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COVER ART BY JULIE HUANG (MEDS 2012)

"Firstly, for those who are curious, it's plasticine, not real brain. I was, however, inspired by the real brain, an organ that at first glance seems simple but is in fact incredibly sophisticated. In this cover, I wanted to capture just some of this complexity. My approach to the brain, therefore, was to use differing media to represent its differing aspects. And like any good approach, I've tried to keep some organization, moving from the gross to the molecular."

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Neurology is one of the oldest yet most enigmatic fields of medicine. The reasons for this are many and this issue of the UWOMJ highlights just a few common explanations.

The first is that the function of the brain is nearly impossible to separate from the *impacts* of its functions. That is, neurological function produces thoughts and behaviours that serve to build communication, relationships, and culture. In this way, neurology cannot be viewed without consideration of psychology, psychiatry, even anthropology. While neurology is not unique in that its function and subsequent dysfunction have implications outside of medicine, it is the extent of this enmeshing that makes neurology particularly fascinating. Naylor, Kudlow and Shu explore this theme in their examination of physical activity on cognitive functioning, and Wang, Suppiah, Jiang, Bahreini and Rhee question the role of sleep in memory consolidation.

A second contributor to the complexity of neurology is the disconnect between structure and function. Consider the heart: its function can be inferred by a careful examination of the valves, the vessels, and the layers of the walls. Analogies have been drawn to plumbing and engineering to help explain the function of the heart. In contrast, the brain affords no such luxury. The structure of the brain offers few clues as to its function. Instead, scientists and clinicians have relied on *dysfunction* in order to explain function. It is through understanding disease that we have come to appreciate the normal function of the brain.

As an historical example, the function of the recurrent laryngeal nerve was discovered when Galen's scalpel slipped during an experiment on a pig.[1] The animal survived the operation, but no longer squealed like his cohort. History could have taken a few roads from here; Galen could have abandoned medicine, chastising himself for suboptimal surgical technique. Instead he asked *why* the pig no longer squealed. In this case, it was not a meticulously crafted experiment that led to discovery, but keen observation and an inquisitive nature.

As Galen found, nature can present data without a structured laboratory environment. This is not to say that neurological discoveries are accidents; it requires someone to notice the phenomenon and probe deeper. The next step is to seek out similar cases, which makes the scientific literature so important. In the grading of evidence, case reports are often viewed as inferior to randomized controlled trials. But sometimes, as Galen found, one case can spark discovery. For this reason, the UWOMJ prides itself on featuring case reports. For instance, Hamidi describes a case of aggressive behaviour that was ultimately attributed to a brain tumour.

The UWOMJ is grateful to the numerous individuals who contributed to this issue, including our editors, feature writers, advisory board, faculty reviewers, and advertisers. With your ongoing support, we will continue to produce issues that will hopefully inspire, inform, and reignite your passion for medicine.

Laura Hinz
Senior Associate Editor

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Interventional neuroradiology and the treatment of carotid artery stenosis and intracranial aneurysms

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Introduction

Cerebrovascular diseases are the third leading cause of mortality in Canada and the United States.[1,2] Recent advances in the field of endovascular surgical (interventional) neuroradiology have enabled the treatment of these conditions using minimally invasive catheter-based technology assisted by radiologic imaging. Boasting a reduction in recovery time and associated pain, these procedures are increasingly being utilized as an alternative to traditional surgical intervention.

When applied in clinical practice, neuroendovascular interventional therapies are primarily used in one of two possible forms: 1) revascularization leading to reopening of blood vessels as used to treat acute ischemic stroke, arterial stenosis, and dural venous thrombosis; and 2) embolization leading to the occlusion of blood vessels as used in the treatment of aneurysms, arteriovenous malformations, and vascular tumors. Utilizing this distinction, an exploration of the most common neurological conditions treated by interventional neuroradiologists – carotid artery stenosis and intracranial aneurysms – will be undertaken.

Origins of interventional neuroradiology

Historically, the roots of interventional neuroradiology can be traced back to the late 1920s, when Egas Moniz used iodides to visualize the cerebral vasculature on radiographs.[3] Several years later, the first attempt at catheterization was successfully completed by Werner Forssmann when he placed a urinary catheter into his own antecubital vein and advanced it into his heart.[4] In 1960, Luessenhop and Velasquez demonstrated that intracranial vessels could be catheterized,[5] and by 1974, these advances had opened the door for Serbinenko to use flow-directed balloon tipped catheters for the treatment of intracranial aneurysms – the first time an endovascular approach was utilized for the treatment of a cerebrovascular disorder.[6] In Canada, the pioneering work in this field was conducted at University Hospital in London, Ontario where Drs. Gerard Debrun, Fernando Viñuela, and Allan Fox established a neuroendovascular centre to test and clinically apply Serbinenko's methods.[7]

Today, the basic principle of all neuroendovascular procedures involves percutaneous entry, usually through the femoral artery, although the brachial and radial arteries are also possibilities. In 1953, a Swedish radiologist, Sven-Ivar Seldinger, introduced the procedure that is now commonly employed to obtain vascular entry by all vascular interventional disciplines.[8] Figure 1 illustrates a modern approach to the Seldinger technique whereby the vessel of

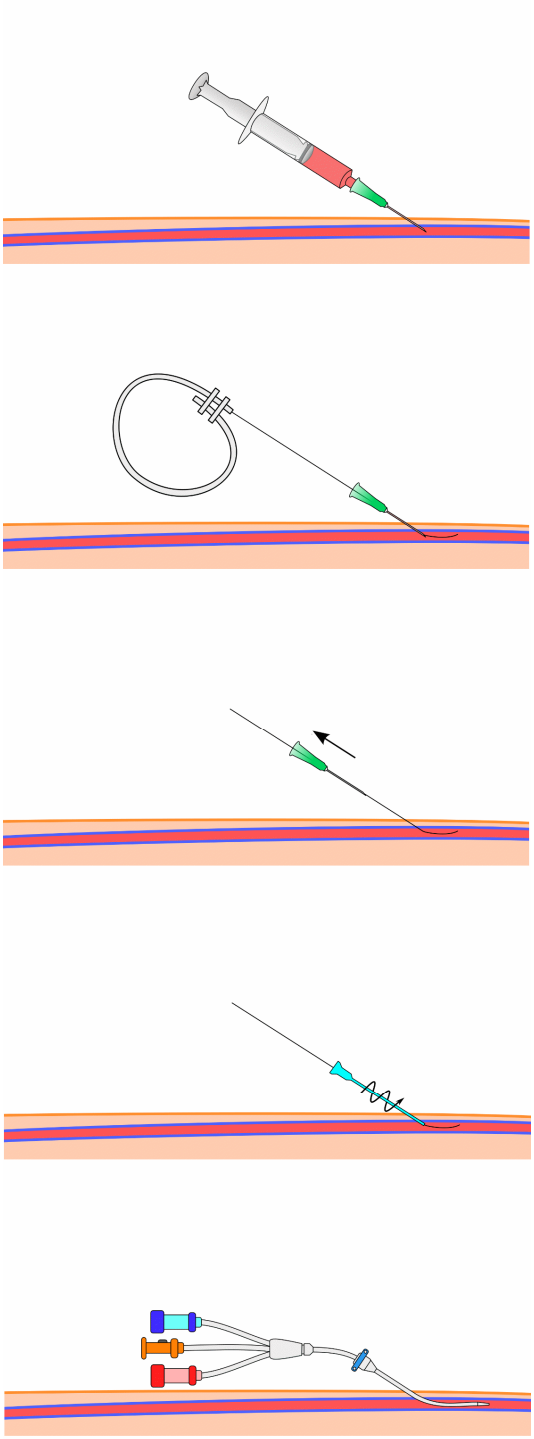

Figure 1. Illustration of a modified Seldinger technique of arterial access through trocar cannulation, guidewire and sheath insertion, and cathether introduction.

interest is commonly punctured by a trocar (hollow needle), and a guidewire is inserted through the needle. The guidewire is used to introduce a catheter (or sheath) which can be used to deliver an array of items to the target lesion. As such, guide catheters can be directed into the supra-aortic vessel of interest to allow for the highly selective delivery of coils, embolic materials, and even drugs into regions of interest.[9] Seldinger showed that his technique could be used to access all arteries in the body via the femoral route,[10] and the current practice of using ultrasound to aid in vessel localization has raised its safety profile.

Revascularization: carotid artery stenting

The application of endovascular techniques is routinely used for the treatment of atherosclerotic disease involving the extracranial carotid, vertebral, subclavian and brachiocephalic arteries. Initially treated using balloon angioplasty, interventional techniques have now progressed to the use of stent-supported angioplasty. As such, this approach is currently offered as a therapeutic alternative to traditional methods of open surgery for patients who have failed maximal medical therapy, or those who present as poor surgical candidates. Although there are numerous cerebrovascular conditions for which revascularization is possible, its use in treating carotid artery stenosis remains by far the most frequent occurrence.[11]

Carotid artery stenting (CAS) is typically performed under conscious sedation using local anaesthetic to enable neurologic monitoring of the patient during the procedure.[12] Following puncture of the femoral artery, selective catheterization of the common carotid artery is achieved. Prior to proceeding, preliminary diagnostic angiography of the carotid bifurcation is done in a minimum of two planes to provide the operator with information about the anatomy of the patient. Anatomical considerations form the basis for choosing between various sizes and shapes of catheters. For example, in older patients, vessel elongation, tortuosity and dilation can necessitate the use of larger-diameter and hence stiffer catheters in conjunction with stiffer guidewires.[13] Patients are intravenously infused with heparin, and once the operator has determined the appropriate interventional strategy, the guide wire is used to cross the stenosed segment. The stent is then deployed and correctly positioned under fluoroscopic control.

Named after an English dentist who invented the device in the late 19th century, stents are metallic structures designed to maintain vessel patency. Self-expanding and balloon-expandable stents are available for use, and these devices are either composed of a thermal expansion alloy (nitinol) or stainless steel. Although numerous designs exist, stent selection does not appear to influence patient outcome.[12] Nonetheless, there are several drawbacks regarding the use of stents in treating cerebrovascular disease. Firstly, stent placement can initiate a robust cellular response, resulting in intimal hyperplasia that can cause restenosis of the affected area. The overall restenosis rate (>50% decrease in vessel diameter) one year following CAS has been reported to be as high as 20.8% in some trials.[14] Additionally, stents are highly thrombogenic and patients are recommended to undergo several days of preoperative treatment with aspirin and clopidogrel. Not surprisingly, experimental evidence suggests oral aspirin (325 mg/day) and clopidogrel (75 mg/day) display a synergistic effect on platelet aggregation inhibition, antithrombotic activity, as well as preventing restenosis.[15,16] Finally, the risk of embolization caused by procedural manipulation poses a significant risk to the patient. MRI studies suggest that upwards of 15 percent of patients develop new ischemic lesions in the brain following interventional stenting of CAS, although half are asymptomatic.[17] To reduce the microembolic burden associated with stenting, embolic protection devices (EPDs) are increasingly being used. Currently, two types of cerebral protection strategies can be employed: 1) distal protection in the form of an occlusion balloon or filter; or 2) proximal protection in the form of flow interruption or reversal devices.[18]

Embolization: intracranial aneurysms

An aneurysm is a dilation of a vascular structure and is particularly troublesome when it occurs in the cerebral circulation, as rupture can often cause catastrophic loss of neurologic function and death. The larger arteries at the base of the brain are predominantly affected, likely due to their unique morphology – thinner walls, lack of external elastic lamina, and lack of surrounding supporting tissue.[19] Traditionally, surgical obliteration of aneurysms has been the gold standard treatment, while endovascular intervention was typically reserved for patients who are medically unsuitable for surgery or for those who refuse open surgery. For example, the location of some aneurysms, such as the intracavernous carotid artery and basilar apex, dictated a preference for endovascular intervention if possible.[9] Today, the majority of aneurysms are treated using coils.

Embolization is typically carried out with the patient under general anaesthesia, and arterial access is achieved as outlined above for CAS. Numerous strategies exist for the endovascular treatment of intracranial aneurysms depending on the nature of the lesion. Commonly, aneurysmal occlusion is achieved by the use of the Guglielmi Detachable Coil system (GDCs).[20] The aneurysmal sac is densely packed with coils until no further angiographic filling is seen. Approved for use in 1995, GDCs are electrolytically detachable platinum coils that offer the operator the advantage of being able to withdraw coils from the aneurysm and reposition them if the initial result is less than satisfactory. Alternatively, stents can be used as a scaffold to support detachable coils, particularly in the case of wide-necked aneurysms, as shown in Figure 2. In this scenario, a stent is deployed across the neck of the aneurysm, and the coils are delivered into the aneurysmal lumen via a microcatheter passed through the stent interstices. Occasionally the size and shape of the aneurysm precludes it from being embolized by coils or surgically clipped, and therefore balloon occlusion of the parent artery is undertaken to stop all

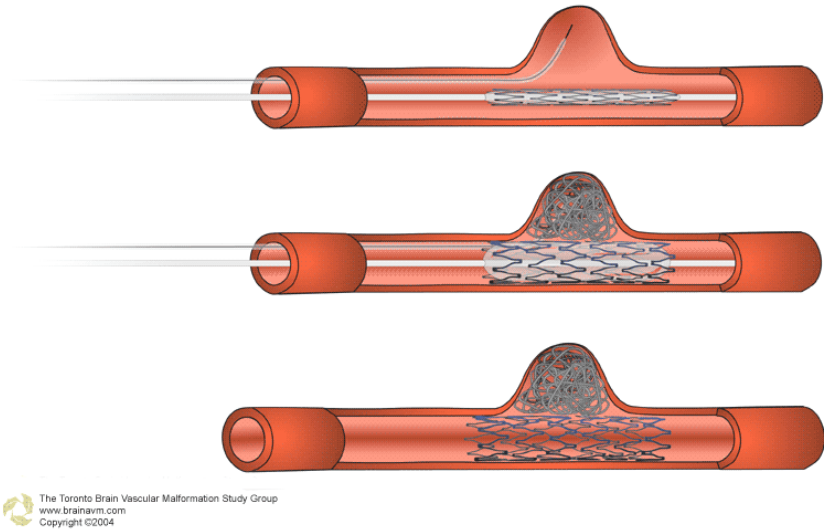

Figure 2. Stent serving as scaffold to support detachable coils in treatment of a wide-necked aneurysm. (Used with permission.)

blood flow to the aneurysm.[21]

Conclusion

The past decade has seen an explosion of minimally-invasive procedures undertaken to treat various cerebrovascular conditions. Currently, randomized trials evaluating the benefits of endovascular treatments are ongoing. As technological advances are made, the safety and efficacy of these procedures are expected to improve. In this manner, techniques employed by interventional neuroradiologists offer a promising alternative to current therapeutic paradigms.

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Alzheimer's disease: a review of diagnostic criteria

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Introduction

Dementia is a syndrome in which affected individuals have impairment of memory and at least one other cognitive area, for example, orientation or comprehension.[1] The diagnosis of dementia corresponds to a variety of etiological domains, from cerebrovascular disease to neurodegenerative disease. However, Alzheimer's Disease (AD), which is a neurodegenerative disease of uncertain origin and pathogenesis, is the most common form of dementia in the elderly.[2]

First described by Alois Alzheimer in 1906, AD is a currently incurable neurodegenerative disease that primarily affects adults. Estimated to affect over 4 million Americans, AD places a heavy burden on the healthcare system.[1] It is very unusual for this disease to occur in individuals less than 60 years of age, and it is reported to have a slight predilection towards affecting women rather than men.[3] Early AD typically presents with an insidious onset of mild cognitive impairment, often in the form of short term amnesia, which may be confused with the effects of aging or stress.[3] This is followed by progressive functional and cognitive impairment in multiple domains, with some studies reporting that the mean survival post AD diagnosis is around 3-8 years,[4] depending on factors such as the severity of cognitive impairment and functional deterioration.[5] In later stages, AD can manifest with non-cognitive neurological symptoms, such as myoclonus and seizures. The progress of AD clinically is often measured by mental status scales such as the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating Scale.[3] However, these scales have their own limitations in terms of corresponding with the rate of clinical decline.

Currently, the only definitive way to secure a diagnosis of AD is through histopathological examination of brain tissue.[3] However, this is neither feasible nor is it practised clinically except for confirmation of diagnosis at autopsy. Rather, the mainstays for establishing a working diagnosis of AD are clinical assessment criteria. In this paper, we explore these tools and discuss their shortcomings in AD diagnosis. We also review some of tests that are useful in differentiating AD dementia from other major types of dementia.

Clinical criteria for a diagnosis of Alzheimer's Disease

While a number of diagnostic criteria for AD based on clinical grounds have been proposed, two major sets of clinical criteria are used in North America to reach a working diagnosis of AD. Both these criteria take into account some well established features of AD, such as the history of insidious onset and progressive course of deterioration, as well as evidence of cognitive impairment in multiple areas.[3] Conducting a detailed cognitive and general neurological examination and evaluating the level of cognitive impairment and dementia using the MMSE provide the essential clinical information to which these criteria may be applied.

NINCDS-ADRDA criteria

In 1984, a task force established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) put forth a set of clinical criteria for diagnosis of probable AD.[6] These are provided in Table 1. Additionally, the criteria put forth by the same group for possible AD, where the degree of suspicion is lower than with probable AD, are also provided in Table 1.

Probable Criteria

- Dementia established by clinical examination and standardized brief mental status examination and confirmed by neuropsychological tests
- Deficits in two or more areas of cognition
- Progressive worsening of memory and other cognitive function
- No disturbance of consciousness
- Onset between 40 and 90 years
- Absence of other systemic or neurologic disorder sufficient to account for the progressive cognitive defects

Possible Criteria

- Atypical onset, presentation, or progression of dementia without known etiology
- Presence of another potentially causative systemic or neurologic disorder that is not thought to be the etiology of dementia in this case
- Progressive deterioration in a single cognitive domain in the absence of any other etiology

Table 1. NINCDS-ADRDA criteria for diagnosis of AD. Adapted from Feldman et al.[3]

The validity and reliability of these criteria have been investigated by a number of studies, with some yielding optimistic conclusions. For example, one study showed that diagnoses of AD made based on these criteria are confirmed by autopsy in 87% of cases.[7] A study by the National Institute of Mental Health Genetics Initiative found these criteria to have good reliability and validity, with a diagnostic sensitivity of 80%.[8] However, some criticisms of these criteria have also been made. For example, one study showed that the interrater reliability for AD diagnosis using these criteria was only low to moderate.[9] Another study showed that these criteria were not effective in distinguishing frontotemporal dementia from AD dementia in a group of 56 patients.[10] This lack of specificity has been attributed to be a result of inadequate emphasis of the saliency of the amnesia component of AD.[3] Furthermore, since the NINCDS-ADRDA criteria are fairly old, they may not reflect recently discovered biomarkers and genetic findings that can help support an AD diagnosis.

DSM-IV-TR criteria

The other commonly used clinical criteria for AD diagnosis are derived from the current version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) published by the American Psychiatric Association.[11] These criteria are provided in table 2.

1.	The development of multiple cognitive deficits manifested by both: · Memory impairment · One or more of the following cognitive disturbances: aphasia, apraxia, agnosia, disturbance in executive functioning.
2.	The cognitive deficits cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
3.	The course is characterized by gradual onset and continuing decline.
4.	The deficits are not due to another brain, systemic, or psychiatric condition.
5.	The deficits do not occur exclusively during the course of delirium.

Table 1. DSM-IV-TR criteria for diagnosis of AD. Adapted from Feldman et al.[3]

One argument in favour of the DSM-IV-TR criteria is that they do not necessitate neuropsychological testing in making a diagnosis. However, in a study of 200 patients that compared the NINCDS-ADRDA criteria and the then-current DSM criteria (DSM III-R) against the gold standard of histopathological examination, the NINCDS-ADRDA probable and possible criteria together were found to be 61% specific, 96% sensitive, and 85% accurate in detecting AD while the DSM criteria were found to be 51% sensitive, 96% specific, and 66% accurate in detecting AD.[12] Another study showed that the interrater reliability between the NINCDS-ADRDA and the DSM-III criteria are comparable,[13] and an evidence-based review written by the American Academy of Neurology (AAN) in 1994 concluded that both sets of criteria for AD diagnosis were sufficiently reliable and valid and that they should be used.[14] More recent evidence indicates that documenting an objective progression of cognitive decline over a 12-18 month period is both highly specific and sensitive for AD,[3] however, this is logistically hard to execute.

Excluding other causes of dementia

As mentioned earlier, dementia can be present in a wide variety of neurological disease entities. Excluding depression is an important part of diagnosing dementia. Depression is more common in old age than dementia, and is treatable. Chronic pain and medication side effects can also be confused with dementia, therefore, clinical assessments need to be thorough in order to delineate these other non-AD causes of cognitive decline.

Laboratory and imaging technologies can also be helpful in ruling out non-AD diagnoses of dementia. For example, according to guidelines issued by the AAN, brain imaging, preferably MRI, is indicated in those patients with suspected AD.[14] This is important because imaging can reveal structural problems (e.g. hematomas), brain atrophy, and cerebrovascular disease, which can all present similarly to AD. Specific imaging features for AD diagnosis have not been firmly established, though some studies have reported reduced hippocampal volume to be correlated with AD.[15,16] However, there is also evidence that AD and aging exhibit substantially overlapping atrophy patterns in the hippocampus and entorhinalcortex, so age-specific criteria are required.[17] Special imaging techniques (e.g. fluorodeoxyglucose-positron emission tomography) have been developed that can highlight areas of hypoperfusion in AD or that can reveal imaging features that distinguish AD from other diseases causing brain atrophy.[18] However, these techniques need to be evaluated further for their ability to provide information that affects therapeutic decision making; distinguishing between clinical entities whose treatment is the same does not help. They are also not universally available, and they are not routinely used for AD at present.

Laboratory tests are useful in ruling out other factors that can contribute to dementia. For example, B12 deficiency, which affects homocysteine and methylmalonyl-CoA metabolism, is associated with irreversible neurological damage.[19] Hypothyroidism can also contribute to a dementia-like presentation, therefore screening for B12 deficiency

and hypothyroidism is important. However, clinicians should not order multiple laboratory tests unnecessarily: some studies show that this is not a cost-effective process, owing to the relative rarity of a treatable metabolic cause of dementia.[20] Given the right clinical picture (e.g. a patient with chronic alcoholism, in whom B12 deficiency is likely), laboratory tests are warranted. A number of studies have revealed that serum or CSF levels of a beta-amyloid peptide (called Aβ 42), which is suspected to play a role in AD pathogenesis, may be predictive for AD in patients with mild cognitive impairment, but these measurements have not been formally included in clinical practice guidelines yet.[21] Genetic testing does not have a routine role in AD diagnosis, but some evidence suggests that testing for presenilin-1 mutations may be considered on a case-by-case basis in unusual presentations of disease, for example in young patients with a strong family history, when appropriate genetic counselling is provided.[22]

Conclusion

In this paper, we have reviewed some major clinical criteria that are used in making a provisional diagnosis of AD and reported on the literature evaluating the credibility of these criteria. While the NINCDS-ADRDA guidelines have been used for a long time and have been shown to have reasonable validity and reliability, they are lacking in specificity, and need to be updated to incorporate the latest advances in diagnostic technology. Studies have found the DSM-III-R criteria to be comparable to the NINCDS-ADRDA diagnostic criteria, however, there is a clear dearth of research in evaluating the value of the DSM-IV-TR criteria for AD. In addition to these clinical criteria, other tests such as neurological imaging and serum B12 tests, can be valuable in excluding non-AD differential diagnoses of dementia. Given that the DSM-V is slated for publication in 2012, we hope that the AD criteria published therein will incorporate the merits of existing criteria with additional criteria that reflect our expansion of diagnostic knowledge and tools in this area.

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Should physicians be taking cognitive-enhancing drugs?

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With the advent of the pharmacological age, a brave new world where the neurological enhancement of the human mind through chemical substances is no longer confined to the realm of science fiction. Variously described as cognitive enhancing drugs, smart drugs, or nootropics, there is an ever-growing list of drugs on the market that can improve mental function such as memory, attention, motivation, and concentration.[1] While initially researched for the therapeutic treatment of psychiatric disorders such as Alzheimer's and Attention-Deficit Hyperactivity Disorder (ADHD), there is increasing evidence that various stimulants and anti-depressants are being used off-label for the enhancement of mental performance in healthy individuals.[2]

The controversial use of these drugs by university students and the military has been well documented in the literature.[2] However, physicians have not been a focus in the discussion despite being a susceptible demographic group with predisposing risk factors. The high levels of stress, fatigue, and pressure especially prevalent among residents and certain shift work specialties, such as emergency medicine,[3-5] may make the use of these cognitive-enhancers appealing. As a result, a candid discussion of the ethical implications is well warranted. This article examines the relevant ethical arguments that are important in determining whether physicians should be taking cognitive-enhancing drugs.

The wisdom of repugnance: the "yuck" factor

While the use of neuro-altering drugs is widely deemed morally acceptable as a medical intervention in neurological disorders, the use of these same drugs in healthy individuals often elicits guttural reactions.[6,7] The use of amphetamines for narcolepsy is not met with nearly the same outcry as its use by ambitious university students to improve test scores. Once the line crosses from treatment of disease to enhancement of normal function, a fundamental change in acceptability seems to occur. One explanation is that the process of cognitive improvement through a pill is unnatural or inauthentic.[8] However, our use of other more common chemical remedies to enhance cognition is not anything new or fundamentally more "natural." The widespread use of caffeinated beverages is a form of cognitive-enhancement,[9] but has not evoked public scrutiny or protest. Why should the ethical considerations change depending on whether the medium is in the form of a drink or pill?

Some arguments that call into question whether there is anything intrinsically wrong with medicating to enhance cognitive function may border on begging the question, but nevertheless have their implications. If the very principle of medicating the healthy is unethical, then advocating for pharmacological enhancement within a profession where public perception and patient trust is so important may be imprudent.

Maximizing utility and the creation of SuperDocs

The use of cognitive enhancing drugs by physicians can potentially improve the well-being of both physicians and their patients. The well-documented high levels of fatigue, sleep-deprivation, and stressful environments that physicians endure have been shown to lead to lowered vigilance and an increase in medical errors.[10] In a double-blind placebo controlled study with sleep deprived emergency physicians, the stimulant modafinil (Provigil®) was shown to improve cognitive ability by improving sustained attention as well as increasing cognitive control and working memory.[11] It is not a far stretch to consider how more attentive, alert, and cognitively functioning physicians can reduce medical errors, improve productivity, and have the fortitude to be more patient-centred in their approach. Not only would this benefit patients by improving their health outcomes, it would benefit the physician by lowering their levels of anxiety and stress, and may even benefit the health care system by improving physician efficiency. If a hypothetical ideal cognitive enhancer can augment desired and predictable changes in mood, personality, attention, and memory, society as a whole may be better off. From a utilitarian point of view, the potential benefits of cognitively enhanced physicians may be too great to ignore with ever-progressing advances in pharmacological agents.

Primum non nocere

Therapeutic agents have inherent risks and the potential for harm; the maxim of "first, do no harm" remains a fundamental principle of medicine and serves as a reminder of how purported beneficial interventions often have unforeseen and undesirable consequences. While psychotropic drugs such as stimulants and anti-depressants are widely prescribed medications with few side effects,[13] even minimal risks need to be taken into account when used by healthy individuals. While patients with severe symptomatic neurological deficits may tolerate the risks involved, the threshold of risk tolerance is significantly lower for healthy individuals.[14] In the study of the use of modafinil among sleep-deprived physicians, the treatment group found it more difficult to sleep when the opportunity arose.[11] While sleep-deprived physicians could use the drug to maintain attention and cognitive function in the short term, the resulting trade-off may lead to a Faustian bargain. Even worse, the long term effects of these psychotropics are largely unknown.[15] The pendulum would certainly take a devastating swing from benefit to harm if a generation of

medicated and neurologically enhanced physicians were later found to suffer from cognitive decline or memory loss in later years. Unfortunately, when faced with the proposition of obtaining immediate tangible benefits from these neurological enhancers, these hidden costs may not be taken into account when considering their use.[16] Given the propensity of human nature to value short term results, as exemplified by the popular use of sildenafil (Viagra®) and cosmetic use of botulism toxin (Botox®), the potential for the overuse and abuse of these pharmacological remedies is a concern.

"But everyone else is doing it"

One of the most commonly cited issues with the use of cognitive enhancing drugs by university students is its perception as a form of cheating, and one could argue that ambitious residents or physicians who take these cognitive enhancers to "get ahead" violate the sanctity of fair competition on an even playing field.[1] Although the field was never strictly even to begin with due to socioeconomic, genetic, and environmental determinants, improving productivity through artificial pills may undermine the value of effort and hard work.[16] The issue especially becomes problematic if there is an unequal distribution of use amongst different physicians or different specialties. Should use only be recommended for specialties with the highest levels of fatigue, sleep deprivation, and stress? Should only those physicians deemed most in need, namely those with the worst attention and cognitive ability, be prescribed these enhancers?

If there are no regulations in place, unintended and indirect coercive forces may come into play where physicians who otherwise would not have taken these enhancers now feel compelled to do so. If doctors who use the cognitive enhancing drugs achieve improved performance and are perceived as superior by patients or colleagues, this puts increased pressure on and makes it more difficult for those who would otherwise opt out.[1] Furthermore, with the emphasis today on outcomes-based medicine and the importance of hospital ratings on budgets, there may also be external pressure from the employer or administration. In the event that these drugs could approach a pharmacological ideal with maximum benefit and negligible harm, could these cognitive enhancers become as compulsory as scrubbing in to protect the safety of the patients?

Conclusion

While a number of ethical issues are left largely unexplored, such as personal identity, distributive justice, or intangible values, a cursory discussion concerning beneficence, nonmaleficence, as well as autonomy has been attempted. Currently, with our poor understanding of the long-term risks of these cognitive-enhancing drugs, the potential for serious harm seems to outweigh the marginal cognitive benefits observed in healthy individuals. The use of these drugs is likely a reflection of our society and medicine as a practice, where the 'quick fix' is often the most attractive strategy.[1] Alternative solutions certainly exist, such as optimizing shift schedules and improving work-life balance. These strategies present less risk and address the root of the problem: over-work, sleep-deprivation, and fatigue.[19] However, as drug advances are made with improved performance records and as better understanding of the long-term effects become available, the reality is that a growing number of people will practice neurocognitive enhancement in the coming years. The sale of various nutritional supplements that are purported to have cognitive-enhancing function have reached a billion dollars annually in the United States alone, and market demand is projected to rise.[14] Given the easy accessibility of drugs to physicians and compounded with their propensity to self prescribe,[17,20] the discussion concerning the guidelines and regulations for the use of cognitive-enhancing drugs needs to begin now.

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Cognitive impact of physical activity in children and youth

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Introduction

Healthy behaviours learned early in life are more likely to persist into adulthood. As such, there is a strong *prima facie* case for health promotion interventions that target young Canadians. That case is strengthened by the fact that risk factors emerging early in life will take a cumulative toll and could have debilitating consequences on future health.

One such risk factor is physical inactivity. Attention in the past has tended to focus on the relationship of inactivity among adults to increasing prevalence of risk factors for chronic cardiovascular disease, viz. higher rates of obesity, dyslipidemia, diabetes, and hypertension. Today, however, there is growing interest in the long-term effects of inactivity that commences in childhood. As summarized below, physical inactivity is not only linked to the growing epidemic of childhood obesity; contemporary evidence also links higher activity levels to enhanced learning and raises the possibility that exercise may be very important in healthy cognitive development.

The childhood obesity epidemic

Obesity has become increasingly prevalent among Canadian children and youth. Temporal trends can be appreciated by defining a reference population and thresholds, e.g. overweight as body mass index (BMI) above the 85th percentile, and obesity as BMI above the 95th percentile for a reference population. Using 1981 weight distributions as a baseline or reference group, one study of Canadian children aged 7–13 years found that the prevalence of overweight among boys increased from 15% in 1981 to 35.4% in 1996 and among girls from 15% to 29.2%.[1] The prevalence of obesity in children roughly tripled over that period, from 5% to 16.6% for boys and 14.6% for girls.

Particularly in North America, physical inactivity is one of the major causes of obesity. Increased caloric intake is also important, but the two may well interact. For example, Crespo et al. reported that US children who watched 5 or more hours of television per day consumed on average 175 kcal per day more than children watching not more than 1 hour per day.[2] Both organized and unorganized sport and physical activities have been shown to reduce the risk of being overweight by 10–24%, and of being obese by 23–43%, after controlling for sex, family structure, and socioeconomic status.[3] In addition to effects on body fat, cross-sectional studies have shown an association between higher activity levels and increased bone mineral mass and lower levels of tobacco and alcohol use in young people.[4]

Not surprisingly given the progressive increase in childhood obesity, school-based physical activity rates are alarmingly low amongst young people. The American Academy of Paediatrics (AAP) recommends comprehensive, preferably daily, physical education (PE) for children in grades Kindergarten through 12.[4] Despite this recommendation, only 3.8% of all elementary schools, 7.9% of all middle schools, and 2.1% of all high schools in the United States provide daily physical education for all students.[5] Data from Ontario high schools are also discouraging. Between 1999 and 2005, there was a significant linear decrease in the percentage of students who were enrolled in PE: from 70.3% in 1999 to 60.3% in 2005.[6]

Adolescence may be a time of particular concern, as academic pressures increase and many schools favour classroom time over physical education. Indeed, one study examining high school students in Ontario found a steady decline in physical activity between 14 and 18 years of age.[7] However, even pre-adolescents are not active enough. In 2002, approximately 82% of Canadian children aged 9 to 12 were not active enough to meet international guidelines for normal growth and development.[8]

Gym in schools and academic performance

School-based physical activity interventions are seen as desirable since students are a "captive audience" during weekdays. There has been a presumption in some quarters, however, that time spent outside of the classroom on physical activity may decrease the academic performance of pupils. Fortunately, several studies have shown that time spent on physical education has no negative effects on overall academic attainment.

In one study of 117 Australian primary schools, time spent in physical education was not negatively related to average school attainment in either literacy or numeracy.[9] Similarly, a study from British Columbia found that a school-based intervention offering an additional 15 minutes of physical activity a day did not reduce levels of academic performance among students.[9] Instead, the evidence suggests that physical activity may *enhance* the academic performance and cognitive functioning of young students. One meta-analysis sought to aggregate the results of 44 studies pertaining to physical activity and cognition in children, and found a significant positive relationship.[8] Middle school students (grades 6-8) and elementary age students showed the largest cognitive benefit from physical activity. The type of activity was not a significant moderator variable, suggesting that any type of physical activity had beneficial effects.

Notwithstanding the results of the meta-analysis by Sibley et al.,[10] some newer evidence supports the notion that different forms of physical activity may actually mediate specific cognitive effects. One study examined the performance of 115 healthy adolescents aged 13-16 years on a test

of attention and concentration. Students performed the test after receiving either coordinative exercise, normal exercise, or a classroom lesson. Both the coordinative and normal exercise groups showed enhanced test performance, but coordinative exercise was the most effective. The authors hypothesized that coordinative exercise might lead to a 'pre-activation' of areas of the brain which also mediate attention and other cognitive functions.[11] As well, Coe et al. suggest that intensity may also be a factor.[12] They found that students who performed vigorous activity had significantly higher grades than students who performed none, while moderate physical activity did not affect grades.

Castelli et al suggest that these effects accumulate through an overall fitness effect, rather than being related solely to recent exercise.[13] They examined 259 public school students in third and fifth grades and found that aerobic capacity was positively associated with achievement, whereas BMI was inversely related.

Also relevant are the results of a systematic review of 23 randomized controlled trials addressing exercise and self-esteem. The review found that exercise has positive short-term effects on self-esteem in children and young adults.[14] It has been hypothesized that improved self-esteem may help to reduce or prevent psychological and behavioural problems in children this age group, which may ultimately augment classroom performance.

Mechanisms for the neuropsychological effects of exercise

These positive effects of exercise on learning in childhood and adolescence are striking, and, encouragingly, appear to be generalized to adult disorders. For example, increased physical activity may delay the onset of Alzheimer disease, Huntington's disease and Parkinson's disease. There is also some evidence to suggest that exercise mitigates the pace of functional decline after neurodegeneration has begun. Furthermore, while the mechanisms are not well understood, exercise also seems to have both positive effects on depression and anxiety, among other psychiatric disorders.[15]

As sometimes happens, these empirical findings are still not well-explained by the available basic science. One line of evidence suggests that neurogenesis – i.e. the production of new neurons – is important. Exercise clearly stimulates neurogenesis in a portion of the hippocampus that affects learning and memory.[15] Since these new neurons appear to have lower thresholds for activation, neurogenesis could well underpin some of the positive cognitive effects of exercise. In particular, Pereira et al. showed that after 12 weeks of cardiovascular exercise training, there was an increase in blood flow to the hippocampal region in rodents and humans.[16] This increase was positively correlated with improved rates of learning a hippocampus-dependent task. While a variety of growth factors appear to play a role in mediating these blood flow effects, no specific therapeutic role for those factors has been elucidated thus far.

An alternative explanatory approach – less relevant to children and youth – is to focus on the risk factors for cognitive decline and delineate those that could be related to physical activity. Among the risk factors for cognitive decline are hypertension, hyperglycemia, insulin insensitivity and dyslipidemia, a cluster of features encompassed by the 'metabolic syndrome.' Exercise reduces the impact of all these risk factors. Thus, whether through direct central neurological effects or through neuro-protective effects mediated in part by mitigating cardiovascular risk factors, exercise seems likely to shape neurological development across the life course.[15]

Future directions

According to Canadian estimates for 2001, the economic burden associated with physical inactivity was $5.3 billion.[17] Thus, interventions targeting physical activity have the potential to show large 'returns on investment'. As already argued, the logical place to start promoting physical activity is childhood, in part to combat the epidemic of obesity among children and youth. Indeed, we know that children who are obese in their preschool years are more likely to be obese in adolescence and adulthood and to develop diabetes, hypertension, hyperlipidemia, asthma, and sleep apnea.[18]

Greater levels of physical activity among children and youth may also lead to enhanced cognitive functioning. However, much more can be done to elucidate mechanisms and clearly delineate exercise modalities. Whereas human studies have emphasized frontal-brain-dependent tasks (i.e. executive function), animal studies have focused on hippocampus-dependent learning and plasticity. There also remains a need for clarification as to which types of exercise, and at what duration and intensity, will have the optimal impacts on cognitive outcomes. Confounders abound in observational studies; physical activity levels may be associated with other mediating variables such as socioeconomic status. Thus, to fine-tune the various interventions, formal randomized trials are essential with standardized outcome measures.

It seems defensible, however, to proceed sooner rather than later with policy shifts that will promote physical activity among children and youth. From a policy standpoint, we applaud Ontario's Healthy Schools program. It was announced in 2005 that every Ontario elementary student will take part in a minimum of 20 minutes of daily physical activity. This initiative aimed to complement existing physical education classes that occur twice or three times a week for 30 to 40 minutes for elementary students.[19] We would strongly encourage similar policies for middle and high school students.

Last, we also encourage the development of a rigorous agenda of basic, translational and applied research that will clarify how best to promote physical activity across the life course.

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Reflux, revolution, and the role of forgotten research in medical paradigms

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Introduction

The conventional view of science as a plodding, methodical process free of entrenched interests and proceeding solely on the basis of observable facts permeates popular thinking. Scientists are often seen as seekers of truth, garbed all in white, using their sheer brainpower to piece together the innumerable parts of whatever grand puzzles capture their respective imaginations. In truth, though, science often progresses not only by evolution, but by revolution as well. In his seminal work of scientific sociology, "The Structure of Scientific Revolutions,"[1]Thomas Kuhn put forward the notion of the paradigm shift as the major mechanism for scientific change, and although the term has been popularized – almost to the point of losing its original meaning – it still retains immense relevance for the analysis of current events in the scientific and biomedical realms.

Kuhn posited that research into a particular scientific or medical problem takes place within the context of a research programme, an overarching framework that dictates the shape of the overall problem, as well as the nature of the specific results needed to solve it. It is perhaps best compared to a partially-solved jigsaw puzzle, in which the dimensions of the puzzle are clear, and the shapes of the missing pieces are discernible – one only has to find the missing pieces that fit into particular spots to complete the puzzle and construct a coherent image. However, sometimes one is left with puzzle pieces that don't seem to fit anywhere, and empty spots for which suitably-shaped pieces cannot be found. In this case, one is forced to question whether the attempt at the puzzle is, indeed, correct, or if perhaps the puzzle depicts something entirely different and needs to be rebuilt from scratch.

Such is the case with science as well: data that pose challenges to the dominant framework accumulate, and important research questions go unanswered by the research programme currently underway. A new theory is put forward that accounts not only for the previously established results, but also for the conflicting data that troubled the dominant paradigm, and while the new approach may not answer every remaining question, it does provide a direction for further research to follow. However, as will be demonstrated shortly, there is often considerable opposition to the introduction of a new paradigm. Careers and fortunes are often staked upon a widely-held paradigm, and even though researchers may have the best of intentions, the words of Max Planck too often hold true: "a new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it."[1]

The case of peptic ulcers

The classic example of a paradigm shift in medical thinking relates to the etiology of peptic ulcers. Originally described by Marcello Donati in 1586,[2] gastric ulcers in particular came to be attributed to the acid milieu of the stomach, encapsulated in the famous proclamation of the Croatian surgeon Karl Schwatz: "No acid, no ulcer." Factors which increased the amount of acid, such as stress and spicy food, were naturally seen as contributing to the pathogenesis of the dread disease. However, blaming acid alone for the incidence of ulcers left several important facts unexplained. For one thing, until the advent of effective antacid medication, the prescribed treatment was often ineffective. More fundamentally, as early as 1875, it was proposed that bacteria had a role to play in the development of peptic ulcers, and in the late 1950s, it was recognized by some clinicians that ulcers could be successfully treated with antibiotics. The Greek physician John Lykoudis, for example, discovered that his chronic ulcer problem went into remission after he treated himself with antibiotics for a bout of gastroenteritis. He later took out a patent on his antibiotic ulcer preparation and attempted to publish an article in JAMA, only to be summarily rejected.[3] Lykoudis was eventually fined 4,000 drachmas (about $900, accounting for inflation) by the Greek medical disciplinary committee for his unorthodox treatment,[4] and the bacterial theory of peptic ulcers resumed its usual lowly place in the dominant paradigm until the work of Marshall and Warren in the 1980s finally set into motion the wheels of scientific revolution and established that gastric infection with *H. pylori* was a major cause of peptic ulcers.

What this paradigm shift serves to highlight is the role of forgotten research, the undercurrent of data supporting alternate etiological factors that were never incorporated into the dominant paradigm. That this research is generally ignored – or censured, as in the case of Lykoudis – is, in retrospect, difficult to justify scientifically, but ultimately understandable. Before the attribution of peptic ulcers to acid and acid alone, research in this area was in what Kuhn called the pre-paradigm phase, in which there is no consensus on a research programme, but the research being conducted is nonetheless valid and scientific. When the consensus of an acid etiology was reached, research began operating in the second phase of Kuhn's hierarchy: normal science, in which experiments and studies are conducted with the aim of filling in the missing pieces of a defined puzzle. Concurrent with the ascendancy of a particular paradigm is the frequent abandonment of earlier, pre-paradigm directions in research, not because of inherent invalidity, but because circumstances are such that further exploration is unfeasible: researchers may change to

a different field of study, there may not be sufficient supporting knowledge or technological gadgetry to investigate a theory, or sources of funding may shift to approaches that support the alternate, ascendant theory. When a dominant paradigm is established and other theoretical approaches are no longer *en vogue*, it is easy to all but forget the historical context that gave rise to the current situation, especially when the next generation of researchers comes through the ranks having not even been informed of any alternative theories to the dominant one.

Forgotten though they may be, alternate theories and dusty old data often survive in some form or another. In some cases, researchers outside the mainstream may continue to investigate older approaches, earning the scorn of their colleagues and collecting very little in the way of grant money and prestige. Alternatively, a researcher may, like John Lykoudis, discover quite accidentally through his or her own personal experience, that the current paradigm is lacking. Furthermore, an older theory may be resurrected when contemporary researchers independently turn up data that force them to dig through the literature for theories that might explain their findings. Thus, forgotten research has a vital role in maintaining one of the ultimate principles of scientific enquiry – that current knowledge is always subject to revision.

Forgotten research in neurology

Neurology is certainly a field that has its share of unsolved problems. The causative factors behind such diseases as epilepsy, ALS, and Parkinson's are still mostly unknown, even if we have made progress towards understanding their pathophysiology. Of all the theories currently circulating that attempt to explain some aspect of neurological disease, there is perhaps none as recently controversial and widely-publicized as the vascular theory of multiple sclerosis (MS), which contests the widely-held notion that MS is predominantly an auto-immune phenomenon. While this author is not in a position to comment on the ultimate validity of the theory, or the degree to which it explains the phenomena it claims to account for, an analysis of the issues surrounding the theory and the potential it has for sparking revolutionary science is worth contemplating.

As was the case for peptic ulcer disease, there have seemingly always been multiple theories accounting for the pathogenesis of MS. As early as 1839, just a year after the first recorded pathological description of multiple sclerotic lesions, it was noticed that MS lesions appeared to involve altered vasculature or hemodynamics, an observation that was later made by Charcot himself.[5] Intriguingly, an experimental study in dogs published in 1935 claimed that when the cerebral veins were artificially obstructed, lesions developed that were "so striking [in similarity to MS lesions] that the conclusion appears almost inevitable that venular obstruction is the essential immediate antecedent to the formation of typical sclerotic plaques."[6] The conclusion at the time was that such obstructions were likely a result of thrombosis, and as a result, treatment with anticoagulants was attempted, with mixed results.[7]

In the years following the second World War, there was increasing recognition that the inflammatory component of MS could be amenable to treatment. In 1969, researchers carried out a placebo-controlled study of adrenocorticotropic hormone (ACTH) in patients suffering from exacerbations of MS, and found that it was an effective symptomatic treatment.[8] This paved the way for decades of further research into pharmacotherapeutical initiatives aimed at curbing the inflammatory process. The vascular component was all but forgotten, and today, the majority of drugs used to treat MS target the immune system, and although they are often touted as breakthroughs, retrospective studies have shown that they have only modest effects on established disease and somewhat questionable efficacy in preventing disease progression.[9,10]

The modern attack on the dominant paradigm of MS began in late 2008, when Paolo Zamboni and colleagues showed that a particular set of extracranial venous anomalies were found in MS patients, but not in controls.[11] (It should be mentioned that Franz Schelling had attempted to resurrect the vascular theory of MS in 1986,[12] but his efforts to secure funding for experimentation were frustrated, and it was left to Zamboni to take the lead more than twenty years later.) News spread quickly, and just a few months later, patients were discussing the new findings and seeking treatment for their venous stenoses and malformations at centres all over the world. Internet forums were abuzz with talk of a real breakthrough, as well as the personal anecdotes of those who had undergone treatment and found that it had helped their symptoms improve. In late 2009, Zamboni published the results of an open-label pilot study, which showed that venous angioplasty reduced symptoms and disability measures in those MS patients who had demonstrated cerebrospinal venous insufficiency.[13] Notably, it should be pointed out that Zamboni does not argue that MS is *not* an auto-immune disease, but rather that the insult leading to inflammation and white matter lesions is often vascular in nature, and likely a congenital malformation.[14]

Comparing the timeline of research into peptic ulcers with that of MS, it appears that the two share a similar trajectory. Both have their origins in a stage of pre-paradigm science prior to the twentieth century, an ascendant paradigm and a consequent programme of normal science within the last hundred years, and a period of potentially revolutionary science within the last few decades. In both cases, researchers operating outside the mainstream demonstrated findings compatible with older theories that challenged the dominant paradigm, and in both cases, their findings were met with skepticism. Lest we forget, even Marshall's dramatic demonstration of the ulcerogenic properties of *H. pylori* (in 1984, he drank a culture of the bacterium and subsequently fell ill with an ulcer) was insufficient to convince the majority of clinicians; eight years later, an informal survey showed that two-thirds of gastroenterologists polled were still skeptical of the *H. pylori* claim.[15]

Conclusions

As the debate over MS paradigms rages on, it is instructive to analyze the situation at play and understand what it may mean for medicine in general. Looking back on a century or more of modern medicine, it is likely that at least some answers to the pressing medical questions of our time have already been found, but have been neglected amidst the inevitable turmoil of shifting paradigms, ever-accumulating data, and the cognitive dissonance stemming from overzealous adherence to a particular set of ideas. Luckily, advances in technology and increasing access to more and more sources of historical research data have provided us with a rich reservoir of science to review and learn from. Whatever the final outcome of the MS debate, it is a foregone conclusion that this will not be the last time forgotten research has its last laugh.

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Addendum

A precursor to this article was originally presented to the Harvey Club of London on April 20, 2010.

The author invites readers to submit further examples of forgotten research at a new website created explicitly for this purpose: www.forgottenresearch.com.

Youth, adults and transitional patients with spina bifida: a multidisciplinary approach to facilitating the passage from paediatric to adult care.

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Children and adolescents with spina bifida – a unique population

Spina bifida (SB), meaning "split spine" in Latin, is the most common neural tube defect and the most severe congenital disorder compatible with life.[1] During the third to fourth week of embryonic development, the central nervous system begins as a neural plate and fuses into a neural tube. SB is the failure of this neural tube to close and results in three different categories of defects: occulta, meningocele and myelomeningocele, the latter being the most severe and the focus of this article. Fifty years ago, the prognosis of an infant with myelomeningocele was grim as only ten percent were expected to survive their first year.[2] Today, survival into adulthood exceeds 85% due to advances in the management of complications.[1] While this is certainly a success in neurosurgical medicine, deterioration in adulthood is common in these survivors. One of the greatest challenges remaining is the continuity of care between paediatric and adult services, which requires a functional multidisciplinary team.

Morbidity in the aging SB population is a complex combination of physical, emotional and developmental obstacles. The long term physical effects of SB include muscle weakness or paralysis below the level of the lesion, loss of sensation, and loss of bowel and bladder control.[3] Following repair of the myelomeningocele, 70-80% of infants develop some degree of hydrocephalus, which is treated by implanting a shunt shortly after birth.[4] If hydrocephalus is untreated, or if the shunt later malfunctions, excess fluid may result in permanent brain injury, seizures, or blindness. Unrecognized shunt malfunction is the leading cause of death in adults with SB.[4,5] This is a topic that adult-centered physicians must be educated in when caring for patients with SB.

Concerning the emotional development of children with SB, independent mobility is an important factor in determining quality of life. The level of the lesion corresponds to prospective independent mobility. For lesions above L2, loss of quadriceps and iliopsoas muscle function is typical and wheel chair dependence is expected.[6] However, lower lumbar and sacral lesions are usually compatible with ambulation,[7] for which early physiotherapy and orthopedics consultations are crucial.[8] Ambulation may mitigate the decline in activity through adulthood resulting from obesity, spinal and foot deformities including scoliosis and clubfoot, and respiratory compromise. In a 2004 cohort study of 117 patients, 30% were ambulatory at 30 years follow-up, of which 88% had lesions at L5 or below.[9] This highlights the importance of early intervention and appropriate rehabilitation in response to changes that occur over time.

Another important area of treatment for people living with SB is the lifelong management of urinary incontinence and impaired sexual function.[10] Sexual function may be reduced due to impaired neurological innervation, or the psychological effects of negative self-image and incontinence anxiety. However, there are two common misconceptions that are held more by medical students and doctors than by the young adults themselves: that people with SB cannot be sexually active, and that they cannot have babies.[3] Both are untrue. Healthcare professionals should provide the proper education and counselling of safe sex and contraceptive services and should address the increased risk of latex allergies. Family planning services and pap smears should also be readily available to patients with SB,[3] and must be sensitive and specific to the emotional and physical needs of this unique population.

As recently as twenty-five years ago, young children with developmental problems, including SB, faced an isolated homebound existence or were placed in often inadequate custodial facilities. A literature review also reveals that children with SB commonly have language deficits that often go unrecognized despite average intelligence.[11-14] In response, early interventions focusing on psychosocial and educational models have been emphasized. Failure in independent self-care has been found to be a hindering factor for employment in young adults with SB.[15] It is therefore of vital interest to understand the factors leading to this failure in self care, whether they be physical, emotional, or developmental in origin, and to facilitate functional transition to adult life.

Issues surrounding transition

Knowledge and communication by paediatricians

A study by Binks et al. outlines several barriers that prevent successful health care transition from paediatric to adult medicine for young adults with SB.[16] One key point is that it is often difficult to sever the relationship between the paediatrician and the patient.[16] The paediatrician is seen often, and builds trust and relationships with the entire family; this is the nature of paediatric care. Thus, there is a lack of incentive for all involved to discuss the process of leaving the paediatric system to transition to adult care.[16] This lack of communication inevitably results in a delay of the transition process until paediatric services are no longer applicable or available – in Ontario, when the patient turns 19. This is contradictory to the literature, which suggests that transition should begin as early as possible – by the ages of 14-16.[16]

We believe there are several components necessary to facilitate an effective earlier transition. First, it is essential that the paediatrician must have a realistic expectation of the duration of their patient's care, since their expertise does not always translate to effective management of adults. It is in the best interest of the patient for the paediatrician to relinquish the patient's care.

Second, it is essential that care is taken by the paediatrician, with help of a multidisciplinary team, to prepare the child as best as possible for the physical and emotional challenges of adulthood.[17,18] As mentioned, they include (but are not limited to), sexual health, social behaviours, alcohol and drug use, body image, mobility, employment strategies, anxiety and depression. Here, it is crucial for the information to be tailored to the patient's age and stage of mental and physical development, which highlights the importance of expertise from multiple disciplines.

Third, it has been shown that young adults with SB rarely feel comfortable navigating the adult health care system.[16,17] Therefore, they are less able to advocate for themselves and are hindered in seeking the best possible care. Often, the paediatrician will continue to care for the patient.[17] This has resulted in poorer health statuses of young adults with SB as compared to age-matched Canadians, whereas children with SB have the same health status as their Canadian counterparts.[18] This inequality is due in part to a lack of preparation of the patient by their paediatrician and health care team. Therefore, early in the transition process, the patient must be made aware of the differences between paediatric and adult medicine, as well as the structure and function of the adult medical system.

Training and abilities of adult care providers

The second barrier outlined by Binks addresses the perceived lack of knowledge of adult care providers surrounding the needs of young adults with SB. They may have little to no exposure to childhood diseases or their sequelae in adulthood. Young et al. notes that paediatricians are often concerned that their adult counterparts do not fully understand or appreciate the nature and extent of SB.[19] Additionally, Sawyer et al. found that paediatricians specializing in SB felt that adult care providers did not fully grasp the needs of this population.[17]

An ideal approach to transitioning would allow for several meetings between the paediatrician and future adult care provider, patient and patient's family before the transition begins.[18] These meetings would ensure several things. First, the family physician would receive all relevant information about the patient from three different sources: the paediatrician, the family and the patient. They would be more aware of the patient's ability to manage their condition, as well as the role the family plays in the patient's care. In such a way, the family physician is educated and may prepare to face the specific challenges of dealing with a childhood disease progressing into adulthood.

Transition organization – multidisciplinary approach

The ongoing goal is to ensure that quality health services are available to the patient with SB, given their physical, mental and emotional needs. Therefore, an organized, cohesive and coordinated system must be in place during and after their transition to adult care. Overall health of youth with SB is reported to be much higher than their adult counterparts.[20] This indicates that adults with SB are not receiving adequate care. Professionals seen by patients with SB include nurses, speech therapists, occupational therapists, physical therapists, dentists and many others, but the variety of care received is much richer for children with SB than adults.[20]

Furthermore, in a study by Sawyer et al., several specific issues with the transition process itself were highlighted: the time gap between receiving paediatric and adult care, the sentiment that the adult health care practitioners' skills were insufficient (especially at the beginning), and the lack of reassured permanence of their care.[17] Coordinated multidisciplinary centers could help to address these issues.

Studies have outlined different transition programs which include transition clinics.[20] A study by Westwood, et al. showed that over 90% of children and adults with cystic fibrosis, another disease in which it is common to transition from paediatric to adult care, felt that a transition clinic would be helpful.[21] These clinics unite family doctors, paediatricians, families and patients, and can provide links to additional resources such as counsellors and psychologists. With the current technology in electronic media that is available, the feasibility of meetings between multiple individuals and disciplines becomes possible with conference calling and other internet-based solutions. The scope of practice may no longer be strictly limited by location, as these online networks become available to all professional communities.

The ultimate benefit of such multidisciplinary clinics or teams would be to all patients with chronic paediatric conditions, who, thanks to advancing medical technology, are growing into their adult years.

Conclusion

Shunt problems and spinal cord-related symptoms typically account for a substantial amount of morbidity affecting young adults with SB and may be avoided if recognized early in their course. There are, however, also many important health education, vocational, and psychological issues that are specific to this age group. The transition from paediatric to adult care presents a huge challenge to the health care system itself. It must involve adequate resources and educated health care professionals to enable these paediatric patients to take the appropriate steps towards independence, maturity, and adult fulfillment.

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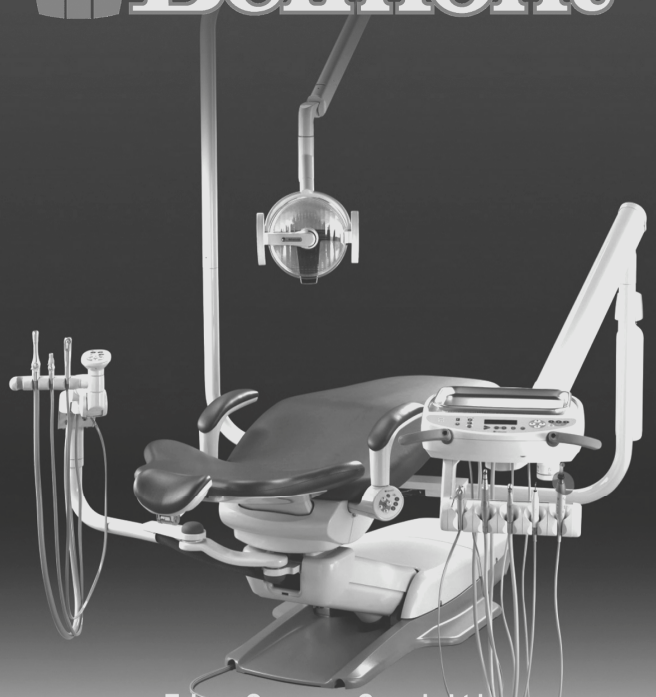

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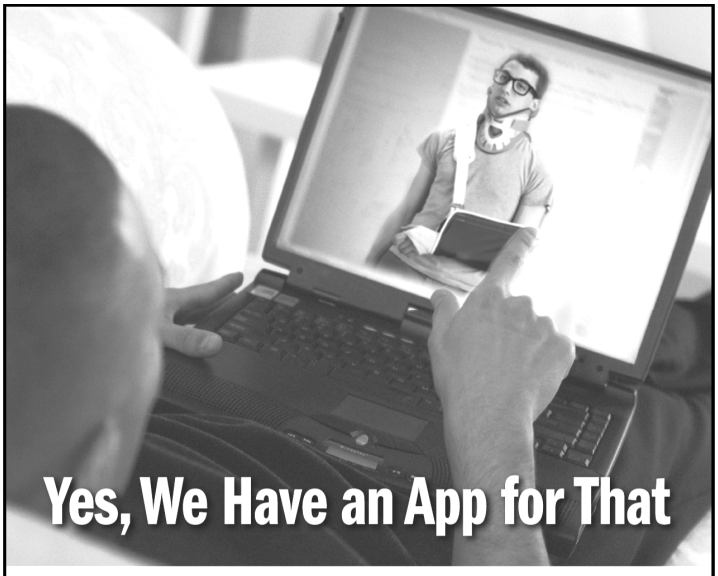

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Neuroprosthetics

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Faculty review: Dr. Tutis Vilis, Department of Physiology and Pharmacology, UWO

Introduction

Neuroprostheses are electronic human-computer interfaces that function to replace or enhance specific aspects of the central nervous system. There are two main types of neuroprosthetics currently in use today: motor and sensory. Technological advances have made possible a wide variety of prosthetic devices that have greatly enhanced the quality of life of many patients who have lost sensory or motor functions.

Sensory neuroprosthetics

There has been a wide interest in neuroprosthetics that replace primary sensory organs. Perhaps the oldest and most successful example of a sensory neuroprosthetic is the cochlear implant. While not a perfect replacement, it has had a tremendous impact in restoring basic auditory function to patients. Research is also underway to develop a visual prosthetic device. However, limitations in current technology and our understanding of the visual pathway present roadblocks in the development of an adequate device.

Seminal work in developing an auditory prosthesis was conducted by French researchers in 1957, and involved stimulation of the auditory nerve with a single channel electrode.[1] Even with this simple setup, the patient was able to distinguish monosyllabic words. More recent technologies informed by our understanding of the auditory system have dramatically improved this performance. For example, the portion of the auditory nerve that runs inside the organ of Corti is tonotopically organized; tones are spatially arranged by frequency. Cochlear implants take advantage of this by breaking incoming sound up into multiple frequency channels. Each channel is fed along its own electrode to the corresponding portion of the auditory nerve replicating the natural function of the cochlea. Just four frequency channels are sufficient to understand speech, which is remarkable considering that roughly 30,000 hair follicles normally stimulate the nerve.[1]

Current implants have up to 22 channels, more than adequate for understanding speech, but still inadequate for auditory tasks such as music perception.[2] A 2001 study in Nature demonstrated that improvements in music perception will require improvements in sound encoding.[3] Not only does the auditory system decompose sound by frequency, it also separates sound into two components: a slowly varying frequency envelope suitable for speech recognition, and a rapidly varying fine structure used in pitch perception and sound localization.

The development of a visual prosthetic has been much more difficult. Firstly, the amount of visual information entering the eyes is more complicated and dense compared to the auditory system. While four frequency channels were adequate for functional hearing, having only four discriminate regions for vision is inconceivable. Researchers have suggested that a 10x10 array of pixels can restore just enough vision for navigation and object avoidance,[4] while as many as 1000 pixels are need to restore face recognition and reading.[5] The retina is also an incredibly compact organ with a receptor cell density that cannot be easily replicated. One group demonstrated that a silicon microarray for nerve stimulation can be machined with electrodes that are 0.4mm apart, although this is still a far cry from the maximal cone density found in the fovea.[6]

Despite the technological challenges of creating an artificial replacement retina, it still remains the primary site of visual prosthetic research for a number of reasons. Firstly, just as the cochlea is tonotopically organized, the retina has a natural spatial organization which simplifies prosthesis design. Secondly, a retinal approach takes advantage of natural visual processing that begins at that level, including colour perception and edge accentuation.[7]

Motor neuroprosthetics

Perhaps the most well known type of motor neuroprosthetic is the artificial cardiac pacemaker. Cardiac pacemakers are devices implanted in the muscular wall of the heart as a replacement for the sinoatrial node, which is required to maintain the sinus rhythm of the heart.[8] Another example of an autonomic neuroprosthetic device is the bladder control prosthesis used in patients with spinal cord injuries. Although still in the experimental stage, neuroprosthetic devices implanted at various areas of the urinary tract attempt to replicate the original function of the urinary tract. Controlled by an external transmitter, the device is implanted at the sacral anterior root ganglia of the spinal cord. Signals sent from the device assist in bladder control, defecation and achieving and sustaining full erections in male patients.[9]

In addition to autonomic devices, there are numerous motor prosthetics under development. The neuroprosthetic device showing the most promise for motor control is an implantable computer chip called the Brain-Computer Interface (BCI). The BCI can be implanted into the grey matter of the brain, the skull or outside the skull. The BCI collects distinct EEG patterns generated by the patient when they imagine specific movements of paralyzed body parts and converts them into signals controlling prosthetic devices.[10] The BCI essentially translates the intentions of the user into movement of the prosthetic device.[11] Figure 1 shows an example of a brain-computer interface currently in clinical trials.

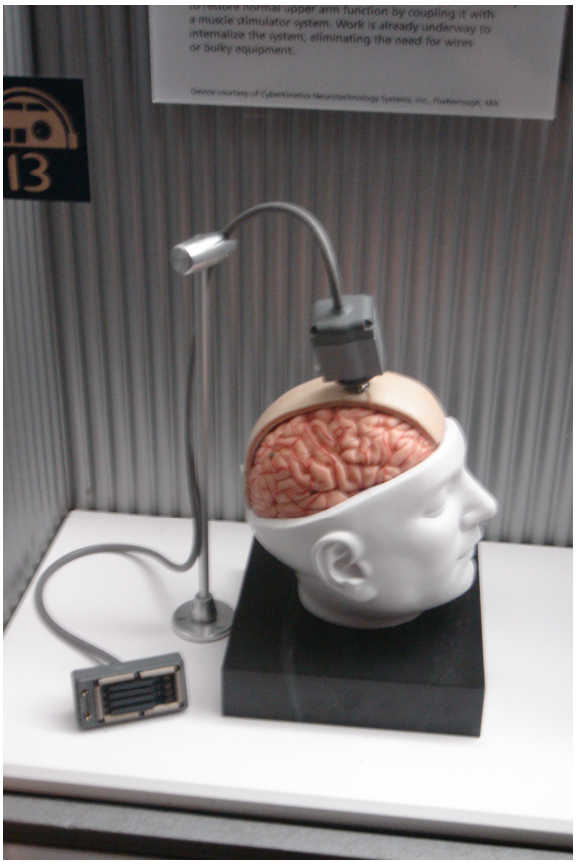

Figure 1. An example of a brain-computer interface.

Conclusions

In addition to the sensory and motor neuroprosthetics that have been discussed above, there is a new area of research focusing on cognitive neuroprosthetics. These devices aim to restore cognitive function to those who have suffered brain injury or paralysis due to trauma and those suffering from Alzheimer's disease and Parkinson's disease. Damaged brain tissue can be replaced by integrated circuits, which would help process information that would normally be done in the diseased region of the brain. [12]

Despite some difficult challenges in designing neuroprosthetic devices, such as the size of the device, power source and material interactions with human physiology, the work done thus far suggests a promising future .

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Excusing "out of control" behaviour: brain tumour-related aggression

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Everyone gets angry from time to time, and for some people, anger seems to be the norm, rather than the exception. However, a relatively sudden shift in character to severe aggression is not considered 'normal.' This kind of aggressive behaviour escalated to an extreme in the case of a 55-year old Eastern European immigrant who, in a fit of rage, beat his wife to near-death with a hammer in 2008.[1] Many similarly unfortunate events occur without attracting the attention of the medical community. This particular event, however, did not go unnoticed, as it involved a brain tumor. The patient has since been incarcerated for his actions, but could it be possible that the observed and documented changes in his behaviour were in fact the result of a tumor or its subsequent treatment? If medicine can provide an organic cause for his actions, should he be found criminally responsible for them? To be exact, should he even be prosecuted for an action he was not legally responsible for? In order to discuss the moral, medical and legal dilemmas that arise from such rare and complex cases, the pathogenesis of tumor-mediated aggression and its legal implications will be further explored.

Case

The patient presented with a one week history of headaches, aphasia and right hemi-paresis. A T1 weighted MRI and subsequent biopsy of the tumor confirmed a large glioblastoma (GB) in the left hemisphere, involving the frontal, temporal and occipital lobes.[1] A glioblastoma is a grade 4 astrocytoma, characterized by high mitotic activity and necrosis or endothelial proliferation.[2] The patient was subsequently treated for six weeks with concomitant radiation and chemotherapy. Throughout treatment, the patients' family complained of new onset paranoia, despite no past psychiatric illness. His family denied any aggressive behavior. In spite of repeated suggestions from his physicians to obtain a psychiatric evaluation, both the patient and his family refused. Although his motor functions improved throughout the treatment, to the utter vexation of his family, his emotional detachment failed to benefit from the shrinking tumor.[1] Upon further requests for psychiatric evaluation, the patient discontinued (or withdrew) from treatment altogether. He was arrested eight months later for savagely beating his wife, in what can only be presumed to have been a fit of extreme, unbridled rage.[1]

Physiology and behaviour

The physiologic functions of the limbic system were discovered in the first half of the twentieth century.[3] Hughlings Jackson had delineated the temporal lobe (specifically, the amygdala) in the early 19th century as the origin for anger, aggression and rage.[4] Studies demonstrating its role in human emotions were performed in 1963 and 1977, showing that stimulation of the amygdaloid nuclei induced a strong aggressive response.[4] A mechanism of aggressive behavior production has been demonstrated in several recent studies on children with epilepsy, which can be extrapolated to those with tumor-associated seizures. These children with aggressive behavior and intractable partial epilepsy demonstrated glucose hypometabolism (which may be indicative of decreased neuronal activity) in temporal and prefrontal areas when compared to control subjects and nonaggressive children with partial epilepsy.[5] It is thought that in normal children, these areas suppress aggression triggered by the activation of limbic structures, and that loss of function in these areas results in loss of frontal lobe control.[6]

It is well documented that tumors of the temporal lobe can cause seizures.[4] Despite the rarity of their occurrence, some of these patients also manifest post-seizure aggression and other behavioral changes, which may be associated with the tumor. In documented pediatric cases, two children (both boys, aged 5 and 13) were found to have excessively aggressive behavior, which improved upon surgical resection of their tumors: a meningioma and a ganglioma, respectively, both in the right temporal lobe.[6]

The patient in this case had cognitive impairments that are consistent with lesions in the left frontal, parietal and temporal lobes. Neuroimaging studies on aggressive and violent offenders have demonstrated a correlation between dysfunction of these areas and aggression and violent behavior. [7]

Social and legal implications

Aggression and the gradation of related emotions have always existed within normal social behavior. It manifests in early infancy, as children procure from their caretakers the attention needed to survive.[3] While in most cultures rage and aggressive outbursts are not tolerated, we must, as a society, consider the etiology of this aggression. The rapid transition a person can make from a state of reason to one of uncontrollable anger is rarely appreciated as a possible manifestation of disease.[3] Underlying illness should be considered when the reaction is grossly disproportionate to the provoking stimulus or out of character for the patient. The possibility of a brain lesion leading to acts of extreme violence, while a rare occurrence, can have tremendous implications in the legal approach to such cases.

The role of the physician must be established in treating patients who may potentially harm themselves or others as a result of their changed behavior. The ruling in Tarasoff v. Regents of the University of California (1976)

determined that physicians have an obligation to protect public safety and can or must breach patient confidentiality to warn those potentially at risk of impending danger.[8] As a result, patients who are demonstrating signs of aggressive or violent behavior require careful scrutiny throughout treatment and beyond, from both health care providers and family, in order to prevent a tragic outcome.

In addition, the role of medical forensics in the judicial system is of increasing importance, as science and medicine are increasingly able to describe biological influences in the development of criminal behavior. Advancements in neuroimaging, such as CT and fMRI have afforded scientists the ability to search for organic causes of aggressive and violent behavior.[7,9] In fact, the use of neuroimaging in criminal trials has increased as part of an attempt to mitigate penalties during sentencing hearings.[11] However, not everyone is convinced of its use in a justice system based on free will. Some argue that searching for a root cause in every situation will decrease criminal liability. However, mitigating factors should not be ignored for the sake of upholding an unaccommodating penal system. Our judicial system relies on the principle of fundamental justice: when personal freedom will be restricted, the State has the onus to prove intent and act (*Mens rea, actus rea*). [10] Thus, Greene and Cohen (2004) believe that:

> [N]euroscience will likely have a transformative effect on the law, despite the fact that existing legal doctrine can, in principle, accommodate whatever neuroscience will tell us. New neuroscience will change the law, not by undermining its current assumptions, but by transforming people's moral intuitions about free will and responsibility.[11]

The Canadian Criminal Code, Part XX.1, states that "A person can be found not criminally responsible by reason of mental disorder."[12] The legal test applied requires that the accused did not appreciate the nature and quality of the criminal act or omission or know that it was wrong. Therefore, physicians must be educated and have an enhanced awareness of the emotional and behavioral ramifications neurological disease and dysfunction may pose. In fulfilling their duty to advocate for patient welfare, physicians can promote new approaches, both medically and legally, to such situations, and potentially prevent wrongful convictions.

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Profile of Dr. Michael Strong

Gordon Tsang (Meds 2012) and Joyce T. W. Cheung (Meds 2013)

Dr. Michael Strong is the current Director of the London Motor Neuron Diseases Clinic at the London Health Sciences Centre and the Arthur J. Hudson Chair in ALS Research. Commencing July 1st, 2010, Dr. Strong is stepping into the role of Dean of Medicine & Dentistry.

Dr. Strong is truly one of Southwestern Ontario's own, having been raised in Leamington, Ontario. His father, a microbiologist, worked as the director of the quality control program for Heinz Canada and then as a teacher at St. Clair College in Windsor. His mother worked as a nurse. Both had strong influences on Dr. Strong's decision to attend Queen's University, pursuing a degree in biochemistry, and his eventual enrolment in medical school soon thereafter. After receiving his M.D., Dr. Strong pursued training in neurology in London, Ontario, and post-graduate training at the National Institutes of Health, Maryland, which he described as "three of the best years of my life."

> "When I initially began my residency training, it was not with a view towards becoming an academic. I came to the University of Western Ontario after receiving my M.D. because I wanted to be a clinical neurologist and the program offered here was amongst the best in Canada. I was, however, aware of the strength in clinical research in dementia at the time, so this had a role as well in the decision. Interestingly, the interview process for acceptance into the neurology training program reflected the focus of the program on training the next generation of clinical academics, so it was pretty close as to whether I would be accepted or not. Not surprisingly however, given the strengths of the program, I fairly quickly found that I did have a considerable interest in the more academic aspects of Neurology. This was in large part due to the mentorship of Dr. Arthur Hudson, my predecessor and head of the ALS clinic at the time.
>
> Following completion of my residency training, I undertook a three year research fellowship at the NIH. I wanted to culture motor neurons to see if we could develop a model of ALS in vitro. Being at the NIH, we were afforded a great opportunity to undertake experiments that were high risk, but that, if successful, could potentially be very high yield. I was successful in both developing a model of culturing rabbit motor neurons — something not previously done — and in developing a new rabbit model of ALS."

Since then, Dr. Strong has won many prestigious awards and honours including recently being awarded the Sheila Essey award for ALS research in 2005 from the American Academy of Neurology and the Forbes Norris award in 2008 from the International ALS/MND Alliance. He is the only Canadian to have ever won both awards.

With such a strong dedication to and interest in basic science research in his own career, we asked Dr. Strong if he would be making any changes to the Schulich medical curriculum with regards to the balance of clinical and research components:

> "Dean Herbert has left us with a very good educational program at Schulich; I hope to maintain and build upon that. I am also interested in promoting our research programs, and moving these to greater international recognition. When someone talks about the NIH, for example, there is immediate name recognition of various labs and research areas. While this does exist to some degree for Schulich, I would like to expand this considerably.
>
> Our new president, Amit Chakma, is also very interested in making UWO known internationally. The best way to do that is to promote a few areas that can become renowned globally. Usually, that is achieved through a combination of strong educational and academic programs. The benefits of such a direction for Schulich are multiple. We have to remember that we are living in a time of incredible scientific advancement, where technologies such as those embedded in genomics are dramatically changing not only how we practice medicine, but what our patients expect of us in terms of scientific knowledge. So the advantage of educating students in a milieu of this caliber is that it will help to equip our students with the skills and the necessary comfort level to be able to process all the information that is available, or at least understand how to begin to interpret it.
>
> It isn't my intent to push for every student to become academically focused, but I do want to allow for those that are to have the opportunities to develop their interest, much like the experience I was afforded. Both educational and academic programs are integrated and necessary, and our goal is to develop physicians highly interested in both areas."

Current students are faced with difficult a dilemma – how much of our time do we invest in clinic and how much in research, if any. We asked Dr. Strong why he decided to pursue a clinical career, given his strong research background:

> "A large part of it was a personal motivation: my father had died from cancer and he was treated in

London, so that experience was ingrained in me. To be honest, I didn't like the specialist that was treating [him], but then again, he couldn't have done anything to make me happy considering the situation. My mother was also a nurse, and I saw her dedication to the healthcare profession as I grew up.

Another positive influence was my biology teacher in grade 13, who had a Ph.D. from India. Since Ph.D.s from foreign countries were not recognized at the time, he taught biology at my school. He promoted innovative teaching that was ahead of his time. One of my projects was to work on the brain with a pathologist at the hospital, looking at different areas of the brain using routine histological techniques and trying to see if there was some sort of anatomic correlate to the different lobes and functions. Pretty ambitious stuff for a high school student!

It was also during this time that my father struggled with cancer, and on his hospital bed, he asked why I wasn't thinking of going to Queens to study biochemistry. You have to understand that at that time, virtually all students in my high school ended up in either Windsor or London, with a very few making it as far away as Toronto. Not at all like today. In hindsight, it was his way of telling me not to set boundaries for myself. It was also around that time that I considered going into [the] priesthood, because I enjoyed working with people. A weekend at the seminary pretty much clarified where my career was going to head."

Your current responsibilities as a clinician-scientist and administrative leader sound very intimidating. What is a typical week in your shoes like?

"Each week is highly variable. Key to this however is my family. There are various activities that are seasonal and I try to organize my time around them. During the summer, I enjoy gardening with my wife, Wendy, and we play golf, often as a family. When my kids were younger I would take a week off to either go camping with them or spend time at a cottage. Eventually, as the kids became older, I could leave for a month at a time, and during that we camped all over Canada and the U.S. I was able to share time with my children that I will never get again. Better yet, the hospital didn't fall down simply because I wasn't there. It really was a great time in our lives.

With regards to my average week, I can't actually recall having one! It is one of the great pleasures of being a clinician-scientist in that there are so many different challenges. I try as much as I can to get to my lab, so generally start each day at 7 by killing off some paperwork, and then complete the day doing the same. In between is when I get to the lab or clinic."

With such a great balance between clinical work, research, and a great family life, we had to ask what motivated you to apply for the Deanship?

"I loved my life, so it was not a quest for something better. One of the reasons is that I do believe our next generation of physicians has to be very comfortable with balancing life, integrating science, and being a physician. We have an aging population that we have to deal with and we need people that are comfortable with balancing many things because it will not be easy in a time of tight fiscal resources. There is a significant research and academic component to our field. It's a difficult time in research, but we want to be able to take next generation of academics and tell them we can survive recessions and setbacks.

I've done a lot of work to address our ability to do clinical research. We're in a financial sector that is constantly squeezed. Our centre is supposed to do cutting edge research but we're even struggling to deliver healthcare. I helped develop the Lifecycle Research Network (LRN), which is model for doing clinical research on a large scale across many different cities in the Southwestern Ontario area. The next thing to do as Dean is to bring about more push towards this."

Dr. Michael Strong

As a scientist, you are always on the cutting edge of new research. Where do you see your research career heading in the next 10-15 years, after your tenure as Dean?

"It's difficult to know if my research career will be like it is now. If you had asked 10 years ago, I certainly would not have predicted that my lab would be

leading in the areas in which it currently does. The most difficult challenge for me while a Dean will be ensuring that I and my lab not only continue to lead, but that we keep abreast of all of the developments. If I get to the point in 10 years where I am no longer doing this, then I will need to seriously consider whether it might be time to take a step aside and hand it to the next generation. So, when all is done, I don't know if I'll be back in the lab, but I will be back doing clinical work."

Do you have any advice for current medical students on finding a balance between work and family?

"What you're establishing here is a life, and your habits will last a lifetime. Finding ways to enjoy your life is critical. There is a social side of being a medical student. There are lots of activities that are already in place for many of you, so my advice is to keep it up! You are all self-selected to be physicians. Finding a balance is a lifelong struggle. You'll get older, wiser, have families, kids…and their life becomes a part of yours. It's very difficult to balance all of that. We want you to know that we can provide role models, just as our previous generation has done."

For more information about the Lifecycle Research Network, visit http://lawsonresearch.com/clinical_research/lifecycle_research_network.html.

Status epilepticus: a neurological emergency

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Epidemiology

Based on United States data, it is estimated that 6,500 to 15,000 people in Canada each year will have generalized convulsive status epilepticus (GCSE),[1,2] with a mortality of 20%.[3] The incidence of GCSE is highest in the first decade of life and after age 60.[3]

Definition

Epidemiological literature defines status epilepticus as a fixed and persistent seizure lasting at least 30 minutes,[4] the time interval after which irreversible damage occurs to neurons. However, clinically it is important to initiate treatment before 20 minutes and a more practical definition is: "either continuous seizures lasting at least five minutes or two or more discrete seizures between which there is incomplete recovery of consciousness." [5]

Clinical features

Initially, patients with status epilepticus will present with obvious seizure symptoms, such as tonic, clonic or tonic-clonic movements. However, as the condition progresses the clinical manifestations become subtle and the only signs of an underlying disorder may be minor twitching or in some cases no motor activity.[6] Electroencephalography (EEG) monitoring will be required to detect cerebral epileptic activity. EEG is also useful in distinguishing status epilepticus from pseudoseizures, also known as nonepileptic status. Pseudoseizures clinically resemble a seizure, but do not show epileptic activity on EEG and may be precipitated by suggestions or commands. It is the other main condition in the differential diagnosis of multiple seizures and is implicated as the cause about half the time.[7]

Physiologic changes that occur in GCSE can be temporally divided into two phases: Phase I (0-30 minutes) in which compensatory mechanisms are still intact, and phase II (>30 minutes) when more serious symptoms develop due to a failure of the compensatory mechanisms. This classification is clinically useful because the development of phase II symptoms should prompt admission to an intensive care unit. (See Table 1).

Pathophysiology

The pathophysiology of status epilepticus remains largely unknown. An insight into the possible mechanism of SE came from reports of patients who consumed mussels contaminated with domoic acid, an analogue of the excitatory neurotransmitter glutamate.[8] This incident suggests that excessive activation of excitatory receptors can cause status epilepticus.

Other evidence demonstrates that status epilepticus can be caused by substances, such as penicillin, which antagonize the neurotransmitter GABA.[9] GABA is the main inhibitory neurotransmitter in the brain and so failure of effective inhibition may lead to prolonged seizures. Ultimately, status epilepticus involves a disorder of the body's normal mechanism to terminate a seizure, which can be due to excessive excitation or lack of inhibition.

Causes - acute and chronic

The causes of status epilepticus can be divided into acute and chronic. It is important to distinguish between them since the prognosis, management and response to treatment differs.

Acute causes of status epilepticus include metabolic disturbances (e.g. electrolyte imbalances, renal faillure, sepsis), CNS infection, stroke, head trauma, drug toxicity and hypoxia. Chronic processes that cause status epilepticus include preexisting epilepsy, discontinuation of antiepileptic medication or sub-therapeutic levels of medication, and seizures due to chronic ethanol abuse. Other processes such as CNS strokes and tumours can present with status epilepticus after a latent period of weeks to years.

Cases of status epilepticus due to chronic processes respond well to anticonvulsant medication. In contrast, seizures due to acute causes are typically difficult to control and have a higher mortality.[10]

Management

The management of status epilepticus includes standard measures that would be implemented in any medical emergency, including evaluation of the airway, breathing and circulation. The next steps in management are to order blood work and administer glucose, thiamine and antiepileptic drugs.

Relevant investigations to order include: CBC, electrolytes, calcium, magnesium, liver function, kidney function, serum levels of antiepileptic drugs, toxicology and clotting parameters. A lumbar puncture should be performed if infection is suspected.

Furthermore, two IV lines are recommended for administering glucose, thiamine, anticonvulsant drugs, normal saline and vasopressors. Thiamine is given to patients who are malnourished or have a history of alcohol abuse since they are at risk for Wernicke's encephalopathy.

Some special considerations in the management of GCSE are in order:

- A priority in management is maintaining a patent airway and adequate ventilation.

- Patients should be protected from injury, however, restraints are not recommended as they may cause fractures.
- Arterial-blood gas measurements are useful and often show a metabolic acidosis, which will correct itself once the seizures stop; sodium bicarbonate should be used only in extreme situations.[11]
- Hyperthermia occurs frequently in about 29-79% of patients and should be treated immediately with passive cooling.

Phase I	COMPENSATORY MECHANISMS REMAIN INTACT
(0-30 minutes)	Extreme adrenaline or noradrenaline release
	Cerebral blood flow and metabolism increase
	Hypertension, hyperpyrexia
	Hyperventilation, tachycardia
	Lactic acidosis
Phase II	COMPENSATORY MECHANISMS START FAILING
(> 30 minutes)	Cerebral autoregulation reduced
	Respiration depressed
	Cardiac arrhythmia
	Hypotension
	Cerebral edema
	Hypoglycemia, hyponatremia
	Kidney failure, rhabdomyolysis
	Disseminated intravascular coagulation

Table 1. Physiologic changes during GCSE.[14]

Principles of drug therapy

The initial treatment of GCSE is combined IV lorazepam and phenytoin; it controls 80% of seizures in patients with GCSE.[12]

Benzodiazepines are fast-acting, potent antiepileptic drugs, and include diazepam, lorazepam, midazolam, and clonazepam. Diazepam and lorazepam may both be considered in initial therapy, however lorazepam is preferred because of its duration of action of 12-24 hours versus diazepam's 15-30 minutes duration of action.[13] Adverse effects of IV benzodiazepines include respiratory depression and hypotension.

Phenytoin is usually administered intravenously after a benzodiazepine (e.g. lorazepam). Adverse effects associated with phenytoin are cardiac rhythm disturbances (incidence of 7%) and hypotension (incidence of 29%). IV phenytoin may also rarely cause "purple glove syndrome" a tissue injury caused by venous irritation resulting in extravasation.

Phenobarbital has a depressant effect on respiratory drive, level of consciousness and blood pressure. For these reasons, it is recommended only when benzodiazepine and phenytoin therapy fails, and administration should ideally be carried out in an intensive care unit.

Status epilepticus that does not respond to a benzodiazepine, phenytoin or phenobarbital is considered refractory and will require therapy with propofol and/or midalozam.

Out-of-hospital Treatment

In situations when IV administration of drugs and monitoring equipment are not available, treatment options include parenteral or rectal diazepam, sublingual lorazepam and intramuscular midazolam.

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Diagnosing the elusive stiff-person syndrome

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Introduction

Stiff-person syndrome (SPS) is a rare neurological disorder involving episodic spasms often preceded by sudden stimuli, progressive stiffness of the limbs and trunk, and axial rigidity. Diagnosis of stiff person syndrome can be elusive due to the fact that patients tend to present with non-specific muscle complaints of stiffness, spasms and cramps.[1] These symptoms have a large differential diagnosis, including infectious, toxic, neoplastic, vascular, genetic and autoimmune,[2] and often other diagnoses are considered before stiff-person syndrome. Additionally, the stimuli-induced spasms, social phobia and anxiety experienced by these patients can expand the differential to include psychogenic movement disorders.[2-4] SPS causes significant disability and in many cases symptom relief can be achieved with treatment.[1,2,5,6] As such, it is important to recognize possible cases of SPS and conduct the appropriate tests for diagnosis. Below is a case report exemplifying an approach to diagnosis of SPS.

Case report

A 66-year-old woman was admitted to the internal medicine service after an 18-month history of complaints of worsening stiffness affecting her lower extremities associated with pain. While the symptoms had started off mild, the patient rapidly progressed to requiring a walker for safe ambulation. The patient's primary caregiver, her son, confirmed this history. Her son also stated that the patient was extremely fearful to attempt walking even when the symptoms were initially mild. The patient denied any symptoms affecting the trunk or her upper extremities. She denied any tremor, apart from that which occurred in the lower extremities upon standing. There were no complaints of autonomic dysfunction. Her speech was normal. By the time she arrived at the hospital, she was no longer able to ambulate even with a walker.

Her past history was positive for a history of anxiety, chronic depression and auditory hallucinations, for which she was followed by the psychiatry service. Other health conditions included hypothyroidism, gastroesophageal reflux (GERD) and osteoporosis. The patient had been treated for her anxiety and depression with a combination of alprazolam 0.5mg three times daily, citalopram 30 mg daily, and risperidone 0.5 mg daily for approximately one year. Other medications included rabeprazole, residronate, and levothyroxine.

Because of the neuroleptic exposure (risperidone), the initial thought at admission was that the symptoms might be secondary to neuroleptic malignant syndrome. However, the psychiatry service saw the patient in consultation and felt that the lack of autonomic symptoms, focality of symptoms and lack of delirium argued against such a diagnosis. The patient did have an MRI of the head and spine performed which was unremarkable. Concerns were also raised as to whether or not the patient might be suffering from drug-induced parkinsonism because of the exposure to risperidone. The neurology service was subsequently consulted for a diagnostic opinion.

When examined by the neurology service, the patient was oriented to time and place, and scored 30/30 on the MMSE. She was noted to have full extra-ocular eye movements, but her pursuit movements were very saccadic in nature. The remainder of her cranial nerve examination was unremarkable. There was no evidence of tremor in the extremities at rest or with action. She was noted to be mildly bradykinetic in the upper extremities, but power was fully preserved. There was mild rigidity in the upper extremities on passive movement. In the lower extremities, the limbs were held in rigid extension, such that it was almost impossible to passively move the lower extremities. Her toes bilaterally were held in continual extension. Her sensory examination was unremarkable to pinprick, and only demonstrated elevated vibratory thresholds at the great toes bilaterally. Her reflexes were 2+ in the upper extremities, 3+ at the knees and absent at the ankles bilaterally. There was no evidence of ataxia. Her gait could not be assessed.

After reviewing this woman, it was felt that stiff-person Syndrome could be the underlying diagnosis. Anti-GAD antibodies were obtained and were positive, supporting the clinical diagnosis of SPS. The patient was subsequently started on treatment with diazepam and baclofen achieving a dose of 15mg four times daily and 25mg three times daily, respectively. The patient noted a reduction in lower extremity tone and has been able to resume ambulation with a walker. The mobility in her legs has progressively improved while her pain has largely resolved with her current medical treatment.

Discussion

Clinical manifestations

Stiff-person syndrome (SPS) is a rare neurological disorder, affecting the neuromuscular junction in a progressive manner, and has a spectrum of clinical presentations.[6] Several forms of SPS exist; the most common is classic SPS, involving auto-antibodies to glutamic acid decarboxylase (GAD).[2,6] SPS, however, is a clinical diagnosis and thus the presence of GAD+ auto-antibodies is not a requisite for diagnosis.[2,6] The classic form of SPS affects twice as many women as men and generally presents in the forth to sixth decades of life.[7] The onset is typically insidious, but progressive in nature. In the early stages of GAD+ SPS, patients

often present with lumbar lordosis and painful muscle spasms induced by stimuli,[2] such as sudden noise, stress or touch.[3,7,8] These spasms can cause falls and patients often experience fear of crossing the street and open spaces.[2] It is currently unknown if the anxiety and phobias associated with SPS are caused by the pathogenesis or in response to the symptoms.[2] SPS can become debilitating, with up to 65% of patients unable to perform routine daily activities due to symptoms of total-body stiffness, fear of falling and anxiety-triggered spasms.[5] Depending on the severity of symptoms or possibly failure of treatment, some patients require walkers or wheelchairs and may even become bedridden.[2,5]

Pathophysiology

In classic SPS, the majority of cases are associated with auto-antibodies against glutamic acid decarboxylase (GAD).[1,2,6] The GAD enzyme is involved with the synthesis of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) from the excitatory neurotransmitter precursor, glutamate.[6] Antibodies against GAD prevent this conversion, thus dampening the GABAergic inhibitor pathway and causing accumulation of glutamate.[6] It is proposed that the muscular symptoms of stiffness and spasms result from the auto-antibodies affecting interneurons in the spinal gray matter and intracortical inhibitory neurons.[6,9]

Glutamic acid decarboxylase is most abundantly present pre-synaptically in the CNS, but is also present in pancreatic ß cells.[2,6] Interestingly, SPS is highly associated with autoimmune type I diabetes mellitus.[2,6] In fact, the majority of patients diagnosed with SPS either have diabetes or will subsequently develop it.[2] While many diabetics have auto-antibodies against GAD, these auto-antibodies target a different epitope than in classic SPS and are present in low titres.[2,6,8,9] Thus, the vast majority of diabetics do not develop SPS.[2,9] When considering other autoimmune disorders in addition to type I diabetes, up to 80% of SPS patients will be affected by another autoimmune co-morbidity.[6] SPS responds well to immunotherapy, further supporting the autoimmune pathogenesis of SPS.[2]

Treatment

There are two general strategies to treatment of SPS; the first approach is to treat the neurotransmitter imbalance directly and the second is to reduce the auto-antibody titres, treating the imbalance indirectly.[9] In the first case, medications such as benzodiazepines and baclofen can be used to improve GABAergic inhibition.[2,6,7,9] The doses of these medications however are limited by adverse cognitive side-effects.[9] Additionally, monoaminergic inhibitors, such as clonidine and tizanidine, can also improve symptoms.[6]

The second approach applies particularly to GAD+ SPS patients due to the autoimmune nature of their condition. These patient may benefit from immunosuppressive therapy such as steroids and intravenous immunoglobulin (IVIg).[2,6] In a randomized, cross-over study, 16 patients were treated with either placebo or IVIg for 3 months, followed by a 1-month washout period and treatment with the alternative agent for 3 months.[5] Significant improvements in stiffness and heightened-sensitivity scores improved for both groups during the IVIg treatment period.[5] Furthermore, a case has been reported describing significant symptom improvement using rituximab, an anti-CD20 antibody that binds mature B cells and targets them for removal.[10] Plasmapheresis is another option available for treatment of antibody-related SPS.[2,6] This allows direct removal of excess auto-antibodies, however the beneficial effects are short-term.[2,6]

Diagnosis

SPS a very rare disorder, with an estimate of 1:1,250,000 affected.[6] Additionally, because its symptoms lead to a broad differential diagnosis, SPS can easily be mistaken for other disorders.[2] In early stages, patients with SPS often present with reports of intermittent muscle spasm, but have a normal neurological exam.[2] Additionally, if treated with diazepam, the EMG findings associated with SPS – continuous low frequency motor activity – are masked, which can further complicate the diagnosis.[2,5,6,8] As the condition progresses, patients often development phobias and anxiety.[2] This psychological aspect of SPS can lead physicians to look for a psychogenic source for the problem.[2-4] As such, SPS diagnosis can be elusive, but should not be forgotten in this clinical picture. While diagnosis of SPS can be made based on clinical findings, auto-antibody titres for GAD can support the diagnosis.[2,6] Thus, although 60-80% of these patients will have serum anti-GAD antibodies, the absence of such antibodies does not rule out SPS.[1]

Conclusion

Stiff-person syndrome is an important diagnosis to consider when patients present with muscle stiffness, spasms and cramps.[1] Patients with SPS often describe stimulus-triggered spasms and falls, and phobia of open spaces, which may lead clinicians to misdiagnose the condition as psychogenic movement disorder.[2-4] However, it is crucial to test for this condition as SPS causes significant morbidity and, in most cases, can be treated to alleviate symptoms.[1,2,5,6] Furthermore, SPS can present as a manifestation of an underlying neoplasm, such as breast cancer, SCLC, lung adenocarcinoma or mediastinal carcinoma, and may indicate the presence of or predisposition to diabetes.[2]

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The optic nerve: a clinical perspective

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Introduction: optic nerve anatomy

The optic nerve carries approximately 1.2 million afferent nerve fibres which originate in the retinal ganglion cells of the retina.[1] Most of these synapse in the lateral geniculate body, while others are destined for the pre-tectal nuclei in the midbrain and other centres. The optic nerve is approximately 50 mm long from globe to chiasm and can be divided into 4 subdivisions.[2] First is the intraocular segment, which is called the optic disc or optic nerve head. Behind the globe is the intraorbital segment, which is 25-30 mm long. Here the nerve thickens with the addition of myelin sheaths that surround the nerve fibres, a function of oligodendroglia. Interestingly, the optic nerve within the orbit is S-shaped which allows the eye to move without stretching the nerve. The nerve will only become stretched if there is severe proptosis.

After exiting the orbit, the optic nerve enters the optic canal to be directed upward and inward at a 45-degree angle towards its chiasmal destination.[3] This is called the intracanalicular segment, and is approximately 6 mm in length. Last is the intracranial segment, where the two optic nerves meet at the optic chiasm. Here the optic nerve fibres from each eye decussate so that each optic tract carries fibres from the contralateral nasal hemiretina and ipsilateral temporal hemiretina.[3]

Based on the arterial supply of the optic nerve, it can alternatively be divided into two segments, anterior and posterior. The anterior segment is simply the optic disc, which is supplied by the posterior ciliary arteries.[4] There is also a minor arterial supply by an anastomotic circle called the circle of Zinn-Haller.[5] The posterior segment consists of the intraorbital, intracanalicular, and intracranial subdivisions and is supplied by a more complex system of peripheral (centripetal) and axial (centrifugal) vessels.[5,6] Venous drainage of the optic nerve occurs almost exclusively via the central retinal vein.

Examination

Disorders of the optic nerve affect the main components of vision which are contrast, brightness and colour.[3] There are four main tests used to evaluate these components and ultimately optic nerve function.

Visual acuity

This is performed with the aid of a Snellen chart, as the patient reads the smallest line of identifiable letters from a distance of 20 feet (6 metres).

Colour plates

In this test a series of colour plates are used to determine colour recognition in each eye. Loss of signal transmission from cone receptors that are concentrated in the macula through the optic nerve is indicative of optic nerve dysfunction. There can be a marked difference in colour recognition between eyes if there is unilateral optic nerve damage. One should consider that approximately 5% of males have some degree of red-green colour blindness while performing this test.[3]

Visual fields

The simple screening examination is confrontation visual field testing. The examiner stands approximately 1 metre from the patient with each person covering one eye and looking straight ahead. A target finger is moved centrally until seen by the patient and this is repeated in several quadrants. A counting fingers test may be more reliable and automated machine testing is the most sensitive means of detection.

Swinging flashlight test

This is one of the most valuable tests of optic nerve dysfunction available for the general physician. The abnormality detected is a Relative Afferent Pupillary Defect (RAPD), also known as a Marcus Gunn pupil. The key concept is that the optic nerve is responsible for the afferent limb of the pupillary reflex. In a dim room, light shone on a normal eye will result in consensual and contralateral pupillary constriction. The flashlight is then quickly moved to shine on the other eye and if there is optic nerve dysfunction in that eye then both pupils will abnormally dilate.

Optic nerve disorders

Ischemic Optic Neuropathy (ION)

ION is the most common acute optic neuropathy in patients over 50.[5,7] As the name implies it is caused by optic nerve ischemia, and patients classically present with abrupt onset of painless, unilateral visual loss. It can be subdivided into anterior ION (AION) vs. posterior ION (PION) based on the location of the ischemia, or arteritic vs. non-arteritic based on the etiology of the ischemia.

Arteritic AION is caused by systemic vasculitis that affects the optic disc, most commonly from temporal arteritis (TA). Prompt diagnosis and treatment are imperative as TA can be lead to blindness or death. Headache, often severe, is the most common symptom associated with TA, occurring in approximately 50% of cases.[8] Other

	Optic Neuritis	Arteritic ION	Non-Arteritic ION	Acute Glaucoma	Open-angle Glaucoma
Age	<50	>55	50-70	Mean 60	>65 increases with age
Symptoms	Pain, colour vision impaired greatly in affected eye	Possible Symptoms of TA + decreased colour vision	Decreased colour vision	Nausea and vomiting, pain, coloured haloes around light	Painless, visual field contraction noticed late
Signs	RAPD	RAPD	RAPD	Fixed mid-dilated pupil, red eye, hazy cornea, ciliary flush	Cupping of disc
Visual Loss	Progressive, hours to days	Sudden and profound	Sudden, often on awakening	Profound, within hours	Gradual, over many years
Visual Field Loss	Diffuse depression, central scotoma	Altitudinal	Altitudinal		Scotomas, gradual peripheral loss
Optic Disc Appearance	1/3 patients have mild swelling (Normal if Retrobulbar)	Swelling and chalky/white appearance (Normal if PION)	Swelling with associated hemorrhages		Cup:Disc ratio >0.5, or >0.2 difference between eyes

Table 1. Clinical summary of common optic nerve disorders.

classical symptoms include jaw claudication, scalp tenderness, anorexia, weight loss, anemia, fever and visual loss.[5] Elevated inflammatory markers – C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) – strongly suggest the diagnosis, but temporal artery biopsy remains the gold standard and is recommended in all suspected cases. The hemoglobin level should always be considered when reviewing the ESR as anemia may mask an elevated ESR. CRP, on the other hand, is not affected by hematologic factors or age.[5] Treatment of TA is with high dose corticosteroids. The vision loss is often more severe than its non-arteritic counterpart, as 75% of patients with arteritic AION demonstrate visual acuity of 20/200 or worse.[5] Transient visual loss, called amaurosis fugax precedes the profound visual loss in up to 30% of cases.[5]

Non-arteritic AION is the most common form of ION. Caucasians account for 95% of cases,[9] and individuals typically present in their 60's.[10] The exact pathogenesis is unknown. It is a presumed diagnosis that is made when TA is ruled out. Visual loss may be less profound and partial field loss is common. Contrary to what one might assume it is not triggered by an embolic event as in ischemic stoke.[6] There is no proven treatment for non-arteritic AION. Metabolic issues such as diabetic control and hypertension should be considered and treated appropriately.

PION is defined as infarction of the retrobulbar portion of the optic nerve, and accounts for only 10% of cases of ION.[7] It is characterized by a normal appearing optic disc that later becomes atrophic.[11] TA is the most common cause of PION. It is very important to rule out TA in all older patients who present with an afferent pupillary defect or unexplained visual field defect.

Optic neuritis (ON)

ON is characterized by inflammation of the optic nerve. It must be thought of in cases of visual loss in younger patients. Clinical features of ON include visual loss, RAPD, optic disc edema and a classic central scotoma.[12] Most patients improve without treatment, however intravenous steroids may hasten recovery and may reduce the risk of developing multiple sclerosis (MS).[13] An MRI should be done to ascertain the long term risk of developing MS as multiple white matter lesions on an MRI increases the risk of developing MS to over 50%.[14,15]

Glaucoma

Glaucoma is a disease that causes nerve fibre layer loss within the intraocular portion of the optic nerve. Cupping of the disc is apparent before the disc becomes pale. The exact mechanism of glaucoma is not fully understood, but it is highly associated with elevated intraocular pressure (IOP). There are two types of glaucoma, open-angle and closed-angle.

Open-angle glaucoma is a chronic condition account-

ing for the majority of cases. Patients have chronically elevated IOP due to impaired drainage of aqueous humour from trabecular meshwork dysfunction. Visual loss is gradual and is characterized by peripheral visual field contraction and scotomas (blind spots). Generally the patient does not notice the visual field loss until late, which is why screening, especially in those with risk factors is important. Risk factors include increasing age, family history, African-American race and IOP above 22 mm Hg.[1] Treatment is commonly with medications that either decrease aqueous production or increase drainage, and less commonly with surgery.

Angle-closure glaucoma, also known as acute glaucoma, is a medical emergency. It is most often caused by pupillary block between the iris and lens which then bows the iris forward blocking the angle and aqueous drainage through the trabecular meshwork. Complete vision loss can occur within hours. Patients typically present with a red and painful eye, nausea and vomiting, and they see coloured haloes around lights.[1] Examination reveals a fixed, mid-dilated pupil, hazy cornea and firm globe.[1] The iris is mid-dilated because this is where it can be in greatest contact with the lens to cause pupillary blockage and as the pressure rises, it becomes ischemic and remains mid-dilated. Immediate medical treatment with topical pupillary constrictors, intravenous osmotic agents and oral carbonic anhydrase inhibitors is required, followed by a laser iridotomy to allow the aqueous to bypass the pupillary blockage.

Summary

Examination of the optic nerve and understanding its disorders are of great importance to the general physician, as misdiagnosis of optic nerve pathology can lead to permanent visual loss. Table 1 summarizes important differences between the optic nerve disorders that one will encounter as a general physician.

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The other Babinski sign: a brief review of hemifacial spasm

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Joseph Babinski is famous for his 1896 description of the Babinski sign, an abnormal plantar reflex associated with dysfunction of the pyramidal system. He is less well-known for his "other" Babinski sign: paradoxical raising of the eyebrow associated with closure of the eye, a feature typical of hemifacial spasm.

As Babinksi noted in 1905, hemifacial spasm (HFS) is a disorder of painless, involuntary facial twitches confined to the muscles supplied by the facial nerve. While benign, it causes significant morbidity due to excessive closure of one eye, and the social effects of an abnormal appearance.[1] Unfortunately, facial twitches are often attributed to stress or anxiety, leading to a delay in diagnosis.[2] A vigilant search for organic causes is essential when these symptoms arise, as highly efficacious treatment options for HFS are available and can significantly improve quality of life.

HFS occurs more commonly in females (2:1) and has an overall prevalence of approximately 10/100,000. [1] The orbicularis oculi is the site of onset in the large majority of cases.[3] Over months to years, the disease spreads to other muscles. [2] Spasms are described as clonic or tonic, are aggravated by stress, fatigue and anxiety, and persist during sleep.[2] Disease is usually unilateral, and spasms are synchronous in all affected ipsilateral muscles. [2] Bilateral disease occurs in a small minority of cases, and spasms are never synchronous bilaterally.[2]

In most cases, hemifacial spasm is due to arterial compression of the root exit zone (REZ) of the facial nerve. This is similar to the proposed mechanism of trigeminal neuralgia, in which the trigeminal nerve is compressed in the REZ, causing demyelination and recurrent episodes of intense pain.[6] In much the same way, compression of the facial nerve causes spontaneous irregular discharges, leading to involuntary muscle contractions. As well, non-synaptic neural transmission (ephapsis) between branches of CN VII may occur, causing synkinesis.[7]

Most commonly, the aberrant artery is the posterio-inferior cerebellar artery (PICA), the antero-inferior cerebellar artery (AICA), or the vertebro-basilar artery (VB). In one series, these vessels were responsible 61%, 56% and 27% of the time, respectively.[8] The same study found that multiple vessels were responsible 40% of the time.[8] However, up to 25% of the population has vascular loops compressing CN VII, suggesting that this alone is insufficient to produce HFS.[9] Vascular loop decompression surgery via the posterior cranial fossa is very effective in providing relief from spasms. For some patients, relief is almost immediate, while for others it can take up to a year following surgery to see the full effects. This delayed cure suggests that HFS is not only due to mechanical compression. Demyelination of the nerve from the brainstem and hyper-excitability of the facial nerve nucleus due to irritation from neurovascular compression may play a role. The slow reversal of these plastic changes explains the delay.[8]

Several other diagnoses can present in a similar fashion, including benign essential blepharospasm (BEB), focal motor seizures, and craniofacial tremor. These are differentiated largely based on clinical presentation, so a careful history and physical exam are essential. For example, BEB often presents with spasms of the orbicularis oculi and adjacent muscles, which may be difficult to distinguish from HFS. However, BEB is often associated with eye irritation, vague ocular pain and photopobia.[4] If the facial spasms are associated with body tremor, or a family history, craniofacial tremor is more likely.[5] Focal motor seizures are implicated when post-ictal weakness and a greater involvement of the lower face are present.[5] If the clinical presentation is ambiguous, electrophysiologic studies and imaging can aid in the diagnosis.

The characteristic sign of HFS on electrophysoiologic studies is a response in distant facial nerve branches following a stimulus to a single branch. This can be seen, for example, by spread of the blink reflex on stimulation of the supraorbital nerve to muscles other than orbicularis oculi. This is referred to as lateral spread response (LSR) and is attributed to spread of excitation at the site of ephapsis.[11]

Rarely, HFS is caused by tumors, arteriovenous malformations, and venous compression.[10] Because the risk of tumor is low, imaging may not be cost effective when the diagnosis is clear.[2] However, a careful neurologic exam for focal signs is essential, and imaging is suggested if these are present or if conservative management fails. [2] Advanced MRI techniques, such as constructive interference in steady state, are effective at identifying neurovascular contact.[2] Imaging may also assist in surgical planning.[2]

While spontaneous remission of symptoms is possible, it occurs in less than 10% of patients,[2] and significant effects on quality of life usually demand intervention. Several oral medications have been studied, including carbamazepine, anticholinergics, baclofen, clonazepam and haloperidol. However, sample sizes have been small and it is difficult to confidently interpret the results.[2] The effects of oral medications are usually transient,[2] and unacceptable side effects often occur.[1] For many patients, this is not a viable treatment option.

In contrast, many physicians consider botulism toxin (BTX) to be the treatment of choice.[2] While few double-blind randomized studies evaluating BTX for HFS exist,[1] the available evidence is encouraging. Park *et al* described an open-label study of 101 HFS patients, 98.6% of which had excellent results after injection of botulism-A. The mean duration of effect was 16.5 weeks, with a range of 11-40 weeks.[12] In a review of the HFS-BTX literature, Jost *et al* found a total of 37 open case-control studies (N=2295) in

which good to excellent results were reported in 76-100% of patients.[13] Adverse effects include facial droop, ptosis, diplopia, lid edema and ecchymosis,[12] with facial weakness being the most common.[1]

Microvascular decompression (MVD) of the facial nerve is the only truly curative option. It involves freeing the nerve from the compressing vessel(s) at the cerebellopontine angle. The offending vessel is gently mobilized away from the facial nerve and a small, rectangular piece of Teflon sponge is then interposed between the REZ on one side and the aberrant vessel(s) on the other.[8]

While MVD has a high success rate (> 90% in some series), the recurrence rate remains up to 20%.[2] Furthermore, the potential risks are significant, including facial nerve dysfunction, lower cranial nerve dysfunction, intracranial infections, cerebrospinal fluid leaks, and temporary or permanent damage to CN VIII.[2] According to some reports, 7-26% of patients will suffer a degree of temporary or permanent hearing loss.[2] A large study of 668 patients by Park *et al* found that 2.2% of patients experienced permanent hearing loss, with 0.7% of these suffering total deafness.[14]

According to several studies, monitoring of brainstem auditory evoked potentials (BAEP) reduces the risk of hearing loss complications.[8] BAEP monitoring allows surgeons to watch for the increased latency of peak V and decreased amplitude of peak I, which are the early warning signs of excessive stretching of the cochlear nerve and impairment of the cochlear vascular supply, respectively.[8] This allows dangerous maneuvers to be stopped or corrected, and appears to significantly reduce the risk of postoperative hearing loss.[8]

Intraoperative monitoring of lateral spread response (LSR) is more controversial. The goal is to see disappearance of the LSR when the aberrant vessel is moved away from the facial nerve.[4] This can augment surgical decision-making, and some authors suggest that it leads to improved outcomes.[15] In 1987, Moller and Jannetta advocated routine intraoperative monitoring of LSR, contending that this would ensure adequate decompression. If LSR was observed at the end of the procedure, they reasoned, symptoms were likely to persist.[8] Therefore, if the LSR does not disappear following decompression of the most obvious site, a search for a second site can be undertaken.[7] In a study by Mooij *et al*, a second compression site was found in the majority of these cases.[16] Several other authors advocate for LSR monitoring during MVD, including Sekula *et al*, who found that the probability of cure was 4.2 times greater if LSR was abolished during surgery than if it persisted.[15]

Conversely, a number of studies have questioned the value of LSR monitoring. Joo *et al* examined 32 patients who had continuing LSR after MVD. Of these, 21 did not display HFS at 1-week follow-up. The authors argued that demyelination of the REZ may lead to a delay in normalization of electrophysiologic muscle responses, even when decompression is effective.[17] Similarly, Sindou examined outcomes in the longer term and found good results even in patients with persistent LSR at the end of MVD.[8] One third of patients assessed became spasm free only after a significant interval (4 to 12 months). Since delayed effects of MVD are common, he argued, final assessment of outcome should not be made until 1 year post-operative.[8] Neves *et al* noted that, in addition to delayed success, HFS can also recur after an MVD that was successful in terms of LSR disappearance. They found that intraoperative LSR changes did not correlate with HFS relief on the first post-operative day.[7] However, they did find a correlation between absence of LSR at the end of surgery and the long-term efficacy of the MVD.[7] Whether elimination of LSR at the time of surgery predicts a good clinical outcome remains unclear.[4]

Involuntary facial movements are often attributed to stress and disregarded. An awareness of HFS and its presentation is essential, as HFS can result in severe social and functional disability[4] and highly efficacious treatment options exist. However, the benign nature of this disorder requires that these treatment options be carefully weighed. No treatment is without risk, but MVD in particular is an invasive solution that carries a risk of significant disability. A careful risk-benefit analysis must be undertaken in order to balance the potential of symptom relief with the risks of therapy.

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Deep brain stimulation for epilepsy

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Introduction

Epilepsy is a chronic neurologic disorder characterized by recurrent, unpredictable seizures.[1] It is estimated to affect 0.5 – 1% of the world's population.[2] Epilepsy is not a singular condition, but instead a diverse family of disorders with many causes, all of which indicate underlying brain dysfunction.[1] This heterogeneity has important implications with respect to treatment regimens and patient responsiveness. About 35% of patients with epilepsy are refractory to anti-epileptic drugs, and of that group, only a quarter may benefit from resective brain surgery.[3] Deep brain stimulation (DBS) may be a suitable treatment alternative for medically refractory patients who are not candidates for conventional surgical resection.

Procedure

DBS is a neurosurgical technique that uses electrical impulses to modulate or interrupt the inherent electrical activity of deep brain structures. Functional neurosurgeons use stereotactic MRI or CT scans to create a 3D coordinate system, allowing them to precisely locate anatomical targets and map out a suitable trajectory for reaching these targets.[4] An electrode (lead) is implanted in the intended deep brain structure, and a battery-powered implantable pulse generator (IPG) is embedded in a subcutaneous pocket positioned inferior to the clavicle. An insulated extension wire that runs up the neck connects the two devices. The IPG is programmed to relay electric current to the lead, which then stimulates the targeted deep brain areas.[5]

Since acquiring FDA approval for the treatment of essential tremor and Parkinson's disease in 1997,[6] DBS has been used for dystonia,[7] and has shown promise in the management of Tourette's syndrome, obsessive-compulsive disorder, and treatment-resistant depression.[8,9] The success of DBS in treating movement disorders has prompted interest in the potential for DBS as a treatment alternative for medically refractory epilepsy.

Deep brain targets

A brief summary of selected deep brain targets that have been under investigation in animal and human models is presented here.

The substantia nigra pars reticulata (SNR) is known to be an important anticonvulsant site in rats. Pharmacologic animal studies have implicated the SNR as part of a 'nigral control' system for epileptic seizures.[10] Since then, DBS of the SNR has resulted in seizure suppression in animal models, though no human trials have been published to date.[11]

The subthalamic nucleus (STN) directly innervates the SNR, thus providing a rationale for using stimulation to interfere with this neural circuit and disrupt epileptogenesis.[12] Small human trials have demonstrated at least 50% overall seizure reduction using STN DBS.[13-15] Further studies are needed to clearly establish its clinical efficacy and to determine whether the optimal stimulation target is the STN or the SNR itself.[3]

Temporal lobe epilepsy is common in adults and frequently does not respond to medical therapy.[2] While temporal lobectomy is an effective treatment for certain patients, surgical resection is less desirable for patients whose seizures involve bilateral foci and who may suffer memory issues as a result of the operation. An alternative treatment, hippocampal stimulation, has been shown to be effective at reducing seizure frequency in patients with mesial temporal lobe epilepsy (MTLE).[16,17] A double-blinded, randomized controlled study demonstrated a 15% median seizure reduction in four medically refractory MTLE patients for whom temporal lobe resection was contraindicated. No adverse effects were reported, and one patient had a substantial long-term benefit.[16] Another double-blinded trial assessing hippocampal stimulation reported a 50-95% seizure reduction in certain refractory MTLE patients. It is worthwhile to note that this stimulation did not result in memory deterioration.[17]

Stimulation of two thalamic structures, the centromedian nucleus (CM) and the anterior nucleus of the thalamus (AN), has provided encouraging results in human trials. The CM is involved in modulating cerebral cortex excitability, and its location between cortical, limbic and basal ganglia structures makes it an attractive target for disrupting epileptic neural circuits. Recent human trials using CM DBS have reduced seizure frequency by 80-95 % in certain forms of epilepsy.[18,19]

The AN's anatomical connections suggest its potential as a vital target in the control of limbic epilepsy.[11] Several animal studies have confirmed the AN's role in seizure propagation,[20-22] and recent human trials have reported seizure frequency reduction using AN DBS.[23-25] Of considerable interest is the recently published Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy (SANTE) trial: a controlled, randomized, double-blinded trial that examined data from 110 patients in 17 U.S. centres who received bilateral stimulation of the anterior thalamic nuclei. During the first 3 months (double-blinded phase), half the patients received active stimulation and half did not. Those that received stimulation had a median decline in seizure frequency of 40.4%, compared to 14.5% for the control group. Then all patients received unblinded stimulation for the remainder of the trial. After a two year follow-up, 54% of patients had their seizures reduced by at least

half, with 14 patients being seizure-free for at least 6 months.[26]

Complications

DBS is an advanced neurosurgical procedure. The accuracy required and complexity involved makes it prone to complications. Adverse events can be categorized according to those arising from the operation, the implanted hardware, or the electrical stimulation.[27]

The most severe operation-related complication is intracranial hemorrhage. While the risk from implanting a single lead is low, sometimes multiple passages are required to ensure proper electrode placement, increasing the risk of symptomatic hemorrhage. With an average distance of 8cm from the cortical surface to most deep brain targets, utmost care must be taken to avoid major cortical blood vessels. Advances in imaging techniques, combined with thorough surgical planning, should help to ensure accurate lead placement with a minimal number of passages.[27]

Anchoring the electrode to the skull too tightly may fracture the device, causing a short circuit and draining the IPG battery. On the other hand, constant head and neck motions create traction that may cause a loosely attached electrode to migrate from its desired target. Infections around the anchorage site, the IPG site or the extension region may also complicate the procedure and necessitate removal of the entire system. Antiseptic cleaning procedures and prophylactic antibiotics may be used to curb this risk.[27]

Stimulation-related complications include confusion, depression, and mood changes. These may arise from malposition of the electrode. Indeed, many of the deep brain targets are very small, and a misplaced lead, even by a few millimetres, may cause unwanted side effects. However, these events are mostly reversible and adjustable, and no major stimulation-related events have been reported thus far.[28]

Open vs. closed loop stimulation

The majority of the trials referenced in this paper have described DBS protocols of scheduled stimulation, where electrical current is delivered either continuously or cyclically (alternating on-off phases). This technique, referred to as 'open-loop stimulation,' delivers current without reference to ongoing electroencephalogram (EEG) activity.[11,28] Recent data, however, suggest that chronic stimulation of certain brain regions may exacerbate seizure activity.[29] Cyclic stimulation may ease this effect, but it also appears to be less effective than continuous DBS at reducing seizure frequency.[30]

The protocol for using DBS to treat movement disorders is well-established.[6] It relies on the concept of an epileptic brain fluctuating between a functionally normal state and an electrically abnormal one. Continuous stimulation in this context thus acts to reduce the brain's excitability and maintain the functionally normal state. The stimulation parameters for using DBS to treat epilepsy have largely followed those for movement disorders; however, the optimal protocol of DBS for epilepsy has yet to be determined.[11]

An alternate strategy, called 'closed-loop stimulation,' uses real-time seizure detection algorithms designed to interpret characteristic EEG cues representing the onset of epileptiform activity, and deliver electrical stimulation accordingly. There is growing evidence that this type of adaptive stimulation may be effective in humans.[31,32] The development of reliable automated detectors will be required to ensure this method's feasibility.

Future directions

The success of DBS in treating motor disorders, along with its expanding potential in the management of numerous other conditions, including epilepsy, has "brought functional neurosurgery back to an exciting era."[27] To firmly establish the role of DBS for epilepsy, optimal stimulation parameters and deep brain targets must be defined for the various seizure types and syndromes. A better understanding of the mechanisms by which seizures propagate and how electrical stimulation has its effect will help to identify ideal surgical candidates and provide them with another therapeutic option worthy of consideration.

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The role of sleep in memory

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We sleep less than ever before.[1] Occupational stress, familial commitments and an increasing number of distractions make it difficult for us to get the traditional eight hours of sleep. Many success stories about people sleeping only a few hours a day pressure us to think that we need to sleep less in order to be successful. Consequently, sleep deprivation has become such a common phenomenon that some people do not even realize their exhaustion. However, demanding schedules for doctors persist and trainees are forced to learn to sleep less. Apparently, the sleep quality and satisfaction among medical students and residents is relatively low, and many of them try to compensate for their lack of sleep by taking caffeine pills or coffee.[2] Is sleep really something we should strive to cut back on? What are the consequences of frequent sleep deprivation on our ability to learn? In the following paper, we will look at the present knowledge of the role of sleep in memory consolidation.

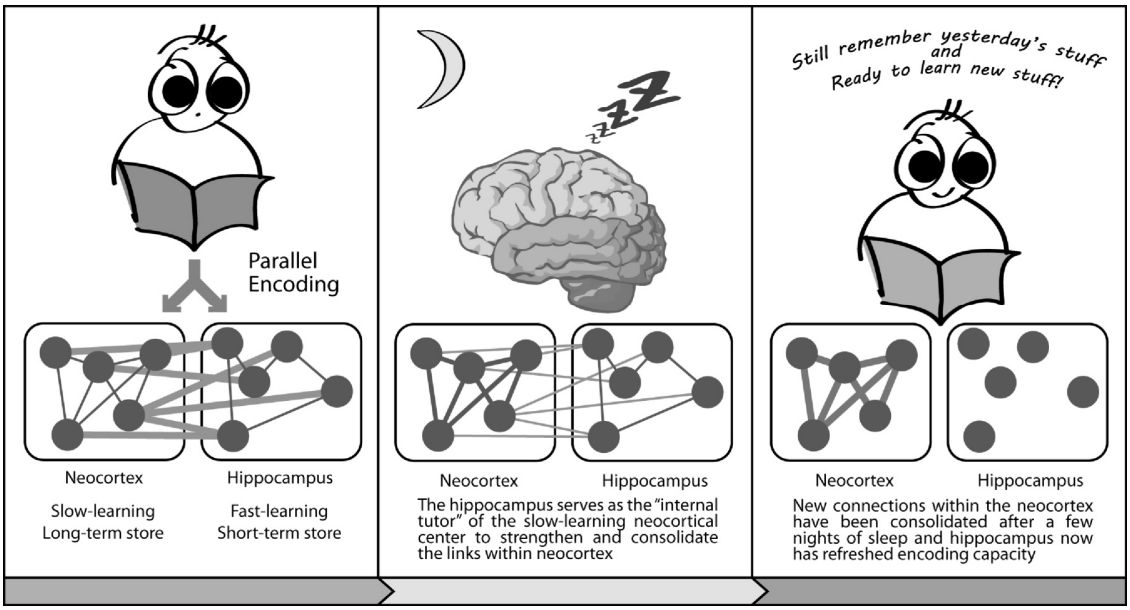
What is sleep? Although often perceived as a passive and inactive period, there are many physiological and neurological changes occurring during sleep. Sleep can be divided into rapid eye movement (REM) sleep and non rapid eye movement (NREM) sleep. The latter can be further divided into light sleep (stages 1 and 2) and slow wave sleep (SWS, stages 3 and 4). Sleep gets progressively deeper from stages 1 to 4. Each sleep cycle proceeds from lighter sleep to SWS and then to REM, and this SWS to REM cycle is repeated several times throughout the night. The first half of the sleep is predominantly SWS, whereas the last half of the sleep is predominantly REM.[3]

One of the most exciting and ongoing debates in the field of sleep research is whether or not sleep contributes to memory and if it does, how so? Memories are initially "encoded" when the brain engages in novel experience and action. These memories, however, require consolidation, which consists of stabilization and enhancement.[3] A large number of studies offer a substantive body of evidence supporting the role of sleep in what is known as sleep-dependent memory processing. Evidence of sleep-dependent memory has been found in many species, including humans and non-human primates, cats, rats, and mice using a variety of behavioural paradigms.[4] These studies offer mixed conclusions about the role of sleep in simple, emotion-free declarative memories. For example, a recent study has shown that facial recognition memory was unaffected by subjects deprived of sleep for 35 hours.[5] However, other studies indicate that both SWS and REM sleep contribute to consolidation of complex, emotionally salient declarative memories. For instance, even though the aforementioned sleep-deprived subjects remembered familiar faces, they had much more difficulty remembering in which of the two sets of photos the faces had appeared.[5] In other words, their memory for the context of the faces was significantly decreased. It is interesting to note that while large doses of caffeine reduced the feelings of sleepiness and improved the ability of the sleep-deprived subjects to remember in which set the faces had appeared, the level of recall was still significantly below the level of the non-sleep-deprived subjects.[5]

There is little doubt that sleep plays a critical role in post-training consolidation of procedural or skill memory.[4] Recent studies have shown that memory stabilization largely occurs during wakefulness, whereas memory enhancement occurs primarily, if not exclusively, during sleep; through this enhancement either previously lost memories are restored or additional learning is produced, both without the need for any further practice.[4] Thus, through sleep, the enhancement phase of memory consolidation causes the active retention of memory instead of its decay.

The enhancement phase occurs during slow wave sleep

SWS is most prominent during early sleep. It is characterized by the appearance of slow oscillations, spindles and sharp wave-ripple field potential oscillations on an electroencephalogram (EEG).[3] These various types of wave activities originate in different centres of the brain and are thought to play a role in memory consolidation. In the hippocampal-neocortical model of memory consolidation, it is proposed that the active memory accumulated during wakefulness is stored as fragments predominantly in the hippocampus as well as in neocortical regions.[6] Studies have shown that by utilizing transcranial direct current stimulation, one can artificially induce increased SWS and enhanced hippocampal-dependent declarative memory consolidation.[7] It is hypothesized that during periods of SWS, slow oscillations originating from the neocortex repeatedly stimulate the newly stored information in the hippocampus and cause their reactivation.[6] This reactivation is associated with the presence of sharp wave-ripple activity as well as spindle activity.[8] The sharp wave-ripple activity originates from the hippocampus, while the spindle activity originates from the reticular nucleus of the thalamus, which travels to the entire neocortex via the thalamocortical circuitry.[8] The process of reactivation essentially allows recently stored memories in the hippocampus to help educate more



permanent stores within the neocortex. This is mediated by spindle activity, which causes changes in calcium permeability of pyramidal neurons (important neocortical neurons in the relay of input into the neocortex).[3] Varying calcium levels have been shown to play a role in the expression of genes that affect long-term plastic changes associated with memory formation and maintenance.[9]

In addition to memory consolidation, SWS has also been shown to aid in the encoding and formation of new memory in the subsequent wakefulness period.[10] It has been well characterized that neuronal synapses possess great plasticity and can alternate between long-term potentiation (LTP) and depression.[3] Calcium influx and delivery of specific receptors to the excitatory synapses facilitate these changes.[11,12] The delivery of excitatory receptors to the synapses increases the synaptic strength and LTP, and this process is found to be more prominent during wakefulness in rats.[11] This indicates that strong synaptic circuits cannot be maintained indefinitely due to limitations on energy, space, and saturation.[11] Hence, the down-regulation of these receptors observed in SWS may be crucial for the homeostasis of neuronal plasticity. However, this does not mean that sleep is devoid of LTP activities, and it is hypothesized that this process occurs during REM sleep. Animal studies have shown that exposure to a novel environment during wakefulness is associated with increased expression of immediate early genes during sleep.[13] They in turn activate several receptors, which induce LTP. The process of "transferring" memory from its temporary hippocampal storage sites to its more permanent neocortical sites has also been suggested to play a role in priming hippocampal structures for the formation of new memories.[14] fMRI imaging studies support this hypothesis by showing significant reduction in hippocampal activity following sleep deprivation during memory encoding activity compared to controls.[14] Furthermore, recent studies evaluating the effect of SWS on the acquisition of temporal memory (memory of when events occur) showed a significant deficiency in temporal memory recall in the sleep deprived group compared to controls.[15] This experiment controlled for confounding variables such as stress from the lack of sleep by allowing a 36 hour sleep 'rejuvenation' period for both groups. Furthermore, it has been shown that even a nap of significant duration, containing SWS, shows significant correlation with enhanced declarative memory.[16] Moreover, physiological and behavior studies have shown the importance of SWS on the consolidation of new and old memories and thus can be thought to play an integral role in the effective acquisition and storage of new information.

The role of rapid eye movement sleep

REM sleep represents the late stage of the sleep cycle. It is characterized by reduced muscle tone and fast, low-voltage EEG waves.[17] Early behavioural studies led to the development of the hypothesis that REM sleep is involved in memory consolidation.[18] Following a period of intense learning, it has been shown that there is an increase in REM density and the number of rapid eye movements.[19] Furthermore, altering the levels of REM during sleep may affect memory acquisition. Donepezil, an acetylcholinesterase inhibitor used for treatment in Alzheimer's, induces an increase in REM sleep. This increase is linked to an enhancement of memory performance.[20] In contrast, a decrease in REM sleep inhibits learning, as seen in REM deprivation studies in both animals and humans. Physiologically, the discharge patterns in the hippocampus during training on a circular track task (a common experimental setup to test for spatial recognition memory) are also mimicked during REM sleep, which suggests that the learned task is replayed while asleep.[21] The increase in the amount of REM sleep post-learning, change in memory performance by altering the amount of REM sleep. and evidence of learning during REM sleep provide support for the aforementioned hypothesis.

Recently the role of REM in memory consolidation has been called into question. The REM depression studies

have been criticized for the use of the "platform-technique," where an animal is placed on a small platform surrounded by water. As the animal enters the REM stage of the sleep cycle, its muscles relax causing it to fall in and thereby disrupting that stage of sleep. This technique produces a high level of stress in the animal, resulting in confounding factors such as hyperactivity, anxiety and irritability. Furthermore, depressed patients treated with monoamine oxidase inhibitors, which block REM sleep, do not show memory impairments.[22] The inconsistent results with respect to the REM sleep-memory consolidation hypothesis have led to a debate in the field, with some suggesting that REM sleep is only important for procedural memory.

Conclusion

Despite the controversial role of REM sleep in memory consolidation, there is no doubt that sleep has a profound influence on how we learn. Medical students are constantly torn between the need to stay up and learn those extra few pages, and getting the sleep required. However, many studies have shown a decrease in memory acquisition and consolidation with a lack of sleep. Although staying up late may help students get the few extra points needed to pass a course, it will hinder the ability to retain what has been learned. Future doctors must optimize learning habits today to take better care of patients tomorrow.

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