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FEATURED ARTICLES

‘Cognitive Maps’
-Onur Tanglay

‘Chronic Sleep Insufficiency’
-Sai Vishudhi Chandrasekhar

‘Episodic Memory Loss in Depression’
-Sydney Jobson

‘Nuances of Neuropsychology’
-Eimear Kyle

INTERNATIONAL YOUTH NEUROSCIENCE ASSOCIATION
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Dear Readers,

Welcome to the second issue of the second season of the IYNA Journal! We greatly appreciate your readership, continued or new.

With the release of this special holiday edition of the journal, we are continuing our policy of exploring an array of neuroscience topics rather than a single overarching theme as in the first season. For the next issue, we have redeveloped our editing process so that authors will get more personal feedback on the articles they write and can improve their writing skills for the future. More information about this will be coming very soon, so keep an eye out for updates!

In the General Neuroscience section, Ryan Bose-Roy discusses some of the positive and negative consequences of the aging brain, Onur Tanglay reveals the importance of neural mechanisms in the process of spatial cognition, and Esthefani Chávez Hinostroza explains the role that genetics and neuroscience share in the manifestation of resilience.

Technology has been ever changing and to provide some insight on new procedures, Alina Davydov and Tobey Le both discuss the implications of using innovative operations to treat formidable mental disorders such as addiction and eating disorders.

Similarly, in the Disease section, Sai Vishudhi Chandrasekhar warns readers about the dangers of chronic sleep insufficiency, Sydney Jobson describes the process of episodic memory loss in depressed patients, and Ali Bauer and Vilena Lee present a medical outline of Alzheimer’s and schizophrenia, respectively.

Finally, Eimear Kyle considers the nuances of neuropsychology in the Research section, Martand Bhagavatula interviews an expert on glioblastomas in the Interview section, and Julia Mayro takes a satirical look into research on effective communication with introverts in the Vitreous Humor section.

We would like to recognize all of our dedicated editors and assemblers for helping us make this issue the success that it is. You can see all of their names and positions on our Contributors page. If you have any questions, comments, or suggestions for us, please feel free to contact us at info@youthneuro.org. We hope you enjoy reading this issue as much as we enjoyed editing it!

Best Regards,

Sojas Wagle - IYNA Journal Editor-In-Chief
Anita Singh, Robert Morgan, Scott Massey - Senior Editors
Aging: Blessings and Challenges
Ryan Bose-Roy

Introduction
As we grow older, we inevitably change. Our brains absorb information by seeing, feeling, tasting, smelling, and hearing new things, which shapes how we experience and view the world. Furthermore, our brains themselves change as we grow older. Neurons begin to show progressive decline, which impacts memory, mood, and daily life in general. A variety of debilitating neurodegenerative disorders are becoming increasingly common as well among older populations. While elders lose their sharp senses and some cognitive faculties over time, the experience that they accumulate over their lifetime can still give us a lot of insight into a variety of issues.

Physical Changes to the Brain

The brain undergoes a great deal of physical change. Initial observations made by researchers revealed that as we age, our brains shrink in volume [1]. This decline happens primarily in the frontal cortex – a region involved in coordinating motor movement-processing higher cognitive skills such as thinking and planning, as well as regulating aspects of personality and emotional makeup [2]. This is specifically due to the rapidity with which the neurons are lost/rapid degeneration of neurons. Studies from half-a-century ago suggested that the cerebral cortex, the wrinkled part of the brain often called “grey matter,” lost roughly 30% of its neurons as it aged, creating the widespread belief that the brain loses 50,000 to 60,000 neurons each day [3].

[Image: Structural MRI scans show the human brain shrinks with age, while the chimpanzee brain stays about the same size.]

[Image: The Aging Brain]

[Image: Brain-damaging conditions affecting the elderly]

[Depression]: can strike a brain in a short period. Depressive symptoms that is important for learning and memory, and can lead to serious health issues. In the front of a person with depression, the cerebellum shows increased activity, which is a sign of short-term memory loss. Reduced neural activity and regional atrophy in the brain, however, can lead to long-term memory loss.

[Alzheimer's Disease]: can start in the brain cells for about 10%, compared to those of healthy people. In the early stages, the brain shows less activity, which is a sign of memory loss. Reduced neural activity and regional atrophy in the brain, however, can lead to long-term memory loss.

[Parkinson's Disease]: can be from a bacterial infection in the nervous system. People who have difficulty with their motor skills, or whose thinking has slowed, may have Parkinson's disease.
This is a gross exaggeration. Current research indicates that not only does the brain lose only a very small fraction of its neurons, but that the remaining neurons form new connections with other neurons, making up for the connections that were lost, offsetting much of the damage [4]. However, there are certain regions of the brain that experience a large percentage of neuronal loss. The nucleus basalis, a region of the brain producing the neurotransmitter acetylcholine, loses 50% of its neurons, perhaps serving as an explanation for slowed visual perception-induced reaction times [5]. The substantia nigra, which produces the neurotransmitter dopamine, loses roughly 35% of its neurons; whereas the raphe nucleus, which produces the neurotransmitter serotonin, loses roughly 40% [6]. The neurodegeneration in the raphe nuclei may have the potential to contribute to changes in circadian rhythms and the sleep-wake cycle among the elderly.

This loss of neurons begins around the age of 30 and progresses steadily for approximately the next 6 decades [7]. Studies conducted during the past two decades have suggested that the prefrontal cortex was most affected by this loss, followed by the striatum, the temporal lobe, and the hippocampus [8]. On average, neurodegeneration occurs at a rate of 5% per decade [9].

However, brains of the elderly make up for this through dendritic sprouting. In essence, the surviving neurons extend their axons and branch out, re-forming the connections that were lost when the precursor neurons died. As a result, older people tend to use more of their brain to accomplish tasks. When young people are shown a picture, and are asked to hold the image in their mind, they activate both their frontal cortex and a small part of their parietal lobe [10]. On the contrary, older people seem to show less activity in the frontal cortex- brain scans indicate that they show more diffused action in their parietal and temporal lobes. In addition, visual recognition in older people is less polar and activity is distributed among both hemispheres of the cerebrum, rather than just one.

**Diseases of the Brain – Dementia**

Although many older people experience a decline in mental faculties, dementia is not a normal part of the aging process. Rather, it is a term given by clinicians for a diverse category of syndromes that include almost 50 different disorders of the brain, all of which result from an unexplained source of neuronal destruction. This cognitive impairment typically manifests itself through memory loss, language and speaking difficulties, motor impairment, and a failure to identify or recognize objects. As a result, people with dementia tend to exhibit odd behaviors and occupational and social dysfunction. The most common causes of dementia result from
Alzheimer’s Disease, Huntington’s Disease, Creutzfeldt-Jakob (“Mad Cow”) Disease, Parkinson’s Disease, and Vascular Dementia (decrease in blood flow to the brain).

Although its prevalence increases minimally with age, dementia occurs in roughly 6-10% of individuals aged 65 years or older; the majority of older adults do not experience dementia [11]. However, it is worth noting that dementia is not something to be taken lightly – Alzheimer’s alone is the 6th leading cause of death in the United States [12].

The hallmark sign of dementia is memory loss. Patients may ask the same question over and over again, forgetting that they had already been answered. They may establish a pattern of misplacing objects, as well as forgetting large parts of their daily routine. In addition, patients may forget common words and have difficulty speaking. They may become disoriented, become lost in familiar places, exhibit poor judgement, or experience mood swings. It is important however, not to jump to conclusions; everyone forgets things, but a dementia patient may take this to an extreme level. Rather than simply losing their keys, they may place them in their refrigerator or even in their washing machine [13].

One of the major challenges in modern neuroscience regards the treatment of dementia-associated disorders. While current medication can temporarily alleviate or lessen the symptoms of disease, they are not the permanent cure. These drugs aim to extend the quality of life of the patient.

Studies have suggested that a commonality among dementia patients, particularly Alzheimer’s patients, is the destruction of neurons releasing the neurotransmitter acetylcholine, which is responsible for the formation of memories in the hippocampus and cortex. Cholinesterase drugs aim to block the enzyme responsible for breaking down acetylcholine, thus increasing acetylcholine levels in the brain. As a result, even though acetylcholine neurons are lost, and the amount of acetylcholine in the brain is not severely impacted. These drugs have shown promise in temporarily restoring the ability of patients to resist sudden changes in behavior, seizures, and depression [14].

Emotions, Learning, and Memory in the Elderly Brain

The loss of neurons in the brain during the aging process causes a net decrease in neurotransmitter release, both due to a decline in their production and a decline in their receptor sites on other neurons. This could likely lead to an increased susceptibility to depression and mood swings. Indeed, nearly 20% of people more than 65 years of age were diagnosed with severe depression, and nearly 1/5th of all suicides occur within the ages of 65 and higher [15]. Although early and accurate diagnosis of depression is critical, this has proven to be difficult to cure because other, physical ailments often take priority during treatment [16].

Synaptic docking sites for the receptor dopamine have decreased among the elderly [17]. This loss of dopamine receptors causes frontal lobe dysfunctions, including a decline in working memory.
The loss of Serotonin (5-HT) - a neurotransmitter crucial for sleep, appetite, depression, and anxiety – has also been associated with late-life depression [19]. Due to this, researchers have begun to design drugs aiming to replace these depleted chemicals, in theory reducing the effects of age-induced depression.

A lack of melatonin production by the pineal gland is also a feature of elderly brains [20]. As a result, sleep disturbances are common among the elderly. Specifically, extreme difficulty in falling or staying asleep, breathing problems, leg movements, and dysfunctional patterns of sleep are more frequent among older people [21]. This lack of sleep is critical. These disturbances have been associated with declining memory, weakened concentration, and impaired functioning during the day [22]. However, research has indicated that an increased intake of melatonin is an effective sleep inducer; a two-milligram, controlled-release melatonin capsule is commonly prescribed as a method of improving sleep [23].

Various aspects of learning and memory are affected in the aging brain. Positron Emission Tomography (PET) Scans indicate that although both young and old use the hippocampus to store memories, the brains of elderly individuals show difficulty in retaining and recalling memories. The elderly brain may try to compensate by activating the frontal lobes to assist in retention, but scans suggest that it is more difficult for older brains to activate these lobes [24].

Interestingly, semantic memory – long term memory that processes ideas not drawn from experience – has been shown to improve as age advances [25]. Semantic memory is observed in the recollection of general facts (such as forks are used for eating), as well as vocabulary and knowledge. Procedural memory – memory governing our ability to carry out actions – typically stays the same during old age [26]. As a result, adults are still able to remember how to perform basic tasks, such as read a clock, and speak a language fluently.

Episodic memory – the memory of events from personal experience – and working (short-term) memory show slight decline in brains of the elderly [27]. The vast majority of cross-sectional studies indicate that this deterioration begins nearly the 20s, and gradually progresses throughout a lifetime. The decline in episodic memory is typically stable until age 65, from where it begins to accelerate [28].

Fortunately, the slight declines in memory associated with normal aging is not a cause for concern; they are not serious enough to drastically change a person’s life. Typical warning signs include forgetting how to carry out everyday tasks, not being able to learn new things, and not recalling the names of loved ones.

It is important to take care of one’s brain to offset and potentially improve memory performance. Studies suggest that socializing, physical activities, and confidence are all key ways to boost function. The American Psychology Association recommends using mnemonic strategies, avoiding distractions, establishing routines, and keeping “to-do” lists as ways to prevent the onset of mental decline [14].
References


Cognitive Maps Part 1: The GPS Within

Onur Tanglay

Introduction

Everyday, we make our way out of our beds to the bathroom or drive home from work or school all without getting lost or relying on our devices for navigation. It has become second nature to interact with these spaces and the objects within them to such an extent that these interactions happen without much thought. There is, however, an integrated network of systems contributing to spatial cognition, allowing us to navigate through the space around us, a skill which has evolutionarily become essential to the survival of both humans, and other organisms. The following will explore the neural mechanisms contributing to the formation of cognitive maps in non-human organisms, including the role of the hippocampus and specialised cells, and examine some of the questions which remain in our quest to understand where we are. Part two of this work will explore the correlates of these mechanisms in the human brain.

A Brief History of Space and Time

Although the notion of a cognitive map was proposed by Tolman in 1948 [1], it was O’Keefe and Dostrovsky’s discovery of the hippocampal place cells [2] in rodents that provided the necessary evidence to fuel research into cognitive maps. Their paper analyzed data of recordings from a small group of cells in the rodent hippocampus, demonstrating their responses to particular locations. An example of this is shown in Figure 1, where it is evident that different place cells in the CA1 region of the hippocampus fire only at certain areas [3]. Further research resulted in O’Keefe and Nadel’s groundbreaking book “The Hippocampus as a Cognitive Map”, which drawing on the experimental evidence and case studies from the 20th century, confirmed that place cells within the hippocampus were the fundamental mechanism behind spatial coding in animals. This subsequently proposed that Tolman’s idea of a cognitive map, allowing extrinsic environmental phenomena to be mapped internally, formed through the action of these place cells [4]. They went on to assert that this cognitive map followed a Euclidean coordinate system, and it was the relationship between the objects in

Figure 1: Each place cell in the CA1 region, represented above as a distinct colour, fires only at certain areas, which make up their firing fields. (Layton, 2015)
the animal’s environment encoded within this map which allowed animals to navigate. However, subsequent work over the next few decades raised various questions over what made place cells fire, as it became increasingly clear that the spatial fields in the hippocampus did not rely on conventional sensory input, since they even fired in the absence of light. This notion was not widely accepted in the scientific community as sufficient evidence over the mechanism was not available. It was a result of Ranck’s accidental discovery of the head direction cells in the subiculum \[6\], which were observed to fire at particular directions the animal was facing, that the cognitive map hypothesis became much more feasible, providing a possible mechanism behind the creation of spatial fields.

As the 1990s saw a shift from the allocentric hypothesis to an idiothetic one, it became commonly accepted that the integration of inputs from both the angular and linear velocity of the head provided feedback on the displacement and orientation of the animal from a given starting point, also referred to as path integration \[7\]. Despite this and many other exciting developments, there still remain significant gaps pertaining to both the origin of spatial fields and the exact brain regions involved.

The Role of the Hippocampus

The hippocampus, albeit overshadowed in humans by the frontal and temporal association areas, accounts for around 10% of cortical volume in many mammals \[8\]. Aside from its significant volume, the hippocampus is widely recognised as a key component for the formation of both spatial and episodic memory (the ability to recall personal events) \[9\]. Hence, the cognitive map within the hippocampus, rather than being exclusively a spatial map, also encodes nonspatial information, providing a temporal context to the overall cognitive map \[10\]. Consequently, rather than being a birds eye view of the local environment, it is a collection of memory systems which represent the external environment internally. This cognitive map is then utilised by the animal through its retrieval of past experience and its use of predicting capabilities, such as exploratory behaviour \[11\].

A contextual approach to examining cognitive maps also reveals further detail into the way in which these cognitive maps are woven into the animal’s behaviour. The sensitivity of place cells to temporal context \[12\] suggests that the hippocampus is able to create and store multiple overlapping maps, activated one at a time, yet which work together depending on the context of the behaviour being carried out. Consequently, if a novel environment is encountered or adjustments are made to a familiar one, new maps can be created or existing ones changed through hippocampal interactions. The latter process, termed remapping \[13\], was still being studied in the 1990s, which still saw exclusive focus on cells in the CA1 of the dorsal, as researchers working in the field were convinced that cognitive maps were of hippocampal origin. However, Menno Witter’s 1989 review on various theoretical and experimental studies regarding entorhinal-hippocampal mechanisms, which identified the topographically arranged interaction between the hippocampus and the entorhinal cortex, \[14\] prompted research into other potential origins. Although the medial
entorhinal cortex (MEC) had been studied previously as an unsuccessful candidate for the origin of place cells [15], a revisit to this area in the early 21st century revitalized research in the role the dorsal MEC in the origin of the cognitive map [16].

**Grid Cells**

Targeting the MEC led to the discovery of grid cells: a neuron type similar to place cells in the specificity of their firing fields. However, unlike place cells, grid cells have numerous firing fields distributed throughout the animal’s environment [16]. Another finding was that the firing fields of each cell formed a hexagonal grid over the space surrounding the animal [17]. The role of these cells seemed paramount to the path integration model, as they revealed information about self-motion (ie distance travelled and time elapsed since start of motion) [18]. Research also showed that unlike place cells, which were subject to extreme remapping, a single map from grid cells could be applied to multiple contexts and spaces, and therefore external objects were not required to ascertain the animal’s position [19]. Since path integration relies on navigation based on a starting point, grid cells appear to be the primary candidates for the mechanism behind this form of navigation. It is only when the environment is resized or stretched that the spacing of the grid is altered, suggesting the presence of an overriding mechanism where disruptive external cues could take over the path integration mechanism [20]. For example, the grid patterns generated by grid cells tend to fall apart in the absence of light [21], suggesting that some external cues are crucial to grid cell dynamics. While this raises questions over the importance of grid cells in navigation, there remain significant gaps in our understanding, and further research is required to fully comprehend the exact role of grid cells. In addition to path integration, activity of grid cells within the MEC has been observed in both spatial and nonspatial contexts which are not related to navigation. For example, a grid pattern is observed in humans in the representation of two-dimensional abstract knowledge, reiterating the nonspatial cognitive maps which exist in the brain [22].

**Questions Ahead**

In the years which followed the discovery of grid cells, an abundance of other functional cell types have been identified in the rodent brain, including border cells in the entorhinal cortex, which incorporate the fixed characteristics of the environment into the fields of both place and grid cells [23]. The challenge which remains is understanding the dynamic interaction between these specialised cells, and how they provide the information on self-motion required to carry out path-integration, and ultimately enable navigation. We still have no clear understanding of how cognitive maps are used. Although the distinct firing patterns of these cells have been recorded and studied, the enabling of these patterns remains to be discovered. This also extends to our lack of understanding of the impact of hippocampal output on the neocortex: how is this abundant range of sensory information used in the neocortex, and are there cells in the cortex which are responsible for this integration? Furthermore, research is needed to understand how this sensory information is
integrated in planning and decision-making behaviour, to gain insight into the practical use of cognitive maps. Previous research has only studied cognitive maps in an enclosed, local environment, and as a result we have no understanding of how cognitive maps are represented in larger three-dimensional environments, such as the organism’s own habitat, and how navigation takes place in these environments, including whether path integration still applies. If future experiments allow such spaces to be observed, we may finally gain an understanding of the significance of cognitive maps. As has been stressed in this article, there is an abundance of research which speculates cognitive maps are means of processing higher cognitive information, and further research is indeed required to study cognitive maps in other contexts than navigation. Consequently, despite having a vast amount of information on the components of the systems involved, it is once again the interaction of these systems which remains elusive to us, as tends to be the case in many areas of neuroscience research.

Conclusion

This article has examined some of the key findings in spatial mapping, including the evolution of our initial hippocampal view to a more global approach in our investigation of the mapping of the external environment in the rodent brain, along with the various specialised cells which have been discovered. Although significant gaps in our knowledge remain, especially in the interactions of these functional cells, new research regularly emerges and will continue to do so in the years to come.

The systems discussed have all been discovered through experiments carried out in non-human mammals, and although some anatomical areas are unanimous amongst all mammals, such as the hippocampus, there are significant differences which question whether cognitive maps are formed and retained in a similar manner, and whether they are crucial for spatial navigation. A review of cognitive maps in humans requires a detailed review of some key experiments which have been conducted, and this will be revisited in part two of this article in the following issue.

References


Neural Basis of Positive Behavior: Resilience
Estefani Chávez Hinostroza

Introduction
Every human being in the course of his life goes through various situations before which he must give an answer in order to maintain his personal stability. This response can be both positive and negative, which will determine the impact that he will have as a functioning member of society, since he will be able to make the choice of behaving assertively or reticently. Given this scenario, this article will explore the neural basis of one of the positive behaviors that deserves to be promoted in individuals: resilience. The science of resilience will be discussed by focusing on the impact that genetics has on resilience, analyzing the neural circuits that influence stress coping, how the process of neurogenesis affects resilience, and finally, the neurobiology of the animal models with respect to resilience.

Genetics in Resilience

The heritability index is an essential element to determine the level of adaptability of an individual in highly stressful situations, which added to their personal history of response to these stressors will define the degree to which they will be able to be or not be resilient.

The hypothalamic-pituitary-adrenal (HPA) axis is one of the components affected by genetics, since the functional variants of the mineralocorticoid receptor and glucocorticoid receptor (GC) genes are involved in establishing the threshold of the HPA axis and regulating its termination in response to stress [1].

In addition, another study reported a link between the genetic variation FKBP5 and the inadequate recovery of HPA axis activity when performing the Trier test in healthy people, demonstrating a risk factor for high cortisol levels and psychopathology with respect to stress [2].

Carriers of the short 5-HTTLPR allele show high rates of risk of depression due to exposure to stressful life events [3]. People with the Met158 allele have higher levels of dopamine and
norepinephrine, which is why they are likely to manifest a greater degree of anxiety and derogatory behavior [4].

At the same time, there are random epigenetic changes that facilitate resilience favoring survival in the face of highly complex events, while those changes related to vulnerability allow for better conduct in more satisfactory periods. The transcriptional mechanisms of resilience show that resilience is mediated by a unique series of changes that allow adaptation, but not the lack of maladaptive changes that occur in vulnerable individuals [5].

**Neural Circuits in Stress Coping**

Understanding the neural circuits that are responsible for resilience begins with fully comprehending the neural circuits responsible for fear, reward, and regulation of emotion. These circuits show how the brain handles unfamiliar situations.

Recent studies show that the conditioning of fear is located in the amygdala, the extinction of fear memory involves the vmPFC, and the fear response that arises in the beginning and the subsequent flexible displacement is related to the activation of a network that gathers the striatum and the vmPFC [5, 6].

The regulation of the emotions of conditioned fear could arise through connections with mechanisms of greater simplicity of extinction of fear [7]. The amygdala intervenes in the capacity of the stimuli produced by exposure to fear and the hippocampus acts on the contextual and temporal factors given by the conditioning of fear.

Evidence has been found that interindividual variability in neuronal responses serves as a reward for anticipation in healthy individuals is linked to the Val158Met COMT polymorphism [8]. Likewise, the optimism of traits regarding resilience may be associated with reward mechanisms. VTA dopamine neurons are activated in response to a reward and are blocked by hostile stimuli [9]. Certain neurons manage to be activated by the absence of expected reward, which is inferred that they are involved in the control of mood [10]. Some investigations refer to the intervention of the VTA-nucleus accumbens circuit in depressive behavior, but there is no consensus on the particular role of dopamine [3].

The neural model of emotion regulation, in which the ventral and dorsal systems participate, is related to patterns of abnormal psychic disorders [11]. The amygdala, the hippocampus, subgenual ACC and PFC are involved in anxiety and mood disorders [12]. A cognitive re-evaluation, a mechanism for regulating emotions, when presented on a daily basis is linked to a higher CRP and, at the same time, less activation of the amygdala in the face of stressors; which suggests that through re-evaluation can be facilitated coping and reduce risks of depression and anxiety [13].
Figure 3. Neural circuitries of fear and reward

A simple schematic of the key limbic regions in the fear and reward circuitries. These regions are highly interconnected and function as a series of integrated parallel circuits that regulate emotional states. Each is heavily innervated by the brain's monoaminergic systems — noradrenaline (from the locus coeruleus (LC)), dopamine (from the ventral tegmental area (VTA)) and serotonin (from the raphe nuclei (not shown)) — which are thought to modulate the activity of these areas. 

a | Fear-inducing sensory information is relayed through the thalamus (Thal) to the amygdala (Amy). The amygdala is particularly important for conditioned aspects of learning and memory, as is best studied in fear models. The hippocampus (HP) has a crucial role in declarative memory, but it probably functions more broadly in regulating emotional, including fear, and behaviour. 

b | The nucleus accumbens (NAc) is a key reward region that regulates an individual’s responses to natural rewards and mediates the addicting actions of drugs of abuse. The prefrontal cortex (PFC) — which is composed of multiple regions (for example, the dorsolateral PFC, the medial PFC, the orbitofrontal cortex and the anterior cingulate cortex, among others) with distinct but overlapping functions — is sometimes also included in the limbic system and is essential to emotion regulation. PFC regions provide top down control of emotional responses by acting on both the amygdala and the NAc (a and b) [5].

Neurogenesis in the Resilience Process

Neurogenesis of the hippocampus is a process influenced by physiological factors as inherent to the environment, whose role has been involved in the response to stress. Evidence has been found that neurogenesis allows greater coping with stress in animals with ablated neurogenesis. On the other hand, the lack of neurogenesis may not vary the ability to react to stress at the time of ablation, but may influence the response to future stressors. In addition, neurogenesis can be part of the resilient attitude in some animals evaluated in experiments, those with high basal neurogenesis or where this can be activated effectively; It should be mentioned that accurate coping allows neurogenesis and increases the possibility of a satisfactory subsequent coping [14].
Neurobiology of Animal Models of Resilience

Experimental studies have determined neural and molecular factors that facilitate susceptibility, which, if eliminated, contribute to stress resistance [15]. It should be noted that this approach proposes that resistance to stress is only a passive process, through which the absence of response from an animal is adaptive, but there is also evidence that active coping strategies influence it, being molecular as behavioral [16]. In the course of stress resulting from social defeat, animals that take less docile postures during the attack show reduced social avoidance, revealing that this behavioral coping strategy can influence aggressive interaction and decrease the effects of stress [17]. This is related to a large number of unique variations in gene expression and chromatin changes in specific brain regions that are not seen in susceptible animals [18, 19].

References


Optogenetic Imaging: Implications in Addiction
Alina Davydov

Introduction
Ever since 1956, when the American Medical Association was the first internationally to recognize alcoholism as a disease, advances in neuroscience and chemistry have allowed for a fairly general understanding of the approximate biochemistry and anatomy involved in a human’s capitulation to addiction. However, recent strides in the field of bioengineering have allowed for a technique known as optogenetic imaging to finally reveal the specifics of the neural mechanisms involved in addiction and suggest possible steps to recovery for those who have succumbed to addiction.

The National Institute on Drug Abuse in the United States has likened the current and predicted impact of optogenetic technology to revolutions in the field of medicine and applied biology like CRISPR-Cas9. Optogenetic imaging works by selectively targeting certain groups of neurons in the mammalian brain that have been genetically modified by viruses integrated with light-sensing channel proteins (Type I opsins), referred to collectively as channelrhodopsins. Because these proteins serve as cation channels, they allow positively charged ions into the neuron, which leads to depolarization – the first step of an action potential in a cell. However, what differentiates these channel proteins from others is that they can be activated via a light stimulus. In addition to propagating an action potential, optogenetic techniques can be utilized to inhibit specific neurons by activating chloride pumps that hyperpolarize the cell and bring it further away from its threshold level.

Moreover, the ability of optogenetic imaging techniques to control intracellular signaling and modulate the strengths of certain neurons can be implemented in the study of the molecular mechanisms responsible of addiction in mammals.

A recent stride in the application of optogenetic imaging to addiction research has been made by the Lobo Lab at the University of Maryland School of Medicine. The team was able to use optogenetic methods to control the neuronal firing of medium spiny neurons (MSNs), the main neurons that are part of the nucleus accumbens. This structure in the brain receives dopaminergic
stimulation from the ventral tegmental area and is a key point in the reward circuit of the central nervous system. The purpose of this research was to test for the existence of a relationship between cocaine-reward behaviors and MSNs. Using mouse models, they were able to delete TrkB, the receptor for a group of genes known as BDNF which is involved in the regulation of the mammalian stress and addiction response. Data obtained through optogenetic imaging showed that there is a distinct difference between D1 and D2 MSNs in that one increases the effects of cocaine on the brain reward circuit, and the other decreases the effects, respectively. This research was only possible because of very precise optogenetic methods and because it provided deep insight into how dopamine receptor cell types affect reward triggers (and thus addiction) in the brain.

The Stuber lab of the University of North Carolina at Chapel Hill employed a different approach in applying optogenetics to addiction research. The team focused their work on the relationship between inhibitory and excitatory signals affecting dopaminergic neurons in the ventral tegmental area (VTA) – a region of the brain that serves as a key relay station for the reward/addiction circuit of mammal CNS. Their results showed that upon optogenetic activation of GABAergic neurons (neurons that produce the inhibitory amino-acid derived neurotransmitter, GABA), the activity of dopaminergic neurons was suppressed in the VTA, further citing the VTA circuit as a central target for addiction remediation.

As a result of such groundbreaking research into the neural mechanisms behind addiction, new techniques that help to reverse the damage caused by addiction have been discovered. An example of such therapies is a recent line of research focused on stimulating the “reflective” structures of the mammalian brain, which allow for retrospective evaluation of the organism’s own actions. These structures include the medial prefrontal cortex, the orbital cortex, and the insula. Inhibition of reflective structures via optogenetic methods has been shown to result in prolonged drug use – a hallmark of addiction.
Not only has optogenetics accomplished a great deal in allowing new discoveries of the neural mechanisms of addiction and the development of potential therapies, but it also has multiple other applications in the field of psychiatric disorders and even trauma-induced disorders (i.e. spinal cord injury). However, there is still much room for improvement. The precision of optogenetic imaging techniques can be further refined to increase the efficiency and decrease the financial burden of implementing optogenetic imaging machines in research facilities and hospitals internationally.

References:


NEW TECHNOLOGY

Treating Eating Disorders Via Microbiota Transplant
Tobey Le

Abstract
While it is difficult to obtain solid statistics regarding the prevalence of eating disorders (EDs), it is estimated that about 5 percent of women and about 2.5 percent of men in the United States suffer from one of these disorders [1]. One of the primary traits observed in those with EDs is difficulty in regulating emotions. These difficulties arise in large part due to a faulty amygdala [2, 3]. Given the general unknown nature of the field of emotions in neuroscience, treatment methods are, at times, ineffective. A potential treatment being studied involves supplementing the patient’s bacterial biome with gut microbiota specific to amygdala function.

Eating Disorders and Emotional Regulation
Eating disorders are a range of mental disorders, such as anorexia nervosa, that are characterized by abnormal eating habits that adversely affect a person’s physical or mental health [10]. While it is difficult to prove, evidence suggests that individuals who suffer from eating disorders generally have great difficulty in balancing their emotions and maintaining healthy outlooks [5]. In lieu of traditional methods of emotion management, these individuals consequently develop EDs as maladaptive coping mechanisms [6]. In order to make significant headway on treatment or even curing of EDs, it is imperative that emotional regulation be taken into account.

Microbiota and the Amygdala
In serious cases that warrant immediate and direct action, it is plausible to inject key microbiota into the gut of someone suffering from an ED through a fecal microbiota transplantation.
(FMT). FMT is a process in which fecal matter from a donor is strained, mixed with saline solution, and injected into the patient, usually through a colonoscopy and similar procedures. Similar procedures have previously proven to be successful in curing ailments such as refractory *Clostridium difficile* infection and irritable bowel syndrome [7, 8]. In previous investigations on microbiota and emotional regulation, the analysis of germ-free mice revealed that large portions of microRNAs in their amygdalae and prefrontal cortices were dysregulated [9]. Consequently, certain microbiota have been concluded to be critical for proper function of these brain regions.

If a patient receives this procedure before the amygdala finishes the bulk of its development, an FMT from a donor with a healthy amygdala could have a major positive impact on brain function later in life. Those suffering from EDs and other anxiety-related disorders only begin to exhibit symptoms during childhood or later, meaning that FMT treatment could plausibly mitigate or even reverse the effects of an underdeveloped amygdala. If administered at the first sight of symptoms, an FMT could drastically reduce the severity of an ED.

References


Chronic Sleep Insufficiency - an Epidemic

Sai Vishudhi Chandrasekhar

Abstract

Sleep is one of the most essential but often overlooked components of modern life. The importance of sleep can be understood from the fact that we spend about one-third of our lifespan sleeping. Sleep has been implicated in learning, memory, restoring body's energy levels, performance and physical health. In order to prevent physiological changes that may predispose individuals to poor health outcomes, sleep of sufficient duration, continuity, and intensity (depth) without circadian disruption is necessary. Chronic sleep deprivation resulting in cumulative sleep debt is a health hazard that has been on the rise. This has been implicated in various disorders such as obesity, diabetes, cardiovascular disorders, stroke and memory loss. Sleep insufficiency is a rising epidemic and awareness about sleep disorders should be spread amongst adults and students.

All of us require sleep, and we all know when we're sleepy! Literature suggests that the average adult should get seven to nine hours of sleep daily. However, a large portion of the population regularly falls short of that requirement. Sleep is a complex, universal, and reversible behavioral state in mammals that is homeostatically regulated with its primary function: providing rest and restoring the body’s energy levels. Following the discovery of rapid eye movement (REM) sleep in 1953, researchers learned that there are three basic states of consciousness: wakefulness, REM sleep, and non-rapid eye movement (NREM) sleep. Human NREM sleep can be classified into four stages, namely, stage I, II, III and IV, representing successively deeper stages of sleep [1]. Further research showed that sleep is not a passive phenomenon as thought by some but an active process involving several brain areas, during which multiple areas in the brainstem and hypothalamus promote wakefulness by actively sending signals to the cerebral cortex (see below).

An important area of the brain that promotes wakefulness is the tuberomammillary nucleus (TMN) that releases histamine as one of its neurotransmitters. The ventrolateral preoptic area (VLPO) and other basal forebrain areas play a major role in the promotion of NREM sleep (see below) by shutting down the arousal centers [2].

Interaction of the pedunculopontine and lateral dorsal tegmental areas with the dorsal raphae nucleus and locus coeruleus is important for REM sleep generation [3]. Furthermore, the circadian rhythm of sleep is controlled by the suprachiasmatic nucleus of the hypothalamus and the
pineal gland. There is a ‘switch’ involved in the transition between these states that researchers call *mutual inhibition*. The areas of the brain that maintain wakefulness by activating the cortex simultaneously switch off the VLPO neurons. Conversely, when VLPO neurons fire rapidly and induce sleep, they also inhibit the arousal centers such as the TMN by inhibiting them [4].

The body regulates sleep in two ways: those being by increasing the level of adenosine in circulation, and through stimulating the suprachiasmatic nucleus, which controls body rhythms. As the adenosine levels build-up in the basal forebrain areas, due to the cells’ activity over the day, the brain acts as a dimmer switch and turns down cognitive processes and responses [5].

Persistent alteration in the quality and quantity of sleep has been implicated in sleep disorders leading to socio-economic consequences, due to chronic fatigue. Sleep deprived people may experience ‘microsleep’ states during which they are perceptually unaware of their surroundings and actions, and thereby potentially endangering their lives and others. Sleep is also implicated in discrimination skills and procedural memory formation, with particular reference to slow wave sleep (NREM) sleep that occurs during early sleep [6,7]. Experience-dependent changes have been observed in the sleeping brain. For instance, when rats were exposed to rich sensorimotor experience in the preceding waking period, the immediate-early gene *zif-268* is upregulated in the cerebral cortex of rats during sleep [8]. Most of behavioral regulation deficits caused by sleep operate through disruption of cognitive functions and self-control [9,10].

Though there are more than 100 identified sleep/wake disorders, sleep complaints can be categorized broadly into five categories: hypersomnia, insomnia, circadian rhythm disorders, parasomnias, and sleep disorders associated with mental, neurological, and other medical disorders. Research that has been conducted over the last 50 years, and the advances made in clinical sleep medicine, have led to more effective treatments for the myriad human sleep disorders. However, an increasing area of concern is volitional or forced sleep deprivation due to work, stress, media and other reasons. Chronic sleep insufficiency is a health hazard relevant to present day life. Some causes can be attributed to work demands, education system, daily stress and medical disorders. Though acute sleep deprivation does not have or manifest any serious disorders, cumulative sleep debt can have serious effects on various body systems. In individuals with a prolonged sleep deficit, genetic changes were observed in the metabolic pathway that is involved in the regulation of cholesterol and inflammation [11] leading to decreased cholesterol transport and increased inflammation.
Cholesterol has long been known to be a predisposing factor to cardiovascular disease. In addition, it has been known to activate immune response [12] and modify glucose metabolism [13]. Epidemiological studies indicate that short or insufficient sleep is associated with increased risk for metabolic diseases and mortality.

An equally disturbing trend is the chronic sleep insufficiency rampant among high school students. A youth risk behavior survey of high school students indicates that only 31% of high school students get the recommended amount of sleep while and students sleeping less than five hours were positively associated with all the 12 outcomes considered, some of which include texting while driving, physical fighting, suicidal ideation, binge drinking, sexual risk-taking, and obesity [14].

Chronic sleep insufficiency is a public health crisis with serious consequences that we must address as a society. Both adults and teenagers are affected by this crisis, which can affect one’s well being in the workplace, at school or at home. Rather than treating sleep as an afterthought, we must strive to sleep the recommended 8 hours a day as frequently as possible, in order to keep our brains and bodies working in optimal condition.

References


Examination of Deterioration of Episodic Memory in Major Depressive Disorder

Sydney A. Jobson

Abstract
This article is a review of selected literature which have explored the factors associated with the link between episodic memory deterioration and Major Depressive Disorder (MDD). It has been definitively established that a direct association between an individual's episodic memory and the hippocampus, a small organ within the limbic system, exists [22]. Episodic memory, or the brain's ability to recreate a specific event, is often coupled with contextual emotions [12]. The limbic system, responsible for emotional regulation, is therefore associated with one's memory. However, it is an impairment of episodic memory, specifically overgeneral memory (OGM), or the inability to recall precise memories from one's autobiographical memory (AM), which is often evident in individuals with MDD [25]. Meta-analyses, MaQueen et al., [14] and Videbech & Ravnkilde [27] show a reduced volume of the hippocampus in depressed individuals, firmly demonstrating that the hippocampus is linked to MDD [27]. Finally, Lemogne et al., [10], and Bäckman, & Forsell, [3] found direct links between MDD and the deterioration of episodic memory. It can therefore be concluded that depression may cause a deterioration of the episodic memory.

Background on Major Depressive Disorder

Major depressive disorder (MDD) or depression is a common but serious mood disorder, affecting 16 million people in the United States and 350 million people internationally [8]. According to Nutt [15] and Andréasson [1], depression produces severe symptoms that may affect the way one thinks, feels, and carries out daily activities such as sleeping, eating, or working. Although the cause of depression is unknown, current research suggests that a combination of genetic, biological, environmental, and psychological factors are likely contributors [2]. Definitive links between depression and episodic memory loss exist [10]. Procedural (implicit) and declarative (explicit) memory are the two forms of long-term memory; procedural memory is the unconscious memory of skills e.g., knowing how to ride a bicycle, and declarative memory is the memory of events and facts,
or memories which can be retrieved consciously, e.g. recalling your wedding day [3]. Declarative memory is comprised of both semantic memory and episodic memory [17]. Semantic memory allows one to recall basic facts learned during one's lifetime, such as knowing the names of countries. Episodic memory complements knowledge recall with explicit memories of experiences and events in a sequential order; in other words, it provides an ability to recreate a specific event from a time in one's life. During recollection, episodic memory generally includes contextual emotions one experienced contemporaneously as opposed to merely explicit facts of the event.

**Overgeneral Autobiographical Memory**

Overgeneral memory (OGM) refers to the inability to recall particular memories from one's autobiographical memory. While attempting to retrieve a memory of a specific event, general memories, the recollection of repeated events, or events lasting long periods of time, are recalled instead [23]. Research shows an association between OGM and certain mental illnesses, including posttraumatic stress disorder (PTSD) and MDD. Although research has been conducted to determine a relationship between OGM and anxiety disorders and personality disorders, none have been found. Yet, OGM has been found to be associated with PTSD and depression. OGM is thought to be exclusive to emotional disorders [25]. In Lemogne et al., [10] 21 depressed participants and 21 control subjects without a history of depression were recruited for the study. The depressed participants had no history of bipolar disorder, psychotic disorder, PTSD, substance use disorder, borderline and schizotypal personality disorder, or any other illness linked with memory loss. At the time of the study, the depressed participants received antidepressants and/or antipsychotics and were presented with a task used to evaluate episodic memory. In the task, participants were requested to recall and describe one positive event and one negative event. To determine if OGM was evident in the participants, the interviewer asked the participants to recall a specific memory that had a duration of less than 1 day and to recall as many details as possible, including: facts, emotional recollections, and the event relative to time and space. The participants were then asked to provide additional responses if the subjects perceived the recalled memory as subjective or objective. They were also asked to provide details that could discriminate between two alike events. Researchers found that each depressed subject scored lower on the task than his non-depressed counterpart [9]. The study suggests that depression negatively affects episodic memory.

**Memory Bias in Depression**

Not only does research suggest that depressed individuals have more OGM, but also that their memories may also be more negative in nature. Williams and Scott [26], produced similar results when studying this same topic. In their study, 20 depressed participants and 20 controls were prompted to recall positive and negative events. The participants were asked to be specific in their description of the memories. The outcome of this study showed that depressed participants took more time to respond to positive prompts than to negative prompts. The depressed participants were also less specific when describing their memories, particularly when retrieving positive
memories. In Bradley et al. [4], explicit and implicit memory biases were evaluated in 19 depressed participants, 17 anxious participants, and 18 control participants. A memory bias is a cognitive preference that may improve or weaken recollection. The bias may affect the time it takes to recall or modify the substance of a memory. The participants were given tasks designed to assess the presence of mood-congruent biases in any of the groups. Mood congruent memory is a process that discernibly retrieves memories that are consistent with one's mood. When certain moods were stimulated, the depressed participants recalled more depressive words than the other groups in the study. The results indicate that depression is associated with mood-congruent biases in memory processes. These negative memory biases can cause further depression [21].

Research continues with the goal of determining additional likely causes of depression, including causes of OGM. Theories on potential causes of OGM concentrate on the role of memory retrieval. Subsequently, these theories have materialized into a model known as Capture and Rumination, Functional Avoidance, and Impairment in Executive Capacity (CaR-FA-X) [19]. The first aspect of this model, Capture and Rumination, pertains to the notion that people with a negative self-image access general memories that they conflate with negative perceptions of themselves, during memory retrieval. This behavior prevents people from progressing to more specific areas of the memory [25]. The second aspect addresses Functional Avoidance which suggests that people who have depressive or PTSD symptoms utilize a coping mechanism in which these individuals avoid specific memories that may elicit emotional distress. However, over time with repeated use, this mechanism becomes ingrained in the retrieval of memories. Because of this, one may not be able to easily access specific memories. The third aspect is based upon impairment in Executive Capacity. This theory posits that autobiographical memory retrieval requires certain cognitive resources including working memory capacity and executive control. People with emotional disorders such as PTSD or depression are shown to have diminished cognitive resources [7].

Likewise, it is commonly known that elderly people often have diminished cognitive abilities [9]. Bäckman and Forsell [3] showed additional cognitive deficiencies in elderly people with depression. In their study, Bäckman and Forsell [3] analyzed 17 depressed people with a mean age of 83.29 years and 51 non-depressed people with a mean age of 83.29 years. The participants were tested on an array of episodic recall and recognition assignments. The study found that depressed elderly adults had greater deficits in recall in comparison to the controls. The study also suggested that elderly people with depression are associated with having a decreased capacity to utilize cognitive resources to improve episodic memory. The results showed that the process of encoding and retrieval are diminished in elderly people with depression. The CaR-FA-X model shows that diminished capabilities of retrieval are strongly associated with OGM [19]. Liu et al. [11] in a meta-analysis studied the results of 22 studies of people with depressive disorders in relation to AM. The study showed that participants with depressive disorders communicated more overgeneralized memories than the controls. The depressed participants also exhibited lengthier recollection times. The study suggests that the participants with depressive disorders had AM deficiency due to the overgeneralization of the memories, as well as longer response times.
The Hippocampus and Depression

OGM, an impairment of episodic memory, is associated with contextual emotion and can be better understood through examination of selected organs in the limbic system. In people suffering from depression, the well-established link between episodic memory and the hippocampus further reveals a reduction in the physiological volume of the hippocampus. [6], [22]. Sheline, et al., [18] suggests that recurrent episodes of depression may lead to hippocampal volume reduction. Tulving and Markowitsch [22] maintain that it is widely recognized that the hippocampus is a crucial component in declarative memory. Their study suggests that the hippocampus is not necessary for the functioning of semantic memory, but is critical in the processes of episodic memory. Bremner et al., [6] states that episodes of depression are associated with heightened levels of glucocorticoids, which have further been associated with damage to hippocampal neurons. The study further found that damage to the hippocampus may also result in episodic memory deficits in depressed people. In the study, 16 depressed participants were treated with an antidepressant. No participant received medication other than an antidepressant. Additionally, no subject had any history of PTSD. The study found that participants with MDD had a statistically significant 10% smaller left hippocampal volume than the controls, without a reduction in whole brain volume.

Similar to the research of Bremner, et al., [6], a meta-analysis by Videbech and Ravnkilde (2004) examined studies totaling 351 participants with MDD or bipolar disorder and 279 control participants. In comparison to controls, depressed participants showed an 8% reduction of volume on the left side of the hippocampus and a 10% reduction of volume on the right side. The study found that hippocampal volume is diminished in participants with MDD, but not in participants with bipolar disorder. MaQueen, McKinnon, Yucel, and Nazarov [14], in a meta-analytical study, used data for 32 magnetic resonance imaging studies of hippocampal volume in participants with MDD. The study found that among participants who have had MDD for longer than two years, or experienced more than one depressive episode, a disparity in the volume of the hippocampus exists between test and control subjects. The depressed participants had smaller hippocampal volumes than those of the controls. However, in participants with less than two episodes of MDD, no difference in hippocampal volume exists. It is apparent that the study suggests that a reduction of the hippocampus occurs in people with recurrent depression or depression lasting longer than two years.
Antidepressants and Other Medications

Additionally, Sheline et al. [18] studied the effect of antidepressants on hippocampal volume in participants with MDD. 38 depressed participants were tested, some received antidepressants and some did not. The results showed there was no significant decrease in hippocampal volume in depressed participants receiving antidepressants. However, participants who had not received antidepressants experienced a reduction in volume of the hippocampus. Sheline et al. [18] and Lemogne et al., [10] both used antidepressants as a variable. Lemogne et al., [10] found a reduction of the hippocampus in depressed participants taking antidepressants. However, Sheline, Gado, and Kraemer [18] found that depressed participants taking antidepressants did not experience a reduction of the hippocampus.

Sheline et al. [18] used magnetic resonance imaging (MRI) to quantify hippocampal volumes in people with a history of depression as compared to controls. 24 participants with a history of depression, and 24 controls completed MRI scanning. Participants with a history of depression had lesser hippocampal volumes than the controls. Moreover, the depressed participants scored lower in a verbal memory test. This verbal test measured neuropsychological hippocampal function.

To mediate decreased neurological functions in people with MDD, interventions such as mindfulness-based cognitive therapy (MBCT) and memory specificity training (MEST) have been used, and furthermore, have been shown to decrease OGM and symptoms of MDD [24]. MEST instructs people to be more attentive to their environments. This results in the person being more attentive to their thoughts and their thought processes. When the depressed person is more attentive to his or her surroundings, the memories of that time period become encoded with greater detail. Multiple studies, including Neshat-Doost et al. [20], and Raes et al. (2009) showed that MEST could decrease OGM in depressed individuals.

It is promising to note that OGM has been shown to be reduced after specific interventions in depressed individuals Neshat et al., (2012). These results could reduce the likelihood that individuals with depression or PTSD would experience OGM. Research shows that modifying this memory style could inhibit OGM as well as certain symptoms of depression from recurring [16].

Conclusion

Behavioral studies, including Lemogne et al., [10], and Bäckman and Forsell, [3] have found direct links between MDD and the deterioration of the episodic memory. It has been firmly established that the hippocampus controls episodic memory [22]. Physiological meta-analytical studies such as MaQueen et al., [14] and Videbech & Ravkilde [27] showed a reduced volume of the hippocampus in depressed people. Because of these findings, it can be concluded that depression may cause a deterioration of the episodic memory. Research accomplished by Raes, Williams, and Hermans [16] is significant in its findings of a successful intervention processes addressing OGM. Additional research should be explored, to analyze the effects of antidepressants and episodic memory.
References


DISEASE

The Spreading of Alzheimer’s Disease Through the Brain

Ali Bauer

Introduction

Alzheimer’s disease was first discovered in 1907 by the German Psychiatrist Alois Alzheimer. The disease has a slow progression affecting one out of ten people over the age of sixty-five. It takes eight to ten years for the disease to reach its critical stage, ending in death, and presently there is no preventive medication [2]. The disease is mainly caused by the accumulation of two unusual proteins that lead to neurodegeneration. Neurofibrillary tangles and senile plaque are the two protein types causing Alzheimer’s disease. They do this by disrupting neurons and destroying important cells necessary for life [3]. Scientists are curious as to what might cure this disease, but a remedy has not yet been identified.

Long Term Damage and the Effects

The condition affects the brain and causes loss of the normal ability to function. Alzheimer’s disease comes in phases and gradually worsens over a long period of time [2]. In the initial stages of the disease, the patient will suffer just from lack of memory. As the disease progresses, the patient will battle loss of language recognition and the ability to make gestures [1]. Death will soon follow, as cells are depleted, and there is no known cure for this deadly disease [2].

Senile Plaque and Neurofibrillary Tangles

Alzheimer’s disease mainly involves two different types of abnormal proteins: senile plaque and neurofibrillary tangles. A large protein, amyloid precursor protein or APP, is found on the surface of neurons. APP is normally sectioned by enzymes which free amyloid beta proteins and then cleared from the body. In the case of Alzheimer’s disease, there is an abundance of amyloid beta due to an imbalance and lack of regulation. The surplus of the protein is assembled together and form senile plaques.

Additionally, the neurons in the human brain transfer information by sending a signal from its soma to the synapse as a form of communication. The information transferred passes through the neuronal skeleton, which is composed of microtubules. The microtubules of the neuronal
skeleton are stabilized by the normal tau proteins. In the case of Alzheimer’s disease, the tau protein becomes abnormal and detaches from the microtubules, breaking apart the vital neuronal skeleton. The defective tau proteins come together and produce filaments in the neuron. Without the skeleton, the neuron unravels and connections between it and other neurons are broken. The unnatural accumulation of tau filaments in the neuron makes neurofibrillary tangles, which eventually destroys the entire neuron.

The plaques and tangles originate in the hippocampus, the area in the brain where memories are formed, and eventually spread throughout the brain. Over the course of many years, the plaques and tangles destroy the hippocampus, and memories, as a result, are harder to form. The tangles and plaques then spread to the front of the brain where language is processed. Neurons are destroyed by the infestation of abnormal proteins, and it is harder for the patient to speak and understand speech. The plaques and tangles continue to progress and attack the section of the brain where logical thoughts are processed. The victim might suffer from hallucinations, as it becomes harder for them to distinguish reality from delusion. Next, the area of the brain in which emotions are regulated gets consumed. The patient loses complete control over their emotional capabilities and mood. Finally, the plaques and tangles travel to the prefrontal cortex, where executive function is regulated. The progressive neurodegeneration of different brain regions ultimately becomes fatal.

The oldest and most impactful memories are forgotten and the brain cannot distinguish between what did and did not happen. Senses are distorted, and their feelings do not correspond to what is happening around them [1]. At the critical stage, balance and coordination is majorly impaired, and, eventually, regulations of breathing and circulation fail. These failures in the respiratory and cardiovascular systems result in death. The lack of preventive measures for the onset of Alzheimer’s leads to the progression of this disease, and inevitably, death [4].
Searching for a Solution

Awareness of the disease has grown greatly over the years, but a cure is still greatly needed. Scientists are investigating the evolution of senile plaques and neurofibrillary tangles and are searching for a solution. With more research being gathered every day, the hope of finding a cure continues to flourish [1].

References


The Neuropharmacology of Schizophrenia
Vilena Lee

Abstract
Schizophrenia is a psychiatric disorder that requires lifelong treatment. The causes of schizophrenia are not certain, however scientists believe that the neurotransmitters dopamine and glutamate play a role in increasing the risk of developing schizophrenia. One method of treating schizophrenia is with antipsychotic medication. Antipsychotic medication works by inhibiting the effects of neurotransmitters (primarily dopamine) on the brain, and this can alleviate symptoms such as mood swings, hallucinations, and delusions.

General Overview
Schizophrenia is a chronic neuropsychiatric disorder. Characterized by severe hallucinations, delusions, cognitive impairment, sleep disturbances, and the inability to make decisions, schizophrenia is detrimental to one's brain and body. Globally, schizophrenia affects approximately 21 million people. Treatment is available; however, the disorder cannot be cured entirely.

Schizophrenia occurs in approximately 1% of the United States general population [1]. However, if a person has a first-degree relative who suffers from schizophrenia, such as a parent or sibling, the chances of him or her suffering from the same disease increase to roughly 10%. Also, the risk of developing the disorder is higher with identical twins. If one twin has schizophrenia, the other twin has a 40-65% chance of development as well. Symptoms of the illness tend to manifest themselves between ages 16 and 30, and people typically do not develop schizophrenia beyond age 45 [2]. Men usually develop symptoms of schizophrenia earlier than women; men will show symptoms of schizophrenia in their late teens and early 20s, while women will begin to show symptoms in their late 20s and early 30s.

Causes
Scientists have not isolated a single cause of schizophrenia. Some research studies suggest that schizophrenia may be due to flawed neuronal development as a fetus [3]. Other studies suggest
that environment, as well as genetics and brain chemistry, interact in such a way that causes an increased risk of schizophrenia. Researchers believe that an issue with naturally occurring brain chemicals, such as dopamine and glutamate, may contribute to schizophrenia due to the discovery of abnormalities in these chemicals in schizophrenia patients [4].

Dopamine and glutamate are neurotransmitters, which are chemicals released by neurons to send signals to other neurons. Dopamine is responsible for controlling the brain’s reward and pleasure centers, as well as regulation of emotional responses and movement. Glutamate is an extremely powerful neurotransmitter, known as an excitatory neurotransmitter. Glutamate plays a role in learning and memory; however, it can also cause cell death when present in excess [5]. Scientists have theorized that both dopamine and glutamate levels in the brain can play a role in developing schizophrenia. By using the drug phencyclidine (PCP) to induce psychotic symptoms, scientists have noticed that by blocking neurotransmission at N-Methyl-D-Aspartate (NMDA)-type glutamate receptors, cognitive disturbances resembling that of schizophrenia can be produced [6]. With dopamine, scientists have theorized that too much of the neurotransmitter can result in the development of schizophrenia. The support of this theory stems from the fact that antipsychotic medications, which can be used to treat schizophrenia, operate by blocking dopamine receptors in the brain [7].

**Treatment**

Even if symptoms have seemingly gone away, Schizophrenia requires lifelong treatment because there is no cure. Antipsychotic drugs are the most common method of treatment for schizophrenia, with the goal being to control and alleviate symptoms at the lowest possible dosage. Antipsychotic drugs are believed to help with symptoms of schizophrenia by affecting the brain’s production of dopamine.

There are two types of antipsychotic drugs: second-generation antipsychotics and first-generation antipsychotics. Second-generation antipsychotics tend to be preferred because they
pose a smaller threat of serious side effects than first-generation antipsychotics, that can have serious long-term side effects, often irreversible. One example of such effects is a movement disorder called “tardive dyskinesia”. This disorder makes one’s facial, tongue, and neck muscles move uncontrollably and can be permanent. On the other hand, first-generation antipsychotics tend to be more generic, thus being cheaper than second-generation antipsychotics. When long-term treatment is necessary, it is not uncommon for a patient to choose to take first-generation antipsychotics over second-generation antipsychotics solely due to price.

Antipsychotic drugs work by altering the effect of certain chemicals in the brain, primarily dopamine. By altering the effect that dopamine has on the brain, antipsychotic medication can reduce the chances of experiencing hallucinations, delusions and extreme mood swings [8]. After starting antipsychotic medication, it can take 2-4 weeks before symptoms are being alleviated. In order to prevent relapses, treatment through medication for schizophrenia is continued long-term. Side effects of antipsychotic drug treatment include drowsiness, weight gain, dry mouth, and blurred vision. Out of 10 people who take antipsychotic medication for schizophrenia, 8 will experience improvement of their symptoms. In the end, the facts stack up to support the presence of a multitude of benefits that antipsychotic medications can bring to schizophrenic patients.
The Nuances of Neuropsychology

Eimear Kyle

Introduction
Neuropsychology is a relatively new subset of the disciplines of neuroscience and psychology. Some may deem it as a fad, but the aim of this article is to illuminate the relevance of this new, exciting field to a wider audience and to explain how the subject matter came to be discussed in the first place. Neuropsychology is defined as the study of the relation between brain function and behaviour. The field draws on information from many disciplines such as neurobiology, behavioural neurology, cognitive psychology, neurosurgery, neuropsychiatry, cognitive science, linguistics and philosophy.

However, its central focus is the development of a science of human behaviour based on the function of the brain. Its contemporary definition is strongly influenced by clinical cases and lesion studies, which form a major part of the existing research and literature on the area. In this article, a brief history of neuropsychology will be outlined and some case studies and recent research conducted in the field will be discussed.

A Brief History

It is clear to us at this point in time that the study of human brain function is essential to our comprehension of human behaviour. This interlinkage of brain and mind is a discussion which can be said to have been initiated by the 17th century philosopher and scientist, René Descartes. Ever since, the subject matter has become increasingly topical and has indeed been expanding rapidly. In actuality, one may think that this link between brain and mental functions should have been easily and early learned, as even primitive man could observe that strong blows to the skull resulted in loss of consciousness and of memory, which often led to significant alterations of perception and behaviour.

The oldest, documented proof of man cognisant of this knowledge comes from the famous Surgical Papyrus, discovered by archaeologist Edwin Smith, written circa 1,600 BC in Egypt [1]. It contains the first known descriptions of cranial sutures, the external brain surface, brain liquor (cerebrospinal fluid) and intracranial

Figure 2. Cases 47 and 48 in the Edwin Smith Surgical Papyrus. (Plate XVII from Breasted I.)
pulsation. Its author further describes 30 clinical cases of head and spine trauma, noting how the brain injuries were associated with changes in the function of other parts of the body, such as spastic hemiplegia, paralysis and micturition, due to trauma inflicted to the spinal medulla.

In western culture, Alcmaeon of Croton, a 6th century BC philosopher and medical theorist, was the first to pioneer the concept of the relationship between the brain and the mind: he identified the brain as the centre of understanding and the essential organ for perceptions, sensations, and thoughts [2]. Hippocrates (460-377 BC) who wrote extensively about diseases of the brain, often made statements showing a clear understanding of the role of the brain vis-à-vis the mind such as in passage ‘On the sacred disease’:

‘Men ought to know that from the brain, and from the brain alone, arise our pleasures, joys, laughter and jests, as well as our sorrows, pains, griefs and tears. Through it, in particular, we think, see, hear and distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasant... I hold that the brain is the most powerful organ of the human body... wherefore I assert that the brain is the interpreter of consciousness...’ [3].

However, even with Hippocrates’ advances which were incredible forward-thinking thoughts for the time, what followed amounted to a considerable amount of regression in the unravelling of the enigma of the spirit, and later, the mind. Plato, a younger contemporary of Hippocrates, thought the soul was immortal, moved from body to body, and was vulnerable to angry gods who could inflict insanity, hysteria or epilepsy, which together composed the “sacred disease.” Aristotle, a student of Plato, agreed with earlier Hindu, Hebrew and Chinese philosophers that the heart was the source of intelligence, emotion and the body’s nerve centre [4]. Galen, the renowned Roman physician (130-210 AD), rejected Aristotle’s ideas and instead studied the ventricles, which were thought to be large fluid-filled spaces inside the brain. He suggested that the ventricles hold pneuma, or animal spirits, that regulate bodily functions such as movement and rete mirabile. These propositions were very influential yet incorrect and hindered the development of neuroscience for centuries, right up to the time of what is commonly termed the scientific revolution and the age of enlightenment that occurred in the 17th-18th centuries.

Now, it is finally time to return to René Descartes. Descartes localised the soul in the pineal gland because it lay deep within the brain, in the midline and was unpaired [see Figure 2]. It is of interest that in neurosurgery journals, Descartes’ views are quoted with respect during discussions on surgery on the region of the pineal gland [5]. This respect was earned by his novel concept of mind-body dualism, which was the idea that the
immaterial mind and the material brain, while being ontologically separate and distinct, interact with one another on occasion. This view, although artless, changed the face of neuropsychology and thus neuroscience, ever since.

Since then, there have been many, varying answers to the question of the 'site of the soul' and the 'seat of consciousness', which are, of course, fascinating, yet largely irrelevant to what we call neuropsychology today. This search for the mind/soul developed into the more empirical idea of phrenology throughout the early 19th century. The main principle behind phrenology is that intellectual abilities and personality traits are correlated with cranial morphology, i.e. bumps and depressions of a person’s head. Although now deemed a form of pseudomedicine, its founder Franz Joseph Gall (1758–1828) and anatomical colleague J.G. Spurzheim (1776–1852) had a number of logical, scientific bases for this thinking, as outlined in the latter’s doctrine [7]. Despite this, two erroneous assumptions transformed their goals into proprietary nonsense; that the morphology of the skull was similar to that of the underlying brain and that their methodology relied almost solely on confirmatory cases and patients [8]. Nevertheless, phrenological thinking played an important part in both the growth of clinical neurology in the second half of the nineteenth century and the development of modern-day neuroscience. Gall’s idea of the localisation of mental function has had a deep and lasting influence – the functional maps of the cerebral cortex which are ubiquitous in neuroanatomy, neurophysiology and neuropsychology textbooks bear more than a coincidental resemblance to phrenological charts [8]. Gall’s assumption that character, thoughts, and emotions are located in specific parts of the brain is considered an important historical advance toward neuropsychology.

After Gall, neuropsychology began to receive more appraisal and confirmatory evidence. Pierre Flourens, a pioneer of experimental methods in neuroanatomy, tested Gall’s theories by slicing away parts of animal brain [9]. Although his cuts were crude and his functional results a bit ambiguous, he demonstrated conclusively that mind and matter were interrelated because damage to certain parts of the brain produced cognitive changes. This localisation of function became even more apparent from the work of both Jean-Baptiste Bouillaud and Paul Broca in the latter half of the 19th century. The former was the first to suggest that the left hemisphere controlled various right-handed tasks and presented cases of speech loss following frontal lesions [10]. The latter also

conducted studies on speech and aphasia. Both scientists completely broke away from Gall’s ideas of phrenology and delved deeper employing and developing a more scientific view of the brain [11].

Wernicke, in the late 19th century, made findings contradictory to the idea that there is a strict localisation of functions in the brain – namely that there is more than one language area and that damage that spares a certain area could result in deficits that are indistinguishable from those resulting from damage to the same area. This challenged the past principles of Bouillaud and Broca, and gave way to a new theory coined as connectionism [12]. The neurologist Hughlings Jackson’s view on the nervous system was also essentially connectionist in nature; the system is an organised and interactive whole with a functional hierarchy on several levels (spinal cord, basal ganglia and motor cortex, frontal cortex) [13]. However, his ideas were too complex for his time and it wasn’t until the mid-20th century that Luria, one of the first full-time neuropsychologists, that a neuropsychology-specific theory was hypothesised. The theory, of a clinical-theoretical nature, included that the brain was composed of Three Functional Units and that there are five stages of development of higher cortical functions [14].

From that point to the present day, the core concept of neuropsychology has been relatively slow in developing. This was in the main due to many neurologists persisting in rejecting the brain-behaviour correlation positions of Broca and Wernicke. To boot, the intervention of two world wars did not help to accelerate progress in the field by any means. Many practitioners of the relevant fields were quite reluctant to combine the areas of neuroscience and psychology and preferred to keep the two areas distinct from one another. Despite this reluctance, neuropsychology became a tangible concept and subject area due to pioneering neurosurgeries such as Milner’s surgically treated epileptics [15] and Sperry’s split brain studies [16], the development of novel psychometric techniques, ongoing technological advancements such as CT, MRI and fMRI and the rise of Experimental Psychology as a new subject area.

The discipline of neuropsychology is indeed an exciting one, as it is steeped in a rich scientific and philosophic history. There are a lot more advances to be made in the field, which are hopefully imminent.

A Case Study

During the expansion of industrialisation and mining in particular, traumatic brain injuries were more prevalent than ever before, leading to more studies to be conducted on the functional effects of such impairments. One of the most renowned neurological cases is that of Phineas Gage, a twenty-four-year-old construction foreman who had a three-foot, 7-inch, 13½-pound iron bar blown through his skull — taking a chunk of his

Figure 4. Computer-generated models showing how the rod went through Gage’s skull.
brain with it — and survived. This happened in 1848 when neuroscientific knowledge was far from extensive and the link between mind and brain still not fully heeded by most. This case was a milestone in the history of neuropsychology as it most plainly demonstrated the effects of personality change due to TBI (traumatic brain injury). The iron rod, which penetrated through Gage’s left cheek, passing behind his left eye, severing his optic nerve and tearing into the underbelly of his brain’s left frontal lobe, forced him to lose consciousness for a mere few minutes. When he had regained consciousness, he was conversing with his fellow workmates as he walked over to an ox-cart with almost no support. Over the next few weeks as Gage quickly regained ability to walk, talk, see (partially) and hear, he seemed to have experienced a phenomenal recovery, as recorded in the July 1850 edition of ‘The American Journal of the Medical Sciences’ [17]. Despite this, his doctor, Dr Harlow, observed that “mentally the recovery certainly was only partial, his intellectual faculties being decidedly impaired, but not totally lost; nothing like dementia, but they were enfeebled in their manifestations, his mental operations being perfect in kind, but not in degrees or quantity.”[18]. According to his colleagues and friends, Gage “was no longer Gage” and transformed from being a once shrewd, virtuous foreman to somewhat irritable and irreverent. This landmark neuropsychological case exemplifies a particular type of cognitive and behavioural defect caused by damage to the ventral and medial sectors of the prefrontal cortex, which has aided our understanding of the link between the frontal cortex of the brain with personality and behavioural traits [19].

Injury

From studies of TBI in more recent years, the specific parts of the brain concerned with cognitive processing have been uncovered. The behavioural impairments which show us these functions range from states of emotional lability, depression, hyperactivity, aggression and elopement. The areas inflicting such dysfunctions are notably the temporal lobe, frontal lobes and more generally, the cerebral cortex.

In a real sense, all neural roads eventually lead to the frontal lobes. There is no other part of the brain where lesions can cause such a wide variety of symptoms [13]. To boot, MRI studies have shown that the frontal area is the most common region of traumatic brain injury [14]. An interesting phenomenon of frontal lobe damage is the insignificant effect it can have on traditional IQ testing. Researchers believe that this may have to do with IQ tests typically assessing convergent rather than divergent thinking. Therefore, frontal lobe damage seems to have an impact on divergent, flexible thinking, and problem solving ability. There is also evidence showing lingering interference with attention and memory even after good recovery from a TBI [15]. Another area often associated with frontal damage is that of "behavioural spontaneity." It was found that individuals with frontal damage displayed fewer spontaneous facial movements, spoke fewer words (left frontal lesions) or excessively (right frontal lesions) [16]. One of the most common effects of frontal damage can be a dramatic change in social behaviour. A person’s personality can undergo significant changes after an injury to the frontal lobes, especially when both lobes are involved. Left frontal damage usually manifests as pseudodepression and right frontal damage as pseudopsychopathic [17].
Bryan Kolb and Ian Whishaw, two famous neuroscientific authors, have identified nine principal symptoms of temporal lobe damage: (i) disturbance of auditory sensation and perception, (2) disorders of music perception, (3) disorders of visual perception, (4) disturbance in the selection of visual and auditory input, (5) impaired organization and categorization of sensory input, (6), inability to use contextual information, (7) impaired long-term memory, (8) altered personality and affective behaviour, and (9) altered sexual behaviour [18].

**Tumors**

Tumors in the brain can affect behaviour in a number of ways. A tumor may develop as a distinct entity in the brain, an encapsulated tumour which can put pressure on the other parts of the brain. Encapsulated tumors are also sometimes cystic, which means that they produce a fluid-filled cavity in the brain, usually lined with the tumor cells. Because the skull is of fixed size, any increase in its contents compresses the brain, resulting in dysfunctions. Even though some tumors such as meningiomas do not invade the brain, they disturb brain function by putting pressure on the brain, often producing seizures as a symptom [19].

Brain tumour patients usually manifest focal neurological deficits and seizures due to this raised intracranial pressure. Although psychotic manifestations are not usually seen, it must be recognized that though rare, these can be the presenting features of intracranial tumours. Where hallucinations, delusions and acts of violence can be seen, the undergoing of craniotomy to remove the tumour and being completely and successfully removed, there was immediate resolution of all psychotic symptoms following the operation [27].

Some other unusual neuropsychological syndromes that can be caused by tumours have been described as follows:
Anomia – the inability to name objects or to recognize the written or spoken names of objects
Aphasia – a particular receptive and expressive impairment in dealing with verbal symbols
Apraxia – impairment in performing gestures or in handling objects properly
Disturbance of spatial orientation and constructional dyspraxia – difficulty in putting objects in proper spatial relationship
Agnosia – disturbance of recognition in sensory modality that is not explained by perceptual deficit [28].

**Recent Studies**

Below is documentation of a few recent studies to give a flavour of the diversity and range of ongoing work:
1. An article revealing the adverse effects of brain injury of a mild traumatic type (mTBI) on the resulting quality of the child-parent relationship, showing a discernible decline in their relationship with their parents. The work was carried out using a sample of 130 children. The key results highlighted the importance of monitoring social outcomes even after minor head injuries [29].

2. A very interesting study recently confirming the strengthened connection that exists between the motor zone and the hearing area in the brain. This study analyzed the brains of musicians and nonmusicians while in resting state using functional magnetic resonance. It was found that musicians have a stronger rs-FC between the right auditory cortex (AC) and the right ventral premotor cortex than that of non-musicians. In addition, this effect was greater in musicians with greater years of practice. It was found that musicians have stronger functional connectivity at rest (rd-FC) between the right auditory cortex (AC) and the right ventral and premotor cortex than non-musicians and this stronger rs-FC was greater in musicians with more years of practice. Further findings would seem to indicate that those musicians who play with both hands have greater autonomy between them – the rs-FC between the brain areas that control both hands correlate negatively with longer practice hours. Here, a definite link between anatomic and functional brain features emerges. [30]

3. An indication that neuropsychological research can result in ever more accurate ways to predict and manage the progression from mild cognitive impairment (MCI) to Alzheimer’s type dementia (AD), the success of reliable cognitive measures is evaluated. It was found that cognitive tests are excellent at predicting MCI individuals who could progress to dementia. The study used meta analyzed data, finding that performance on tests could predict whether patients would progress to AD three years before such an event. This type of information could constitute a major tool in identifying this transition [31].

**Conclusion**

The relationship between neuroanatomy and cognitive function is expressed in all aspects and theories within neuropsychology. The roots of the discipline itself stem from both neuroscience and psychology backgrounds, while case studies illuminate the interlinkage of the two concepts of brain and mind. This article has outlined the discipline’s origins, applications and its current status in research. The relevance of neuropsychology cannot be underestimated, as the behavioural and mental changes following accidental brain injury, neurosurgery, or the unfortunate occurrence of neurological diseases that affect particular brain regions should be of recognition to all. From its beginnings, the study of brain-behaviour-mind has been of great significance and will continue to be for a long time, as there still remains a lot to uncover and comprehend.
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Introduction

With just a 10% three-year survival rate and 90% recurrence rate, glioblastomas are among the deadliest tumors. Most prevalent in adults, the tumor increases in frequency with age and gender, striking men more than women [1]. I recently spoke with Dr. Linda M. Liau, MD, PhD, MBA, a professor, director of the brain tumor program, and chair of the neurosurgical department at the University of California, Los Angeles about her work concerning glioblastomas. She currently works in the field of advances in glioblastoma treatments, and took the time to answer questions regarding the approaches of modern treatments and what the future holds.

Interview

**MB:** Hi Dr. Liau. I’d like to thank you for taking the time to let me interview you. I’m going to start with a couple of intro questions. Have you always wanted to go into the neurosurgical field?

**Dr. Liau:** I decided to go into neurosurgery probably my third year of medical school.

**MB:** You started a lab when you first came to UCLA. What were the research questions you explored when you first began?

**Dr. Liau:** I have always been very interested in Neuroscience, and that’s kind of what I did research on in medical school, and wanted to learn more about the function of the brain and brain recovery. That’s what led me to go into neurosurgery. During my residency, my mom passed away from cancer that had metastasized to the brain, so that’s kind of how I got interested in cancer, and I think a good convergence of those two interests led me to explore research questions relevant to neurological cancer. And I started my lab with the fundamental question of how do you treat and cure glioblastoma.

**MB:** The current standard of treatments for glioblastomas temporarily work, but after 4-6 months the tumor can recur. What would you say is the primary cause of that?
Dr. Liau: I would say that the main cause of the recurrence of glioblastomas is the fact that these tumors are very heterogeneous. Given that it’s not just one cell type, it’s actually a multitude of cell types. So even if you have a treatment that affects, let’s say, a third of the cells, and get a response, the remaining cells that aren’t responding then outgrow and come back, so that’s a problem. It’s not going to be ‘one treatment fits all’, in the sense that because of the heterogeneity of the tumor, not one treatment is going to kill every single cell within a heterogeneous mass. So, I think what we call the “durability of response” is very low. I mean, you have a response but it’s not durable.

MB: So, treatments that do work would work for 4-6 months, and then following the tumor recurrence, would the same treatment work again?

Dr. Liau: It depends. The problem with these tumors is that not only it is heterogeneous within one patient...it’s also heterogeneous over time. So, once you treat that tumor, 4 to 6 months from now, it may be different.

MB: Dr. Bachoo of the Simmons Cancer Center spoke about how new genetic mutations are no longer required for continued tumor growth. What would be the primary reason behind this being the case?

Dr. Liau: So, for instance, for a tumor like a glioblastoma, there’s not just one mutation, or two or three. There’s probably hundreds. If you think about it, there are already a multitude of genetic mutations. And, as those propagate they may continue to mutate, or even in response to treatment they may change in terms of their mutational profile. In general, they may outgrow whatever treatment you are giving to them at that time.

MB: Have you used magnetic resonance imaging (MRI) and metabolic data in advanced treatment plans?

Dr. Liau: Yes, we actually use MRI scans pretty much for all our patients both for planning, for instance surgical resection, but also for determining whether a tumor has recurred or is responding to treatment. So, an MRI is pretty standard. In terms of metabolic data, we do PET (positron emission tomography) scanning. And UCLA is actually a big PET center. We have several cyclotrons here so we have a lot of research protocols that use different types of PET tracers to look for different aspects of tumor metabolism.

MB: You just talked about surgical resection. Would you say that has been among the more successful methods of complete tumor resection in the past?

Dr. Liau: I would say that surgical reception is useful to obtain a tissue diagnosis. In order to obtain a pathological and now a molecular diagnosis. And because of the heterogeneity of the tumor just doing a tiny little needle biopsy I don’t think is reflective of the true pathology of the tumor usually
because you may miss another cell type within there. So that’s one advantage and then the second advantage of surgery is a phenomenon that we call cytoreduction. So if you have a big tumor if you are able to reduce that surgically to the extent to which, for example, if you have trillions and trillions of cells and you are able to reduce it to thousands of cells even though you can’t get every cell, there’s just fewer bulk of tumor that radiation or chemo or any of these other treatments need to work on to get to the cancer.

**MB:** So, it’s been somewhat successful in the past?

**Dr. Liau:** Generally, it does offer some therapeutic benefit but it’s not certainly not the cure for these tumors.

**MB:** Makes sense given the complexity of the tumor. Can you talk about how signaling pathways can be activated constitutively in migrating glioma cells?

**Dr. Liau:** So, a lot of times these signal pathways usually are activated when you have a receptor and you have something that triggers the receptor and then that’s how that pathway goes on. But when they talk about the constituent activation they don’t have the receptor anymore, but they, that process keeps going on due to some mutation in the cell, so even though you have a drug that affects the receptor...once the cells mutate to the point where they are no longer responsive to the receptor and they’re just, you know, operating on their own, then that drug no longer has an effect.

**MB:** Got it. So, in general, signaling pathways have worked for other tumors in general but glioblastomas with the level of heterogeneity and complexity?

**Dr. Liau:** Yeah. And again, the responses aren’t very long and they’re not very durable.

**MB:** Looking at novel drugs like temozolomide \[2\], are they becoming more and more prevalent in revolutionary treatments?

Dr. Liau: Temozolomide is actually now standard of care for glioblastoma. Unfortunately, beyond radiation and temozolomide there really hasn’t been a whole lot else of that has been approved as standard treatment for these tumors. And you know, alkylating agents have been around for decades. I think Temozolomide has gained approval because it’s well-tolerated in general. It’s an oral pill as opposed to a heavy-duty IV chemo. And it’s readily accessible.

**MB:** Are you guys consistently using it?

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*Figure 2: diagram mapping out the chemical structure of temozolomide*
Dr. Liau: Currently, a lot of experimental treatments are given in addition to standard treatments meaning radiation and Temozolomide plus the experimental treatment versus the placebo. It’s not really given in lieu of standard treatment because there’s nothing out there that uniformly is able to affect, for instance, all glioblastomas.

MB: So, molecular cellular therapies as well as local drug delivery being used to complement conventional treatments, in addition to having the original treatment?

Dr. Liau: Yeah exactly, I think that over time there are probably going to be different subgroups of these tumors, some that respond really well to metabolic inhibitors, some that respond to other kinds of signaling pathway inhibitors, some that respond to immune therapies. But it’s not going to be one treatment for all these groups.

MB: Would you say that neurodevelopmental transcription factors [3] drive the growth of glioblastomas?

Dr. Liau: Some of them, yes.

MB: Would you say are there any solutions to really inhibit them in particular?

Dr. Liau: Good question. Transcription factors are hard targets for treatment. They are kind of targets that are deemed less “druggable” than, for instance, a receptor antagonist or things like that.

MB: So, in that situation what would you guys use to inhibit the transcription factor?

Dr. Liau: Depends on the transcription factor. Depends on what type of transcription factor.

MB: And then the dendritic cell vaccination?

Dr. Liau: So, dendritic cells are an antigen-presenting cell. So, they’re actually a cell that is a normal cell in the body. And the concept is that because, for instance, a brain tumor is in the brain. These cells actually don’t get to the tumor, so the antigen-presenting cell doesn’t really have contact to the antigen to produce an immune response. So, the dendritic cell vaccine that we’ve developed is really taking a patient’s own antigen-presenting cells and put them together with the tumor antigens to activate T-cells, which are the cells that go to attack the tumor. And we’ve tried various combinations of ways to activate the dendritic cells. But so far, still using the patient’s own tumor seems to the most efficacious method, probably because of what I have talked about before, the
heterogeneity of the tumor. It’s hard to make a designer vaccine with all these hundreds of mutations that it would work for everybody.

MB: So is there anything that stands out to you about glioblastomas compared to other tumors? You mentioned the heterogeneity as the primary reason.

Dr. Liau: Yes, I think it’s the heterogeneity both in terms of heterogeneity within the patient, the heterogeneity between patients, so if you have a hundred patients with glioblastoma they all have somewhat different cell types and mutations and then also the heterogeneity and the transformation over time so as you treat with one drug then when you go back in and for instance operate on the tumor again that tumor at that point in time actually has changed from the original. So that makes it hard, as you essentially have a moving target in terms of how you are trying to treat.

MB: Oh, I see what you mean. And overall, what would you say is the most revolutionary treatment right now?

Dr. Liau: I don’t think there’s particularly one revolutionary treatment. I think there’s probably, you know, groups of treatments and they’re probably going to work in different subgroups of patients, so I think there’s a concept of, as you talked about, you know, changes in metabolism. So, there’s a thought that for instance if you treat a tumor with an EGA foreign inhibitor, though the inhibitor hasn’t shown a durable effect, it works for a little bit and then a few months later the tumor grows back. What we do see if you treat with the inhibitor for instance...sometimes what that does is it actually changes the metabolism of the cell environment. And then it’s in a more vulnerable state. So, if you go in at that time and hit it with another agent, it’s almost like a one-two punch. And hopefully try to kill the tumor with this kind of combination of a cell signaling inhibitor and a metabolic agent or an apoptotic agent. So that’s I think one category. And another category of treatments are immune-based therapies, things like tumor vaccines, Car-T cells, checkpoint inhibitors. I think each individually may have some efficacy, but I think there’s going to be, in the future probably, you know smarter combinations of kind of immune-based approaches. Probably similar to this, where you need probably two drugs to really melt down the tumor. You may need, for instance, a vaccine to get the T-cells into the tumor but then the T-cells are being suppressed by agents that are immune checkpoint inhibitors that are released by the tumor so you need another agent to block those.

MB: Are you working on new treatments or building off what you have done before?

Dr. Liau: No, we’re working on all these new treatments. We have a huge brain tumor program at UCLA. We have researchers and clinicians working in all these areas, like I said, the metabolic vulnerability, we have immune-based therapies, we have treatments that are targeting cancer stem-like cells. One thought about why tumors come back is because there are these stem cells that are resistant to radiation and actually may be triggered by radiation to become tumors. And we are working on ways to counter those.
MB: So I think that's it. Thank you for taking the time.

Dr. Liau: Thank you.

References


New Research on Effective Communication with Introverts

Julia Mayro

A study was recently conducted at a local university to determine how to most effectively communicate with introverts. Several researchers have come up with new ways for extroverts to interact with introverts without scaring them off or entirely monopolizing the conversation.

Before commencing experiments, the researchers first had to find introverts. They soon realized that the fastest way to find a large group of introverts was to enter the library and recruit any student who voluntarily spent time there for purposes other than school work. The researchers also had to find extroverted people to interact with the introverts. The theater department readily supplied a large number of extroverts. In fact, there were so many volunteers that a number of the theater students were requested to leave. A few suggested that they could act like introverts, but the researchers thought it best to use authentic introverts for the study.

The study focused on how introverts have a lower level of arousal than a typical extrovert. Three introverts participated, and for privacy purposes, they will be referred to as Jane, John, and Jen. All three were sitting alone at separate tables in the library at the time of the experiment, and none of them were aware that an experiment was being conducted. The three extroverts who participated in this study all wanted their true names to be written in the report, but for legal reasons, they will be known as Emily, Elizabeth, and Edward. All three followed a similar script when approaching their assigned introvert. They would sit down at the table the introvert was working at, drop their pencil, let it roll to the introvert's side of the table, and ask, "Could you hand me my pencil?" After being handed their pencil, they would introduce themselves and attempt to initiate conversation. A researcher sitting at a nearby table would discreetly time the conversation until the introvert stopped responding to the extrovert. Emily was instructed to whisper, Elizabeth was to speak at a normal volume, and Edward was to speak loudly. The researchers hypothesized that an introvert would respond more to an extrovert speaking at a lower volume due to their need for a lower level of arousal.

Emily approached Jane and began the conversation at a whisper. Jane willingly returned Emily’s pencil and conducted a polite conversation ending with plans to meet later for lunch. They talked for 12 minutes and 42 seconds which, based on the researchers’ past experiences, was above average. Elizabeth sat across from John. John returned Elizabeth’s pencil, but as soon as she introduced herself, John stood up and mumbled something about needing a book about “library etiquette”. Their conversation lasted 1 minute and 39 seconds which was determined to be not only below average, but also extremely rude. When Edward began his experiment with Jen, he accidently...
threw his pencil at her and used a bullhorn for asking for his pencil back. Jen was startled by the encounter and, without responding, ran out of the library leaving all of her belongings.

The researchers believed their study appropriately supports their hypothesis. They concluded that it is best to avoid bullhorns and throwing writing utensils when working with introverts.
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