

NEUROLOGY NEWSLETTER

COLLEGE OF MEDICINE
CALIFORNIA NORTHSTATE UNIVERSITY

Who is Patient H.M.?



March, 2016

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THE BEAUTY OF HUMAN MEMORY

Along with vision and the ability to communicate, our capacity for remembering is the most cherished of all aspects that make us human. Human memory comes from only one place: the human brain. This may seem like a ridiculously trivial thing to say in the 21st century, but it's important for historical context as it was not always thought to be so. Before the days of Hippocrates (the great father of medicine), the brain was simply thought of as an organ to cool the blood—a bodily radiator and that instead, the heart was the place of thought and memory.

Now, we know that we have more than one type of memory. Under the umbrella term of memory, we have two distinct types known as declarative and nondeclarative memory, each with its own subtypes and a third known as working memory, which can also be described simply as attention. The former is what we normally think of as “memory.” It can be split into semantic memory, or the general knowledge of facts about the world and episodic memory, or the memory of events. On the other hand, nondeclarative memory may seem more primitive in its capabilities. This would be a correct assumption as this form of memory includes the nonassociative learning mechanisms habituation and sensitization, which are reflexes to harmless and noxious stimuli, respectively; the associative learning modalities classical (think Pavlov's dog) and operant conditioning, where a response to a stimuli is paired with a reward or consequence to strengthen the behavior; procedural memory, in which a motor memory can be reinforced through practice, such as learning to ride a bicycle; and finally, priming. It should be noted that declarative memory is recalled through conscious thinking giving it the alternative name of explicit memory, whereas nondeclarative memory is recalled without conscious awareness and thus is also known as implicit memory.



-Matthew Zabel
MS1, CNUCOM
President, CNU SIGN

“Along with vision and the ability to communicate, our capacity for remembering is the most cherished of all aspects that make us human.”

“It is clear that more is to be revealed about the remarkable capacity for our brains to encode and store all aspects of memory along with its inherent fallibility.”

The different modalities of memory contribute a distinct mental function—a specific type of memory trace—to the perception of our environment. It is, after all, the sensory inputs from our environment that give us vivid, rich memories, which make up or at least remind us of, our experiences. Imagine if we did not have the capacity for memory as we know it. We would not recall our happiest memories, or our saddest. We would forget those people most important to us. Ultimately, we would lose our sense of personal identity. And this is exactly what happens in dementia, making it one of the greatest medical challenges facing our species.

Each memory type has its own neuroanatomical correlate within the brain. We know this to be the case from clinical lesions, such as stroke or surgical removal, that target different regions of the brain, leaving that person with an impaired memory modality. For example, as discussed by Rainy Zhang in this issue of The Newsletter in her description of the famous patient H.M., we know that declarative (explicit) memories are encoded, consolidated, stored (as well as in the cerebral cortex) and recalled in the medial temporal cortex, and more specifically in the hippocampal formation. On the other hand, removal of these structures do not affect nondeclarative (implicit) memory function, which seems to rely on separate structures within the brain. Additionally, Letitia Pirau describes a separate amnesic syndrome described by Carl Wernicke where downstream memory networks from the hippocampus become damaged from metabolic stress. It is known as Wernicke-Korsakoff Syndrome, and if managed correctly and timely, it can be reversed. Lastly, Flynn Kaida-Yip presents for us a history of the most feared and most common form of dementia: Alzheimer’s disease.

Researchers are constantly making advances in every aspect of memory neuroscience. Recently, a novel mechanism of how an animal tracks its movement in space and time has been described, earning its discoverers a Nobel prize. This function too can be localized to the hippocampal formation and acts a personal global positioning system, now defined as a kind of spatial memory. It is clear that more is to be revealed about the remarkable capacity for our brains to encode and store all aspects of memory along with its inherent fallibility. We hope you enjoy this issue of the CNUCOM SIGN Newsletter on the impact of this fascinating subject.

-Matthew Zabel

HENRY MOLAISON AND HIS GIFT OF MEMORY

Neuroscience is a rapidly evolving field with scientists who have made incredible advances in understanding the brain’s complex structure and function. With the knowledge that we have today, it is difficult to imagine a neurosurgeon suggesting bilateral resection of medial temporal lobes of a patient and not predicting its critical consequences. That is what happened to Henry Molaison, or better known as “Patient H.M.”.

Henry was born on February 26, 1926. He experienced partial seizures since the age of 7, followed by several tonic-clonic seizures after his 16th birthday. Despite heavy dosage of Dilantin, his seizures



-Rainy Zhang
MS1, CNUCOM

“Henry awoke on that fateful day on August 25, 1953 with an inability to commit new events to long-term explicit memory...and had difficulty recalling events up to 11 years before the surgery...”

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continued to be debilitating enough to interfere with daily living. As such, when his neurosurgeon Dr. William Scoville suggested removing the areas of the brain (hippocampus, amygdala, and entorhinal cortex) that were causing his epilepsy, Henry agreed.

The surgery was a resounding success...to an extent. It significantly decreased the frequency of his seizures, but not without other major complications. Henry awoke on that fateful day on August 25, 1953 with an inability to commit new events to long-term explicit memory (anterograde amnesia – think 50 First Dates and Momento) and had difficulty recalling events up to 11 years before the surgery (retrograde amnesia – think Anastasia and The Bourne Identity).

What followed in the next 55 years resulted in possibly the greatest contribution to neuroscience given by a single patient. Henry was the perfect candidate; he demonstrated a clear before-and-after effect, intact intelligence and other cognitive functions (minimizing confounding variables), and perhaps most importantly of all, a willingness to participate.

Through numerous experiments led by Dr. Suzanne Corkin and her team at Massachusetts Institute of Technology, much of the ground foundation of memory and its function in the brain had been laid. We now know that explicit memory is of separate modality and localization than working and procedural memory. Henry was unable to acquire new recollections of himself (episodic memory) or facts and general knowledge of the world (semantic knowledge), but could form long-term procedural memories (like learning to ride a bike). Thus he could learn new motor skills, such as drawing a reflection of a figure in the mirror, despite being unable to remember learning them.

After many years of service, Henry finally passed on December 2, 2008, but not without first agreeing to donate his brain for further studies at the Brain Observatory at University of California San Diego. There, Henry’s brain was carefully cut and recorded in a series of high resolution neuroanatomical images, enabling it to be viewed microscopically and reconstructed into a 3D digital model.

It is reasonable to assume that a patient who has undergone countless experiments and tests might become frustrated and disengaged with the process. But that was not the case with Henry. He was friendly and courteous, and seemed to enjoy participating in the research. He once said, “What [my neurosurgeon] learned about me helped others, and I’m glad about that.” We could attribute his positive disposition simply to his inability to recall the repetitiveness of his motions, but I believe Henry had insight into his condition and truly wanted to be the gift to neuroscience that he is seen as today.



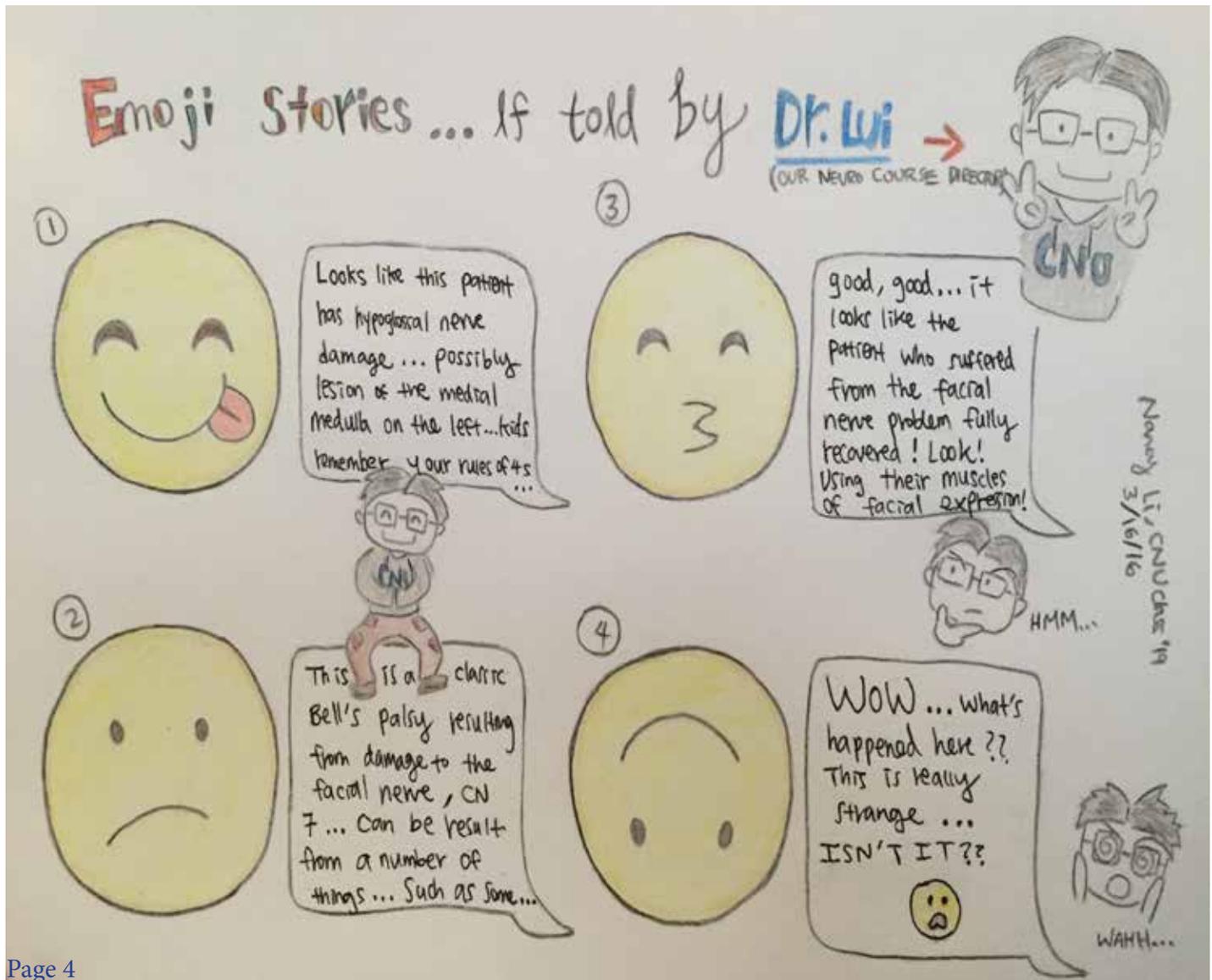


-Nancy Li
MS1, CNUCOM

Mini Neuro Correlations (mentioned in the article):

- **Partial seizure:** begins in one hemisphere. Small part of one lobe is affected with normal consciousness (simple) or larger part is affected with altered or loss of consciousness (complex). Could spread to other hemisphere (secondary generalized seizure). Most common in temporal lobe.
- **Tonic-clonic seizure:** best recognized form of seizure. Generalized seizure. Abrupt onset, LOC w/generalized tonic contraction.
- **Epilepsy:** recurrent paroxysmal uncontrolled hyper-synchronous discharges from an aggregate of neurons
- **Dilantin:** trade name of phenytoin anticonvulsant (tonic-clonic and partial). VG Na⁺ channel blocker. Side effects include hirsutism, gum hypertrophy, and cerebellar ataxia.
- **Hippocampus:** part of limbic system. Functions include memory consolidation and spatial navigation. Degenerated in Alzheimer's disease.
- **Amygdala:** part of limbic system. Functions include motivation, identification of internal state (pain, hunger, thirst), and regulation of emotion.

-Rainy Zhang





-Flynn Kaida-Yip
MS1, CNUCOM

“In 1984, George Glenner and Cai’ne Wong identified the first major protein involved in the brain plaques characteristic of Alzheimer’s disease: beta-amyloid. Four years later, Goedert also identified neurofibrillary tangles made of tau protein aggregates as another pathological marker.”

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“the necessity of caring for a vast aging population in the United States makes finding answers to neurodegenerative diseases an increasingly critical area of research.”

HISTORY OF ALZHEIMER'S DISEASE (FROM AS FAR BACK AS I CAN REMEMBER)

Alzheimer’s Disease is well known as one of the most common neurodegenerative disorders. It was first documented by Alois Alzheimer in 1906. Since then, its definition has changed to exclude the delusions and hallucinations that Dr. Alzheimer originally described as part of the disease. A conference in 1977 also eliminated age restrictions on diagnosing Alzheimer’s disease. In 1984, George Glenner and Cai’ne Wong identified the first major protein involved in the brain plaques characteristic of Alzheimer’s disease: beta-amyloid. Four years later, Goedert also identified neurofibrillary tangles made of tau protein aggregates as another pathological marker.

Discovering these two pathological markers created a target for medications. In 2001, a vaccine that triggered an immune response to beta-amyloid progressed to clinical trials, but the trials ended in 2002 when a significant number of patients developed encephalitis with no observable slowing of cognitive decline. Since then, researchers have developed numerous other vaccines aimed at either active or passive immunization to beta-amyloid. Many of the trials are ongoing, and some have even successfully reduced brain atrophy in comparison to age-matched control patients, but unfortunately with no change in the primary outcome of slowing of cognitive decline. More recently, at the beginning of 2016, a vaccine that targets tau proteins rather than beta-amyloid proceeded to clinical trials. Approaching Alzheimer’s disease through tau tangles may be particularly beneficial as a 1992 study linked tau neurofibrillary tangles rather than beta-amyloid to cognitive decline. Additionally, we are becoming more capable of imaging tau protein in living patients via PET, allowing researchers to obtain more data from the clinical trials.

According to a study conducted by the Alzheimer’s Association, there were an estimated 5.3 million Americans suffering from Alzheimer’s in 2015. Alzheimer’s also accounted for 60-80% of dementia cases that year. Yet, for such a prevalent disease, research has consistently fallen short of finding a cure for this debilitating disease. Studies have, however, successfully identified numerous preventive measures for reducing the risk of Alzheimer’s disease. Exercise, diet, and remaining both mentally and socially active are all important factors. Preventive medicine is always the preferred approach to a disease, but for neurodegenerative diseases such as Alzheimer’s, it is currently the only approach. It is not a hopeless prospect; researchers continue to develop new drugs that reach clinical trials. Even so, the necessity of caring for a vast aging population in the United States makes finding answers to neurodegenerative diseases an increasingly critical area of research.

-Flynn Kaida-Yip



-Letitia Pirau
MS1, CNUCOM

“Mr. John Phillips is a 45-year-old male...when John was asked how old he was, he stated that he was 35.”

“Wernicke-Korsakoff Syndrome, first described by Carl Wernicke, is classically associated with a triad of symptoms: 1) ophthalmoplegia, 2) ataxia, 3) disturbance of consciousness and mental state.”

“confabulation’ – a neuropsychological condition that is the hallmark of Korsakoff psychosis. Patients usually offer... an impossible or implausible history of events.”

WHEN BLACKOUTS ARE MORE THAN JUST ONE NIGHT STANDS

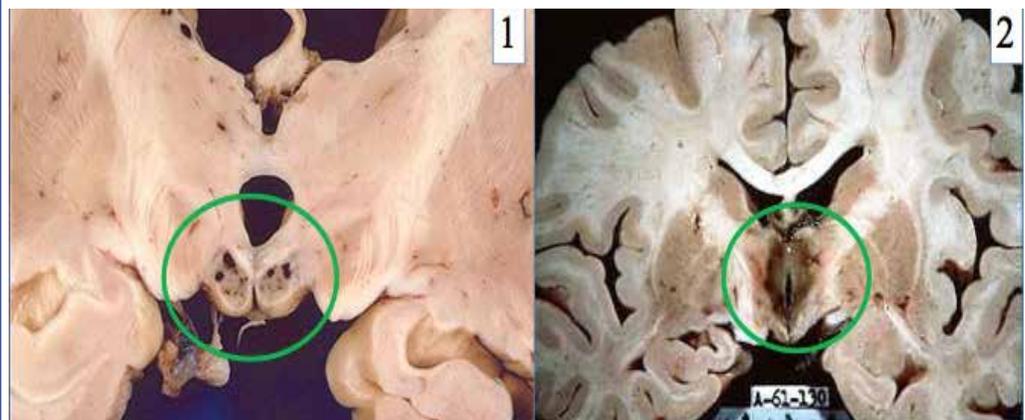
Mr. John Phillips is a 45-year-old male, who presents to the clinic after police found him in a delirious state, rambling in the street with an empty vodka bottle. John stated that he did not know where he was. When the police asked him questions, the man answered bizarrely and inappropriately, saying irrelevant statements such as “he had to go to the store.”

During the physical exam, John presented with a very stunted and hesitant walk, especially when turning directions. His gait was wide and uncertain, with mild ataxia on heel-to-toe walking. Furthermore, the cranial nerve exam presented with bilateral rectus palsy.

Yet the most telling part of the examination was within the cognitive assessment. When asked to do arithmetic, John was able to answer correctly. However, when the physician asked him to recall the name of the hospital, John did not know. Prompted with the first letter of the hospital, John was able to remember the name correctly. Yet, John could not remember how long he had been staying in the hospital. In fact, when the neurologist asked John what he had been doing this weekend, John stated, rather excitedly, that he had been seeing friends in New York City. Much to his surprise, John had already been in the hospital for the entire weekend by that point.

John did not just have memory loss of recent events from the past day. The physician was able to contact John’s family and acquire more details about his current living situation and livelihood. John told the doctor that he still lived in his original home in New Jersey, although he had moved away ten years prior. When the physician reminded John of this, John stated “Oh yes...that’s right.” Furthermore, when John was asked how old he was, he stated that he was 35.

John’s case illustrates the advanced effects of Wernicke-Korsakoff Syndrome. Wernicke-Korsakoff Syndrome, first described by Carl Wernicke, is classically associated with a triad of symptoms: 1) ophthalmoplegia, 2) ataxia, 3) disturbance of consciousness and mental state. In particular, Wernicke-Korsakoff patients suffer from “confabulation” – a neuropsychological condition that is the hallmark of Korsakoff



Wernicke-Korsakoff Syndrome. Mamilary Body Hemorrhage (1) and Periventricular Hemosiderosis (2)

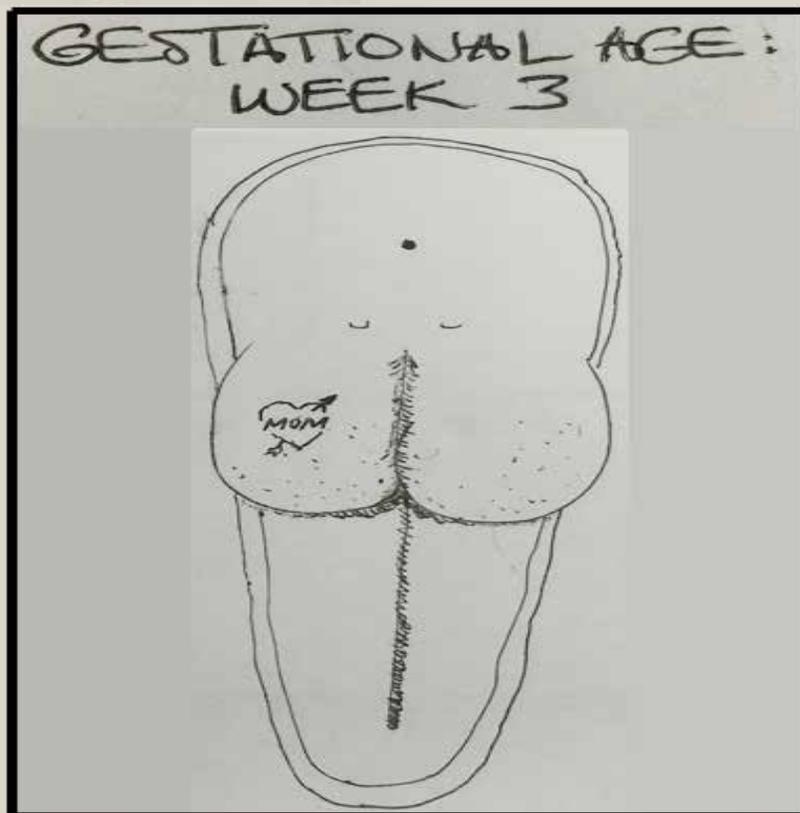
psychosis. Patients usually offer, as in the vignette, an impossible or implausible history of events. Yet, unlike other amnesic disorders, patients who suffer from confabulation appear to be sincere and forthcoming. Wernicke-Korsakoff is usually observed in chronic alcoholics, as a result of thiamine (vitamin B1) deficiency. Thiamine is an important cofactor for pyruvate dehydrogenase, which catalyzes pyruvate to acetyl CoA. Without thiamine, pyruvate is turned into lactic acid, causing lactic acidosis within the CNS and thereby destroying neuronal cells. Petechial hemorrhage and infarction are usually seen in the mammillary bodies, thalamus and periaqueductal gray matter. While the treatment for Wernicke-Korsakoff is IV administration of thiamine, the solution is merely a quick fix – with most patients suffering from chronic memory disorder. Yet, there is a chance for some recovery of cognitive function. That is, if the patient assumes responsibility to maintain continuous abstinence.

-Letitia Pirau



-Glen Geesman
MS1, CNUCOM

MD* by GLENN
GEESMAN



PRIMITIVE STREAKING:
THE UNCOMFORTABLE ACT OF
REMEMBERING YOUR BRAIN WAS
ONCE A BUTT CRACK.

TRANSIENT GLOBAL AMNESIA A CASE STUDY

This is a very interesting clinical syndrome with unknown etiology. It was first described by C. Miller Fisher (the same Fisher who described the Fisher variant of Guillain Barre Syndrome and the Hollenhorst plaques).

The presentation is usually very consistent. It may occur at any age, though more commonly among elderly. There may be some stressful precipitating events such as dental extraction or diving into ice-cold water. The patients will suddenly lose all of his or her memory, especially all anterograde memory and will also exhibit retrograde amnesia for events that occurred many years prior; however, their personal identity is always preserved. Furthermore, they may also still remember their immediate family members. During the episode, that usually lasts from a few hours up to more than 24 hours, the patient will not be able to recall any thing that he or she does or says. The patient will often ask the same question over and over again. Otherwise, they are able to perform all motor tasks including driving, writing, reading, talking and socializing. They will present as definitely not delirious and neurological exams, labs, CT, MRI, EEG and CSF will all be normal.

The recovery is gradual over a few hours as they will start to regain their memory in a telescopic manner (distant memory returns first). The patient typically will return to normal after the event except with amnesia of the period of time during the attack.

No treatment is required and reassurance is all that is necessary. Episodes typically do NOT recur. If it does, a differential diagnosis of transient epileptic amnesia must be considered.

As a clinical neurologists taking calls to the ED and hospital, I see about 4 or 5 cases a year. The pathogenesis is unknown and it is closer in mechanism to a migraine phenomenon.

-Dr. For-Shing Lui MD

SEVERAL INTERESTING CORTICAL SYNDROMES

1) Alexia without agraphia: able to write yet unable to read. Alexia usually coexists with agraphia in patients with aphasia. If the patient has a lesion in the left occipital lobe with involvement of the splenium of the corpus callosum (usually due to a left occipital infarct) then the intact right occipital cortex will be unable to transfer the information through the corpus callosum to the language area on the left hemisphere all the while the patient already has right homonymous hemianopia. The patient also shows intact left language area and left frontal lobe and therefore is able to write.

2) Acquired color blindness (achromatopsia): This is usually caused by a lesion involving both medial temporal occipital temporal areas affecting the "what" pathway of the visual association cortex.

3) Prosopagnosia: inability to recognize familiar faces. It may arise due

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"The recovery is gradual over a few hours as they will start to regain their memory in a telescopic manner...the patient typically will return to normal"

"No treatment is required and reassurance is all that is necessary"

Drowning In Student Loans?

Help come up with a creative name for this newsletter. If picked, the winner will receive a ten dollar gift card to wherever you like.

E-mail your answers to CNUSIGN@gmail.com

Neurology Newsletter, a monthly newsletter published by students in the Student Interest Group in Neurology (SIGN) at California Northstate University, College of Medicine (CNUCOM) is meant to bring abreast information in the ever changing field of neuroscience to ultimately provide our patients with excellent medical care and top-notch patient education. Our website can be found at <http://cnu-comorgs.wix.com/student-groups>. All correspondence should be e-mailed to CNUSIGN@gmail.com.
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to a unilateral lesion in the non-dominant medial occipitotemporal lobe (what pathway) yet it is way more common due to bilateral lesions. Prosopagnosia is the most common symptom of basilar embolism causing bilateral PCA infarct.

4) Pure word deafness: a form of auditory verbal agnosia. It is caused by lesion of the dominant or more commonly bilateral temporal lobes affecting the auditory association areas. The patient has intact hearing (can hear sound) but unable to understand spoken words.

5) Anton's syndrome: a relatively common problem due to bilateral occipital lesion most commonly result of bilateral occipital infarct. The patient is cortically blind yet anosognosic (deny the blindness).

-Dr. Forshing Lui MD
CNUCOM Faculty Advisor
Professor of Clinical Neurology and Neurology Clerkship Director

CLINICAL TRIVIA

Q: How can you differentiate cortical blindness from blindness due to bilateral eye or optic nerve problems?

Please send answers to CNUSIGN@gmail.com

Winners will be entered into a drawing for a free Academic Cafe Entrée

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