 80% of orally administered caffeine metabolizes to paraxanthine (1,7-dimethylxanthine), and about 16% is converted to theobromine (3,7-dimethylxanthine) and theophylline (1,3-dimethylxanthine).

In the first segment of the experiment mice were given doses of saline or caffeine 10 minutes, 30 minutes, 1 hour, 2 hours, or 6 hours before doses MPTP or saline was administered. The saline administration provided a control to compare the effects of the actual chemical. Then the same dose of caffeine or saline was administered 10 minutes, 30 minutes, 1 hour, 2 hours, or 6 hours after the first. The second segment of the experiment involved testing the action of the metabolites. Caffeine, Theophylline, Paraxanthine, or saline was administered 10 minutes before MPTP or saline was administered.

Dopamine levels were measured by extracting the striatum from the right cerebral hemisphere. Caffeine was measured from the trunk blood of mice. Serum and supernatant of brain homogenates were measured for caffeine and its three metabolites. The results showed that caffeine was not only effective in attenuating dopamine depletion when co-administered with the toxin (10 minutes before MPTP), but also 30 minutes before administration. However, when caffeine was administered earlier than 6 hours before MPTP it no longer had a significant effect. When caffeine was administered 10 minutes, 30 minutes, or an hour after, but not 4, 8, or 24 hours after MPTP, striatal dopamine depletion was reduced significantly.

Similarly, in the second segment of the experiment, Caffeine metabolites theophylline and paraxanthine pre-treatments attenuated MPTP-induced dopamine depletion in mice. Caffeine not only has a neuroprotective effect against this model for PD, but acts in this role in a range of 2 hours before and after MPTP administration. However, there are differences in how caffeine is metabolized in humans versus rodents. The half life of caffeine is around 2.5 to 4.5 hours in humans, but about an hour in rodents. The longer half-life of caffeine in humans suggests its neuroprotective effects may be greater than those in rats. Caffeine seems to hold great promise in preventing the damaging effects of Parkinson's disease—news that should make any coffee or soda addicted readers happy.

— Devyn Buckley

ORIGINAL PAPER: Xu K et al. Neuroprotection by Caffeine: time course and role of its metabolites on in the MPTP model of Parkinson's Disease. Neuroscience. 167:2, 475-481. 2010
Every day, we find ourselves making countless decisions, some of which are nearly reflexive, and others that require further reasoning and perceptive abilities. This decision-making process also includes our introspective ability—the capability to reflect on a particular decision and determine whether or not it was a correct one, a capacity that varies across individuals. In a recent study published in Science Fleming, et al. display evidence of a possible neuroanatomical basis of this introspective ability.

In the study, introspective or “metacognitive” sensitivity refers to “the ability to discriminate correct from incorrect perceptual decisions.” Its accuracy, or lack thereof, will later direct an individual’s behavior and action. It was hypothesized that individual differences in these abilities would be reflected in anatomy of brain regions responsible for this function. In order to test this hypothesis, the variability in metacognitive sensitivity between individuals was objectively quantified and related to interindividual differences in brain structure, which were measured with magnetic resonance imaging (MRI).

The study consisted of 32 healthy human subjects, who participated in a two-part, forced-choice task. The first part of the task, a series of visual judgments, was meant to provide a measure of objective performance, and the difficulty of said task was varied on a per-participant basis to keep performance at a constant level (71%) near sensory threshold. The second part of the task required that the participants provide ratings of confidence in their decisions after each trial, rated on a one-to-six scale, with participants encouraged to use the whole scale where one = low relative self confidence and six = high relative self confidence. These ratings were used to determine metacognitive ability at an individual level through the construction of a type II receiver operating characteristic (ROC) curve.
Astrocytes Regulate Breathing

Among the key findings from the study is that astrocytes in the respiratory chemoreceptor regions of the brainstem help regulate breathing by acting as pH sensors. This was achieved by testing whether or not astrocytes in the respiratory chemoreceptor regions of the brainstem help regulate breathing by acting as pH sensors.

To observe the astrocytes in question, the scientists engineered rats to express the Case 12 gene, a Ca²⁺ indicator. The gene was expressed in the chemoreceptive region of the medulla (VS) in the rats tested. When the pH was decreased by 0.2 units in the VS, Ca²⁺ concentration increased instantly in the rats. Astrocytes adjacent to the VS

The area between the major diagonal and an individual’s ROC curve is a measure of the ability to link confidence to perceptual performance (Aroc).

Two distinct measures were then used to find whether the variability shown in introspective judgments could be predicted by variability in brain structure. First, gray-matter volume was measured from T1-weighted anatomical images, and second, the fractional anisotropy (FA) of white matter was measured from diffusion tensor images (DTI). It was found that an individual’s metacognitive ability (Aroc) was significantly correlated with gray-matter volume in the right anterior PFC. Furthermore, gray-matter volume in this region did not correlate with task performance. It was also found that FA (a measure of white-matter integrity) in the genu of the corpus callosum was positively dependent on Aroc.

These regions might contribute to metacognition in that anterior subdivisions of the PFC have been implicated on high-level control of cognition and are well placed to integrate supramodal perceptual information with decision output, a process thought to be key for introspective ability. Additionally, patients with lesions to the anterior PFS show deficits in subjective reports as compared to controls, which is consistent with the theory. These findings, though they provide no direct causal relation between these neuroanatomical areas and metacognitive sensitivity, do however provide an initial window to the biological basis of the ability to link objective performance and subjective confidence.

—Lauren Joseph

in the chemoreceptive retrotrapezoid nucleus (RTN) showed long, continuous Ca²⁺ responses. These acidification-induced Ca²⁺ excitatory responses were also demonstrated in in vitro preparations of brainstem slices which showed several pH-sensitive astrocytes near the blood vessels in the VS.

By inhibiting RTN neurons with tetrodotoxin (to block sodium channels) and muscimol (to block GABA receptors) the researchers showed that the Ca²⁺ excitation of the astrocytes was not merely a response to excitation of nearby neurons in the RTN. While the RTN neurons were being treated with tetrodotoxin and muscimol, Ca²⁺ responses in reaction to acidification still occurred in RTN astrocytes. Additionally, activation of the RTN neurons beside them did not induce Ca²⁺ elevation in RTN astrocytes.

As it turns out, this Ca²⁺ excitation in the VS is modulated by adenosine triphosphate (ATP). A 0.2 unit decrease in pH causes a continuous release of ATP from the VS. Testing with ATP-hydrolyzing enzyme apyrase eliminated pH-evoked Ca²⁺ excitation, and the addition ATP receptor antagonists markedly decreased such excitation. Three different antagonists were tested, that reduced the Ca²⁺ signals by 80%, 82% and 83%. These findings suggest that ion-gated ATP receptors might play a role in this mechanism.

The excitation is spread among the chemoreceptive astrocytes via gap junctions, but predominantly through release of ATP by exocytosis. Blocking astrocyte gap junctions with concentrated carbenoxolone reduced acidification-induced Ca²⁺ excitation by about 43%, but inhibiting ATP production and release essentially eliminates excitation. In addition, RTS neurons’ resting potentials were not affected by decreased pH, but their pH-induced depolarizations decreased markedly when treated with a apyrase, and also when treated with an ATP receptor antagonist. The neurons’ pH sensitivity appears to be the result of prior ATP release.

This study also employed optogenetics to investigate the chemoreceptive VS astrocytes. A mutant version of light-sensitive channelrhodopsin-2 was combined with a far red-shifted fluorescent protein (AVV-sGFAP-ChR2(H134R)-Katushka1.3) and expressed in rats. Cultures and brainstem slices with the incorporated AVV-sGFAP-ChR2(H134R)-Katushka1.3 showed increases in astrocyte Ca²⁺ concentration when exposed to 470 nm light. Astrocytes with the optogenetic construct incorporated showed immediate ATP release and prolonged depolarization of labeled RTN neurons was observed upon activation.

Anesthetized, artificially ventilated rats with their vagus nerve fibers surgically divided and transduced with AVV-sGFAP-ChR2(H134R)-Katushka1.3 on one side of the ventral brainstems were tested to observe the respiratory effects of pH-induced Ca²⁺ excitation. When the VS was exposed to light of the proper wavelength, respiratory activity was generated from apnea in the rats. Recordings from the phrenic nerve demonstrated increased amplitude when rats breathing normally were optogenetically stimulated. An ATP receptor antagonist inhibited the response of the respiratory system to optogenetic stimulation of the astrocytes. The side of the VS that was not transduced did not respond to illumination.

This study serves to highlight the role of astrocytes in chemoreception that was once thought to be reserved for particular neurons in the medulla and pons. Their anatomical location - in close proximity to arteries going into the brain - allows them to keep track of what enters the brain. Clearly, they are vital components in maintaining homeostasis.

— Natalie Banacos

Sports-related Concussions and the NFL

by John Batoha and Evan Stein
By November of 2009, the National Football League season was winding down, and with a playoff berth and a shot at the Super Bowl on the line, each new contest meant more than the last. “These are the games you don’t get back,” observed Pittsburgh Steelers wide receiver Hines Ward.

With only four weeks left in the season, teams like the Arizona Cardinals and Ward’s own Pittsburgh Steelers were prepared to put anything on the line for a victory – except their starting quarterbacks. Ben Roethlisberger of the Steelers and Kurt Warner of the Cardinals stayed on the bench that Sunday, both looking on as their teams lost heartbreaking games. Each looked completely healthy; Roethlisberger had even practiced the Thursday before. But both had sustained in-game concussions a week earlier, and in the wake of recent reports about the dangers of repetitive head trauma, elected not to play.

Unlike more apparent injuries like a torn ligament or broken bone, concussions can be hard to define, let alone diagnose. But as more information about the dangers of concussions – and their long-term implications – emerges, more people are paying attention to this particularly insidious injury.

Sports-related concussion (SRC) is a common injury in a wide variety of contact sports. It has been commonly defined as any alteration in mental status experienced as a result of head-jarring trauma that may or may not include a loss of consciousness (LOC)⁹.

A concussion, also known as a mild traumatic brain injury (MTBI), can result from either a direct blow to the face or head, or as the indirect result of an impulsive force transmitted to the head⁶, where abrupt acceleration or deceleration impacts the brain against the skull⁷.

Long-term neuropsychological impairments associated with SRC include deficits in memory, attention, and concentration, as well as a decrease in reaction time and cognitive processing speed⁶, ⁷. Even repetitive subconcussive hits, or minor trauma-induced injuries, that accumulate over time may eventually lead to similar cognitive impairments⁵.

A particularly concerning aspect of SRC is that athletes who sustain one concussion are four to six times more likely to suffer a second one than athletes without a history of concussions⁴, ¹⁰. Guskiewicz et al also found that subsequent concussions have relatively lower injury thresholds, thus making the athlete more susceptible to a second injury⁴. This disparity seems to disqualify the notion that the increased likelihood of a second concussion is due entirely to a genetic predisposition to the injury.

Long-term cumulative effects of SRC have also been identified in De Beaumont et al.’s transcranial magnetic stimulation (TMS) study investigating motor cortex inhibition in concussed football players². Their study provides significant evidence that previously concussed athletes who sustain additional concussions exhibit long term motor system abnormalities². Their conclusion – that subsequent concussions exacerbate this dysfunction – provides further evidence that the adverse effects of SRC are cumulative.

But while repetitive concussions can cause cognitive function to slowly wither, the injury can be deadly in the short term too. Consider a situation common in high school football games. Time is expiring in the first half and a teenage standout is tackled hard. The hit sends him to the ground and though his head bounces off the turf, he shakes it off and gets up. At halftime, he mentions to a teammate that he feels lightheaded and dizzy, but does not tell his coach.

In the second half he seems fine, but after receiv-
ing several routine blows to the head, he collapses on the field. Four days later, he is pronounced brain dead at a local hospital. The autopsy shows subcortical ischemia, diffuse brain swelling, and a subdural hematoma.

This young athlete fell victim to a deadly condition called second-impact syndrome (SIS)\textsuperscript{3, 6}, a rare but serious condition that occurs when an athlete does not fully recover from a previously sustained concussion before receiving a second blow to the head. Real cases mirroring this vignette occur each year and until athletes and trainers alike gain a better understanding of the dangers and symptoms of SRC, these tragedies will continue.

The Center for Disease Control and Prevention (CDCP) has estimated that between 50,000 and 300,000 athletes in the United States sustain concussions within one athletic season\textsuperscript{1}. Even this striking number may grossly underestimate the true incidence of concussive events; the CDCP study only included athletes who experienced a loss of consciousness. Moreover, various studies concerning SRC reveal an alarmingly high rate of under-reporting of concussions by the athlete, attributable to a lack of education, awareness, and appreciation of a concussion as a serious medical condition.

Other reasons for the underreporting of concussions by the athlete include the feeling that the injury is too insignificant to report, external and internal pressure to continue playing, and simply the failure of the athlete or trainer to recognize the symptoms of SRC\textsuperscript{3, 6}.

Easily overlooked, subtle symptoms such as headache, dizziness and lightheadedness can all indicate SRC; other symptoms include poor judgement, photophobia, and difficulty concentrating. Further complicating the diagnostic process, these common indicators often seem insignificant to the athlete, and overlap with unrelated etiologies like dehydration, lack of sleep, overtraining and hypoglycemia. Moreover, the symptoms – already ambiguous enough – often have a delayed onset up to several days after the time of injury\textsuperscript{6}.

In the past, concussions were diagnosed only when an athlete experienced LOC or amnesia; however, studies have now provided significant evidence that LOC and amnesia alone are insufficient for assessing the severity of, and recovery from, a concussion. To address these concerns, experts have abandoned the concussion-grading system and return-to-play guidelines, leading to the rise of a two-fold classification system\textsuperscript{6}.

This new system classifies MTBI as simple or complex, based on how long the athlete’s symptoms persist. A simple concussion is diagnosed when an athlete recovers within 7 to 10 days. A complex concussion occurs when the athlete has prolonged and persistent cognitive deficits, sustained multiple concussions, or suffers from sequelae such as convulsions or an LOC lasting more than 1 minute\textsuperscript{6}. One inherent shortcoming of this classification system is that concussions cannot be properly diagnosed until the athlete fully recovers from all signs and symptoms. Delayed onset symptoms also render this classification system impractical in the acute setting\textsuperscript{6}.

But while the cognitive deficits following SRC have been discussed at length in recent years, the pathology that underlies these phenomena has remained an enigma. It seems intuitive, for scientists and athletes alike, that repetitive head trauma could damage the brain, but until recently, no one was quite sure how to prove it. A slew of recent studies, many focused on retired NFL players, have raised some disturbing questions about why these deficits arise, and just how drastic their implications can be. Though still incomplete, the studies are beginning to indicate that what arises from repetitive concussions is not merely a collection of cognitive deficits, but a unique, pervasive, and ultimately fatal pathology.

John Grimsley, a former linebacker for the Houston Oilers, shot himself in the chest while cleaning his gun in February of 2008. While authorities initially ruled the death an accident, Grimsley’s family and friends were shocked that he could be so careless. They emphasized his skill with guns, and insisted that he had used them countless times without incident. They recounted observing changes in Grimsley, most notably a decline in his mental health, for some time. They also reported that the standout linebacker’s personality had shifted drastically in his last years. Long known as a passive, even-keeled man, he had become emotionally unstable, and sometimes even violent.

Disturbingly, several parallel cases have emerged in recent years which, taken together, begin to build a coherent set of symptoms in retired NFL players. Justin Strzelczyk, a former Pittsburgh Steeler, led police on a high-speed chase for over 40 miles in 2004 before eventually crashing his car into a tanker truck. He had reported repeated hallucinations prior to the incident.

Fellow Steeler Mike Webster died in 2002 at age 50 after bouts with depression, drug addiction, and
homelessness. Like Grimsley and Strzelczyk, he had sustained countless blows to the head over the course of his career. These representative tragedies are only a handful of the incidents that together reveal an extensive pattern of symptoms and deficits in retired NFL players. Their collective symptoms: dementia, memory loss, and emotional instability, had been reported before. Dementia Pugilistica, or “punch drunk” syndrome, and had already been observed in boxers.

As pathologists began examining the brains of the NFL players, they noticed clear abnormalities in their brain tissue similar to those observed in “punch drunk” fighters. Most notable were massive aggregations of tau protein, a common marker in several major neurological disorders, including Alzheimer’s disease (AD). Now, physicians refer to this premature buildup of tau, and the substantial behavioral abnormalities that accompany it, as Chronic Traumatic Encephalopathy, or CTE.

Both the symptoms and the histology of CTE manifest like a premature form of Alzheimer’s. Distinguishing between the two can be difficult; a formal diagnosis of either can be made only upon postmortem examination. But where Alzheimer’s involves a buildup of both tau protein and accompanying beta-amyloid plaques, the brains of CTE patients only contain tau.

Although the neurobiological markers of CTE have become clearer, physicians are still struggling to describe the exact mechanism of the neurodegeneration. Some have suggested that inflammation and oxidative stress brought on by the force of the impact may cause tau to aggregate. Others have pointed to studies suggesting that genetics may play a role in an athlete’s susceptibility to concussions, and consequently, in CTE. Apolipoprotein E (ApoE) may make people more susceptible to the ill effects of concussions, exacerbating the effect of each blow. But even with the precise biochemical processes unknown, the psychological effects of CTE, and its characteristic physical markers, are impossible to ignore.

Despite the high profile cases that have emerged, and the neurological evidence to corroborate it, not all athletes are buying it. “I could see some players or teammates questioning, like, “It’s just a concussion,”” wide receiver Hines Ward told the Boston Globe. “I’ve been out there dinged up; the following week, got right back out there. I’ve lied to a couple of doctors saying I’m straight, I feel good, when I know that I’m not really straight.”

Though the toughness and machismo of many athletes constitute perhaps the toughest hurdle in addressing CTE, it was largely the efforts of a former football player that helped bring the dangers of repetitive concussions to light. In the late 1990’s, Chris Nowinski was a sociology concentrator at Harvard College, and an exceptional defensive lineman on the football team. He recalls sustaining several concussions during his career there. After graduation, Nowinski began a stint with the World Wrestling Entertainment (WWE) circuit under the pseudonym Chris Harvard, a pretentious anti-hero who would often enter the ring reading a book.

He sustained several more concussions during his time with the WWE, finally suffering one from which he felt he never quite recovered. Experiencing headaches, memory problems, and bouts of emotional instability, he moved back to Boston, taking a desk job until his symptoms subsided and he could re-enter the ring. But the symptoms persisted and the concerned wrestler began doing some research. He discovered reports of dementia pugilistica, and wondered if the mental deterioration described in boxers could occur in other athletes. He enlisted the help of Robert Cantu, a neurosurgeon at the Boston University School of Medicine, and the two co-founded the Sports Legacy Institute to determine if other athletes were susceptible to the disease. With both their publicity and their funding building, the Boston group began to study the pathology and long-term neuropsychological effects of repetitive concussions.

What they have already found has been striking. Ann McKee, a Boston University neuropathologist, has discovered CTE in each brain of the four retired pros she’s examined. And these results, however remarkable, are no anomaly. A pathologist at the University of Pittsburgh, Bennett Omalu – the first to document neurodegeneration in an NFL player – has found evidence of CTE in eight of the nine NFL players he’s examined. As case studies continue to mount, the researchers began to find support even in the macho world of the NFL, where the striking data had begun to raise concerns among players. To date, over 150 athletes, including at least 40 NFL players, have agreed to donate their brains to Boston University for a postmortem examination to search for pathology. As the body of evidence that repetitive concussions can lead to CTE grows, the dangers of playing football at the professional level have become harder to refute, even for players.

But that doesn’t mean the NFL isn’t trying. Even as the heartbreaking stories of former athletes were
beginning to garner national attention, the NFL administration was doing everything in its power to downplay the dangers of concussions. When Omalu published his paper on CTE in 2005, the NFL demanded an immediate retraction, claiming that the study was inconclusive and misleading. They hired their own team of independent experts to evaluate the effects of repetitive concussions – a move described by some as reminiscent of the tobacco industry’s early attempts to downplay the role of cigarettes in lung cancer.

But amidst the building evidence, their contentious response found fewer sympathetic ears, and the NFL finally began to address the concerns about concussions. It disbanded its team of hired experts, agreeing instead to work with the Boston researchers to investigate CTE. Even more recently, league officials have begun to work to keep players better informed about the symptoms and effects of concussions. The New York Times reported in 2010 that teams would be required to hang an informational poster about concussions in their locker rooms. Baltimore Ravens lineman Matt Birk discussed the development with a Times reporter, “To put it out there in writing in the locker rooms, at least it’s publically acknowledging that ‘hey this is real’. There’s risks in everything you do and this one is real. You can’t sweep it under the rug anymore.” But even as the NFL began to address concerns, the most disturbing piece of information to date about CTE emerged:

Owen Thomas, the captain of the football team at the University of Pennsylvania, hanged himself in his apartment in April 2010. A postmortem examination revealed characteristic Tau aggregations in his brain, leading to the diagnosis of CTE – the first for a college player. Owen had never sustained a concussion11.

References
Genius or Insanity?
An Investigation of Creativity and Mental Illness

By Frank P. DeVita
Introduction

Oftentimes, creative individuals are plagued with various psychological afflictions ranging from depression and autism spectrum disorder to schizophrenia or bipolar disorder. In fact, these afflictions have beset people such as Salvador Dali, Pablo Picasso, Sylvia Plath, Earnest Hemmingway, Pyotr Tchaikovsky and many others. A combination of mental illness and creativity spans across many different media and its bearers personify the struggle that arises from straddling the line between genius and insanity. Yet it is this paradox that has produced some of history’s greatest innovations. Only now are we beginning to understand the underlying mechanisms behind what many may be defined as both a gift and a curse. In fact, there is a neurological and psychological link between creativity and mental illness that may begin to resolve the line between genius and insanity.

Creativity is defined by the Oxford English Dictionary as, "the use of the imagination or original ideas, especially in the production of an artistic work." Through humanity’s existence, creativity has been an important factor in the evolution of global culture through its manifestations in science, visual art, music, design, architecture, politics and war. It can be argued that these human innovations start with a latent spark of creativity that evolves into a brilliant flame - but where does this spark come from? Creative potential seems uniquely human as no other species can match the human imagination.

Defining and Investigating Creativity

Creativity was defined very recently as, "the ability to produce work that is at the same time novel and meaningful, as opposed to trivial and bizarre." In many circles, creativity is deemed concordant with divergent thinking, the thought process used when a problem is solved by multiple unique solutions. It is thought that an increased ability to think divergently, may imply enhanced creative potential, and this ability is investigated through various psychological tests. Batteries such as the Torrance Tests of Creative Thinking (TTCT) present a series of tasks in picture generation to a subject who must then generate pictures from partial drawings and generate original works with a given set of shapes. A selection of the Berlin Intelligence Structure Test (BIS) also contains a figural battery with line drawing in addition to a verbal battery that asks for novel uses of various objects and a numeric battery that requires generation of unique number sequences. In both series of tests, higher scores reflect an ability to create unique solutions to single problems and, in theory, are results of heightened creativity.

Over time, these tests have gauged human cognition, and led to conclusions about intelligence and the creative thought process. Raymond Cattell and John Horn stated that human intelligence is compartmentalized into fluid and crystallized ability. The fluid component grounds critical thinking, problem solving, pattern recognition and learning, while the crystallized grounds retention of facts, formulae and other malleable information. Additionally, John Carroll thought that the mind functions within a general intelligence, combining the fluid/crystallized dynamic with perception, processing and specific specialized abilities. Researchers administering divergent thinking tasks have found that there are significant correlates among a defined set of these specialized abilities and divergent thinking, specifically fluency (the number of valid responses), originality (the frequency of valid responses), flexibility (number of unique categories produced), switching (ability to shift between categories) and elaboration (extensive nature of responses). These factors are dynamically interacting in each individual, and certain combinations theoretically serve as the foundation for divergent and creative thinking. For instance, subjects who exhibit high fluency scores often demonstrate increased flexibility of thought and the ability to create an increased number of uncommon solutions on the tests. Creative individuals have
an uncanny ability to perceive related stimuli, understand them with great variation, and generate unique outputs through words, music, paint, prose or other media. This ability to make novel associations about incoming stimuli is the purest essence of human creativity on the macroscopic level.

**Extremes in Creativity**

Associational ability also is affected by a widely investigated phenomenon called latent inhibition (LI). It is the varying capacity of the brain to focus on stimuli previously experienced as irrelevant or insignificant. LI can be quantified as the ability to learn to ignore irrelevant stimuli and focus on important parts of the incoming sensory stream. For example, in an environment with noise and other distractions, latent inhibition allows us to focus on and perform a specific task efficiently while ignoring the distractions – akin to reading with the television or radio on, but still understanding the reading. Thus, more attenuated/decreased latent inhibition can lead to a reduced ability to focus properly and/or learn by associaton efficiently. Essentially, LI is a filter that keeps the brain from being distracted. Decreased LI can then cause increased sensitivity to one’s environment. In the context of creativity, decreased latent inhibition can allows an individual to perceive their environment as markedly more novel. The brain is not ignoring irrelevant stimuli, but rather interpreting it repeatedly and uniquely multiple times over. This is a crucial component of divergent thinking and forms the groundwork for making grandiose free associations about one’s environment and possibly the basis for creative thought.

Latent inhibition is reduced to different extents in different creative individuals, which may enable their unique cognitive abilities. LI is measured and related to creativity through a combination of auditory and visual discrimination tasks. Subjects are first separated into “pre-exposed” (PE) and “nonpre-exposed” (NPE) groups, and are presented with audiovisual tasks. The NPE group is presented with an audio sample of syllables and a video clip that flashes a yellow circle before a target syllable, and the subject must learn to associate the appropriate sound with the visual stimulus. The PE group is first presented the same audio sample combined with white noise, then separately presented with the same audiovisual task as the NPE group. LI is measured as the speed of learning the syllable stream (the conditioned stimulus) is paired with the yellow circle (the unconditioned stimulus). Classically, the nonpre-exposed group learns faster than the pre-exposed group, demonstrating higher levels of latent inhibition. This shows that pre-exposure to a stimulus lessens the ability to form concrete associations with that stimulus. In relation to creativity, this deficit in associational ability may enable increased free association. Creativity has been evaluated with respect to latent inhibition through LI and divergent thinking tasks plus an arts and sciences creative achievement evaluation. It was shown that pre-exposed modest creative achievers have higher levels of latent inhibition than their nonpre-exposed counterparts, and that pre-exposed highly creative achievers score comparably to their nonpre-exposed counterparts. This demonstrates reduced latent inhibition among pre-exposed highly creative groups and contributes to an overall trend of increased creativity correlated with attenuated latent inhibition.

Interestingly, reduced latent inhibition is also linked to the psychopathology of schizophrenia (SZ), creating a curious psychological link between creativity and mental illness. There are many environmental, genetic, neurobiological, psychological and familial factors that lead to the development and expression of schizophrenia. However, it has been observed that latent inhibition is improved in medicated schizophrenic compared to unmedicated schizophrenic patients, and more so impaired in those who had recently experienced their first psychotic episode. This sheds light on the psychotic processes associated with schizophrenia, by which patients express irrational paranoia, delusions of grandeur, and disconnected thought patterns. As a result of their decreased filtering and attenuated latent inhibition, SZ patients perceive the world as markedly more novel, strange or even malicious as a result of their hypersensitivity to the environment. However, there is more to be learned here. While a individual with SZ may believe their peers are going to kill or hurt them, may assume the consciousness of a celebrity, or perceive human emotion from static objects, they are demonstrating divergent thinking on overdrive. Since their latent inhibition is critically lowered and the incoming information stream remains relatively unfiltered, radical thoughts and associations become second nature. Although these thoughts are peculiar, their foundation still lies in divergent thinking. Although schizophrenic thought demonstrates the problems in extreme divergent thinking, these thoughts are arguably creative at their very core.
Real World Evidence

Many may think that there is greater madness in the arts as compared to the sciences, and in fact, artists may express a greater lifetime prevalence of mental illness as compared to natural scientists and social scientists.¹⁴ This greater instance of mental illness in artists through their lifetimes may be accounted for by an environment that values decreased objectivity, rationality and precision as compared to fields in the natural and social sciences, where there are more standards, laws and constraints. Interestingly, the mental condition of an artist often manifests itself in the technical aspects of their artwork, and this is most easily seen in the visual arts. Mandlebrot’s fractal theory¹⁵ addresses this idea of “self similarity,” stating that irregularities in small parts of an object reflect the overall composition of the whole. This also applies to the creativity and mental illness argument in that the part is the technical attributes of an artistic work and the whole is its creator.

This notion of self-similarity by fractal theory was investigated in three forms of art: formal (exhibiting compositional emphasis), symbolic (exhibiting social realism or narration) and emotive (exhibiting abstract expressionism). Formalists such as Picasso and Matisse, exhibited the lowest instance of lifetime mental illness, while symbolic/surreal painters such as Hopper and Cezanne fell at the median, and emotive modern artists such as DeKooning and Rouault demonstrated the highest instance of lifetime mental illness.¹⁴ Formalists show a more rigid and defined technical style despite abstract subject matter, which reflects their more stable mental state. Their art is a result of careful, methodic manipulation of conventions to create unique works that although strange at times, are certainly technically well defined. The symbolic/narrative painters exhibit comparable technical efficiency, but their output is a result of a somewhat warped perception of the real world that allows them to turn the average and real into the surreal, embodying a more feral psyche. The emotive painters exhibit overtly original technique in their abstract expressions that is very difficult to define and create a sense of confusion and awe in their paintings. These artists show the highest rates of mental illness, reflected by their eclectic techniques. Other painters not included in the study also embody this phenomenon. Salvador Dali, arguably the most prominent surrealist painter in history, was a victim of paranoid personality disorder and erratic personality disorder based on his unusual behavior and personal accounts.

This phenomenon is not unique to visual art. A creativity and mental illness trend is also present in music and writing. Classical composers such as Tchaikovsky and Shumann have been linked to affective disorder¹⁶, and instances of compulsive disorder and depression were present in the lives of jazz musicians Miles Davis and John Coltrane.¹⁷ Renown novelist and pioneer of confessional poetry Sylvia Plath and was afflicted with psychosis that drove her to commit suicide at home in the presence of her children at the tender age of 30, while fellow writer Earnest Hemmingway also succumbed to suicidal depression. This evidence suggests a real-world presence of a link between mental illness and creativity.

Biological Creativity and the Link to Mental Illness

While psychology has provided much to understanding divergent thinking and creativity, there have been advances in neurobiology that strive to bolster theory with functional evidence. In investigating the biological basis of creativity, studies have been converging on the thalamus, the brain’s relay station and sensory gating system before the prefrontal cortex. The thalamus contains a plethora of chemical recep-
tors for the neurotransmitter dopamine, and specifically, the dopamine D2 receptor has been studied with regard to neurobiological creativity. Imaging studies (MRI/PET) have revealed significantly higher densities of D2 receptors in the thalamus relative to other parts of the brain (the only place with a higher density is the striatum), and they enable the filtering function of the thalamus to prevent information overload in the cortex.8 These dopamine pathways play a critical role in creativity in that D2 receptor density and thalamic D2 dopamine binding potential (D2BP) decrease as divergent thinking test scores increase.8 This suggests that subjects who score high on divergent thinking tasks also may exhibit decreased D2BP in the thalamus and a smaller amount of D2 receptors. D2 dopamine binding in the thalamus may then have an important role in thalamic filtering and divergent sensory processing.

The dopamine system is dysfunctional in schizophrenia. It becomes hypersensitive, over active and particularly, dopamine binding in the striatum increases with intensity of positive psychotic symptoms. These include hallucinations, delusions and disordered thought.2 Interestingly enough, the dopamine pathways rendered dysfunctional in schizophrenia, bipolar disorder and (albeit to a lesser extent) depression show significant overlap with the thalamus and striatum – brain areas seemingly important for creativity and divergent thinking.2 Additionally, decreased D2BP and reduced D2 receptor density in the thalamus are included in the molecular pathology of schizophrenia.28 Studies show that as cortical and limbic D2BP decreases, intensity of positive schizophrenic symptoms increases,8 thus establishing the role of the D2 receptor in this mental illness. Although very controversial, this emergent piece of evidence links psychological and biological creativity through the dopamine brain pathways and D2 receptors. An analogous negative correlation also exists between divergent thinking test scores and D2 receptor density in the thalamus. D2 density is lower in subjects who score high on divergent thinking tests.8 Thus, a biological link between creativity and mental illness is brought to light. Since both schizophrenic pathology and divergent thinking exhibit decreased D2 receptor density and DA binding potential, this suggests that there are associations between some of the underlying mechanisms of creativity and mental illness.

Given the above testament, it can be argued that the ability to think creatively arises from an increased capacity to make free associations of stimuli in the external environment. Also, given that the thalamus has an elevated level of D2 receptors, it has been suggested that decreased D2BP decreases thalamic ability to strictly filter the incoming stream of information flowing rapidly to the prefrontal cortex.9 Thus, the prefrontal gating system goes awry, allowing for input of an unfiltered stream into the frontal lobe, which could be the neurological basis for creativity. This makes sense with respect to neurobiology, as decreased filtering by the thalamus facilitates information flow to the prefrontal cortex and the frontal lobe, where input is available for free association. Since the creative mind has taken in more information, it can create more original associations as a function of mathematics – if there is more information to be strewn together, there will be more output. The incoming information stream coupled with an open sensory gate in the thalamus may create the conditions for the infamous and elusive creative spark, but for some, the spark can lead to psychosis. What then chooses the path?

**Proposition of a Continuum**

In a Harvard study, intelligence was investigated with respect to latent inhibition in a group of pre-exposed individuals from a latent inhibition diagnostic to investigate IQ’s role in creativity.11 After re-administration of latent inhibition tasks and creative achievement evaluations, individuals were given an IQ test, and it was found that those who demonstrated higher levels of creative achievement also demonstrated reduced latent inhibition. Trends in IQ accounted for 20% of the variance of the results, and IQ was a significant variable. In further investigation, the group’s eminent creative achievement (ECA) was analyzed. The researchers defined this as publishing/sale of a novel, book or poetry, sale of recorded music, patented construction of a prototype invention, private exhibition of original artwork or scholarship/prize for a scientific discovery. The group analyzed consisted of 4 artists, 5 composers, 2 writers, 2 inventors, 3 dramatists, 7 scientists and 2 choreographers, whose IQ and latent inhibition scores were compared to a control group. These eminent creative achievers showed markedly lower levels of latent inhibition than the controls and were seven times more likely to demonstrate attenuated latent inhibition. Pertaining to IQ, it is suggested that a score of 120 is the threshold for creativity11, and in comparing the IQs of the subjects, 84% of the creative achievers had an IQ score greater than 120 while only such was the case for 44% of the control group.
Further statistical analysis demonstrated a higher instance of reduced latent inhibition in eminent creative achievers with an IQ greater than 120.

This data and the previously presented neurobiological and psychological ideas suggest that attenuated latent inhibition is associated with both high creativity and mental illness, with IQ serving as a possible modulating factor. These extrema of creativity and mental illness may exist in a continuum linked by latent inhibition and modulated by IQ. Reduced latent inhibition is associated with schizophrenia in multiple cases, but may also be related to an increased likelihood of creativity. Furthermore, there are other correlations between creative individuals and schizophrenic patients in latent inhibition and divergent thinking tasks. Without the modulating function of IQ, all creativity could be explicitly synonymous with psychosis, but this clearly is not the case. Intelligence may serve as the mediator between an individual’s susceptibility to psychosis and ability to be creative. This also suggests that intelligence may influence how each individual’s mind responds to and functions under attenuated levels of latent inhibition, which relates back to the defined set of abilities associated with creativity mentioned earlier.

Final Thoughts

What does all this mean in a larger context? Principally, it expands our knowledge of the mysterious realm of psychosis and neural function. Through the psychopathology of mental illness, we are better able to understand what is happening in the brain at the level of neurophysiology, which will prove important in understanding the brain as a system. While we can diagnose and treat all mental illnesses, we do not understand the complete brain mechanisms of all of these disorders. Breakthrough molecular neurobiology has and will continue to help us further understand these conditions and open up possibilities for treatment at more localized levels. If we are able to understand specific receptor-ligand mechanisms, neurochemistry, neuroanatomy, and neurophysiology of various mental illnesses, we will be better able to better treat them. In the context of creativity, this evidence further allows us to understand and investigate our established metaphysical and psychological ideas under a microscope. Modern understanding of the mechanisms of mental illnesses allows us to develop new treatments and prophylactic interventions to prevent disorders before they even start. More interestingly however, is the idea of manipulating these mechanisms for our benefit once we fully understand them. Theoretically, it may be possible one day to modulate brain function from the level of genes and molecules, opening the door to a new realm of self-enhancement by molecular intervention. Just think, one day you may be able to take a pill to access the cognitive plane of Pablo Picasso or Ludwig van Beethoven for just a few hours.

In 0.19 seconds, the Google search engine retrieves over 9,600,000 results concerning I-Dosing, the newest Internet fad that is taking the world’s youth by storm. The next time you hear someone talking about drugs, you might get confused when you hear them talking about crazy beats and soundproof headphones. However, an increasing number of people are listening to sound files that are specifically designed to alter an individual’s state of consciousness and induce a ‘high’ that is claimed to mimic the psycho-physiological effects felt after the administration of an actual psychoactive drug; this “drug trip” is called I-dosing. To feel optimal effects, the user is advised to wear stereo headphones, lie down in a comfortable position in a dark room, close his or her eyes, and drift off into the world of digital-drugs. As ludicrous as I-Dosing may seem, the scientific foundation for digital-drugs dates back to as early as the mid nineteenth century.

The Biological Basis Behind Binaural Beats

The human brain, being a dynamic and adapting organ, has the capacity to rapidly alter its electrical activity in response to incoming information. In 1839, the perceptive ability of the brain to encode and react to exogenous stimuli was manipulated by German physicist Heinrich Wilhelm Dove, the father of the binaural beat phenomenon\(^2\). Since their discovery, binaural beats have been implemented both clinically and experimentally to assess the audio-perceptive abilities and integrity of corticovisual tracts.

In general auditory situations, when a sound of a particular frequency hits one ear earlier than the other, the brainstem auditory processing areas, the superior oliv, inferior colliculus, and lateral lemniscus, detect the difference in auditory stimulation time and estimate the direction a particular sound is coming from\(^4\). However, when the two ears are simultaneously presented with a sinusoidal sound of a slightly different frequency, as in binaural beat stimulation, the slight frequency difference is not what is perceived. Instead, the result is a sinusoid whose interaural time difference changes slowly. Consequently, this frequency difference between the two tones creates a binaural beat, a sound that seems to move in space. If this resulting movement is rapid, the beat will “fill the head” rather than being perceived as coming from a particular location\(^5\).

For example, if the left ear is presented with a sound of 110 Hz while the right ear receives a frequency of 100 Hz, the sound perceived by the auditory system will be of 105 Hz while the binaural beat will be of 10 Hz\(^5\). Once the binaural auditory beat travels to the brainstem’s superior olivary nucleus, where specialized nuclei that encode binaural stimulation are located, a beat of neural activity is generated\(^4\,7\).

Welcome to the Digital Highway: Advocates

As a ‘cognitive arousal’ technique, the administration of binaural beats demands a general knowledge of the electrical behavior of the brain. Typically, electrical brain activity can be sorted into five frequency-based categories. Gamma waves (30-100Hz; usually 40Hz) are the brain’s highest frequency electrical waves and are present during multimodal processing of sensory information. Beta waves (14-30Hz) and alpha waves (8-13Hz) typify wakefulness and conscious cognitive function (pad). Alpha frequency waves occur at more relaxed cognitive states while beta waves are produced at higher arousal states. Delta and theta waves characterize an unconscious state. Delta waves (1-4Hz), the lowest-frequency brainwaves, promote dreamless sleep, and theta waves (4-8Hz) are associated with REM sleep, meditation, and creativity\(^8\).

When a binaural beat is of the same frequency range as any one...
of the five brainwaves, it is claimed to be capable of altering an individual’s state of consciousness by stimulating the reticular-thalamic activating system, a neural system responsible for cognitive arousal. Studies conducted with EEGs have shown that binaural beats of a theta wave frequency will induce a feeling of drowsiness in a listener. Conversely, binaural beats in the beta wave range will cause the listener to become more aroused and alert, with enhanced memory and task performance.

Advocates of the use of binaural beats for cognitive manipulation are convinced of its potential therapeutic effects. Robert Monroe, founder of the Monroe Institute, developed multi-layered sound files that manipulate brain waves and transform the brain into a state of “hemispheric synchronization,” an occurrence in which both hemispheres of the brain are in unison with each other. Research director of the Monroe Institute, F. Holmes Atwater, markets the Institute’s product by describing HemiSync as an “audio guidance program… for obtaining altered states of consciousness”. There are also a few published articles concerning the investigation of HemiSync in clinical settings. In preoperative settings, it was shown that patients undergoing surgery required significantly less anesthetic if they listened to a HemiSync sound file. Further, in preoperative-associated anxiety, nearly half of patients benefited from listening to binaural beats.

HemiSync, having been developed before I-Dosing, set the stage for the future of digital brainwave manipulation. I-Doser Labs, one of the many designers of marketed binaural beat audio, has even developed a proprietary program to present their audio stimuli. The user interface of the I-Doser program is organized into folders, with the parent folder labeled “Dose Files.” These dose files, lasting from ten to forty minutes, range from hallucinogens to club drugs and opioids. When asked about how the program works, I-Doser explains, “each audio track contains [our] advanced binaural beats that will synchronize [your] brainwaves to the same state as the recreational dose. Mixed with [our] advanced auditory pulses are soothing backtracks of ambient soundscapes to help the brain induce a state of mood lift, euphoria, sedation, and hallucination.” However, I-Doser Labs does not have everyone convinced.

You Are Only as High as You Want to Be: Skeptics

Although there are studies publicizing the application of binaural beats to cognitive arousal purposes, many are skeptical of these claims and point out how few legitimate, peer-reviewed scientific papers document affects on brain state. Boston University professor Dr. Barbara Shinn-Cunningham describes the true application of binaural beats as a prognostic tool to identify the brain’s ability of spatial hearing and auditory encoding. Dr. Shinn-Cunningham relates methods of ‘cognitive arousal’ to other common methods to alter consciousness, such as meditating or simply listening to relaxing music. She asserts that in most situations, binaural beats do not induce any considerable difference in brain wave behavior. The brain is an easily manipulated organ, and differences in electro-cognitive activity can be a result of simply “thinking.” While effects of binaural beats may be significant statistically, Dr. Shinn-Cunningham says the effects of binaural stimulation on brain activity are smaller than the effects of more overt cues in music, such as the rhythmic beats that we all dance to and hear consciously.

Additionally, many experiences of a psycho-physiological ‘high’ being felt by I-Dosers could be due to a placebo effect and may not even simulate the high resulting from a recreational psychoactive drug. Although it has been shown that drugs do have an effect on brainwave activity, it is not known if these effects can be replicated by binaural beats alone. Furthermore, drug activity on the brain is largely dose dependent, making the approximation of the effects of binaural beats on the brain hard to measure in comparison to a real high.

Regardless of the disagreements concerning the impact binaural beats have on cognitive arousal, the major ethical issue is the message I-Dosing is sending to unsuspecting individuals pursuing the Internet. Although I-Dosing and other methods of brain wave manipulation may not be dangerous or even effective, there is a concern that these methods of digital stimulation will act as gateway drugs. It is up to the user to decide whether to go digital or not.

References


Introduction

Fooling our own brains is an appealing concept: everyone enjoys optical illusions, magic tricks and riddles. But can fooling our brains help heal our bodies? When it comes to taking medicine, people have consistently proven themselves to be highly suggestible. The color of pills, the number of pills and the brand of pills can influence our assumptions about the medications we are taking. We tend to think that capsules are stronger than pills, and that injections are more powerful than medicine taken orally¹. Even surgery has been evaluated for its potential placebo effect: in one experiment on arthroscopic knee surgery, both the osteoarthritis patients receiving the operation and those who just got an incision and stitches showed significant decreases in knee pain¹,².

The preferred test to prove the effectiveness of an experimental drug evaluates whether or not its effects can beat those of a placebo in a double-blind, placebo-controlled, randomized trial. Many experimental drugs fail this test, or often the placebo trial may give the drug a run for its money. So, if the placebo is so difficult to beat and is devoid of side-effects, then why not use it as the treatment itself? This question is being raised by physicians, researchers and bioethicists: can safe, affordable treatment be found in fake medicine?

How To Trick Your Brain

By definition, the placebo effect is a physiological state brought on when one anticipates a health-related result from biologically irrelevant treatments or procedures. The placebo effect can target several different neurological systems, thus the wide range of possible effects: analgesia, mood improvement, and even immunosuppression¹.

Brain pathways involving dopamine are important in understanding the placebo effect. Dopamine is a neurotransmitter that lets us associate a stimulus in our environment with a reward, and it is released when we are engaging in behavior that will bring about that reward. Dopamine activity in the nucleus accumbens (NAC) is evident when pain relief is expected, and people who show more activity in the NAC when expecting a monetary reward are more noticeably affected by placebos³.

A second contributing neural system is known as the endogenous opioid system. Our brains release their own opioid substances in response to pain (endogenous opioids) and when that is not enough, doctors prescribe painkillers with similar chemical structures. So how do we know that natural opioids are involved in the placebo effect? Naloxone, a substance that blocks opioid receptors, has been shown
to prevent placebo analgesia, demonstrating the placebo's reliance on our brain's natural painkillers. Knowing this, conditioning studies have been able to demonstrate that expectation of pain relief is associated with the release of opioids in the brain. One such study used morphine, an opioid painkiller, and ketorolac, a non-steroidal anti-inflammatory drug (NSAID). Subjects were conditioned to expect either morphine or ketorolac injections. After getting two real injections, they received saline placebos that triggered analgesic responses similar to the drug they had been administered previously, whether they expected pain relief or not. Injections of naloxone, independent of the subjects' expectations of receiving a painkiller, decreased pain tolerance significantly.

Both opioid and dopamine systems rely on cognitive and conditioning factors. For instance, when taking a biologically active substance, the effectiveness of a placebo that physically resembles an active drug will be increased in both humans and animals. We are conditioned to respond to the physical act of taking medicine, but we hold an expectation in our minds of what the active drug is supposed to look like. Conditioning factors refer to drug conditioning - giving a subject a certain number of doses of a drug before replacing it with a placebo. The cognitive part of the effect is introduced when the subjects are given expectation cues, being led to think that they are or are not taking a particular substance. In terms of anatomy, the anterior cingulate cortex seems to play a role in both systems, and is activated in the placebo groups of analgesia, anxiety relief and mood improvement studies.

In addition to the dopamine and opioid systems, the serotonin system has also been proven to play a role in the placebo effect. The involvement of this system in the placebo effect is often observed in experiments concerning depression, although it is difficult to have a true control for the placebo groups of these studies because the subjects have often had outside intervention like counseling. Nonetheless, changes in brain glucose metabolism have been observed in similar regions of the brain in subjects taking fluoxetine, an antidepressant, and subjects taking a placebo.

**Tricks for Treatment**

The broad range of effects that have been produced by placebos are evident in their wide experimental use. Although they tend to treat the symptoms rather than the cause, the inherent lack of side effects makes placebos prime candidates for treating a variety of ailments. Research is being directed toward finding a useful place for placebos in medicine.

Effective methods to use placebos as painkillers are being investigated. A 2001 study demonstrated that subjects tolerate pain better when they can actually see that they are being given an analgesic. When test subjects received the opioid receptor-blocker naloxone after the seeing themselves injected with the NSAID ketorolac, their pain tolerance was the same as it was after only receiving a hidden injection of ketorolac. In May, the Boston Globe reported on a study published in Science last year in which patients given cream to put on their arms showed much less pain-related activity in their spinal cords when told that the treatment they had been given was in fact a powerful painkiller.

Even surgical placebos - sham surgeries - have proven effective, perhaps most notably in Parkinson's patients. One study looked at patients who had had electrodes for deep-brain stimulation treatment implanted in their brains. One group of patients was told that the treatment was functioning, and another group was told that the stimulator had been dialed down. The patients who believed that their electrodes were working expected improved motor performance to result from deep-brain stimulation. Although they were never given the treatment, these patients associated the fake subthalamic stimulation with better motor performance and were able to move their hands faster. The necessary brain changes occurred within minutes. In another study, after injecting Parkinson's patients with medication that would help relieve muscle stiffness, the subjects were given a placebo and their subthalamic brain activity was monitored. Individual neurons in this brain region became less active so that the patients' muscles could relax and function more easily.

Though it is an unpredictable disease, and thus difficult to control for in placebo studies, multiple sclerosis (MS) has been another potential candidate for placebo remedies. Multiple sclerosis is an autoimmune disease in which the body attacks the myelin insulation covering its own nerves. In a trial of interferon-β-la treatment for MS, the group given a placebo showed a twenty percent decrease in areas of inflammation due to the body attacking its myelin, expressed as MRI lesions, compared to their baseline MRIs. Epilepsy, a similarly unpredictable condition, has been shown to respond to placebos. The placebo groups of anticon-
vulsant trials regularly show significant (more than fifty percent) reductions in seizure frequency.

Placebos may also be used to address cognitive issues associated with aging. In a study of healthy adults aged 65-85, subjects taking what they were told was a cognitive enhancement pill performed better on cognitive tests than the group of subjects that had not taken any pills. In one Alzheimer’s study, fifty percent of the placebo group had shown either improvement or stability in their condition six months into the trial. It is interesting, then, that Alzheimer’s has been demonstrated to deter the placebo effect, perhaps because of frontal lobe impairment.

**Tricky Business**

The placebo effect is a neurobiological phenomenon that has the potential to aid in the treatment of a number of disorders. The wide range of neural systems it affects gives it the potential to serve as treatment for a great variety of conditions. Research directed toward finding medical uses for the placebo effect will undoubtedly be put under great ethical scrutiny before being used clinically.

Placebos are not a new concept. They were used as early as the 16th century in the form of fake holy objects given to people believed to be possessed. If the victims were upset by these false relics, priests would know that the possession was imaginary - only a real relic was thought to bother a possession victim. By the late 1700’s, placebos were used medically, but merely to placate patients. This “undoubtedly led to the tainted reputation of placebos and placebo effects that persisted until very recently.”

When the randomized control trial experimental design became popular after World War II, it became apparent that people responded positively to placebos. In fact, Henry Beecher declared that thirty-five percent of patients responded well to placebos. This is no doubt an exaggeration, as confounders were not fully taken into consideration, but nonetheless placebos have become a big research topic in recent years.

A principal ethical issue surrounding placebo medicine is informed consent - the patient’s right to understand their treatment. The fact remains that placebos involve deception by definition. It can be argued, however, that this deception is merely putting the effects of mental and emotional states on the body’s well-being to use. Interestingly, the deception can actually be lessened by letting the patient in on the fact that he or she is taking a placebo without ruining the effect. The treatment can still work because there is a healing element of the treatment routine itself: simply being seen by a doctor and taking medicine promote recovery. Unfortunately, over an extended period of time, extinction of the body’s conditioned recovery response to this routine can occur. To maintain the placebo’s efficacy in the face of extinction, a physician could explain that he or she does not fully understand the mechanisms of the prescribed drug (a placebo) but is recommending it on the grounds that it will not cause the serious side effects associated with the better-understood treatment option.

Another potential benefit in introducing placebos into clinical use would be a reduction in health care costs. As well as being free of side effects, placebos are very inexpensive. A recent study in psoriasis patients showed that corticosteroids administered in smaller-than-standard doses interspersed with placebo doses could prove a better, safer treatment plan than regular, standard doses of the same medication. “You’re talking about many, many, many millions of dollars a year in drug treatment costs. If [doctors] can produce approximately the same therapeutic effect with less drug, then it’s obviously safer for the patient, and I can’t believe they wouldn’t want to look into doing this,” Robert Ader, the leader of the study at the University of Rochester remarked in the Boston Globe. In that respect, placebo treatments irrefutably address two major problems facing the health care field today.

**Conclusion**

The placebo effect is an intriguing neurological process involving many facets of the brain: chemically, cognitively, and anatomically. The diverse range of systems that appear to be involved in placebo phenomena account for the usefulness of placebos in many different kinds of clinical trials. As the highest standard for pharmaceutical testing, the effective use of randomized, double-blind, placebo-controlled trials has prompted those in the biomedical field to ask why placebos are not used as medications themselves. While treating symptoms more than causes, the relief achieved with a placebo might contribute to the body’s ability to heal itself. If this becomes a real movement in medicine, informed consent may not end up being a problem: perhaps patients will come to accept the possibility that they could be issued “fake” medication for their own benefit. Studies have shown placebo effec-
tiveness in disorders ranging from depression to multiple sclerosis to Parkinson’s disease. On their own or alongside the medications they are imitating, placebos seem to have great potential in helping patients get safer, more affordable health care.

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Brain Research and National Defense

How Neuroscience Funding by the Department of Defense is Going to Revolutionize Science, Technology and Computation by Aisha Sohail

Formed in 1958 in response to the successful Soviet launch of the Sputnik satellite into space, national defense department agency DARPA (Defense Advanced Research Projects Agency) has been responsible for research into breakthrough, though often highly speculative military technology. The Eisenhower administration implemented ARPA with three concrete goals: to get us into space, protect us from Soviet missile attacks, and develop technology to detect Soviet nuclear tests. As a national security agency, DARPA has been funded entirely by taxpayer money1.

As a result of DARPA-concentrated efforts, the United States launched Explorer I on January 31, 1958. Despite breakthroughs in military technology such as the unmanned combat air vehicle Boeing X-45, the M16 Assault Rifle, useful radars and lasers, DARPA’s discovery of ARPAnet in 1973 is probably the agency’s most far-reaching and revolutionary invention as it eventually lead to the develop-
ment of the Internet and what we now know as the World Wide Web. Although DARPA’s mission statement has remained the same, the agency has undergone a series of name switches between DARPA and ARPA as dependent upon additional responsibilities assumed during wartime industry.

Since then, DARPA has evolved into an agency that supports research bordering on the realm of science fiction. Recent project solicitations include BaTMAN (Biocentricity and Temporal Mechanisms Arising in Nature) – which aims to better understand the spatio-temporal universe, and, from there, “transform biology from a descriptive to a predictive field of science”; and RoBIN (Robustness of Biologically-Inspired Networks), which aims to, “create a dynamic biologically-inspired network of scientists and other experts for crisis response and complex decision support”. These two projects highlight a unique trend in military research: the desire to develop a greater understanding of biology to gain advances in national security. This editorial will examine how advances in defense-funded research of brain biology, or neuroscience, will revolutionize military technology and all sciences that require intensive computation.

**History of DARPA and neuroscience**

Many of DARPA’s projects involve the funding of neuroscience research. A google search of the subject reveals several papers examining the ethical, social, and legal issues posed by the burgeoning field. One such Nature editorial titled “Silence of the neuro-engineers” spawned in 2003 with the intrepid byline: “Researchers funded by a defense agency should stop skirting the ethical issues involved”. This editorial urges neuro-engineers to evaluate synergies between the goals of military research and neuroscience. The editorial also recommends DARPA-funded neuroscientists be more open to answering questions from opponents of the development of such technologies in order to “achieve a better quality and balance with researchers’ engagement”.

Dr. Jonathan D. Moreno, an ethics professor at University of Pennsylvania and editor of Science Progress magazine, is another relevant source on the subject. Dr. Moreno published a book titled Mind Wars in 2006 to review DARPA’s recent accomplishments in neuroscience and offer his expertise on the ethical questions posed by defense funded neuroscience research. Along with the Nature editorial, Moreno also notes that most DARPA-funded neuroscientists are reluctant to debate the potential military uses of now extant technologies called brain machine interfaces. Dr. Moreno empathizes by saying that defense-funded neuroscientists have an “understandable reluctance to jeopardize relationships with research funding sources”, especially with the added sensitivity to defense disclosures in the post 9/11 and WikiLeaks era. Given the nature of this research, DARPA-funded neuroscience appears secretive and obscure to the public.

Despite the secretive nature of DARPA researchers, Moreno’s persistent exploration into the subject reveals a history of DARPA-funded neuroscience research that raises novel ethical, legal, and philosophical issues. Past defense projects demonstrate military interests in the workings of sleep and sleep-inhibiting pharmaceuticals such as Modafinil that can enhance cognition while replacing sleep in order to build better soldiers. DARPA also funds the development of brain prostheses that allow for more efficient information processing and storage in subjects. This research has ignited a new generation of bioethical and philosophical debates between the humanists apprehending a robot apocalypse and the transhumanists hoping to achieve a positive Singularity.

A potentially intrusive DARPA patent is one in which a wireless neuroimaging module with portable monitors that offer both neural and vascular signals, which would ultimately be capable of reading the private brain states of its potentially unwilling subjects (See DARPA patent # SB031-010 for “Wireless Near-Infrared Devices for Neural Monitoring in Operational Environments”). The patent reads: “The market for non-intrusive portable monitoring by means of non-invasive brain monitoring offers a most exciting and significant break-through, impacting many industries. Early adapters are expected from the military for training under stress; medical-head trauma evaluations; educational-diagnosis of learning disabilities; and law enforcement-for interrogation.”

Moreno concludes his book by encouraging the ethical regulation of neurodefense technology that could be misused to threaten public health and privacy. The American government has already faced significant criticism due to reports of torture and other inhumane interrogation tactics at Abu Ghraib and Guantanamo Bay. In a response to public disapproval, the Obama administration took efforts to shut down Guantanamo as one...
of its first acts, and would likewise benefit from conducting open-ended discussions about neurodefense technologies to prohibit the implementation of publicly unpopular defense policies.

**DARPA and Universities**

In my significant coursework at Boston University’s (BU) Cognitive and Neural Systems (CNS) department, I have come to notice that most of the technology research at the department is financed by DARPA. Pooling most of its money from DARPA, NIH, and CELEST (Center for Excellence in Education, Science, and Technology funded by the National Science Foundation) the department accrues roughly $6-7 million dollars a year in funding. This funding exclusively directs the research of roughly 25 post-doctoral students and approximately 40 other graduate students. A reliable source within the department confirms that DARPA funding amounts to roughly $2-3 million of the department’s fiscal budget. This figure means that a national defense agency directs roughly 50% of the systems-level neuroscience departments’ research, and 25% of the department’s post-doctoral research. These funds cover the direct and indirect costs of 4 to 6 post-doctoral researchers involved in defense research through CNS. According to this source, computational neuroscience laboratories at other top-level schools such as MIT receive even more of their funding from military agencies. MIT allows its defense research to be classified, and laboratories such as the Draper and Lincoln laboratories in Cambridge take full advantage of that privilege; BU on the other hand requires all research to be publishable.

**SyNAPSE Project**

One of BU CNS department’s more lucrative projects is called the Systems of Neuromorphic Adaptive Plastic Scalable Electronics, or the DARPA SyNAPSE project. Featuring articles in Wired, NewScientist, engadget, and Singularity magazine hplus, the program promises to develop “a brain inspired electron ‘chip’ that mimics that function, size, and power consumption of a biological cortex.” This chip will use neuroscience inspired architecture to simulate cognitive abilities such as perception, planning, decision-making, and motor control. Funds allocated by DARPA to prime contractors HP, HRL, and IBM have been granted only to BU, Stanford, and a handful of other laboratories.

One way to develop such a chip is through the discovery of a memristor, a type of computer that uses neuron inspired architecture to compute. The discovery of memristors has the potential to revolutionize the electronics marketplace by allowing for highly efficient and relatively inexpensive computation. Any technology that can benefit from faster processing that requires less power—cell phones, personal computers, game consoles, supercomputers, robotics, etc.—would ultimately benefit from the discovery of this missing circuit element. Neuroscientists will be especially thrilled with the ability of such technology to process large data sets.

**How does the memristor hardware work?**

First theorized by Leon Chua in 1971, ‘memristor’ is short for memory resistor, and it works by registering how much current has passed through a circuit. A memristive circuit effectively stores information by measuring the change in electrical resistance when current is applied. This effect can be compared to a neural synapse, which uses electrical gradients formed by the influx and efflux of sodium and potassium ions across the cellular membrane to transmit signals. The success of memristor computation depends significantly on the sensitivity of the resistor: a memristor with a high resistance can be interpreted by the computer as a “1” in processing terms, and a low resistance can be interpreted as a “0”. It would be a bit silly if neurons only had binary outputs to relay since the number of neurons required to compute a simple motor task would take an infinite amount of time. Needless to say, biological and memristive processing is more efficient than traditional binary processing.

In the past two years, HP has successfully demonstrated the use of memristors using two layers of titanium oxide to create heat-induced differences in resistance between the two layers. Controlling this heat-current allows the computer to record data. Earlier this year, the work of Dr. Wei Lu at University of Michigan confirmed that memristors indeed simulate synapses as electrical synaptic connections either strengthen or weaken depending on the timing of firing of two memristive circuits. This appears to occur in a Hebbian fashion—just as two neurons that fire action potentials concurrently are more likely to pass future messages, a memristive synapse also becomes more likely to pass later messages between two elements that are often simultaneously ac-
Why do we need memristors?

The current generation of computational devices suffers from an upper threshold for computational efficiency because processors cannot execute a program faster than they can fetch instructions for its execution via RAM (Random-access memory). Although increasing clock speed and transistor density, and adding processors and features such as cache memory has allowed for an exponential increase in computing capacity until now, processing beyond the clock speed of a few gigahertz is still too power-expensive. Hence the justification for development of memristors: if we want continued exponential growth of computational processing, next-generation devices will need to integrate memory and computation into one step, much like a biological SyNAPSE.

The human brain contains about 10 billion neurons, and each neuron is connected to other neurons through an average of about 10,000 synapses—a big number, but a finite number, nonetheless. DARPA’s SyNAPSE project is committed to scaling memristor technology to biological levels and once accomplished, surpassing biological computation is the next logical step in the technological revolution wrought by memristive devices.

Memristor chips function like flash memory and retain data even after a computer is turned off while consuming less energy, requiring less silicon and fewer transistors. Since individual memristive circuits hold their own memory and processor, memristors hold the ability to tremendously expedite data processing and consequently hold the key to accelerating advances in all scientific fields, especially neuroscience. Just imagine that: a brain-inspired device being used to discover deeper complexities of its very inspiration!

Other implications of faster-than-brain computation

As a technological retailer, HP’s primary interest is in the marketing of memristors for cell phones, videogames, computers, etc. For the rest of us, however, the creation of a mere chip that can compute better than any human could bear immense philosophical weight. For example, a memristive computer with more synapses than a human brain could technically hold enough associative memories to be able to pass a Turing test. A Turing test employs an interrogator who asks written questions to decide whether its subject is a human or machine. Surprisingly, there has been no machine to date that can convincingly pass the test and successfully mimic a human enough to actually fool one, though the discovery of the memristor will probably change that.

In addition to this philosophical weight, neural modelers will also have to bear the financial implications of such a discovery; many computational neuroscientists will be forced to decide whether they choose to work at designing neuromimetics (i.e. brain-inspired technology) or strictly modeling neurobiological circuit processes. As a young neuroscientist (and self-proclaimed gadget junkie), I have to admit myself feeling conflicted at times between the two fields: I would consider neuromimetics a more lucrative field in the sense that technologies created through it will revolutionize the everyday lives of most people who rely on computational devices. As such, neuromimeticists will probably make more money, have more media exposure, and accordingly, acquire even more funding. In fact, this has prediction has already proven valid if we perform some simple calculations on the financial statistics mentioned earlier: if 50% of CNS’s funding, or about $3 million dollars, is distributed in direct/indirect costs to 5 post-doctoral defense researchers, each defense researcher has a crude average of $600,000 in funding (which may not seem like a lot, but is entirely sufficient for computational modelers who often do not require expensive hardware). On the other hand, CELEST funding amounting to a roundabout of $4 million is distributed between the other 20 post-doctoral biological researchers, which allows for an average of only $200,000 per postdoctoral researcher. Although these calculations are approximate, the glaring contrast between the amount of funding awarded to both parties is too asymmetrical to be ignored.

Despite this pronounced imbalance in funding, I recognize that my loyalty is to discovering how brain processes give rise to emergent properties such as dreams, emotions, desires, beliefs, and ultimately, consciousness—seemingly infinite complexities that machines may never even be capable of reproducing. Neuroscience researchers may be apprehensive about the increasing difficulties for computational neurobiologists to compete with the amount of funding that defense agencies can offer to biomimetic projects such as remote sensing software designed for PackBot robots deployed in Iraq (as engineered by the brilliant minds at BU’s very own CNS Tech Lab). As we all know, acquiring sufficient
funding for research is the bane of most scientist’s careers. It seems
only inevitable that systems level neuroscience departments will
start producing more and more bionic research with little compa-
rable growth in biological modeling research if developing neuro-
morphic technology is considered so much more profitable.

So what can we do to change this disparity? The root of the
problem is buried deep within the workings of our governmen-
tal system and the priorities our government chooses to assign
to developing cutting-edge military technology as compared to funding
biological research. In 2010, DAR-
PA’s proposed budget is 3.25 bil-
lion dollars, whereas the National
Institute of Mental Health (NIMH)
is appropriated less than half that
amount by the NIH. Continuing the
wars in Iraq and Afghanistan is of
little everyday concern to most
Americans; the research of neural
dynamics that eventually leads to
the eradication of schizophrenia
and depression, however, could po-
tentially help over 25 million peo-
ple in the United States alone.

Conclusion

I surmise that the impact that memristors have on neuroscience
research should generally be a posi-
tive one. Allowing for the study of
brain computation at a speed that
is faster than the speed of brain
computation will enable faster data
processing, and thus, faster output
of research.

Nevertheless, the impact DAR-
PA funding has on neuroscience
still deserves monitoring as it could
direct resources away from brain
research. As artificial computation
becomes faster than the speed of
brain computation, neuroscience
funding could be easily redirected
toward developing applications
inspired by neural design. Under-
standing complex brain mecha-
nisms such as consciousness and
advancing research in organic neu-
ral circuits will certainly prove use-
ful not only in solving the myster-
ies of complex brain diseases such
as schizophrenia, depression, and
epilepsy, but it will also contribute
to the human understanding of bi-
ological networks and how they can
be integrated into a “Theory of Ev-
erything”. Brain mechanisms have
already proven to be infinitely more
complex than any artificial intelli-
gence design we could even dream
of programming, and it would be a
shame to waste any more time in
determining them. As such, neuro-
scientists should reserve the right
to question whether their research
is directly relevant to discovering
the processes of the brain and will
it help people in need?

This editorial is not against
artificial intelligence inspired by
neural mechanisms; it is merely
a suggestion for a separation be-
tween biological neuroscience and
neuromimetics in order to ensure
that discovering the laws of neu-
robiology is at the forefront, espe-
cially as it becomes more and more
profitable to create technologies
inspired by neural models.

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General Anesthesia: Molecules to Pink Elephants

by Grigori Guitchounts
Introduction

“Gentlemen, this is no humbug,” the surgeon John Warren is said to have declared to the audience at Massachusetts General Hospital after William Morton’s first successful demonstration of general anesthesia on October 16th, 1846. Before then, surgery was a miserable experience for both patient and surgeon. The term anesthesia – literally meaning “without sensation” – was first used by the ancient Greek surgeon Dioscorides and resurrected by Dr. Oliver Wendell Holmes after the demonstration at MGH.

Anesthesia has indeed transformed medicine and while great improvements have been made in the clinical aspect of anesthesia since the 1840’s, the mechanism by which anesthesia produces reversible changes in central nervous system function have remained a mystery until recently.

In the past decade, anesthesia has grown to be used in various medical settings outside the operating room. Children undergoing Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scans, or endoscopy are often sedated or anesthetized to assure cooperation and the required immobility2,3. Likewise, electroconvulsive therapy, long considered more torturer than treatment, is now being used with the aid of general anesthesia as an effective treatment for medication-resistant depression and schizophrenic affective disorders.4

However, despite the multitude of benefits to medical procedures that anesthesia has provided, it remains a somewhat dangerous and toxic procedure, usually involving postoperative delirium5 and sometimes cognitive dysfunction6; even more frightening is the fact that one in 750 patients remain aware during general anesthesia7. The intravenous general anesthetics etomidate and propofol are widely appreciated for their anesthetizing properties, but are also associated with unfavorable toxicities. Patients develop “propofol infusion syndrome” after prolonged exposure to the drug; this is associated with dysrhythmias, lipemia, fatty liver, metabolic acidosis, and rhabdomyolysis8. Etomidate causes adrenal suppression, putting patients at high risk of mortality9. More common side effects include respiratory depression, hypotension, and postoperative nausea and vomiting.

It is therefore critical for safety and the progress of medicine that better drugs and methods be developed for use in general anesthesia. This review focuses on the goals of general anesthesia, the theories behind its mechanism of action, and studies of the structure and function of the GABAA receptors that mediate anesthetic action.

Goals of General Anesthesia

The basic idea of general anesthesia (GA) is to make the patient unaware of the surgical trauma and unmoving, and to allow the surgeon to perform his job with precision. More specifically, the goals of GAs are to reversibly induce immobility, amnesia, and hypnosis (unconsciousness) in the patient; a fourth and often debated goal is analgesia, which some argue is an irrelevant measure since the patient is unconscious during anesthesia.

The three goals have dissociable correlates in the brain; amnesia, consciousness, and immobility are mediated by different neural systems and therefore respond differentially to drugs. Potency of inhaled anesthetics is assessed using a scale of concentra-
tions required to suppress patient response to certain stimuli. Potency is inversely related to the amount of anesthetic required – as measured by alveolar concentration – to reach certain behavioral goals like immobility after a noxious stimulus or no response to spoken commands. The most commonly used scale is the Median Alveolar Concentration (MAC or MAC-immobility), which measures end-respiratory concentration of anesthetic for which half of the patients do not withdraw in response to a surgical incision. Other common scales include MAC-awake, a concentration that prevents physical response to spoken comments, such as to squeeze the doctor’s finger; and MAC-BAR, a concentration of anesthetic that blocks autonomic responses like blood pressure or heart rate changes to a surgical incision.

That the behavioral end-goals of amnesia, unconsciousness, and immobility require different concentrations of anesthetics (i.e. they have different MAC values) and that the ratios of MAC-awake to MAC-immobility vary among different volatile anesthetics, suggest that the three behavioral end-goals are mediated by different neural mechanisms.

Immobility

A common assumption has been that all anesthetic effects are mediated by the central nervous system (CNS) above the brainstem. However some studies have implicated the spinal cord as key to producing immobility. Experiments in goats, whose unique circulatory system makes it possible to isolate the forebrain’s circulation from that of the brainstem and spinal cord, have shown that immobility is in fact produced primarily by the spinal cord. Selective administration of isoflurane to the brain raises the concentration required to suppress movements in response to noxious stimuli threefold. In contrast, administration of isoflurane to only the body (brainstem and below) induces immobility at the concentrations required for whole animals. So while the brain is able to induce immobility, it is not required, nor is it the primary actor.

Hypnosis

Hypnosis is defined as the impairment of perception and awareness, or loss of consciousness – a critical component of general anesthesia. Loss of consciousness in anesthesia is remarkably similar to stages of sleep. Functional magnetic resonance imaging (fMRI) studies show that the brain regions affected by sleep or anesthesia overlap significantly. Studies of the brain during sleep may therefore inform what we know of GA-induced unconsciousness.

The thalamus acts as a major relay center in the brain, passing sensory information from the outside world up to cortex. In the awake brain, thalamocortical neurons receive depolarizing input from arousal nuclei in the ventrolateral preoptic area, VLPO, which allows them to faithfully pass along information to cortical neurons in a single-spike tonic firing fashion. In contrast, during sleep the ascending arousal input to thalamocortical cells is inhibited. Thalamocortical cells lacking this depolarization enter an oscillatory firing mode, generated by $I_h$ and $I_{Ca}$, which subsequently prevents the transmission of signals to cortex.

The most obvious similarities between sleep and loss of consciousness under anesthesia aside, the two states share nearly identical EEG signatures (i.e. spindles and delta waves), suggesting that the thalamus is involved in sleep as well as anesthetic-induced loss of consciousness. However, general anesthetics do have widespread molecular targets, such as GABA receptors, which are found in a large number of inhibitory cortical interneurons. It remains unclear whether their effects in the thalamus (specifically on the reticular system) are necessary and/or sufficient for loss of consciousness.

Amnesia

The hippocampus and surrounding medial temporal lobe (MTL) structures are responsible for the formation and consolidation of episodic memories. The hippocampus is therefore a likely target of general anesthetics. The formation of memory depends on the integrity of Long Term Potentiation (LTP), which requires functioning NMDA receptors. It follows that inhibition of NMDA receptors by general anesthetics, such as cyclopropane and ketamine, would impair memory. Some studies also implicate the amygdala, which processes affective information and is strongly connected to the hippocampus.

THEORIES OF ACTION

Lipid vs. Protein

At the beginning of the 20th century, Hans Meyer and Charles Overton observed a correlation between the potency of anesthetic agents and their solubility.
in olive oil. The Meyer-Overton rule predicts that the more hydrophobic the anesthetic, the higher its potency. From the Meyer-Overton rule, it followed that all anesthetics must act through a common mechanism, probably in the cell membrane, which is a hydrophobic lipid bilayer, and that anesthetics somehow disrupt that bilayer. And while most people agreed that the final result of the perturbation of the cell membrane was a conformational change in the structure of membrane proteins, none of the lipid theories explained how this could happen. It was not until the latter half of the 20th century that research emphasis turned to the interactions between anesthetics and proteins themselves. In an important set of experiments, Franks and Lieb showed that the lipid-free enzyme luciferase could be inhibited by anesthetics following the Meyer-Overton rule: the higher the hydrophobicity of the anesthetic, the more potently it inhibited luciferase. While anesthetics target diverse molecules, such as PKC, transmembrane ion channels have received the most attention. Research since then has focused mostly on the hypothesis that anesthetics enhance the action of inhibitory ion channels (GABA and glycine receptors) and inhibit excitatory ion channels (Serotonin type 3; nicotinic acetylcholine; and glutamate receptors). For example, electrophysiological studies have shown that the GABA receptor is a major target of intravenous general anesthetics, such as propofol and etomidate.

Current work is focused on the structure-function relationships of the target ligand-gated ion channels (i.e. how the molecular structure of a receptor mediates its ion-conducting function) in order to elucidate the molecular mechanism by which such channels open and close; and the sites at which anesthetic agents bind and affect those channels. While the former has been of interest to the entire neurobiology community since the 1950’s, when Hodgkin and Huxley proposed a model of the action potential that depended on a mystical conduction of ions across the cell membrane, the latter promises the more practical improvement of clinical outcomes for patients undergoing general anesthesia. With the elucidation of the pharmacologic interactions between proteins and anesthetics, researcher-physicians may soon have at their disposal better drugs that produce minimal side effects and toxicity.

THREE GROUPS OF ANESTHETICS

General anesthetics have been classified into three groups based on their relative potencies for behavioral endpoints and effects on the EEG.

Group 1: Etomidate, propofol, and barbiturates

Etomidate, propofol, and barbiturates produce amnesia and hypnosis at doses far lower than those for immobility (reviewed in ref 17). These drugs act via GABA receptors, the most abundant inhibitory ligand-gated ion channels in the brain. Convincing evidence for their action via GABA receptors comes from mutation and transgenic animal studies.

Etomidate’s action via GABA receptors has been confirmed in studies utilizing its chirality. R(+)-etomidate is 20 times more potent at inducing Loss of Righting Reflex (LORR) in animals, a surrogate test of consciousness, than S(-)-etomidate. Likewise, the R(+) enantiomer modulates GABAARs 20 times more potently than does the S(-) enantiomer.

Moreover, mutations on the GABAAR subunits affect GABAAR electrophysiology and in vivo responses to anesthetics similarly. For example, mice with a methionine residue in place of asparagine at the 265 position on the β3 subunit exhibited a four-fold reduction in sensitivity to propofol and etomidate anesthesia, specifically immobility. The same point mutation reduces anesthetic modulation of the receptors in electrophysiology studies. The same mutation on the β2 subunit did not affect immobility or hypnosis, but reduced sedation in mice. Furthermore, mice lacking α5 GABAAR subunits were insensitive to etomidate’s amnesic effects. And while the β3(N265M) mutation reduces hypnosis and immobility response, it preserves the undesirable effect of respiratory depression, showing that GABAARs are not etomidate’s only target in the body.

Group 2: Nitrous oxide, cyclopropane, and ketamine

Drugs in Group 2 act mostly via glutamatergic NMDA receptors, as opposed to GABA receptors. Glutamate is the most abundant excitatory neurotransmitter in the brain, so it’s no surprise that inhibition
of glutamate receptors would produce anesthetic effects, which among the Group 2 drugs are mostly analgesia, weak hypnosis and immobility\textsuperscript{17}.

As with etomidate, ketamine chirality has been used to correlate its anesthetic effects with NMDA receptor modulation. S-ketamine was 1.9 times more potent in inhibiting NMDA receptors in hippocampal slice preparations than was R-ketamine; the same effect was observed in vivo\textsuperscript{17}.

Horace Wells noted nitrous oxide’s (NO\textsubscript{2}, “laughing gas”) analgesic properties while attending a demonstration in 1845; Wells’ own demonstration of nitrous oxide’s anesthetic properties at MGH was deemed a failure. Transgenic animal studies have shown that NO\textsubscript{2} also acts via NMDA receptors. Transgenic mice lacking the ε1 subunit (homolog of the human NR2A) of the NMDA receptor do not exhibit immobility or loss of righting reflex under NO\textsubscript{2} administration\textsuperscript{24}.

However, using an NMDA antagonist MK-801, Stabernack et al.\textsuperscript{25} showed that inhibition of NMDA receptors is not sufficient to produce anesthesia. Administration of MK-801 alone reduced MAC but did not produce immobility\textsuperscript{25}.

**Group 3: Halogenated volatile anesthetics**

The halogenated volatile anesthetics, usually isoflurane, sevoflurane, desflurane, and halothane, are the least selective of the general anesthetics. These anesthetics affect the GABA\textsubscript{A}Rs, two-pore K\textsuperscript{+} channels, NMDA and 5HT3 receptors, Na\textsuperscript{+} channels, and other targets\textsuperscript{26}.

**STRUCTURE AND FUNCTION OF CYS-LOOP LIGAND-GATED ION CHANNELS**

Studies show that the GABA\textsubscript{A} receptor is a major target of halogenated volatile anesthetics and intravenous anesthetics such as etomidate and propofol. The GABA\textsubscript{A}R is a member of a large family of ligand-gated ion channels known as the cysteine loop family for the cysteine loop that all family members share; other members include the 5HT3, glycine, and nACh receptors. Most of what is known about the structure of the GAB\textsubscript{A}R comes from studies of the nicotinic acetylcholine receptor:

**Nicotinic Acetylcholine Receptor**

Serious investigation into the structure and function of the nAChR began with the studies of the Torpedo electric ray nAChR\textsuperscript{27,28,29,30}. Electron microscopy revealed that the receptor is composed of five subunits organized around a central pore. Molecular cloning showed that each subunit consists of four α-helical transmembrane domains (TM1-4). TM2 lines the pore, TM1 and 3 are next to it, and TM4 faces the membrane. Importantly, TM2 is able to interact with hydrophilic molecules since it faces the water-permeable pore, while the other transmembrane domains interact with the hydrophobic cell membrane\textsuperscript{31}.

Advances in genomics have produced large libraries of eukaryotic and prokaryotic genes that are available for analysis. Interestingly, these libraries have brought to light a large number of cysteine-loop LGIC genes conserved in prokaryotes\textsuperscript{32}. One such advance was the discovery of the Acetylcholine Binding Protein (AChBP) found in the snail Lymnaea stagnalis, where it mediates neurotransmission. Even though AChBP is water-soluble and lacks the transmembrane domain of mammalian nAChRs, it nonetheless forms a homopentamer with distinct acetylcholine and nicotine binding sites\textsuperscript{33}. As expected from prior experiments, ligand binding occurs at the interface between subunits, with different affinities for acetylcholine, nicotine, and the agonist carbamylcholine. While ligand binding induces local conformational changes, studies of signal transduction in a system that lacks the transmembrane domain that is integral for the study of channel gating have to be interpreted with caution.

In contrast with AChBP, which is a good model for the extracellular domain of the nAChR, the Erwinia chrysanthemi (ELIC) and Gloebacter violaceus (GLIC) channels reveal the minimal structural requirements for a functional LGIC in the Cys-loop family. Even though ELIC and GLIC share only 16\% and 20\%, respectively, of the sequence with the nAChR, their structures are remarkably similar\textsuperscript{34,35}. GLIC is activated by protons, while ELIC’s activating ligand has not been discovered yet. The X-ray crystallography structures of ELIC and GLIC are valuable because they are thought to show the closed and open conformations of the protein, respectively. Hilf and Dutzler suggest that the difference in the two conformations can explain the mechanism of gating (channel opening). Specifically, it is the difference in orientation of TM2 and TM3 α helices and the extracellular β sheet between the GLIC and ELIC structures that Hilf and Dutzler base their hypothesis on.

Similar to the pores of other cation channels, the
GLIC pore-lining TM2 domain is composed of hydrophobic bulky residues; the intracellular half is filled with polar residues such as serine and threonine, making this part of the pore hydrophilic. Cation selectivity arises most likely from a conserved ring of glutamate residues on the intracellular end of the pore; this “intermediate ring of charges” is also found in the Torpedo and muscle nAChR. 

**GABA A Receptors**

The GABA A receptor is the major inhibitory ligand-gated ion channel in CNS neurons, found in all layers of the cerebral cortex, the hippocampus and the rest of the limbic system, the cerebellum, thalamus, and brainstem. The receptor is composed of five subunits arranged pseudosymmetrically around a central ion-conducting pore. Nineteen subunit varieties have been cloned to date, which theoretically allows for a tremendous amount of diversity of expressed receptors. However, not all possible combinations have been found assembled, and indeed the majority of the neuronal receptors are composed of a, β, and γ subunits. Nevertheless, the abundance of subunit varieties, as well as subunit-dependent localization of the receptors in the brain make GABAARs a promising target for drug discovery.

Upon activation by GABA, the receptor pore conducts Cl- and bicarbonate ions, hyperpolarizing the neuron and thereby reducing the action potential firing rate. GABAARs are thought to be the major target of several general anesthetics, including etomidate, propofol, alcohols, halogenated volatile anesthetics, and barbiturates. The understanding of how these and other drugs affect the GABA receptor is essential for improvements in anesthetic drugs and treatments of CNS diseases.

### Structure

Using a forced subunit assembly method, Sigel and colleagues determined that receptors composed of α1β2γ2 subunits (the major isoform) are arranged γ2β2α1β2α1 counterclockwise when viewed from the synaptic cleft. Each of the five subunits making up a GABAAR contains a large N-terminal domain, four transmembrane domains (TM1–4) and an intracellular domain between TM3 and TM4. The receptor conducts ions in an all-or-none fashion, transitioning among the open, closed, and desensitized states. Ligand binding is described in terms of an allostERIC model in which ligands bind and affect the protein at sites distinct (and sometimes far) from the GABA site. These allostERIC sites may be found in the extracellular and transmembrane domains of the GABAAR.

### Extracellular Domain

GABAARs have two binding sites for GABA, each in the extracellular domain at the interface between the α and β subunits; GABA binding at these sites opens the Cl- pore. Baumann et al used point mutations on linked subunits to differentiate the contributions of each site to channel gating (using free subunits does not indicate which of the two α/β interfaces has the desired mutation), showing that the α/β site where α is adjacent to γ is more sensitive to GABA; and conversely that the α/β site where β is adjacent to γ is more sensitive to the competitive antagonists bicuculline and muscimol.

Classic benzodiazepines enhance inward currents produced by GABA binding. Benzodiazepines bind with high affinity at the interface between α and γ subunits, sites homologous to GABA’s at the two αβ interfaces. Rusch and Forman showed that benzodiazepines enhance GABA currents by enhancing GABA gating as opposed to binding. Using the Monod-Wyman-Changeux allostERIC model, they were able to conclude that benzodiazepines are high-affinity but low-efficacy co-agonists, in stark contrast to general anesthetics such as etomidate, which are low-affinity high-efficacy agonists. The differences between benzodiazepine and etomidate agonism are further highlighted by single-channel studies. These studies show that etomidate lengthens the mean single-channel open time, whereas benzodiazepines do not; although single channels did open more frequently in the presence of benzodiazepines or etomidate.

### Transmembrane Domain

A diverse set of organic compounds has been shown to act by binding to sites in the GABAAR transmembrane domain. These include alcohols, neurosteroids, barbiturates, volatile anesthetics, etomidate, and propofol.

### Alcohols

Alcohols enhance GABA-induced currents in αβγ GABAARs, and reduce currents in receptors with
ρ1 subunits\textsuperscript{41}. Mihic et al (1997) constructed chimeric receptors containing sequences from the GABA ρ subunit and the glycine receptor α1 subunit (a close homolog of αβγ GABAAR). They were able to identify a region of 45 amino acids between TM2 and TM3 that are necessary and sufficient for enhancement of currents by ethanol and enflurane. Specifically, the α1S270 and β1S265 in the TM2, as well as α2A291, β1M286, and β3N265 in the TM3, were critical to ethanol's enhancement of GABA currents.

Barbiturates

Barbiturates are CNS depressants, and have been used through the 20th century to treat conditions such as insomnia, anxiety and epilepsy; and in the OR as inducers of anesthesia (their history is reviewed in ref 55). Like etomidate, pentobarbital enhances GABA currents at low concentrations and activates GABAARs directly at high concentrations\textsuperscript{52}; at even higher concentrations (millimolar) pentobarbital blocks GABA currents.

Etomidate and Propofol

At clinically relevant concentrations, the potent intravenous anesthetic etomidate enhances activation of GABAARs by GABA (lowers EC50)\textsuperscript{56}. This interaction directly activates GABAARs at higher concentrations, in the absence of GABA\textsuperscript{56}. These two types of activation suggest that GABAARs have two types of etomidate sites – high-affinity sites that enhance GABA sensitivity and low-affinity sites that directly activate the receptor. These observations suggest an orthosteric model where etomidate binds to the same site as GABA to directly activate the receptor (and an allosteric site to enhance GABA activation). However, using electrophysiological methods and the Monod-Wyman-Changeux allosteric model, Rusch et al. (2004) showed that a single class of sites can explain both enhancement and direct activation, concluding that etomidate's affinity for the receptor changes depending on the receptor's state (open or closed); the open receptor has a high affinity for etomidate, whereas the closed receptor has a low affinity\textsuperscript{56}.

Evidence that etomidate acts at the interface of the α and β subunits comes from experiments using a photoactivatable etomidate analog, [3H]azi-etomidate, which labels the amino acids αM236 (TM1) and βM286 (TM3).\textsuperscript{57}

Mutations of these residues to tryptophan (which is bulky and hydrophobic like etomidate), α1M236W and β2M286W, mimic etomidate presence. Stewart et al used these mutations to show that one class of sites is sufficient to explain etomidate's effects.\textsuperscript{58} The β2M286W mutant was insensitive to etomidate direct activation and had zero GABA enhancement by etomidate, consistent with one type of modulatory site. In contrast, the α1M236W mutant showed reduced GABA potentiation by etomidate compared to wild-type but increased direct activation. These opposite effects seem to suggest two classes of etomidate sites, but are nevertheless consistent with the interpretation of one class of sites: etomidate's efficacy is reduced in the α1M236W mutant, but direct activation appears to be enhanced because the mutant has high spontaneous activity, which lowers the energy barrier required for channel opening.

Propofol has been thought to act near the TM2 domain at α1Ser270/β2Asn265 and TM3 domain at α1A291/β2M286. Cysteine protection experiments showed that propofol protects all four of these residues, but only β2M286 in a dose-dependent manner, implicating this residue as the propofol binding site.\textsuperscript{59} However, Siegwart et al showed that the mutants β3M286W as well as β3N265M significantly reduce propofol enhancement of GABA currents and direct activation by propofol.\textsuperscript{53} Propofol's varying effects on receptors composed of different forms of the β subunit may be useful in drug discovery or modification.

New or Improved Drugs

Going forward, two major branches of research must be pursued to ensure success in the development of new anesthetic drugs. These are the study of the structure and function of LGICs, as well as their subunit compositions and localization in the human brain; and drug discovery, including high-throughput assays of novel agents and chemical modification of existing drugs such as etomidate.

Efforts to improve etomidate include methoxy carbonyl- (MOC-)etomidate, which is designed to be metabolized quicker than etomidate\textsuperscript{60} and carboetomidate, which is a significantly weaker inhibitor of adrenal cortisol synthesis\textsuperscript{61}. The goal of these chemical modifications is to remove etomidate's toxic properties while preserving the anesthetizing ones.

Another approach is drug discovery. Recently, Lea et al (2010) reported a high-throughput screening of compounds that interact with apoferritin, a soluble protein that mimics the GABAAR's interaction with an-
esthetics. Of 1280 compounds, about 1% were hits. Obviously further electrophysiological, metabolic, and clinical characterizations are necessary before any of those compounds can be used as general anesthetics.

Conclusion

While surgeons and patients have enjoyed the availability of general anesthesia for over 150 years, scientists have not made progress in elucidating its mechanism of action until quite recently. That paradigm shift came in the 1980s, when Franks and Lieb showed that anesthetics act via proteins, not the lipid membrane; research since then has focused primarily on ligand-gated ion channels that mediate fast synaptic transmission in the CNS.

Numerous techniques are available for the study of the structure and function of LGICs, including electron microscopy, cysteine substitution, point mutagenesis, and x-ray crystallography. Our current conception of the 3D structure of the GABAAR is largely based on x-rays of the nicotinic acetylcholine receptor and its homologs. While the overall structure appears to be conserved among the Cys-loop receptors, the fine details (including single amino acids) are different. Until we have a definite idea of GABAAR’s 3D structure, including the orientation of the transmembrane domains where general anesthetics act, our interpretations of experimental data will remain murky. Nevertheless, the past decade’s progress in research on new or improved anesthetics is bound to continue in the next.

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The resection of Patient H.M.’s bilateral medial temporal lobe (MTL) structures in 1957 produced a deficit in encoding new episodic memories, leaving short-term memory, non-declarative memory, and other cognitive functions intact\textsuperscript{15}. The discovery of the relationship between MTL damage and the development of anterograde amnesia has provided evidence that these areas are responsible for memory processes. Animal models have also supported the hypothesis that these areas play a major role in memory function, using lesion methods that have replicated H.M.’s bilateral damage to the hippocampus and the surrounding MTL cortices\textsuperscript{20}. Although animal models of memory research have provided ample evidence in support of this hypothesis, the development of human brain mapping techniques, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), diffusion tensor imaging (DTI), magnetoencephalography (MEG) and transcranial magnetic stimulation (TMS), allow researchers to apply the findings from animal studies and Patient H.M.’s case to investigate both spatial and temporal aspects of the neural network underlying the human memory system, and more specifically, the role of this memory network in spatial navigation.

Due to the evidence provided by animal studies, clinical cases and H.M.’s case, two hypotheses regarding the role of MTL structures in declarative memory have been suggested. The declarative memory hypothesis, proposed by Squire and Zola-Morgan\textsuperscript{44}, posits that the MTL is critical for declarative memory processes only, whereas non-declarative memory components engage areas outside of the MTL. Two years later, Cohen and Eichenbaum\textsuperscript{14} proposed a competing relational memory hypothesis, stating that in addition to being crucial for declarative memories, the MTL structures are also important for acquiring associations among items together in time or across time and for encoding sequences of episodic events. Several studies have been performed using animal models, but a confounding problem with animal studies on episodic memory is that animals cannot explicitly describe their declarative experience after performing their task, which is a critical aspect when studying declarative memory.

In a study to provide a solution to this problem, Schenden et al.\textsuperscript{40} used fMRI and a serial reaction time task (SRTT) to actively test both hypotheses in humans by seeing if the activation of the MTL is dependent on the subject’s conscious awareness of learning sequences. As predicted by the declarative memory hypothesis, the MTL structures should not be activated when a subject is unconsciously aware of learning a sequence of events. In favor of the relational memory hypothesis, this study provided significant fMRI evidence that the hippocampus is activated regardless of the subject’s conscious awareness when learning higher order sequences during the SRTT. Since the SRTT has both spatial and temporal memory components, the activation of the hippocampus during sequence learning, regardless of the subject’s conscious awareness, supports the hypothesis that the hippocampus is involved in binding sequential information and events into a distinct episodic experience. These studies thus provide evidence that hippocampus, along with the surrounding MTL structures, are involved and critical for learning associations of both spatial and non-spatial stimuli across time and for learning sequences of events. Though these findings suggest a role of the MTL in association and sequence learning, these studies have yet to find the role of the MTL in disambiguating between overlapping sequences of episodic events.

The role of the MTL in encoding and retrieving overlapping experiences both spatially and non-spatially have been further studied in animals using invasive techniques including single-cell recordings and selective MTL lesions. With accumulating evidence that the hippocampus is involved in encoding information about different types of episodic experiences.
in the same location, Wood et al.\textsuperscript{45} studied the aspect of encoding overlapping spatial experiences in rats by using a T-maze alternation task in combination with single-cell recordings of the hippocampal CA1 pyramidal cells. Taking into account the number of hippocampal neurons that are specifically influenced by running, head and movement direction, Wood et al.\textsuperscript{45} found that two-thirds of the cells fired differentially when the rat was traversing through the common, central stem of the maze for both left- and right-turn trials. Significant differences between cell firing rates for both left- and right-turn trials provided evidence that CA1 cells show a selective response for both location and context of the trial type, despite the overlapping components of animal’s behavior and pathways traveled. In 2007, Lipton et al.\textsuperscript{29} investigated the role of the dorsocaudal medial entorinal cortex (dMEC) neurons in the disambiguation of overlapping spatial experiences. Similar to Wood et al.’s\textsuperscript{45} study, rats were trained to perform a T-maze alternation task; however, in addition to recording the activity of the CA1 neurons, they also recorded the activity of the dMEC neurons while the rats were performing this task. An interesting robust pattern of firing of the dMEC neurons, more so than the CA1 neurons, exhibited specificity for distinguishing between trial-types (left- and right-turn trials), whereas the CA1 neurons showed a stronger response to the location of the rat within the T-maze. These findings support the MTL’s role in encoding and disambiguating between overlapping spatial events.

Agster et al.\textsuperscript{2} provided complementary evidence that the hippocampus is also involved in the disambiguation of overlapping events with non-spatial stimuli. In this study, rats were presented with two alternating partially overlapping sequences of six odors. Both sequences began with a distinct odor (odor 1a or 1b) followed by another distinct odor (odor 2a or 2b), indicating what sequence they were going to follow (either sequence a or b). Odors 3 and 4 in both sequences were kept constant to provide the degree of overlap and ambiguity between the two sequences. Odors 5a and 5b were used as a test probe, known as the critical choice point, to indicate whether or not the rats could successfully disambiguate between the two partially overlapping sequences. By comparing the performance of the control rats to the rats with selective hippocampal lesions, experimenters found that rats with hippocampal damage were significantly impaired when attempting to successfully disambiguate between sequences at the critical choice point (odors 5a and 5b). This finding suggests that at the critical choice point, the hippocampus is required to recall information from the earlier segment of the sequence in order to successfully disambiguate between sequences after experiencing the overlapping ambiguous component (odors 3 and 4). The findings from these animal studies suggest and support the hypothesis that the hippocampus is critical for encoding and retrieving the information necessary to disambiguate between overlapping episodic representations of spatial and non-spatial events. Given the significant evidence provided by these important animal studies, investigators sought to apply these findings to study the role of human MTL in the encoding and disambiguating between overlapping representations of events by using human brain mapping techniques.

An advantage of fMRI research, as opposed to animal studies, is that fMRI provides investigators with a non-invasive tool to obtain a high spatial, but moderate temporal resolution of brain activity when subjects engage in cognitive tasks. These important techniques allow researchers to spatially map and locate what brain regions are active relative to the task the subjects are performing. With regard to the MTL and its involvement in sequence learning and retrieval, Ross et al.\textsuperscript{30} applied fMRI to investigate if the role of the human hippocampus in sequence learning and sequence retrieval. During the scan, subjects encoded and learned two overlapping (OL) and two non-overlapping (NOL) sequences, each consisting of six cropped faces per sequence. In addition to the four conditions, two random groups of six randomly presented faces were also intermixed to serve as controls for this study. Importantly, post-scan tests revealed that there was no significant difference between difficulty and number of errors made in each condition (100% correct in OL, 98.6% correct in NOL), thus showing that the subjects successfully learned each sequence. Analyzed fMRI data showed hippocampal activation regardless of the degree of overlap of information, thus suggesting a role of the hippocampus in both encoding and retrieval memory processes. Further analysis provided evidence that there was greater hippocampal activity for OL than NOL condition in both the encoding and learned phases of the study, as well as greater hippocampal activity for OL than NOL at the critical choice phase. These findings suggest that overlapping sequences of events demands a greater activation of the hippocampus during retrieval because participants are required to recall the necessary information from the earlier component of
the sequence to successfully disambiguate between overlapping episodic events.

In a similar study, Lehn et al. hypothesized that the MTL is sensitive to recalling naturalistic sequence of events, and aimed to evaluate the contribution of the subregions in the human MTL to the recall of temporal sequences of related events. To test their hypothesis, participants watched a novel movie depicting "true-to-life" characters and "life-like" events, explicitly telling them that they would be tested on this information the next day. During the scan, participants were presented with four scenes, either from different time points (retrieve/reconstruct test) or close together in time (infer/logic test), from the movie and then were asked to place them in the correct order in which they occurred. After each test, subjects reported their level of effort (1 = little effort, 5 = a lot of effort) and the strategy they used to reconstruct the sequences of events (remembered the order, used logic, or other). Intermixed with these two test conditions, a control condition asked the subjects to evaluate a simple math equation. The results from this study showed a significantly greater activation of the hippocampus and the parahippocampal cortex (PHC) during the retrieve test when compared to the infer and control tasks. In combination with the behavioral reports, activity in the right hippocampus was positively correlated with the accuracy of sequence recall, whereas the bilateral PHC activation did not. Most importantly, when comparing the data from the retrieve to the infer tasks, significant bilateral activation of the hippocampus and the PHC during the retrieve trials reflects various mnemonic processes including the retrieval of temporal order, recollection of spatial and non-spatial contexts, and scene and landmark recognition, concurrent with similar studies.

Though these findings of MTL activation for different aspects of sequence learning and retrieval have implied that these structures are critical for encoding and integrating episodic events across time, perception, attention, executive function and connectivity studies have provided insight to a network of areas outside of the MTL that also importantly contribute to the support of normal functioning of these memory processes.

In order to understand the network involved in integrating various types of sensory information into an episodic experience, we must investigate the anatomical and functional connections of MTL to surrounding cortices. Similar to the human prefrontal cortex (PFC), anatomical connections of prefrontal cortex (PFC) in rhesus monkeys to the MTL have been identified using the retrograde tracer horseradish peroxidase. Barbas and Blatt identified ipsilateral projections from the hippocampal complex (hippocampus, presubiculum, and parasubiculum) to distinct areas in the lateral, medial and orbital PFC. Further analysis of their results have shown that the medial PFC receives the most input from the hippocampal region, suggesting the role of the medial PFC in mnemonic processes. Outside of the MTL, anatomical connectivity studies in rhesus monkeys have identified projections from the early and late stages of sensory processing cortices to both the PFC and the OFC, suggesting that these areas integrate, converge and communicate the necessary information for constructing and retrieving episodic memories.

In humans, white matter connections, integrity, degree of diffusivity and the direction of diffusion along white matter tracts can be assessed using DTI. In a study of the relationship between episodic memory and white matter integrity, Charlton et al. measured the mean diffusivity (MD), fractional anisotropy (FA) and white matter hyper-intensities (WMH) of the distributed network of white matter pathways supporting episodic memory in normal aging participants. Results revealed a significant decrease in immediate and delayed memory performance, as well as a decrease in FA and an increase in MD and WMH as age increased, further supporting a similar finding from a DTI study on the relationship between white matter and LTM in adolescents. Interestingly, this study showed that hippocampal volume did not decrease when compared to baseline, thus suggesting that hippocampal atrophy does not significantly contribute to LTM decline in normal aging subjects. This finding suggests that memory decline is not specifically related to hippocampal atrophy, but may be attributed to the reduction of integrity of the white matter connections between the PFC and the MTL. Though these anatomical connectivity studies identified that the PFC, OFC, sensory cortices, and MTL structures communicate critical information for normal memory functioning, the specific role of these areas and their contribution to navigational processes were later investigated.

Computational models of the PFC’s involvement in goal-directed actions and connection to the hippocampus provide evidence that these areas must integrate and communicate information in order to successfully navigate a spatial environment. In support of these models, Churchwell et al. studied the prefrontal-hippocampal pathway in rats and its role in the navigation of a modified Hebb-Williams maze.
To test the contribution of the medial PFC, OFC and the hippocampus in spatial navigation, researchers utilized a deactivation procedure involving lidocaine infusion to these specific areas. Rats with deactivated medial PFC, as well as rats with deactivated hippocampal cortex, were significantly impaired when encoding and retrieving the necessary information to successfully navigate through the maze to the goal box. However, the rats with OFC deactivation did not show any disruption of memory processes, suggesting a dissociation of function in spatial navigation between the OFC and medial PFC. These findings suggest that the interaction of the medial PFC and the hippocampus is critical for encoding and retrieving crucial contextual information, concurrent with evidence from an MEG study on the prefrontal-hippocampal pathway. Although there is an ample amount of evidence from animal studies showing that the hippocampus is critical for spatial navigation, other studies have suggested that the OFC and medial PFC differentially contribute to long-term memory processes.

In a review of the dissociable functions of the medial and lateral OFC, the authors provide evidence that patients with OFC damage display an impairment in decision making, choice responses, complex reasoning, and rule switching relative to reward values. Simple delayed match to sample tasks reveal an enhanced activity in the medial OFC, whereas the lateral OFC exhibits enhanced activity when subjects perform a delayed non-matching task. Such evidence of the lateral OFC being involved in non-matching processes suggests that this area is involved in the flexible expression of a behavioral choice in the context where an outcome is ambiguous. With the OFC showing a flexibility of response choices relative to stimuli-reward associations in novel and familiar contexts, its role in spatial navigation appears to be evident. However, when studying the OFC in humans, PET has been shown to be advantageous when compared to fMRI. Studies have proven that fMRI is susceptible to signal-loss as a result of the sinus cavities in this area, thus making it difficult to investigate the OFC's contribution to memory processes. Frey and Petrides utilized PET, an invasive imaging technique that involves the injection of a radioactive isotope, to examine OFC activity while subjects encoded abstract, non-spatial, non-verbal drawings. The researchers hypothesized that if the demand for active encoding increases, activity of the OFC must increase as well. Four encoding conditions were implemented, ranging from a minimal, control encoding task (condition 1) to a maximal encoding task (condition 4). In conditions 1 and 2, subjects viewed random single presentations of familiar stimuli, whereas in conditions 3 and 4, subjects viewed random single presentations of novel stimuli. However, condition 4 subjects were instructed to explicitly memorize the novel stimulus during scanning. A surprise subsequent recognition memory test was administered to participants after each scanning condition, which was used to assess their encoding performance. In support of their hypothesis, PET analysis revealed that as encoding demands increase, activation of the OFC increases as well. Importantly, there was no other area within the frontal cortex that was significantly activated during encoding conditions. This finding suggests a relationship between OFC and the level of encoding novel material, which also supports OFC anatomical connections to the MTL in the rhesus monkey. Concurrent with OFC studies on memory organizational strategies, condition 4 and subsequent memory results show that a greater use of verbal and semantic association strategies of partici-

"a confounding problem with animal studies on episodic memory is that animals cannot explicitly describe their declarative experience"
pants to memorize material resulted in a better recall of the material. Although Frey and Petrides did not observe any other significant activity in the frontal cortex, they hypothesized that the PFC, an area involved in executive functions, differentially contributes to various mnemonic processes.

The role of PFC in delayed non-match to sample tasks has provided insight to a dissociation of function between the dorsolateral and ventrolateral PFC. A result from this study demonstrates that the dorsolateral PFC is responsible for holding onto the information of a stimulus in the absence of that stimulus and motor planning of goal-directed behaviors, whereas the ventrolateral PFC is involved in making decisions and judgments based on the stimulus information that is actively monitored by the dorsolateral PFC. Although dissociated in function, both areas are highly connected and are critical for normal memory functioning. Such a connection between these areas allows the communication of the necessary information to select the appropriate response in familiar and novel contexts. Another critical function of the PFC in memory was identified in clinical cases involving patients with frontal lobe damage. One deficit these patients exhibit is an impaired ability to freely recall lists of pictures or words. Interestingly, further examination revealed that these frontal lobe patients lacked an organizational strategy when attempting to recall a list of words by randomly recalling words instead of grouping words together. Parallel to this finding, Badre et al. provided significant fMRI evidence that the PFC is organized hierarchically and is critical for executive functions and cognitive control in both abstract and concrete contexts, a critical component of spatial navigation in a novel environment. Patients with PFC damage were tested using four types of higher order cognitive processing tasks consisting of a response task, feature task, dimension task and a context task. Each task was designed to assess and test the hierarchical organization of the PFC and its function in concrete and abstract contexts, respectively. Analysis of the fMRI results shows an interesting organization and dissociation of function between the anterior and posterior PFC. Patients with anterior PFC lesions were affected more on abstract than concrete tasks, whereas patients with posterior PFC lesions were affected more on concrete than abstract tasks. Though these clinical cases provide ample evidence of the PFC's involvement in memory, widespread damage to other areas found in these patients may also contribute to impaired memory processes. A solution to such a problem when investigating the relationship between a brain area and its function is by applying a non-invasive technique with a precise temporal and spatial resolution such as TMS to human brain mapping studies. An important aspect of TMS is that single or repetitive pulses (rTMS) transiently disrupts normal brain activity when applied to a given brain region, thus inducing a 'reversible lesion'.

In order to assess the time course of the dorsolateral PFC's involvement in memory formation, Machizawa et al. applied a double-pulse TMS to both the left and right anterior inferior frontal gyrus, as well as to the control vertex site, during the encoding of sequences of words. Behavioral probes showed that participants who received TMS pulses to the PFC were significantly affected when encoding and consolidating sequences of words, which paralleled the subjects decrease in recognition accuracy. Results strongly suggest that the left inferior frontal gyrus is crucial for long-term memory consolidation and the creation of an organizational mnemonic strategy to remember words, a finding similar to Frey and Petrides. Another TMS study investigated the role of the dorsolateral PFC in memory-guided responses during a spatial recognition task. Application of rTMS to the participant's right dorsolateral PFC resulted in a decrease in performance on spatial recall probes, thus suggesting a role in spatial memory. However, it is important to note that the authors attribute this deficit of spatial recall in subjects to the impairment of preparation and execution of the memory-guided motor response and not to a deficit in retrieval. Evidence of the critical involvement and contribution of the PFC in memory formation, retrieval strategies, and memory-guided responses provides strong evidence that these areas are equally as important as the MTL structures when navigating to a destination of our choice. In a recent fMRI study of remote memory for spatial relations and landmark identity in former taxi drivers with Alzheimer's disease (AD) and
encephalitis, Rosenbaum et al. revealed a network of areas that differentially contribute to the support of spatial memory functions. The focus of this study was on two patients with widespread damage to areas involved in mnemonic processes. Patient S.B.'s widespread atrophy of the hippocampus, parahippocampal cortex, occipitotemporal cortex, inferior parietal and orbitofrontal cortex was a result of AD, whereas Patient I.R.'s atrophy of the hippocampus, left parahippocampal cortex, and anterior temporal cortex was a result of viral encephalitis. Both patients were matched for age, education, and both served as taxi drivers in downtown Toronto for approximately 42 years. Controls were matched for age and education. Performance results from experiments requiring both patients to mentally navigate through remote memories of spatial layouts suggested that despite MTL atrophy, only a limited proportion of old allocentric spatial memories are spared and accessible. This finding suggests that remote memories are stored and accessible outside of the MTL, supporting fMRI evidence from a study on MTL activity during the recall of remote semantic memories. A major dissociation in performance regarding landmark identification and landmark memories was found between Patients S.B and I.R. Patient S.B.'s landmark agnosia was identified during the recognition and identification landmark task. The inability to perceive and imagine familiar landmarks was attributed to his occipitotemporal cortex damage, a region found to be involved in object recognition. Importantly, when both Patient S.B. and I.R. were required to learn and navigate through a novel environment, Patient S.B. was significantly impaired when identifying alternate routes between start and end points after a delay, whereas Patient I.R. performance improved from five errors to no errors on the second day of testing. In addition to S.B.'s landmark agnosia, significant atrophy of S.B.'s right hippocampus, involved in spatial memory, provides evidence of why this patient could not encode and navigate through the novel test environment. This study provides evidence of a relation between widespread brain atrophy and memory dysfunction when navigating through environments; however, it does not reveal the active memory network underlying navigational processes in healthy individuals, and does not directly test how one disambiguates between routes that share common elements.

In everyday life, we rely on a widespread network of brain areas to successfully navigate from one place to another. However, because there is a degree of overlap of streets between these familiar routes, we often make mistakes when trying to navigate to our intended destination. In order to successfully reach our point of interest, our brain must overcome this interference by separating, or disambiguating, between overlapping pathways. In a recent study performed in our lab, Brown et al. studied the effects of contextual retrieval on the disambiguation of well-learned overlapping navigational routes. The researchers postulated that the hippocampus and parahippocampal cortex would be activated for the retrieval of contextual cues and associations which aids in the successful disambiguation between routes, and that the OFC would also be activated when subjects were required to make the correct response after traversing the overlapping component of the maze. Prior to scanning, participants learned to successfully navigate through overlapping (OL) and non-overlapping (NOL) mazes. The OL conditions consisted of six mazes that were split into three pairs. The OL mazes had distinct start and end points, but converged in the middle to provide the degree of overlap between these mazes. Importantly, after traversing down the overlapping hallways, subjects were required to make the correct decision at the critical choice point (where the mazes diverged) to reach the correct end point relative to where they began. The NOL condition consisted of six distinct mazes, with no overlapping components. Unique spatial cues were provided in each hallway for both conditions to serve as contextual cues that allowed the participants to identify the specific maze they were in and which end point they have to navigate to. Post-scan interviews consisted of question regarding their use of landmark objects, how they identified the mazes, and the strategy they employed to make the correct decision at the critical choice point after navigating through the overlapping hallways. fMRI analysis of the first hall period showed a greater activation of all three hypothesized brain areas in the OL condition when compared to the NOL condition. This finding suggests that these areas are important for the retrieval of spatial context, which supports evidence from similar studies.

At the critical choice point, the right hippocampus and right parahippocampal activation, as well as bilateral OFC activation, was also greater for the OL than NOL condition. Right hippocampal and parahippocampal cortex activation suggests the retrieval of distinguishing contextual features from the first hall period, where as the OFC activation reflects the participants selection of the correct navigational re-
response based on the contextual cues and associations retrieved by the MTL. In addition to these areas, the medial parietal and retrosplenial cortices were also active in both first and critical halls. Based on the retrieval strategies used by the participants, both areas have been suggested to play a role in thinking about one’s future, autobiographical memory, and response planning, thus aiding in the successful disambiguation of overlapping routes.

Groundbreaking evidence from animal studies on memory has facilitated an overwhelming amount of research on the human memory network. Although it was believed that the MTL was specific to memory processes, human brain mapping techniques allowed investigators to identify a network of areas that are equally important and critical for supporting spatial navigation. More importantly, studying spatial navigation allows researchers to breakdown this simple, yet complex process that we engage in everyday. Dissecting this phenomenon provides researchers with a better understanding of how we successfully navigate through our environment, as well as understanding the similarities and differences of neural activity across species during a spatial navigation task. With the use of human brain mapping techniques, the relationship between mnemonic processes and brain areas can be further investigated safely and accurately. However, one must be wary when interpreting an author’s evidence and conclusions. Thus, I propose that when reading these studies, one should always read with a critical eye and mind, questioning and comparing result and methods to avoid any misinterpretation of the data. Despite these caveats, as task designs and brain mapping technology advances, researchers hope to decode and model this neural network underlying all cognitive processes with accurate and valid evidence.

References


Evolutionary Psychology on the Couch

by Devyn Buckley
Evolutionary psychology (EP) is the predominant lens of interpretation in psychology today and is expanding into the general public as a contemporary thought trend. As you may guess, it attempts to apply Darwin’s Theory of Evolution to the field of psychology. It explains observed behavior in contemporary humans as results of hard-wired predispositions produced by natural selection. While speculation has its merits, many of E.P.’s claims seem reactionary and guided by an agenda, as is evidenced by the claims’ poor believability and the lack of data that support them. As a result of an ideological polarization occurring between modern religious extremists and their counter Darwinian fundamentalists, E.P. performs logical acrobatics to justify its speculation as fact. I aim to demonstrate the logically fallacious nature of E.P. and its ideological character, particularly as a counter-ideological reaction to the social sciences, religiosity, and feminism.

The Evolution of Psychology

The multitude of previous schools of thought in psychology mostly relied on the premise that the human mind was a malleable thing. Many disciplines emphasized psychological malleability out of a dual motive for truth and social justice. Even John Scopes, who was favored by scientific intellectuals in the 1925 Tennessee vs. Scopes trial, which accused him of un-lawfully teaching evolution in Tennessee, taught from the textbook Civic Biology, which made racist suggestions and endorsed ideas such as sterilization of epileptics and the mentally feeble from the then popular field of eugenics. Anthropology and craniometry had long sought to justify social inequities on both the racial and class levels by making them natural law.

Freudian psychologists emphasized the influence of early childhood and the multiplicity of conflicting motives within an individual psychology. The Behaviorists at the turn of the 20th century held the radical position that all aspects of psychology, including personality and intelligence could be attributed to variations of Pavlov’s conditioning, or learning strictly in terms of reward and punishment. In the 1950’s, humanism provided an almost limitless encouragement of self-actualization, positing that a well-socialized, happy being was attainable through unconditional positive regard and a general atmosphere of goodwill. Meanwhile Cognitive psychology overlapped greatly with neuroscience and studied the structures underlying cognition. The passing of time and the formation of new schools of thought did not reject each system, but dethroned it as the principle means of psychological analysis as soon as the next came along.

E.P. emerged at the end of the 20th century, first in the form of Sociobiology. It began around 1975 when Edward O. Wilson proposed that human psychology, in addition to physiology, could be explained in terms of evolutionary adaptations in his book Sociobiology: The New Synthesis. It was initially unpopular due to a fear of returning social injustice. It reemerged under the new title of E.P. in the 1990’s with books such as The Adapted Mind (1992) by John Tooby and Leda Cosmides and David Buss’s Evolutionary Psychology: the New Science of the Mind (1995).

Reaction to the “Social” Sciences or the SSSM

Dylan Evans and Oscar Zarate, who write in Introducing Evolutionary Psychology, published 1999, that
“In the future, the study of human psychology will be completely transformed by the Darwinian approach... it won’t be called ‘Evolutionary Psychology’. It will just be called ‘psychology.'” David Buss titles one of his papers, "Evolutionary Psychology: A New Paradigm for Psychological Science." The Handbook of Evolutionary Psychology, edited by Buss describes E.P. as a "scientific revolution, a profound paradigm shift in the field of psychology," and a "paradigm within biology itself." All prior schools of thought are dismissed. In The Handbook, Buss labels socio-cultural outlook “mainstream psychology,” which he defines as being “partitioned into subdisciplines—cognitive, social, personality, developmental, clinical, and hybrid areas such as cognitive neuroscience,” that E.P. reveals to lack "logical or scientific warrant." To all of them Buss grants a false premise: the human mind is a “blank slate”. He states, “The human mind can no longer be conceived as it has been in mainstream psychology as a blank slate onto which parents, teachers, and cultures impose their script.” Buss refers to non-evolutionary explanation as the “myth of cultural causation.” All non-evolutionary facets of “mainstream psychology” are united under the appellation of the Standard Social Science Model (SSSM), meaning that they attempt to explain aspects of human behavior by external influences rather than internal predeterminations. Those opposing the revelation of sociobiology by Wilson are described in the Handbook as “intellectuals wedded to the blank slate.”

While previous approaches did not rely on biological explanations, largely out of technological limitations, to say they viewed the human as entirely a blank slate would be a stretch, excepting the behaviorists. Freud, for one, acknowledged uncontrollable impulses and the strength of unconscious instincts. Additionally, despite the radicalism of the Behaviorists, their conditioning experiments were integral to an understanding of learning and cannot be dismissed. Steven Pinker quotes philosopher Nelson Goodman in the foreword of The Handbook to describe alternative psychological explanations as “a pretender; an imposter, a quack.” According to him, they are utterly false because they rely on “similarly, frequency, salience, and regularity” to make conclusions about behavior; explanations Pinker states are “in the eye of the beholder.” They do not address the “why” of behavior. However, the same methods are employed by E.P. in their observation of behavior in order to devise explanations for its existence. What they claim as evidence uses the same observational techniques deemed “quack” in order to legitimatize it, namely it observes and interprets behavior in the mode of a soft science. Furthermore, if observation is in the eye of the beholder, then wouldn't claims concerning un-observable behavior 100,000 years ago be even more so? The only difference then is that E.P. imagines itself to supersede the others because it provides a creation story for behavior, rather than stopping at what is observable and imagines itself to be a science because its vocabulary incorporates biological terms.

I, Robot

Right at the time of Darwinism’s reawakening a revolution was occurring in technology affecting fields from computer science to biology. The mind became the brain the more the brain could be measured. David Marr, a British neuroscientist helped interpret the visual processing system from a computational standpoint. Noam Chomsky’s 1968 study of infants demonstrated the existence of innate linguistic capabilities, revealing the power of inborn mechanisms or modules within the mind, signaling the commencement of the cognitive revolution, or the mechanistic treatment of the mind. Module is a term often used in technological and economic fields because it deals with highly structured mechanisms. It is a general systems concept, meaning, it refers to “complexes of elements or components, which mutually condition and constrain one another, so that the whole complex works together, with some reasonably clearly defined overall function.” Neurological modules exist mostly within the realm of comprehending physical relations, analyzing visual data, processing speech and emotion. These are all areas with minimal variability among individuals in the same way that the pumping heart is more or less unvarying. E.P. grasped the notion of modularity and applied it universally to the point that the human being is a preprogrammed machine. Pinker states that “the brain is not just like a computer—it is a computer” and that “the evolved function of a psychological mechanism is computational.”

Universal modularity seems to go against neurological fact and observed behavior. Modularity is not synonymous with cognition. It details rigid, pre-programmed, unchanging systems. Pinker writes "humans are intelligent not because we have fewer instincts, but more." Instincts are innate for every member of the species, yet, human behavior and personality vary vastly among individuals. How can such
a high degree of flexibility exist in an organism entirely composed of modular instinct? Either each individual possesses her or his own set of instincts or there is a multitude of strongly deviating mutants. This is not to say that modularity does not exist within the human mind, only that the model of its universality fails. Modularity may operate within the realms of language, perception, and emotion, while other more complex psychology involves the interaction of memory, feeling and consciousness, without being the product of a rigid, preprogrammed and definitive process.

A modular system works in a deductive fashion—arriving at a conclusion through a rigid reasoning system with a defined premise. The human consciousness, on the other hand, behaves mostly in an inductive fashion. That is, conclusions are not reached through linear computation, but through a constant modification of experience and probabilistic determinations. Self-awareness is the critical ingredient to non-modularity. Jerry Fodor, a cognitive scientist and original proponent of modularity, gives the example that, although we cannot force our modular visual system to stop perceiving an optical illusion, the fact that we can understand that it is an illusion and reject it or modify our relationship to it illustrates complex cognition outside of modularity.  

The computational model of the human mind seems incongruous with observation, yet E.P. denies it for reasons unconscious to itself. E.P. reacts as it did to the social sciences, to religious and western notions. It represents a facet of the polarization marking this era between scientism and metaphysics.

The Fall of Man

Metaphysics deals with non-quantifiable experience such as philosophy, art, literature, psychology, contributing to E.P. Such an outlook comes from the desire to push against age-old western notions of human nature, particularly those revered by religious extremists. Evolutionary psychologists label them as stubborn, irrational, and imposing to the acquisition of a truth.

Western Culture finds humans to have some elect quality that gives them superiority not only in skill but also in essence over animals. E.P. tries to destroy the notion of the elect human being by placing him within the animal kingdom, but with such over-emphasis that it frames human nature as uniform and instinctual, ignoring the defining factors of humanity: self-awareness and culture. It attempts to crush any utopian notion of a human-invented paradigm toward which we progress, by over-emphasizing negative aspects of human behavior. The Handbook of Evolutionary Psychology takes a missionary tone, stating that “E.P challenges the foundations of crucial enlightenment values.”

Daniel Dennet, a philosopher and advocate of Dawkins’ strict adaptationism, explains in Darwin’s Dangerous Idea natural selection as a “universal

“We have the power to turn against our own creators”  
- Richard Dawkins, The Selfish Gene
acid”: universal referring to its global explanatory power and acid to its corrosion of traditional Western belief.¹²

It is a testament to the power of cultural influence as well as to the influence of the unconscious to observe that while E.P. fights traditional western values, it maintains them in its methodology. As regards love of reasoning, they are in full conformity, for they treat their conjectures as absolute truth, indicating none other than a total faith in the purity and omnipotence of their human reasoning. As regards the elect status of the human being, it is evident that they see their school of thought as superior to any other and in this manner treat themselves as a chosen elect. As regards the notion of paradigm, they treat their system as finalized and refer to it as paradigmatic. Additionally, evolution itself is often treated as purposeful, directed, and perfect. The adapted machine understanding of the human mind conforms not only to the desire for a paradigm, but also to the desire for an anthropomorphic, willful designer found in the religious psychology. The religious personality is explicitly evident in Pinker’s own statement: “Darwin's prophetic vision is being realized.”¹⁵

Most fascinating of fallacies, however, is E.P’s dualistic understanding of human nature despite its determinism. Rejecting cultural influence and free will, evolutionary psychologists perceive what Ivan foreworns in Dostoyevsky’s The Brothers Karamazov that without God “everything is permitted.”¹⁴ God, in this case, can be understood not only as metaphysical impetus for morality, but also as the concept of free will. To preserve morality, evolutionary psychologists separate self from self and ethics from nature. In How the Mind Works Pinker states that science and ethics are “two self-contained systems...science treats people as material objects and its rules are the physical processes that cause behavior through natural selection...ethics treats people as equivalent, sentient, rational, free-willed agents...” ¹⁵ He proposes two separate, equal, and entirely contradicting ways to understand the human being. Dawkins states in The Selfish Gene that “we have the power to turn against our own creators”, the genes.¹⁶ Pinker writes of his choice to never have children and how it is an “evolutionary mistake,” but that if his “genes don't like it, they can go jump in the lake.” What kind of a machine has the power to defy its hardware? What modular, goal-oriented, reductionist system creates a being that can behave counter to its biological fitness? If ethics are not metaphysical or religious delusions, but possess real value, then how are they separate from the supposed biological determinism that shapes all thought and behavior? The paradox arises from the profound error of rejecting the essence of human existence, partly out of radicalized counter-ideology to religion and traditional Western beliefs; that essence being metaconsciousness or the feeling of “I” that is so intimately infused with the also rejected concept of culture. They are not to be denied in simplistic systematization, as their rejection leads to impossible paradoxes and incongruities with human experience.

How can a trait be biologically determined if it is not necessarily expressed? Steven Gould addresses the conundrum in The Mismeasure of Man, stating, “if innate only means possible...then everything we do is innate and the word has no meaning...flexibility is the hallmark of human evolution.” He goes on to say, “we should be wary of...viewing all brain capacities as direct adaptations...additional capacities are ineluctable consequences of structural design, not adaptations...our vastly more complex organic computers were also built for reasons, but possess an almost terrifying array of additional capacities—including, I suspect, most of what makes us human.”¹⁸ Thus, there are basic structures which are universally found, but complex, variable behavior made possible by basic structures is not a modular adaptation, but an expression of an incredible plethora of possibilities. A potential to act one way or the other renders both possibilities essentially non-determining.

Once the existence of systematized thinking is discovered, people accuse it of masking truth in the rigidity of its dogma, and shatter it by revealing a complete opposite of its creed to be true, and in their excitement fall unknowingly into another system as fierce as the first in its conviction and as sensitive towards criticism. Polarized against the SSSM, traditional Western notions of human nature and anti-scientific religious extremism, E.P. falls into the error of counter-ideology. E.P. forcefully defends conjecture out of ideological imperative rather than objectivity and claims conjecture as fact through faith in its dogmatic axioms.

Boys versus Girls

E.P. focuses primarily on sex and supposed sex differences. The most frequently used words in the titles of over 800 articles in two journals, Ethology and Sociobiology and Evolution and Human Behavior include sex, differences, human, and male in that order from 1997-2002 and attractiveness, sexual, facial,
sex, men, female, male from 2003-2008 in that order. E.P.’s narrow window of focus indicates an almost fanatical devotion to naturalizing sex stereotypes as Robert Wright, who initially popularized E.P. in his book The Moral Animal, predicted it would. 

E.P. defines the biologically determined or programmed mating strategies of men and women to be inherently opposing. The textbook Psychology and Life outlines the perspective of E.P. to be such, citing Buss stating “Human males could reproduce hundreds of times a year if they could find willing mates. To produce a child all they need to invest is a teaspoon of sperm and a few minutes of intercourse. Women can reproduce at most once a year and each child... requires a huge amount of time investment and energy... the basic problem facing a male animal is to maximize the number of offspring he produces by mating with the largest number of females possible...but females have the problem of selecting...the biggest, strongest, smartest, most highest-status, most thrilling mate... but also the most committed...” Men, as Buss posits, have an evolved strategy to "seduce and abandon as many women as possible...” and the female strategy is to seek out resources and men of high-status. In essence, women are commitment loving and child-oriented, whereas men are stunted by commitment in the pursuit of their biological imperative to impregnate as many youthful, attractive women as possible.

Women seek resources, status, and "men who are older," according to Buss. In the scheme of E.P. the words "willing mate" are unnecessary, but used to preempt extreme controversy, as happened when Craig T. Palmer and Randy Thornhill, whose paper "Why Men Rape," stated rape was not in its essence a violent act, but "natural, biological phenomenon." They advised the New York Times, "a woman's risk of attack rises along with her hemline, and her willingness to socialize without the company of 'male protectors.'" They suggested men be instructed to repress natural feelings to prevent the act. Like other violent criminal acts, rape is not a global behavior, or an evolved trait, but one behavior out of many coming from a cognitively flexible species.

E.P. perpetuates stereotypes and sexual inequities by making the dream of social justice a farce in the face of fact. By claiming that certain behaviors are innate and modular, the human will becomes ineffectual to change them. A double standard is, thus, justified in which the male is irresponsible, freewheeling, and self-indulgent, while the female is a natural caretaker, a fullfiller of responsibilities, and bearer of burdens, most specifically child-rearing. To EP, female sexual desire is stupefying, if not ignored completely, and the monogamy of men is seen as a female victory or effeminacy. Christopher Ryans, author of Sex at Dawn, titles an entry on his blog on Psychology Today’s website, “Why Does Female Orgasm Exist?” and states how its existence has baffled evolutionary psychologists. David Buss’ book Why Women Have Sex presumes in its title the perplexing nature of the female pursuit of sex. Yet a sexual desire in women would seem more evolutionarily advantageous.

While the premise of E.P. is that an observed behavior is adapted, they refuse to acknowledge female orgasm as an adaptation, but regard it as an enigma or as vestigial. This demonstrates the a priori nature of their beliefs, which shape interpretation through a pre-established conviction of gender roles, making them decide what is or is not an adaptation by preference. If females had choice in selecting mates of high-status, then wouldn’t they have just as much of a choice in pursuing sexual pleasure and preferences? The confusion over female orgasm is really confusion over whether females have choice in pursuing sex or not. E.P. grants women choice only when it allows them to explain the evolution of a pre-existing stereotype.

E.P. is the naturalizes of female objectification, and makes women natural means to ends in the eyes of men, rather than a fellow human being whom they relate to, empathize with and depend on. Their perspective places the male as a champion of fitness and esteems him through a worship of his potential to massively procreate. Warlords and keepers of harems who enslaved women are cited as examples of male fitness and sexual strategy. Psychology and Life gives as an example of a Moroccan despot, King Ismail the Blood Thirsty, who possessed many harems and fathered over 3,000 children, ignoring the fact that a warlord from several hundred years ago is not an exemplar for the biologically determined psychology of every human male anymore than a stay at home dad from the 21st century is. Buss cites the Turkmen of Persia to justify women’s resource-oriented strategy and men’s sex-oriented one: the males in the wealthier half of the population left 75 percent more offspring than males in the poorer counterparts. Interpreting this as a fulfillment of evolutionary roles ignores the entire cultural background which was, like the majority of societies throughout history and the world, possessive of women, selling them into marriage and denying them equitable societal status. To say that the enslavement,
domination, and objectification of women is natural justifies sexual inequity and preempts social change. The same textbook Psychology and Life lists exemplary power hierarchies as: “parent-child, teacher-student, doctor-patient, boss-worker, male-female.” This exemplifies attitudes of E.P. 22

The aggressive anti-feminist tone of E.P. is illustrated by Ryan who states, “boys will be boys, and men will be the way they are, despite the many ways our society tries to make them change.”23 Ryan quotes Donald Symons saying “The sexually insatiable woman is to be found primarily, if not exclusively, in the ideology of feminism, the hopes of boys, and the fears of men.”

The stereotypes naturalized by E.P. are facts of current culture. Women are shown to be “resource obsessive,” pursuing shoes, handbags and men with great wealth. A popular T-shirt depicts a man and woman getting married with the words “game over” underneath. A poster for the show Entourage on Spike, the men’s channel, shows two female bodies in bikinis outlining authoritative male figures in suits with the caption, “where every guy can get some.” The Evolutionist describes it as “a flood of magazines and television programmes celebrating the distinct features of “maleness” - ogling, drinking, fighting, playing football...” It describes this as a reaction to the failed attempt to modify male behavior by sociologists.6

An article in The Economist titled “Sex, Shopping, and Thinking in pink” argued that women were evolutionarily programmed to enjoy shopping and to be attracted to pink, a color designated feminine in Europe and America around 195027, since it signified the color of berries and emotional states on faces, making them good empathizers.28

Once again, the errors lie in the foundational mistakes of E.P. The dismissal of obvious social and cultural phenomena does not come from reason, but from adherence to dogma and a desire to make stereotypes irrefutable. What they designate as evidence is behavior selected by them to be interpreted with a priori conclusions. Perhaps a uniform history of denying women equal career opportunity could have made attaching oneself to an economically stable, older man more conservative for women. Equitable social and economic status for women is fairly new, and limited geographically. A cross-cultural examination may reveal universal cultural phenomena but a biological reality. The poor status and treatment of women, for example, is similar throughout history and throughout culture. Would this not lead to similar behavioral phenomena?

A study in Psychology and Life involved over 16,000 participants from 52 nations about their interest in “short-term sexual relationships,” in which men reported greater desire for sexual variety than did women.22 The survey does not validate an evolutionary narrative, but reveals merely what those participants at that point in time and space revealed about their personal motives. Take this as a testament to the nature of surveys: “In 1953, Alfred Kinsey, Ph.D., the famous sexuality researcher, found that nearly 40 percent of the 5,628 women he interviewed experienced at least one nocturnal orgasm (orgasms during sleep), or “wet dream,” by the time they were forty-five years old. A smaller study published in the Journal of Sex Research in 1986 found that 85 percent of the women who had experienced nocturnal orgasms had done so by the age of twenty-one, some even before they turned thirteen.”29 The dramatic increase was not due to a biological change, but a change in what participants stated about themselves and also, likely, changing societal attitudes about women’s sexuality.

E.P.’s most fatal error is its denial of humanity. It places women and men in psychological sexual conflict in which they must attempt to trick one another to achieve satisfaction. Buss states “One of the key insights of evolutionary psychology is that humans have inherent conflicts of interest with other individuals, with members of their own family, with members of the opposite sex, and members of their own sex,” and describes his major interest as “topic of conflict between the sexes.”6 E.P. attitude sees all elements of nature in conflict, including the supposed modules within oneself or “scores of instincts assembled into programmes and pitted in competition,” as described by Pinker. This misinterprets not only the relation between the genders, but evolution as a whole and critical aspects of a social humanity.

Adaptation can result from mutually beneficial relationships between individuals who share the same needs. The parts of the brain, as well, work very nicely together, not because they are in competition, but because their harmony gives rise to a well functioning whole. In the system of E.P. there is hardly need for men to fall in love or for women to experience orgasm, as Ryan notes, yet this occurs anyway. Why not incorporate them into one’s evolutionary schema? Perhaps men and women form lasting bonds out of mutual emotional and physical need as many seem to do. Maybe it is through supporting these needs together that ensures the success of both? Though we may only speculate, isn’t it probable that cave people
in their small social groups facing a threatening climate similarly needed steady bonds with other members both to survive as well as ensure the health of their offspring? Perhaps the attentiveness of a man to his mate and offspring ensures their success more than those who abandon them to the environment? It would seem the thing of greatest need in small groups struggling to survive would be trust and ritual culture.

Perhaps E.P. could be more appreciable if had a set of varied narratives, but it does not. Its emphasis on conflict neglects the various complex emotional and social needs that are satisfied by relationships unique to human beings. Relations between the genders are about more than just procreation, and successful human procreation is about more than just copulation. By treating people as animals, not only in taxonomy, but in essence of spirit, we lose the defining quality of humanity—that is, the self-awareness and all the psychological complexity that comes with a reasoning and emoting conscious.

To Err is Human

It is important to remember that in the noble quest to uncover the basis of our psychology, we sometimes overlook our psychology. The influences of other people, as well as the motives of the unconscious, present the greatest obfuscations to truth, while at the same time are least detected, by virtue of the very fact that they are not conscious. Societal convention and self-serving belief, the two often one in the same, constitute the great Lochness of the depths of the unconscious, powerful, ageless, and hidden, churning the waters of consciousness in the minds of even the most earnest. In the excitement of a new school of thought, it is often easy to forget that the present is also part of history and that the current era, since it is always the most modern, does not signify an arrival at final truth, but the most current contribution to a succession of imperfect perspectives. Deconstructing E.P.'s methods one finds the symptoms of the ideological or religious personality, whose most integral aspect the circular logic of faith. E.P.'s assumptions concerning biological determinism and modularity are in opposition to the facts of behavioral flexibility, the humanity of self-awareness, and culture. Its beliefs are often counter-ideology to the social sciences, religiosity, and feminism. Understanding what is false is one way of understanding what is true. Deconstructing E.P. illuminates the social politics of our era and practices a critical skepticism that aids scientific objectivity.

6. The Evolutionist (1996) [Interview with David Buss, author of _The Evolution of Desire_]. Darwin@LSE.
Does the Brain Run Algorithms?

by Kayla Ritchie
Introduction

Computation, or information processing, can be defined as that which describes the changes which occur in the natural world. Typically an algorithm or equation, such as the ones used in neural modeling, are employed for such processing due to their ability to describe the behavior of a system according to certain dependent and independent conditions. Due to the recent increase in processing capacity of modern computers, neuroscientists and computer scientists have attempted to model large scale brain architectures that include entire populations of neurons, or in the case of a team of Swiss researchers, the entire human brain, in hopes of simulating the processes in the brain to a point that higher cognitive functions would arise from the models. While this is an exciting prospect, it is unclear whether running the “Brain Program”, would actually yield genuine cognitive processes, simply because the brain is not necessarily a digital computer, and its functions not necessarily computational. In this paper, I pose the question: Does the brain run algorithms? I will argue that this question stems from a deeper uncertainty of whether cognitive processes are computational, and explore the implications that this may have on our ability to model the mind with computers.

What is an algorithm?

For the purpose of this article, it is appropriate to use a general purpose definition with a few clarifications. First, an algorithm must consist of precise, unambiguous steps which require no subjective interpretation, and, resultantly, the execution of the algorithm must always yield the same outcome given a particular set of inputs.

Intentional Use of Algorithms

While executing even the simplest tasks such as brushing one’s teeth, or navigating to a desired, familiar destination, application of an algorithm is essential for successful completion of the task. More complex tasks, such as using the quadratic formula, require similar use of step-by-step processes. However the algorithms we draw on to accomplish such everyday tasks are learned through many experiences of trial and error; each algorithm was developed indirectly through intentional, goal-driven behavior, and so is not inherent to the architecture of the brain. In other words, the processes which govern the underlying functions of the brain, i.e. protein synthesis and the physical and chemical basis for generating action potentials are neither learned, nor controllable through intentional behavior. Such processes are inherent in the physics of the system.

Computer algorithms

Though a general purpose dictionary will explain that an algorithm consists of a step-by-step problem solving procedure, the computational meaning of the word has not yet been agreed upon. Computation, in its most basic definition, occurs in a system which is designed to process information in the form of simple symbol exchange, as in the 0-1 coding paradigm used in digital computers. A certain combination of such formally defined symbols correlates to certain commands, which can take the form of stepwise algorithmic functions.

In most modern computers, this symbol exchange corresponds to the presence or absence of electrical current. Hardware is designed so that input generates current fluctuations in a vast array of transistors, which eventually leads to some output mechanism. This output can be expressed, for example, through a mechanical device that takes the current fluctuations and converts them to light on a monitor. It can also be converted into signals that direct the motion of the mechanical arm that writes on the hard disc. Note, however, that transistors are not strictly necessary for a formal symbol exchange. Theoretically, any system upon which a formal symbol definition can be imposed can be a computer.
What is the difference between human and computer algorithms?

The human method of following an algorithm requires consciousness. Humans are consciously aware of the task that they are supposed to complete, and use the meaning of their instructions to drive their behavior. Computers run algorithms in a completely different manner due to their lack of consciousness. The computer “performs” algorithms simply through following a formal symbol definition that precipitates changes in the hardware and software. Though both humans and computers can use the same exact algorithm to find the value of variables in a quadratic equation, the processes which underlie their behavior are radically different. But the question still remains: Are there any nonconscious algorithms (i.e. computational processes) in the brain?

What things in nature are potentially capable of algorithmic behavior?

In the post-Newtonian era, all of us can observe a natural process, such as a rock falling from a cliff overhang, and can imagine a basic set of laws or equations which could accurately model the rock’s motion. It is also clear to us that the rock is not following an algorithm, which could look something like this:

```
val determined by force of gravity and mass of rock }
Until(terminal_velocity == velocity)
Move towards center of the earth at terminal_velocity
}
```

Why is it clear to us that the rock is not following this algorithm? For one, we know that a rock does not have an input/output system. It neither has way of measuring its own velocity, nor a way to alter its velocity, and so could not follow the do... until instruction, or any of the others. Additionally, a rock does not propel itself; rather, gravity exerts a force on the rock that causes it to move in a particular direction at a particular speed. In other words, we know that a rock cannot detect its progress, and aside from not having a propulsion system, it wouldn’t be able to execute commands if it did have a propulsion system.

But does there exist anything in nature that does follow algorithms? Immediately, it should occur to us that there is one prime candidate: Life. Even the most basic life forms have organization which functions as an input/output system. Paramecia have the ability to sense changes internally and in the environment, and thus can perform certain behaviors, e.g. food acquiring. Yet this by itself does not indicate that any algorithm is being followed. Biological processes are unique in their input/output organization, but this does not contradict the fact that all things that occur are still based on chemical and physical processes. A cell membrane is not selectively permeable because it detects each substance on its exterior and passes judgment on whether or not to let it through, but because the substances that make it through are small enough to pass, and do so because of a chemical gradient, or because they are chemically suited to pass through a specific channel. Similarly, a cell membrane is not round because the cell actively maintains its shape due to the fact that this enables higher internal organization, but rather because it is the lowest energy configuration of the hydrophilic heads and hydrophobic tails of each phospholipid molecule in the membrane. In other words, there are no instructions written somewhere to govern these behaviors; they are results of physical and chemical processes.

Unfortunately, accepting that all things are results of physical and chemical processes does not by itself refute the proposal that the brain is computational. Indeed, it is still possible to assert that all things in nature are intrinsically computational.

Is everything intrinsically computational?

This viewpoint has been furthered by such prominent philosophers as Daniel Dennett, who proposed that evolution was an algorithmic process. Others debate this claim, however. John Searle, an opponent of this type of thinking stated in his book The Rediscovery of the Mind, “...notions such as computation, algorithm, and program do not name intrinsic physical features of a system. Computational states are not discovered within physics, they are assigned to the physics”.

In order to understand this, let us remember that computation can be defined as a system of information processing that relies on the mindless exchange of symbols, i.e. the use of syntax. In much of his
work, Searle vehemently points to the fact that syntax is a formally defined system which is imposed upon a natural system. By this he means that the voltage levels of a computer which we encode as 0’s and 1’s, and in fact all state changes in any natural system, are not in themselves indicative of anything. Rather, as observers assign symbolic meanings to each state. In this sense, nothing is intrinsically computational.

Considering any given pattern found in the brain, we could readily ascribe a computational interpretation. But this does not mean that the brain is a digital computer, or that it has a separate “program level”, as has been the assumption since Marr proposed a model of the brain that separated the neurobiology from the other “higher” functions. As Searle said, “You don’t need to suppose that there are any rules on top of the neurophysiological structures.”

What does it mean for computer science models of the brain if the brain isn’t algorithmic?

If the brain lacks any intrinsic algorithmic processes, then there is no algorithm we’ll invent that will recreate any fundamental processes in the brain. Computational models that emphasize a top-down approach may be valuable for academic fields that wish to use brain-like behavior for the purpose of improving mechanical and computational systems. But the top-down method of devising a computational model that represents the relationship between higher level brain architectures and behaviors will fail to provide an ultimate explanation of how the brain works. Methods that operate under the mistaken assumption that the brain contains “programs” of behavior which are somehow distinct from neurobiology will never offer explanations of how behaviors actually arise from the neurobiology, and so are limited in their ability to realistically portray what the brain actually does.

**Could a network of Ordinary Differential Equations constitute real consciousness?**

Top-down approach aside, there are those whose efforts revolve around reconstructing the brain from the bottom-up using computers to simulate its most basic components. Networks of ordinary differential equations have been used to mimic the changes in individual neurons as they fire. But even this only provides a simulation of the processes that occur in the brain. There is still this assumption that the physiology that causes the brain to function is somehow incidental. On the contrary, the physicality of any system is what causes it to behave as it does. To suppose otherwise is unscientific. Thus efforts like Tom Markram’s Blue Brain project may succeed in simulating all processes in the brain perfectly, but such a feat would not amount to creating a mind any more than simulating a tornado will amount to creating a tornado¹.

**Conclusion**

With a certain degree of complexity, it is often difficult or impossible to decipher the processes of a system. Because the human brain is radically more complex than most natural phenomena, attempts to explain the operations and physical processes which cause a brain to function fall victim to these difficulties. Often times when such a system is encountered, descriptions which focus on behavior, that is, on the input-output relationship displayed by the system, are put forward, rather than explanations which are based purely on physical properties of the system. An indispensable tool used in nearly all math and science, the algorithm, is often used to generate similar input-output relationships in a virtual environment.

Upon first examination, it seems obvious that brains “run” algorithms, simply because a brain appears to us as a black box function, i.e. an entity which, when given specific input, produces specific output with some predictability². However, the same could be said for many other natural phenomena, such as a projectile moving through the air, or the formation of phospholipid membranes. Each of these systems can be reduced to a set of inputs or initial conditions, which after a series of steps or computations that are defined by physical rules produce a predictable set of output. Indeed, one can write algorithms which describe the behavior of each of these systems. But we have seen that our unique position as observers creates the notion of a symbol, and this predisposes us towards believing that nature contains its own inherent language of computation. Were it not for the philosophical analysis of such problems, we would forever be limited in our ability to understand the universe.

Though the implications of the brain’s lack of intrinsic algorithmic processes may seem inconsequential, many areas of research operate under the assumption that the brain is a computer. Of course, the majority of these projects are not concerned with creating a truly
conscious mind, but rather focus on developing applications for small-scale artificial intelligence software, in which a simulation of behavior is appropriate. Projects that do aim to create a conscious mind, however, may be faced with severe difficulty unless they adapt their methods to reduce or eliminate the modeling of higher-level structures in the brain. Henry Markram’s Blue Brain project, for example, is attempting to model the brain at the molecular level, and so has a much higher chance of creating a mind than if he were to model the brain at a higher-level. In addition, there may be success in attempts to build a physical recreation of the brain with synthetic materials analogous to the biological ones. This approach would excel not only because it emphasizes the importance of the brain’s physicality, but also because it would enable a view into the precise relationships and connections between the parts of the brain, and possibly explain how such relationships contribute to consciousness.

Current research programs that wholly embrace the philosophical considerations related to science are rare. Even Boston University’s own Cognitive and Neural Systems department barely considers the myriad philosophical problems associated with the study of the mind. Institutions that care only about the utility of the fruits of an experiment dominate the realm of scientific funding, as they should. What these institutions (and the scientists who appeal to them) tend to forget is that robust theoretical deliberation improves the chances of practical, scientific success. It should be the aim of every research effort, then, to develop a solid theoretical paradigm that places their experiments in context, and clearly defines the domain in which results may appear. Still, the scientific study of the mind is relatively young. With any luck, neuro-researchers will begin to recognize the significance of the philosophy of mind in time to guarantee the success of their scientific endeavors.

Notes:
1. That is not to say that it will not provide valuable data on how the brain works. Simulations are created and used for their ability to supply vast amounts of knowledge about a particular system, knowledge which may be otherwise inaccessible. But that is the extent of their abilities.
2. The mathematical definition of a function requires that specific input will always produce the same output, that is, the relation must be totally predictable. While it can be assumed that minute processes which occur in the brain during normal operation respond predictably to given inputs, the unpredictability of processes in the brain as a whole (due to the vast number of contingencies within the brain) causes us to view the brain’s responses as probabilistic rather than deterministic. Note however that if by some terrific feat of neuroscience we could view how all of these contingencies interacted, it may be more appropriate to think of the brain as deterministic.

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