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Meeting Abstracts

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Keynote Presentations

Normal and Abnormal Spatial, Temporal, and Category Learning and Memory Consolidation: Multiple Roles of the Hippocampus

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Abstract

This talk provides a self-contained summary of neural models of normal and abnormal learning and memory consolidation in which the hippocampus plays an important role. As heuristically described in the Multiple Trace Theory of Moscovitch and Nadel, the role of the hippocampus in some learning processes is time-limited, but in others more enduring. This theme raises the question of why and how several different kinds of learning processes all include hippocampal resources. The talk will describe neural models of cognitive, adaptively-timed cognitive-emotional, and spatial navigational processes that all involve the hippocampus in learning and memory consolidation processes, but which differ in the extent of hippocampal involvement as memory consolidation proceeds. It hereby provides mechanistic explanations of the differences that have been experimentally reported about hippocampal involvement. Many psychological and neurobiological data are explained in a unified way by these models, including data about clinical disorders like medial temporal amnesia and problems with allocentric navigation.

Opposing Roles of Peripherally-Derived γδ T Cells and Tregs in Epilepsy Pathogenesis

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Abstract

The pathophysiology of drug-resistant pediatric epilepsy is unknown. We carried out a flow cytometric analysis of inflammatory leukocytes in resected brain tissues from 29 pediatric patients with genetic (focal cortical dysplasia) or acquired (encephalomalacia) epilepsy. We found significant brain infiltration of blood-borne inflammatory myeloid cells and memory $CD4^+$ and $CD8^+$ T cells. Significantly, pro-inflammatory (IL-17- and GMCSF- producing) γδ T cells were concentrated in epileptogenic lesions and their numbers positively correlated with the patient's seizure frequency and severity prior to surgery. In contrast, the numbers of regulatory T cells (Tregs) inversely correlated with disease severity. Correspondingly, using the kainic acid model of status epilepticus, we show ameliorated seizure activity in both γδ T cell- and IL-17RA-deficient mice and in recipients of Tregs, while Treg depletion heightened seizure severity. Moreover, both IL-17 and GM-CSF induced neuronal hyperexcitability in brain slice cultures. These studies support a major pathologic role for peripherally-derived innate and adaptive pro-inflammatory immune responses in the pathogenesis of intractable epilepsy suggesting an autoimmune component to chronic epilepsy and increased research on the potential use of immunomodulatory therapies for disease therapy.

Study of Neuropathology of Neurological Disorders: Novel approach

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Abstract

Most neurological conditions are diagnosed clinically. Subjective in neurological diagnosis introduces errors, delayed or incorrect treatment. Investigators are making efforts to develop techniques that remove subjectivity and allows accurate objective diagnosis at an early stage. We developed one of those techniques. It is called the single scan dynamic molecular imaging technique (SDMIT). The technique uses positron emission tomography (PET) to detect, map and measure neurotransmitters released acutely during cognitive or behavioral processing in the live human brain. It allows detection of impaired neurotransmission at a very early stage to help make a diagnosis of the conditions in which these transmitters are dysregulated. The technique exploits the competition between a neurotransmitter and its receptor ligand for occupancy of the same receptor site. In this technique after patients are positioned in the PET camera, a radio-labeled neurotransmitter ligand is injected intravenously and the PET data acquisition started. These data are used by a receptor kinetic model to detect, map and measure neurotransmitter released dynamically in different brain areas. Patients are asked to perform a cognitive, behavioral or emotional task while in the scanner and the amount of neurotransmitter released in different brain areas measured. By comparing it with the data acquired in healthy control volunteers during performance of a similar task, it is determined whether release of a neurotransmitter is dysregulated in the patients and whether the dysregulation is responsible for clinical symptoms. Finding of a significant dysregulation would confirm diagnosis of many neurological conditions including, Parkinson's disease and many forms of dementia. Since this technique measures neurotransmitter released under conditions of cognitive stress, it can detect changes at a very early stage, when dysregulation of is not expressed at rest but manifests only under conditions of cognitive overload.

Mast Cells and Endoplasmic Reticulum Stress Contribute to Cerebrovascular Pathobiology

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Abstract

Strokes contribute to significant childhood mortality in a genetically inherited condition, sickle cell disease (SCD), due to a point mutation in hemoglobin leading to red blood cell sickling under low oxygen. The underlying vascular pathobiology contributing to stroke remains unknown. We examined if mast cell activation and endoplasmic reticulum stress underlie cerebrovascular dysfunction in SCD. Mast cells are in close proximity to the vasculature and cause endothelial activation, plasma extravasation, and vascular dysfunction (Gupta & Harvima, Immunol Rev 2018). Vascular dysfunction in sickle cell disease (SCD) is accompanied by increased expression of P-selectin. Treatment with Crizanlizumab, an antibody against P-selectin, led to significantly less sickle cell-related pain crises (Ataga et al., NEJM 2017) highlighting the role of endothelial P-selectin in vasoocclusive crises (VOC). Earlier studies demonstrated that mast cell activation with morphine or ischemia/reperfusion stimulates endothelial E- and/ or P-selectin expression. One of the known triggers of endothelial dysfunction, inflammation and oxidative stress is endoplasmic reticulum (ER) stress. We hypothesize that in a sickle microenvironment, mediators derived from activated mast cells stimulate endothelial P-selectin expression via ER stress leading to increased blood brain barrier (BBB) permeability. We isolated MCs from HbAA-BERK and HbSS-BERK, control and sickle mice, respectively; incubated them *in vitro* and collected mast cell conditioned media (MCCM) from HbAA MCs and HbSS MCs. Normal mouse brain microvascular endothelial cells (mBMECs) were treated with unconditioned MCCM, HbAA MCCM, or HbSS MCCM to examine the effect of mast cell activation on endothelium.

We observed increased mast cell activity in HbSS mice evinced by significantly higher plasma and skin histamine levels, compared to HbAA mice ($p < 0.02$ for both). Mast cells from HbSS mouse skin showed significantly increased expression of histamine compared to HbAA skin mast cells ($p < 0.04$).

mBMECs incubated with HbAA and HBSS MCCM exhibited about 3 and 6-fold increases in P-selectin expression, compared to unconditioned culture medium, respectively ($p < 0.0001$ for both). Therefore, mast cells in culture release substances that stimulate P-selectin expression which is further increased by mast cells from sickle (HbSS) microenvironment. Preincubation of mBMEC with 5 microM salubrinal, an inhibitor of dephosphorylation of elongation initiation factor-a, which reduces ER stress, significantly inhibited HbSS MCCM-induced P-selectin expression on mBMEC ($p < 0.0001$) to the level induced by HbAAMCCM. In contrast, salubrinal did not inhibit HbAA-MCCM-induced P-selectin expression on mBMEC, suggesting that in a sickle microenvironment mast cells contribute to P-selectin expression via ER stress.

We next examined mast cell activity on endothelial permeability *in vitro* on mBMEC monolayers and *in vivo* in the brain

of HbSS mice. mBMECs incubated with HbSS MCCM showed a significant increase in Evans blue leakage compared to unconditioned or HbAA MCCM ($p < 0.0001$ for both), which was inhibited by preincubation of mBMEC with 5 microM salubrinal prior to incubation with HbSS MCCM ($p < 0.0001$). *In vivo* female HbSS mice showed a significantly increased leakage in the brain of FITC-dextran injected through tail vein compared to HbAA mice ($p < 0.01$). HbSS mice treated with 1 mg/kg salubrinal demonstrated inhibition of FITC-dextran leakage in the brain compared to vehicle ($p < 0.05$). Thus, ER stress contributes to increased BBB permeability in HbSS mice. We observed activated degranulating mast cells in the brain parenchyma of HbSS mice. In HbAA mice, quiescent mast cells were confined to the meninges of the brain but not seen in the parenchyma. Together, these data suggest that mast cell activation contributes to BBB permeability in a sickle microenvironment via ER stress-mediated P-selectin expression. In turn, this mast cell-initiated activity in the brain may underlie the pathobiology of stroke in SCD. Inhibitors of mast cells and P-selectin have been tested clinically leading to reduced VOC in SCD without known adverse events. Therefore, mast cell activation induced P-selectin via ER stress may serve as treatable targets for reducing the risk of stroke in SCD.

Precision Behavioral Management (PBM®) of Reward Deficiency Syndrome (RDS), the Construct that Underpins All Addictive Behaviors

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Abstract

Worldwide, daily there are several millions of people increasingly unable to combat their frustrating and even fatal romance with getting high; for some 'high' may be just experiencing "normal" feelings of well-being. The National Institutes on Alcohol Abuse and Alcoholism and on Drug Abuse (among others) conduct and fund outstanding research using sophisticated neuroimaging and molecular genetic applied technology to improve understanding of the intricate functions of brain reward circuitry and resting state functional connectivity, that is purportedly playing a key role in addiction symptomatology. In the international addiction medicine community, there is controversy as to the ultimate definition of addiction involving ASAM, ISAM, on one hand and other psychological and World Health organizations on the other hand. From a neuroscience perspective, while it is widely accepted that dopamine is a major neurotransmitter implicated in behavioral and chemical addictions, there remains controversy about how to modulate dopamine clinically in order to treat and prevent various types of addictive disorders. While for the most part Medication Assisted Treatment (MAT) promotes dopamine blockade or unintentional dopamine down–regulation in the long term, adherence and relapse prevention has been poor. However, harm reduction is a major societal benefits obtained through MAT [1]. This is especially true even for buprenorphine–naloxone combinations. It appears, though, that a prudent approach may be a biphasic short-term blockade (harm reduction) followed by long-term dopaminergic upregulation, with the goal of enhancing the functional connectivity within the brains reward circuitry, possibly targeting the reward deficiency [2] and the stress-like anti-reward symptomatology arising in the context of addiction (relapse prevention or intervention). Such phenotypes can be characterized using the patented Genetic Addiction Risk Score (GARS®) [3]. Dopamine homeostasis may thus be achieved via customization of neuronutrient supplementation (putative prodopamine regulation) based on the GARS test result along with a behavioral intervention developed by our group, dubbed "Precision Behavioral Management" (PBM®). The session will be delivered in terms of scientific development of PBM and clinical applications including genetic mining data in approximately 1000 probands and neuroimaging in humans and even animal addiction models. In one particular study, directed by MCGL, participants (n = 35) are in current addiction treatment with a Howard University or local community buprenorphine provider. To date it was found that Chi square analysis showed that the RDS scores (based on a 29 item questionnaire) positively correlated with Trauma ($X2 = 6.804$; $p = 0.033$; two tailed). The correlation is moderately high (Cramer's $V = 0.454$). Preliminary genetic analysis of 25 participants showed that

100% had GARS scores equal or higher than 4, characterized according to the Addiction Severity Index as at risk for drug addiction. Sixty percent were also at risk for alcohol addiction, with GARS scores equal or higher than 7. The scientific goal is to induce dopamine homeostasis through epigenetic manipulation without compromising harm reduction especially in Opioid Use Disorder (OUD) [4].

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The Shadow of Vitamins and Health

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Abstract

Vitamins are a group of organic substances that are in small quantities essential to normal metabolism. Vitamins are divided into two categories: fat soluble (A, D, E, and K) and water soluble (Bs and C). They cannot be synthesized in the human body or the rate of synthesis is inadequate for maintenance of health, therefore, they must be obtained from the environment, such as food. Deficiency in a vitamin may cause a disorder. Supplementation of multivitamins is believed to be beneficial in maintaining individuals in a good healthy condition, enabling them to have longevity and preventing them from developing a disorder. Unfortunately, overdose of a vitamin may be ignored which may cause a medical problem. The belief of "the more the better" for taking a vitamin may not be true in this regard.

Featured Presentation

Lack of Evidence for a Role of BMAA (β-N-methylamino-L-alanine) in Human Neurodegenerative Disease

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Abstract

The compound BMAA has been postulated to play a causative role in four neurodegenerative diseases: Amyotrophic Lateral Sclerosis/Parkinsonism Dementia Complex (ALS/PDC) found on Guam, and ALS, Parkinsonism, and Alzheimer's disease that occur globally. The BMAA hypothesis is based on four contentions: 1. BMAA caused ALS/PDC due to consumption of animals that contained large quantities of cycad seeds where cyanobacteria-produced BMAA had bioaccumulated; 2. All of these diseases are sufficiently similar to enable BMAA to cause them; 3. Environmental exposures to BMAA are sufficient to cause the diseases; and 4. BMAA acts by producing neurofibrillary tangles due to its incorporation into proteins in place of serine and this is proven by animal studies and the existence of BMAA in the brains of sufferers of both ALS and Alzheimer's. There are now data that collectively contradict these contentions. Analysis of the identical Guam food using more definitive analytical methods have shown no BMAA present. There are major differences between these four diseases in terms of the types of aberrant proteins and/or affected regions of the brain, and no evidence that one agent could induce them in different individuals. Analytical studies have often not identified BMAA in the environment, and when found, were quantities approaching the amounts thought to have induced ALS/PDC. Several well-designed, definitive studies have failed to find BMAA incorporation into proteins. Animal studies have used unrealistically high dose levels, and in the case of rodents, inappropriate routes of administration. Studies using accurate analytical

techniques have not identified BMAA in the brains of former ALS or Alzheimer's patients. The BMAA hypothesis as a causal factor for neurodegenerative diseases has not been verified.

Pathological Markers of Alzheimer's Disease

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Abstract

Alois Alzheimer's 1960 postmortem report of his former patient indicated shrunk brain. This observation is consistent in autopsy reports over the years (and decades) and also supported by structural imaging results. Using this as a consensus effect of Alzheimer's disease, we present a model to track pathological changes in the brain with respect to time. This work successfully characterize the prediction and diagnoses of Alzheimer's disease by comparing variations in the models predicted pathological-Marker results.

Pathway Level Codon Bias among Synonymous Rare Variants is Associated with Alzheimer's Disease Imaging Biomarker

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Abstract

Background: Neuroimaging data can be utilized along with genetic information to improve our ability of detect Alzheimer's disease (AD) and characterize its pathogenesis. Though synonymous codons synthesize the same amino acid sequence, synonymous variants have been implicated in a number of diseases including neurological, cancer, heart, and more specifically AD. A growing body of evidence suggests variation among synonymous codons leading to codon bias can impact protein abundance, conformation, and function. One form of codon bias occurs when a synonymous codon is represented more often than another leading to biases in terms of codon frequency throughout the genome. Other codon biases can be in the form of optimal and non-optimal codons, which have stronger and weaker codon interactions, respectively. Furthermore, codon bias can present itself within a gene, in other words the 5' and 3' ends of genes can be biased with different synonymous codons. Although rare variants within specific pathways have been shown to be associated with AD, it remains unclear how pathway specific rare variants that affect codon bias are implicated in the disease.

Methods: Data (whole-genome sequencing and MRI imaging) used in this study was obtained for 750 non-Hispanic Caucasian participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. Rare variants were annotated based on specific types of codon bias (i.e. frequency or optimality) and binned into pathways using BioBin. An association test between the pathways and an AD-related neuroimaging phenotype (e.g. entorhinal cortex thickness) was performed using SKAT-O.

Results: Rare variants that affect codon optimality towards the 3' ends of genes in the p53 signaling pathway were associated with the imaging phenotype (FDR < 0.05). This association was not observed when including synonymous variants that affect optimality or the frequency across the full length of the gene.

Conclusions: While previous work has pointed to a connection between p53 and AD, this study is the first to suggest they are linked via rare variants in synonymous codons. Moreover, codon bias that affects certain regions of genes may play a role in the pathogenesis of AD and can be used to improve statistical power when performing pathway-based association tests.

Developing Mobile Software that Uses Visual Mapping Techniques as Habit-based Assistive Technology for Individuals with Alzheimer's disease and Alzheimer's Related Dementias and their Caregivers

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Abstract

One of the most important insights in the neuroscience of memory is the idea that there is more than one memory system in the brain. Conscious memory, often called declarative memory, or everyday memory, is based on active learning and memorization, and is dependent on the temporal lobe region of the brain, including the hippocampus. When the hippocampus and related brain structures are damaged or destroyed, as in the case of Alzheimer's disease, the individual loses the ability to learn and remember new information and to access recent memories. By contrast, habit learning occurs when information is stored unconsciously, through repetition and trial-and-error learning. A different region of the brain, the neostriatum, is thought to underlie habit learning. We now know that humans have a robust capacity to learn and retain new information unconsciously, retaining habit memory even when conscious or declarative learning is impaired. Thus, memory-impaired individuals can learn and retain information normally when the task does not require explicit memorization.

MapHabit, Inc.'s use of habit memory is foundational for the implementation of our patent-pending software which takes advantage of the intact habit memory system to bypass the impaired hippocampal declarative memory system. With repeated experience, memory-impaired individuals can learn to routinely utilize their visual maps. The innovative use of the brain's habit system can be an effective way for caregivers and memory impaired individuals to organize and schedule daily activities, to reduce stress for both individuals, and provide memory-impaired individuals the opportunity for more independence and autonomy.

Lithium to Prevent Dementia: A Review and Call to Action

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Abstract

Lithium is an agent with established neuroprotective qualities, considerable epidemiological evidence supporting its use as a dementia prophylactic, and was strongly debated to be part of the UK's national dementia strategy. Yet it has failed to enter regular clinical use for this purpose – not for lack of evidence, but rather arguably for saturation of poor quality evidence and aborted peripheral clinical trials. This presentation presents a review of the story of lithium's almost rise to fame, and argues for a fresh approach.

Psychological and Behavioural Patterns of Stigma among Patients with Dementia: A Cross-sectional Study

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Abstract

Rationale: The aim of this study was to test the psychological and behavioural patterns of stigma (self-esteem and social participation) and their relationship to self-stigma, patient activation for engaging in self-care among patients with dementia.

Methods: This was a cross-sectional study in tertiary-level hospital and out-patient unit.

Participants: A consecutive sample of 89 outpatients with dementia. Inclusion criteria were as follows: diagnosis of dementia, age 55-95 years, no diagnosis of psychosis, and no need for urgent medical procedures.

Outcome measures: Study measures included Mini Mental State Examination, a self-administered questionnaire to assess the Rosenberg Self-Esteem Scale (SES), the 3 subscales of 36-question Short Form Health Survey (SF-36; Social Function, Role Physical, Role Emotional), Self-Stigma Scale and Patient Activation Measure (PAM-13).

In previous qualitative study, we found that psychological and behavioral patterns of stigma varied according to patient's levels of illness-related self-esteem as well as attitudes towards social participation. For quantitative consistency, we used the SES scale to measure self-esteem and the SF-36 subscales to measure social participation. We then divided participants into 4 groups by exhibited psychological and behavioral patterns: Group (A) (high SES/high SF-36), Group (B) (high SES/low SF-36), Group (C) (low SES/high SF-36) and Group (D) (low SES/low SF-36).

Results: Using analysis of covariance after controlling for age and sex, there was a significant difference in self-stigma levels between the four groups ($p < 0.001$). We observed the highest mean self-stigma levels in group D. Group D also had

significantly lower PAM-13 scores than those of groups A ($p < 0.001$) and B ($p = 0.02$).

Conclusions: The psychological and behavioural pattern of group D was found to be associated with higher levels of self-stigma and poorer patient activation for self-care.

Exploring Alzheimer's Disease Mouse Brain Through X-ray Phase Contrast Tomography: From the Cell to the Organ

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Abstract

Alzheimer's disease (AD), the most common form of dementia, is a progressive neurodegenerative disorder associated with aberrant production of beta-amyloid (Aβ) peptide depositing in brain as amyloid plaques. While animal models allow investigation of disease progression and therapeutic efficacy, technology to fully dissect the pathological mechanisms of this complex disease at cellular and vascular levels is lacking.

X-ray phase contrast tomography (XPCT) is an advanced non-destructive 3D multi-scale direct imaging from the cell through to the whole brain, with exceptional spatial and contrast resolution. We exploit XPCT to simultaneously analyze disease-relevant vascular and neuronal networks in AD mouse brain, without sectioning and staining. The findings clearly show the different typologies and internal structures of Aβ plaques, together with their interaction with patho/physiological cellular and neurovascular microenvironment. XPCT enables for the first time a detailed visualization of amyloid-angiopathy at capillary level, which is impossible to achieve with other approaches.

XPCT emerges as added-value technology to explore AD mouse brain as a whole, preserving tissue chemistry and structure, enabling the comparison of physiological vs. pathological states at the level of crucial disease targets. *In-vivo* translation will permit to monitor emerging therapeutic approaches and possibly shed new light on pathological mechanisms of neurodegenerative diseases.

The Essential Role of Biofilms in Alzheimer's Disease

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Abstract

Biofilms are made by microbes and are exceedingly common in nature. On examination of pathological specimens from the hippocampi in Alzheimer's disease (AD) brains, biofilms have been observed both intra and extra-cellularly. It is highly probable that the microbes that create the biofilms in AD are spirochetes of either Lyme or dental origin. *Borrelia burgdorferi* of Lyme disease and *T. denticola* (representative of the dental organisms) have been found by PCR analysis, and *Borrelia burgdorferi* has been cultured from AD brains. Simultaneously with making biofilms *in vitro*, these cultivated *Borrelia* have been shown to make beta amyloid precursor protein (ABPP) and amyloid beta (Aβ) in pure culture. Comparatively, in the intracellular location *in vivo*, the Aβ (formed by the spirochetes while making biofilm), when meshing with tau protein, causes tau to be phosphorylated by a known interaction. When tau is hyperphosphorylated tau (p-tau), it no longer functions to stabilize neuronal dendrites, and those dendrites disintegrate. Extracellular biofilms are coated with Aβ (which is antimicrobial). Further, those biofilms attract Toll-like receptor 2 from the innate immune system; this molecule attempts to kill the spirochetes, but is ineffective, because it is unable to penetrate the biofilm. NFkB, one of the intermediates in the MyD88 pathway generated by TLR2, catalyzes beta amyloid converting enzyme which, in turn, catalyzes beta and gamma secretase that cleave ABPP to Aβ. Consequently, in the formation of biofilm, Aβ is created; and, in the TLR2/MyD88 response to the "spirochete-coated" biofilm, Aβ is also created. Finally, p-tau, the other major element of the pathology, is directly related to the creation of the biofilms. Biofilms are thus integral to the pathology of AD.

Sex Differences in Alzheimer's Disease: Female Susceptibility and Therapeutic Opportunity

Liqin Zhao

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Abstract

Alzheimer' disease (AD) disproportionally affects women more than men. Of current AD cases, more than two-thirds are women. After age 65, the lifetime risk of AD is 1 in 6 for women whereas 1 in 11 for men. Moreover, age-stratified analysis reveals that AD is at least two times more prevalent among women than among men across all age groups, indicating that the higher incidence of AD in women cannot be simply attributed to the longer life expectancy of women. Despite these clinical indications, the biological bases underlying such sex differences in AD vulnerabilities remains poorly understood. This presentation will discuss our recent study aimed to elucidate sex disparities in metabolic aging of the brain focusing on 2 major areas – energy and amyloid metabolism – that are most significantly affected in preclinical development of AD. Our findings provide a mechanistic rationale for female susceptibility to AD and suggest a potential therapeutic opportunity for AD prevention and risk reduction in women.

Multicentric Cryptococcomas Mimicking Neoplasia

Adrian Kelly

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Abstract

With regards fungal mass lesions in the CNS they are, as a group, extremely rare. In this group cryptococcomas are the most commonly seen and are often included in the differential diagnosis of multicentric space occupying lesions in immunocompromised hosts. While crypococcomas are known to occur in both healthy and immunocompromised individuals they are more commonly seen in the latter where *Cryptococcus neoformans* is the typical agent. This contrasts the species seen in immunocompetent hosts where *Cryptococcus gatti* occurs more commonly.

These lesions are commonly 3 mm – 10 mm in diameter and occur in the basal ganglia due to the organism spreading via the Virchow-Robbins spaces surrounding the small perforator vessels as part of contiguous spread from a basal meningitis. Although most frequently associated with HIV infection, patients with chronic renal disease, vascular conditions, hepatitis B or C, alcoholism, diabetes mellitus and oncological diseases may also succumb to this infection and present with cryptococcomas.

In rare cases a chronic granulomatous process may lead to formation of a mass lesion (cryptococcoma) that has a tumoral appearance. Metabolites released by *Cryptococcus* can inhibit the migration and function of leukocytes and promote survival and localized replication of the pathogen, thus facilitating chronic granulomatous inflammation and cryptococcoma formation.

Tracing Cognitive Disease to Global Representations: Neurological Etiologies Affecting the Self Construct

Denis Larrivee

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Abstract

Improvements in medical care have significantly extended life expectancies, upwardly shifting demographic indicators of an elderly population sector worldwide. Coupled with falling birth rates, however, they have also greatly increased numbers of patients suffering cognitive deficits. World Health Organization projections, for example, indicate that by 2050 more than 20% will fill this sector, with considerably higher percentages in developed nations, placing large numbers of individuals at risk. Current evidence now indicates that several of the most prevalent cognitive diseases impact the phenomenal construct of the self, diminishing the capacity to unify brain and bodily operation. Disturbances of the self, for example, mark diagnostic evaluation of the schizophrenia patient, affecting such symptoms as an abnormal sense of the body, loss of ego boundary and a confused sense of agency. Similarly, degenerative processes in Alzheimer's Dementia progressively diminish the control of self-circuitries in the default mode network over regional operation. How these properties are impaired is unknown but in higher organisms key influences likely center on motor plans that are autonomously executed on behalf of a coded, neural self-representation. This concept of self, evoked when the body is dynamically engaged in intentional action, has been traced to the notion of the motor image, a covert action sequence undertaken only mentally and so simulating a non-executed action. Accordingly, this talk will explore current evidence linking the deterioration of the self-construct to a loss in planning and executing motor behavior through the motor image.

In vitro Pharmacological Characterization of [^{3}H]TZ3321 Binding toward Sphingosine-1-phosphate Receptor 1(S1P1), a Promising Target for Neuroinflammation

Sumit Joshi, Hui Liu, Qianwa Liang and Zhude Tu*

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Abstract

Introduction: S1P1 plays a key role in neuroinflammation, and emerges as a promising target for imaging and therapy for neuroinflammatory diseases [1]. We reported that a promise PET radiotracer [11C]TZ3321 could be used for quantifying S1P1 expression in different inflammation diseases, including the rat EAE model of multiple sclerosis (MS), the ApoE-/- mouse artery wire-injury model, and the rat carotid injury model [2-4]. Currently we are working on the FDA approval of [11C]TZ3321 for human use. Herein, we report *in vitro* characterization of its tritium counterpart [3H]TZ3321 binding toward S1P1.

Methods: The binding affinity of [3H]TZ3321 was determined by saturation binding assay using human recombinant S1PR1 membrane incubated with serially escalating doses of [3H]TZ3321 (ranging from 1 to 32 nM). The nonspecific binding was determined by adding 10 μM cold TZ3321. Samples were counted after incubation. For competition binding, cold TZ3321 and S1P (0.01 - 10 μM) were incubated with S1PR1 membrane in presence of [3H]TZ3321 (8 nM) for 15, 30, or 60 min.

Results & Discussion: [3H]TZ3321 bound to the human S1PR1 with high affinity (Kd = 8.4 ± 0.6 nM) (Figure 1). At optimization condition of incubating for 15 min, Ki values were 6.3 ± 0.2 8.1 ± 0.1 nM for S1P and cold TZ3321) (Figure 2).

Conclusion: The data suggested [3H]TZ3321 to be a promising radioligand for *in vitro* measure of S1PR1 in postmortem human brain tissue, indicating that PET with [11C]TZ3321 could be a biomarker for assess the neuroinflammation response in MS patients.

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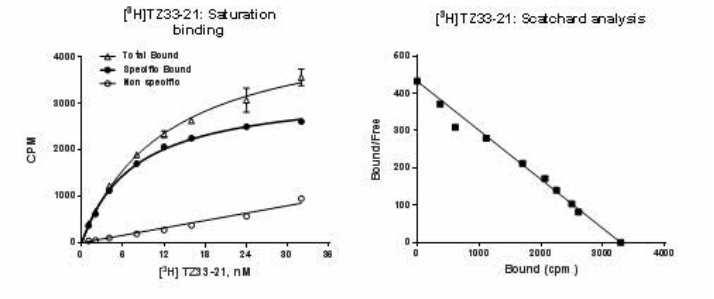

Figure 1: Saturation binding curves and Scatchard analysis of [3H]TZ3321 to hS1PR1 membrane.

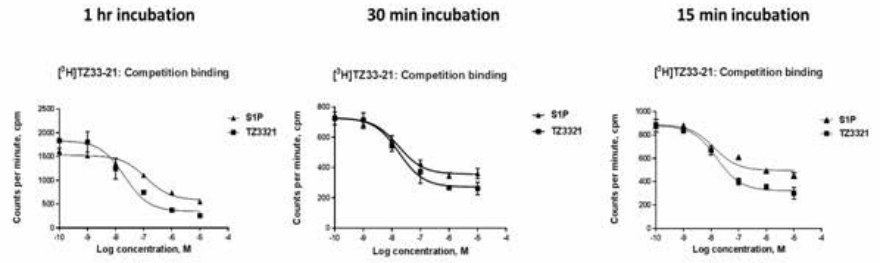

Figure 2: Competition binding curves of [3H]TZ3321 to hS1PR1 membrane.

The Role of Codon Bias and Elongator in Neurological Disease

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Abstract

The George laboratory studies a devastating childhood neurological disease called familial dysautonomia (FD). As both a neurodevelopmental and neurodegenerative disorder, patients are born with an emaciated peripheral nervous system that progressively deteriorates over time, with most patients dying as young adults. FD is caused by mutation in ELP1, a gene encoding the scaffolding protein for a multi-subunit complex called Elongator. In lower organisms, this highly conserved complex is essential for interpreting an aspect of the genetic code known as codon bias. Our recent work demonstrates that Elongator serves a similar function in mammalian neurons and that many FD symptoms ultimately result from a compromised ability to read codon bias. As such, we are identifying cellular and molecular pathways that depend on Elongator for regulating protein production, and that may serve as unique targets for therapeutic intervention. The fact that allelic variation in multiple Elongator subunits also contributes to other, more common neurological diseases including autism spectrum disorder, amyotrophic lateral sclerosis (ALS), Rolandic Epilepsy, and intellectual disability, suggests that neurons may be more dependent on codon-biased genes that other cell types. Thus, in addition to broadening our basic understanding of the genetic code itself, our work is providing new insights into the molecular mechanisms that neurons may specifically depend on to regulate protein levels.

Drosophila Melanogaster: A Robust and Cost-Effective Model to Screen Therapeutics for Neurodegenerative Disorders

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Abstract

The fruit fly, *Drosophila melanogaster*, is commonly used in biomedical sciences as a model system to study human disorders. About 70% of human disease genes possess a Drosophila homolog. Drosophila models of neurodegenerative diseases including Alzheimer's disease (AD) and Huntington disease (HD), present us with an efficient and cost-effective platform to screen for therapeutics prior to embarking on studies in mammals. Several Drosophila models of HD differing in polyglutamine repeat lengths are available to conduct intervention and mechanistic studies. These flies mimic HD in terms of decreased lifespan, decreased locomotion, and increased photoreceptor degeneration. Also Drosophila models for Alzheimer's disease, which overexpress Aβ42 and MAPT (Tau) are available. We have been working with these two models in our laboratory and tested the impact of botanical extracts and their putative active compounds on the phenotypes of AD and HD. In this presentation, a summary of our data on the impact of *Rhodiola rosea* and cinnamaldehyde on phenotypes of Alzheimer's disease and Huntington's disease in *Drosophila melanogaster* models will be presented.

Function and Dysfunction of the Neuropatho- Signature Protein TDP-43

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Abstract

More than 98% of amyotrophic lateral sclerosis (ALS) and 50% of Frontotemporal lobar degeneration (FTLD) are associated with mis-metabolism of the RNA-binding protein TDP-43, resulting in ALS-TDP and FTLD-TDP, respectively. TDP-43 proteinopathies causes ALS-TDP and FTLD-TDP through gain-of toxicity at the early stage of their pathogenesis and loss-off function at the later stage. We will present some of our works utilizing different mouse models, primary mouse hippocampal neurons, and pyramidal neurons derived from genetically engineered mouse ES cells to study the neuronal functions of TDP-43 and its dysfunction in ALS-TDP and FTLD-TDP.

Autoimmune Biomarkers and AI Algorithms could Lead to New Diagnosis and Treatment Options in Neurodegenerative Diseases Such as Glaucoma

Franz Grus

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Abstract

Glaucoma is a chronic neurodegenerative disease and one of the leading causes of blindness. The elevated pressure cannot explain the disease in all patients. In glaucomatous human retinae, we could demonstrate some significant proteomic biomarkers by LC-ESI-MSMS and antibody microarrays. Several of those markers provide hints for an involvement of the immune system. Therefore we used several bead based mass spectrometric approaches for immunoproteomics. We could show alterations in serum antibody profiles of glaucoma patients against optic nerve and retinal antigens, upregulations (e.g. anti-HSP60, anti-MBP) and downregulations (e.g. anti-14-3-3) have been described. These markers were validated by antigen microarrays and are consistent in independent study populations. Additionally, the changes in antibody profiles could be used as highly sensitive and specific marker for diagnostics purposes. Using algorithm approaches from artificial intelligence and connections of different neural networks including deep learning approaches, we could demonstrate a sensitivity and specificity of more than 93%.

Early diagnosis and intervention in risk patients would offer the chance of early treatment and to slow down the progression of disease. Furthermore, it could be shown that the intravitreal injection of some of these antibodies shows a neurorecovery in glaucoma animal models.

We hypothesize that the homeostasis of the autoimmune system plays an important role in recovering and protecting those RGS in early damage. Using these markers could allow a beneficial translation into clinical routine for diagnosis and personal treatment.

Tuberculous Hypertrophic Pachymeningitis-A Review

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Abstract

Tuberculosis infection of the central nervous system is diagnosed in a variety of forms which include tuberculous meningitis, tuberculomas and tubercular abscesses, tuberculous vasculitis, tuberculous encephalitis, tuberculous subdural empyema and spinal tuberculosis. In addition each of these diagnoses may present with secondary complications which include hydrocephalus, cranial nerve palsies and stroke. Considering tubercular meningitis specifically it is noted to be the most common diagnosis of central nervous system tuberculosis occurring most frequently in young children and individuals with untreated HIV infection. The classical form of tuberculous meningitis is as a basal meningitis comprising thick exudates which as the disease progresses complicates by causing hydrocephalus and infarcts secondary to an obliterative arteritis of the small perforator vessels. A much rarer form of tuberculous meningitis is as a pachymeningitis affecting the meninges of the cranial vault. In certain cases the inflammatory response may become exuberant leading to a hypertrophic form of pachymeningitis where considerable nodular or linear thickening of the dura mater occurs. This hypertrophic reaction may be localized or extensive and the extent of the disease as well as its location dictates the presenting symptoms. Histologically granulomatous change with caseous necrosis and Langerhans giant cells are seen in the tuberculous form of the disease. We present a mini review of hypertrophic pachymeningitis with emphasis on the tuberculous form of the disease.

Keywords: Tuberculous hypertrophic pachymeningitis; tuberculous meningitis

Effects of Music Aerobic Exercise on Autonomic Nervous Function among the Residents in Long-term Care Facilities

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Abstract

Aim: Two-thirds of residents in long-term care facilities do not exercise regularly, leading to a rapid decline in physical functions. This study designed a music aerobic exercise (MAE) program in 3 times per week at 50-minute sessions for 12 weeks and examined the effects of this program on the autonomic nerve function of residents in long-term care facilities.

Methods: The participants in three long-term care institutions were randomly assigned into experimental group (n = 33)

and control group (n = 15). Heart rate variability (HRV) parameters were measured. All the participants received pre- and post-tests.

Results: Before the intervention, both groups revealed no significant differences of the HRV parameters. After 12 weeks of practice, the difference of changes (post-test minus pretest) among those who participated in MAE significantly decreased Mean HRT (Z = -1.85, p = 0.035). The residents in the MAE group also revealed a significantly higher post-test value of RMSSD (parasympathetic nervous system activity) compared to the pretest (Z = -1.68, p = 0.045), and a borderline significant increase in the ratio of LF/HF (Z = -1.19, p = 0.12) (balance of autonomic nervous system activity).

Conclusion and Implications for Practice: The 12-week MAE significantly decreases Mean HRT and increases RMSSD in residents of long-term care facilities. A future goal is to recruit a larger group of subjects to participate in the MAE program, and monitor the environmental influences in further clinical practice and studies.

Keywords: Institutionalized residents, Heart rate variability, Music aerobic exercise, Long-term care facilities, Autonomic nervous function

Different Senescence Associated Secretary Phenotypes in Exosomes of Plasma and Urine in Elders with and without Degenerative Brain Diseases

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Abstract

We have previously shown that aging was associated with epigenetic CG methylation of certain immune genes (Yang Y, et al. 2017. *Oncotarget* 8(30): 48591-48602), white noise could help stabilize agitation of Alzheimer disease patients (Yeh L, et al. 2018. *J Nurs Res* 26(1): 2-9), and regular exercises enhanced immune regulatory differentiation and circulating brain-derived neurotropic factor (Yang Y, et al. 2015. *Biomed Res Int* 2015: 135893). This study postulates that elders with and without degenerative brain diseases have altered senescence associated secretary phenotypes (SASP) in blood and/or urine, and exercise may improve the SASP profiles. In an active aging program, we have recruited elders with and without brain degenerative diseases for a regular exercise for 12 weeks, and performed pre-test of SASP including 28 cytokines and chemokines in blood and urine. In comparison to young adults (age before 30), elders older than 60 have significantly higher levels of IL-8, IP-10, MCP-1 and MIP1a ($P < 0.05$) in exosomes derived from plasma. In urine exosomes, elders older than 60 have significantly higher levels of GRO, IL-6, IL-8, IP-10 and MCP-1 ($P < 0.05$). Interestingly, most of the SASP chemokines (GRO, IL-8 and IP-10) detected in exosomes of urine were not detectable in drop through solution cut-off by a 30 nm filter, rendering the possibility to detect aging biomarkers in urine exosomes. This presentation will also compare the SASP chemokines of exosomes between elders with and without degenerative brain diseases, and determine whether a regular exercise improves the SASP of urine in the near future.

Neuromodulatory Roles of Oxytocin in the Activity of Neuroendocrine Immune Networks

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Abstract

Oxytocin (OXT) is mainly produced in the supraoptic nucleus (SON), paraventricular nucleus (PVN) and several accessory nuclei in the hypothalamus. In response to environmental challenges, OXT is secreted into the brain and blood to regulate social behaviors, personal relationship, feeding and autonomic activity, suppress anxiety and social stress and promote lactation and childbirth. Recently, immunological functions of OXT have emerged as an important defense mechanism of the body through both the central and peripheral approaches, such as cardioprotection, antibiotic activity and wound healing. Based on our review works, "Oxytocin-secreting system: a major part of the neuroendocrine center regulating immunologic activity" and "Approaches mediating oxytocin regulation of the immune system", we further examined the relationship between activities of the oxytocin-secreting system and other hypothalamic-pituitary-immune axes in rats. The preliminary results showed that neurotoxic lesion of the dorsolateral region of the SON to reduce OXT production significantly caused atrophy of lymph nodes, the thymus and the spleen. In the hypothalamus, increase in CRH and decrease in TRH occurred in the PVN, and GnRH in the medial preoptic area

of the hypothalamus tended to increase. Plasma vasopressin increased significantly while thyroid hormone (T4) and interleukin -1/6/10 decreased. In response to surgical stress, CRH reduced significantly accompanying with increased OXT secretion in the hypothalamus. Taken together, the OXT-secreting system can directly regulate the activity of the immune system while coordinating other components of the neuroendocrine immune network to achieve immune defense functions.

Cortical-Subthalamic Beta-frequency Signaling Supports Movement in Healthy Individuals, but Impairs Movement in Parkinsonism

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Abstract

Beta frequency (~12–30 Hz) activity in motor cortex (MC) and subthalamic nucleus (STN) is related to motor output. Because MC β-power is pathologically elevated in parkinsonian states, it has been identified as a putative biomarker of symptom severity and considered a potential control signal for closed-loop/smart deep brain stimulation (DBS). In recent experimental work, we targeted DBS to the STN of parkinsonian rodents while collecting neural field potentials. During high frequency (150-250 Hz) stimulation, mean MC β-power was suppressed whether or not the treatment alleviated symptoms, but variations about that mean changed with DBS efficacy. In asymptomatic rats, MC β-power was strongly anticorrelated with gait speed; in parkinsonian rats, including those being treated unsuccessfully, MC β-power was independent of gait speed. Thus, the magnitude of MC β-power is less relevant than it having a strong relationship to movement intensity, and effective DBS restores that relationship.

With the role of β-power unclear, several groups are instead focusing on β-coherence between MC and STN. We report that during low intensity movements, alterations in MC-STN β-coherence are small and unrelated to behavior. However, in healthy rodents during self-directed behavior reversals — eg. quick stop followed by rapid acceleration — MC-STN β-coherence is prominently elevated. In contrast, parkinsonian rodents performing self-directed behaviors exhibit suppressed MC-STN β-coherence. These results suggest that in healthy animals, intense motor activity is mediated partly via strong β-frequency signaling from STN to MC; in parkinsonian animals, the β-frequency signals in STN are aberrant, and motor activity is enabled by their suppression.

Children with Autism Spectrum Disorders: Comparison of Montessori Therapy and Treatment by Special Pedagogue

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Abstract

In last 10 years, a frequency of symptoms of Autism spectrum disorders (ASD) in Europe increased more than twice. Up to date, no effective treatment of ASD exists. The aim of this study was to compare different types of therapies for ASD in 2–5 years old children. The study sample consisted of 100 children, of them 29 considered as healthy, and most of others (N = 62) received different kinds of therapies: Montessori therapy (N = 26), attendance of special pedagogue (N = 21), or others. We used the Munich Denver functional scale to assess children psychomotor abilities after two years of therapy. Multiple logistic regression models adjusted for age, compliance of development to age norms, and initial diagnosis of a child were built to assess the association between a types of the therapy with improvement of psychomotor functions. We observed a significant improvement of all psychomotor abilities in children attended different therapies. Montessori therapy and attendance of special pedagogue improved three of five investigated abilities. Montessori therapy was especially effective for improvement of hearing (Odd ratio, OR = 19.3 [95% confidence interval, CI 1.69;221.1] and fine motor skills (OR = 46.14 [2.81;757.1]), while attendance of special pedagogue was more effective for improvement of gross motor skills (OR = 8.26 [1.35;50.3]), however, these differences were not statistically significant. We concluded that attendance of a therapy is essential for children with ASD, but specific type of a therapy should be matched for needs of each child individually.

Experiences of Latinx Families with a Child with Autism: Cultural Considerations

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Abstract

While the number of children diagnosed with ASD increases, so does the amount of caregivers raising them. Parents of children with autism report immense levels of stress that affect their psychological well-being, family, and marriage systems. Few studies have examined the cross-cultural differences in the experiences of raising a child with ASD. Marginalized populations lack the necessary information to make health, mental health, and childcare decisions, have poor patient/provider communication and rely frequently on informal social networks and the Internet for information that may be inaccurate and inconsistent. Latinx parents may face additional barriers such as limited English proficiency (LEP). Culturally and linguistically diverse parents of children with ASD experience a high risk for poor healthcare decision-making, significantly later diagnosis of ASD, greater difficulty accessing and utilizing ASD and related services, and perceptions of lower quality in the healthcare received. This presentation examines the experiences of Latinx caregivers and raising a child with autism, including implications for helping professionals, assessment protocols, and treatment planning.

Advantages of Early Screening for Risk of Autism, Rehabilitation Through Behavioral Parenting Training and Early Intervention O.T.A. for Children with Autism Spectrum Disorder (ASD)

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Charles University, Czech Republic

Abstract

Early detection of autism spectrum disorder is an important criterion for possible outcomes of rehabilitation care. In early age it can cause necessary changes in brain connectivity and start development by regular and well-targeted stimulation of skills relevant for autism to activate connections of the brain areas that would have worked only on a limited scale or would have not been activated at all. It is important to create a connection based on the spontaneity of the child with ASD, to support the natural frequency and quality of eye contact and to raise interest in human speech which transmits social information as well as facial expressions – theory of intersubjectivity. Intervention based on positive parent-child interactions (parent as main therapist) can optimize child development and activate mirror neurons (responsible for the ability of "gestalt" design). Inducing primary intersubjectivity and powering attachment behavior affects motivation, theory of mind and executive functions. O.T.A. is also used for children over 3 years. However, new connections are then based on old patterns of behavior, which must be reeducated, rewritten memory map of the brain, the results are significantly lower. Intervention initiated optimally within 2 years, can optimize the development on a much wider scale by stimulating key skills that trigger important psychological processes. The results of a longitudinal pilot study of the intervention O.T.A. with 16 toddlers with ASD show that low-cost therapy can be effective. To validate these results, the methodology is currently being tested on 100 children, comparing after two years.

How Can We Support Conversations about What Autism Means to Clients, Within a Concerned System?

Yvanna Coopoosamy

National Health Service, UK

Abstract

This presentation invites delegates to consider the ethical, clinical and systemic challenges of talking about what autism means to diagnosed clients. A 3-step therapy activity is presented as a possible framework for facilitating such discussions within a child and adolescent mental health service context. Children and young people who are assessed for autism are often at the center of a concerned system. Consequently, consideration of their lived experience and the development of their identity can be difficult for those supporting them to hold in mind. The challenges of accessing an autism assessment and relevant support services is often an overwhelming experience for parents. Services in turn are positioned as a support for the impact of autism, with time constraints on the space available to fully explore the meaning of a diagnosis with children and young people. This presentation further explores the questions raised by the publication on 'Creating space for meaning-making conversations with children and young people following an autism assessment'. For example, whose job is it to ask children or young people what they think about their diagnosis of autism? Does this conversation need to occur? When would such conversations occur?

Overall, the presentation aims to initiate debate amongst the clinical community and interested parties on what should be privileged when supporting children and young people diagnosed with autism?

Effects of Health Qigong Exercise on Heart Rate and Frequency of Heart in Parkinson's Disease Patients

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Abstract

The purpose of this study was to investigate effects of Health Qigong on heart rate and frequency of heart (HR + fR) in Parkinson's Disease patients. HR + fR included the measurements for heart rate(HR) and breath rate (BR), 36 moderate PD patients (N = 36) were randomly divided into experimental and control groups; 16 PD patients were placed in the experimental group which the prescribed medication plus Health Qigong exercise will be used in as intervention. The other 16 PD patients set up as the control group were treated only with regular medication. 10 weeks intervention had been conducted for the study, and participants completed the scheduled exercises 5 times per week and 60 minutes each time (10 minutes for warm-up, 40 minutes for the exercise, and 10 minutes for cool-down). Heart rate and frequency of heart (HR + fR) was collected before, during, and after the intervention. Comparisons were made between the experimental and control groups through the Repeated Measures ANOVA. The results showed significant. There were no significant differences between the two groups on gender, age, and course of differences ($P < 0.05$). The study concluded that Health Qigong exercises could reduce HR and BR, enhance their oxygen uptake, and increase the metabolism of PD patients.

Parkinsonians Syndromes Associated with Cognitive Deficit: A Molecular Imaging Update

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Abstract

Parkinsonian syndromes include, besides idiopathic Parkinson's disease several other neurodegenerative type of diseases called atypical parkinsonian syndromes. These are either part of synocleinopathies (like dementia with Lewy body or multisystem atrophy) or part of tauopathies (progressive supranuclear palsy and corticobasal degeneration). In the absence of a clinically approved alpha-synuclein or tau-targeted positron emission tomography tracer, the abnormalities associated with these diseases can be assessed using F18-FDG PET and 123I-ioflupane (Datscan) SPECT. Typical images appearances and the utility of quantitative evaluation for Datscan images will be also reviewed.

Remodeling of Lumbar Motor Circuitry for Recovery after Spinal Cord Injury

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Abstract

Retrogradely-transported neurotrophin signaling plays an important role in regulating neural circuit specificity. Here we investigated whether targeted delivery of neurotrophin-3 (NT-3) to lumbar motoneurons (MNs) caudal to a thoracic (T10) contusive spinal cord injury (SCI) could modulate dendritic patterning and synapse formation of the lumbar MNs. *In vitro*, Adeno-associated virus serotype 2 overexpressing NT-3 (AAV-NT-3) induced NT-3 expression and neurite outgrowth in cultured spinal cord neurons. *In vivo*, targeted delivery of AAV-NT-3 into transiently demyelinated adult mouse sciatic nerves led to the retrograde transportation of NT-3 to the lumbar MNs, significantly attenuating SCI-induced lumbar MN dendritic atrophy. NT-3 enhanced sprouting and synaptic formation of descending serotonergic, dopaminergic, and propriospinal axons on lumbar MNs, parallel to improved behavioral recovery. Thus, retrogradely transported NT-3 stimulated remodeling of lumbar neural circuitry and synaptic connectivity remote to a thoracic SCI, supporting a role for retrograde transport of NT-3 as a potential therapeutic strategy for SCI.

SD-OCT Study of Retinal Morphological Changes in Patients with Parkinson's Disease in Different Clinical Stages

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Abstract

Background: The retinal morphological change has been detected in Parkinson's disease. However, the previous studies had the controversial conclusion. The aim of this study was to observe the changes of retinal morphology in patients with Parkinson's disease with different clinical stages by spectral domain optical coherence tomography (SD-OCT).

Method: Forty-eight PD patients and thirty-six healthy controls (HC) were enrolled. Subjects were assessed for retinal structure using SD-OCT and general ophthalmic examinations.

Results: The PD group was divided into three subgroups by the Hoehn and Yahr scale: H-Y I stage group, H-Y II stage group and H-Y III stage group. The mean deviation of visual field had a significant difference among the four groups. The macular retinal thickness (MRT) and macular volume (MV) were obviously decreased in PD patients. And the further statistical analysis showed that the difference appeared between H-Y III stage group and HC group. The other subgroups had no differences compared with the HC group.

Conclusion: SD-OCT examination can detect the changes in retinal morphology in PD patients, and they may not be found the difference until the patients are in the middle stage of PD.

Key Ingredients of Effective Cognitive Rehabilitation Training

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Abstract

In this interactive workshop, a clinical neuroscientist and cognitive psychologist will present and demonstrate seven elements to make cognitive rehabilitation training more effective: repetitively practiced, delivered by a clinician (not a computer), intense, targeted, sequenced, progressively loaded, and with dynamic feedback. These elements have been critical components of the cognitive rehabilitation intervention the presenters use and in the studies they have published and presented on the efficacy of the intervention.

Much more than brain games, effective clinician-delivered cognitive rehabilitation training can remediate learning struggles, recover cognitive functioning following traumatic brain injury, increase self-esteem and confidence, and improve quality of life across the lifespan. The human interaction in effective cognitive training is grounded in Feuerstein's theory of structural cognitive modifiability, or the potential of an individual's cognition AND synaptic strength to be changed by mediated experience. This interactionist approach to a cognitive intervention aligns with the therapeutic perspective.

In this session, we will first present the framework of our model and then highlight neuropsychological and neuroimaging research results from our studies with children and adolescents with learning disabilities, with soldiers and civilians recovering from traumatic brain injury, and with adults over age 55 with age-related cognitive decline. Then, we will lead interactive demonstrations of training exercises and give participants instructions on how to integrate the seven key techniques one at a time. Finally, we will share case studies that highlight human interest stories representative of more than 100,000 lives who have been changed by this cognitive rehabilitation training intervention.

Lifestyle Modulators of Neuroplasticity: How Physical Activity, Mental Engagement, and Diet Promote Cognitive Health During Aging

Cristy Phillips

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Abstract

The rapidly expanding elderly segment of the world population will approximate 2.1 billion by 2050. Juxtaposed against

this burgeoning segment of the population will be an increased risk for cognitive decline. Unfortunately, these mild cognitive impairments portend the onset of disability even before dementia becomes clinically manifest. Given that pharmacological treatments that mitigate dementia remain elusive, alternative behavioral therapies are increasingly garnering widespread attention. In fact, the results from translational studies demonstrate that modifiable lifestyle factors such as physical activity, cognitive engagement, and diet are therapeutic strategies that can be used to optimize cognition during normal and pathological brain aging. Bolstering this notion are studies demonstrating a relationship between lifestyle factors, brain structure and function, and cognitive function in aging adults. These benefits stem from the ability, at least in part, of physical activity and diet to modulate common neuroplasticity substrates in the brain (neurotrophic signaling, neurogenesis, inflammation, stress response, and antioxidant defense). Similarly, cognitive engagement enhances brain and cognitive reserve. Thus, the aims of this presentation are to 1) articulate the common mechanisms are to explicate the relationship between modifiable lifestyle factors, neuroplasticity, and optimal brain health during normal and pathological aging, 2) identify putative mechanisms that contribute to positive brain aging, and 3) highlight future directions for scientists and clinicians. Undoubtedly, the translation of cutting-edge knowledge derived from the fields of exercise and regenerative medicine will advance our understanding and enhance clinical treatment interventions as we endeavor to facilitate optimal brain aging and cognition during aging.

Dr. Douyon's BrainFit™: Using Gamification to Prevent and Manage Neurological Diseases

Philippe Douyon

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Abstract

According to the CDC 75% of our healthcare dollars are spent on chronic diseases. The four modifiable health risk behaviors responsible for much of the illness, suffering, and early death are lack of physical activity, poor nutrition, tobacco use, and alcohol. These risky behaviors cause the chronic diseases which contribute to a lot of neurological disorders. As of 2011 greater than 100 million Americans were suffering from a neurological illness. By 2030 it is estimated that the costs of dementia and stroke alone will be more than $600 billion annually (2014 dollars, not adjusted for inflation). These increases in disease are occurring despite improvements in medications. Technology offers us the opportunity to have a lasting impact on patients where medication cannot.

Technology allows us to teach and empower patients in new and creative ways. It allows us to impact their behaviors and track their progress. Technology allows us to influence their lives on a daily basis without having to be physically in their presence. Using Dr. Douyon's BrainFit™ app we will explore some of the benefits technology has in preventing and managing chronic diseases.

Feasibility Test of Virtual Reality-based Visual Perception and Cognitive Rehabilitation Service

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Abstract

Patients with brain damage experience difficulties with activities of daily living (ADL) due to motor function and visual perception impairment. These brain-injured patients need ADL training or task-oriented training in the actual environment. Most existing approaches to intervention in patients with visual perception impairment involve evaluation-oriented treatment tools or intervention through a two-dimensional computer program. This study sought to evaluate the feasibility of virtual reality (VR)-based programs using questionnaires for healthy elderly (HE, n = 11), chronic stroke patients (CSP, n = 7), and stroke patients with visual impairment (SPVI, n = 4).

ADL contents consist of living room, kitchen, veranda, and convenience store scenarios that approximate real home environment, and were organized through rehabilitation specialists (consisting of neurologists, physiotherapists, occupational therapists). The contents included tasks such as turning lights, organizing drawers, organizing the kitchen, watering the plants, and buying things at convenience stores. Oculus Rift CV1 was used to apply training in VR systems. The questionnaires were revised to include 13 items in the evaluation of the augmented reality system of Nielsen.

The average related to the degree of understanding and difficulty of the content is 4.05. The average value of the questionnaire

related to vividness, interaction, and immersion is 3.95. The value related to rehabilitation purposes and fun factor of the program is 3.9. The overall results were higher in the following order: SPVI, CSP and HE. The VR rehabilitation service of this study is an efficient service that can promote the function, interest and motivation of stroke patients.

Redefining Spasticity and Its Rehabilitation: Insight from Use of Optokinetic Chart Stimulation

Benjamin Chitambira

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Abstract

Background and Purpose: In patients with traumatic brain injuries (TBI) and stroke, spasticity is defined from the affected muscles' view point. Velocity dependent stretch responses have been implicated mainly in flexor muscle groups. Acceleration optokinetic stimulation stimulates the anti-gravity extensor system in the brain with resultant EMG recordings in the extensor muscles. Preliminary evidence suggests that optokinetic chart stimulation (OKCS) may prevent spasticity. A brain anti-gravity extensor system based view point of spasticity has developed as a result. The aim is to discuss OKCS effects on spasticity and offer a proactive rehabilitation approach to spasticity.

Methodology: OKCS consists of moving an optokinetic chart of repeated colors of the rainbow in front of a patient. From 20 centimeters in front of a patient's face, the chart is moved from side to side for 3 minutes, up and down for 3 minutes and then forwards and backwards for 3 minutes.

Results: In 3 TBI patients with spasticity, use of OKCS resulted in reversal of spasticity and restoration of voluntary movements. In a case controlled series of 10 participants with complete paralysis as a result of partial anterior circulatory strokes, none of the OKCS participants developed spasticity of the affected upper limb. Four of the 5 conventional physiotherapy participants developed spasticity of the affected upper limb. The differences in spasticity were statistically significant ($P < 0.05$).

Conclusion: OKCS shows preliminary efficacy in preventing spasticity. Its stimulation of anti-gravity extensors may explain this through reciprocal inhibition of flexors. Further research is recommended to explore this hypothesis.

The Chinese Medicine and Acupuncture for Children with Cerebral Palsy

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Abstract

Objective: One: To investigate the effect of Jian-Pi-Yi-Shen and Tong-Du-Xing-Nao-Acupuncture on brain plasticity and motor development in children with cerebral palsy.

Two: To evaluate the effect and mechanism of acupuncture and moxibustion on cerebral palsy. Three: The nerve repair effect of acupuncture on cerebral palsy.

Methods: In this study, 146 cases of brain injury and 1078 cases of cerebral palsy were included by randomized controlled study with ICF (GMFM, Peabody fine motor function, Gesell, muscle tension, joint activity, ADL, TCD, skull B ultrasound, head CT/MRI, SPECT, DTI) evaluation method.

Results: One: the recovery rate of extracellular space (92.3%) was significantly higher than that of the control group (70.8%) ($P < 0.05$), TCD total efficiency (79.3%) was significantly higher than that in the control group (51.8%) ($P < 0.05$). Jian-Pi-Yi-Shen and Tong-Du-Xing-Nao-Acupuncture to promoting the development of neurological and cognitive movement under 6 month's children, effectively reduce the neurological sequelae.

Two: The total effective rate of the children with cerebral palsy was 87% in the acupuncture group, which was significantly higher than that of the control group ($P < 0.01$). The total effective rate of CT/MRI was 59.55% in the acupuncture group and 13.25% higher than that in the control group ($P < 0.01$). The total effective rate was 91.3% in the 1 year follow-up group, which was significantly higher than that in the control group ($P < 0.01$). The FA value of white matter fiber bundle was significantly higher than that of acupuncture at 60 times ($P < 0.05$). The recovery rate of ultrasonous brain injury (86.7%) in acupuncture group was significantly higher than that in control group (64.4%) ($P < 0.05$). The recovery rate of SPECT in acupuncture group was 96.4%, which was significantly higher than that in the control group ($P < 0.01$).

Conclusion: Acupuncture rehabilitation not only promote the development of white matter and gray matter in children

with cerebral palsy, but also promote the brain function of children with cerebral palsy remodeling and compensation, and promote social adaptation, language and other cognitive function development, children with cerebral palsy movement and Fine motor function development and recovery, improve the children's self-care ability.

A Case of Paradoxical Embolism Causing Anterior Spinal Cord Syndrome and Acute Myocardial Infarction Following the Intradiscal Oxygen-ozone Therapy

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Abstract

An old female who burst into flaccid paralysis of the lower extremities, accompanied by losses of pain and temperature sensation below T4 level, during an oxygen–ozone injection for disc herniation. Half an hour later, she suffered from chest pain. MRI showed a hyperintense area in the thoracic spinal cord from T2-10 level on sagittal T2WI. The ECG showed ST-segment elevation in V1-V6 leads. She was diagnosed with spinal cord infarction and ST-elevation myocardial infarction (STEMI). Transthoracic echocardiography with saline contrast showed the existence of a large patent foramen ovale (PFO) correlated with the detection of massive microbubbles in the left atrium. We discuss the potential role of paradoxical embolism through PFO as a possible mechanism of spinal cord infarction and myocardial infarction after intradiscal oxygen–ozone therapy.

Major Economic and Psycho-social Changes Experienced by Retirees in Selected Counties in Kenya

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Abstract

Retirement is a state of being out of or withdrawal from an active work-life. It can happen due to health reasons, voluntary retirement or after reaching mandatory retirement age which in Kenya is 60 years. Employment provides economic and social network that fulfills an individual's sense of belonging. Majority of employees face overwhelming challenges as they get to terms with post-retirement expectations and the reality of life during retirement. Many employees do not adequately prepare for their life during retirement. Kenya, like most other developing countries, is in the process of formulating retirement policies.

This study focused on different economic and psychosocial changes facing retirees after retirement. A purposive sampling strategy was adopted to draw a sample of retirees from selected counties in Kenya. A structured questionnaire was used to get information on the economic and psychosocial changes experienced by retirees.

The study revealed that retirees experienced various challenges related to their economic and psycho-social well-being. They either had reduced income (pensionable) or zero income (without pension). In their new circumstances, retirees reported either being resilient thus overcoming retirement challenges and being better-off, or were overwhelmed by the changes in retirement and hence reported being worse-off than while in employment. In conclusion, both employees and employers should jointly plan for the retiree's life after retirement, during their life in employment. Their retirement preparedness will avoid the mental health vulnerability that result from absence of, or diminished economic and psychosocial challenges experienced during retirement.

Post-Stroke Delirium: Prognostic Variability Between Anterior Circulation Strokes and Posterior Circulation Strokes "SEEK and DESTROY!"

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Abstract

Delirium is a common complication of stroke. It is not only under-diagnosed but also undertreated. Untreated post-stroke

delirium may render permanent damage to the brain and can also considerably increase mortality.

Aim: To observe and compare spontaneous progression and prognosis of post stroke delirium in anterior and posterior circulation strokes.

Method: A total of 37 patients were selected who had been admitted to the hospital through the ER following acute stroke episode and were clinically judged to be having developed delirium. Memorial Delirium Rating Scale (MDRS) was used for delirium assessment and applied on the patients on 2nd and Rating 5th post-admission day.

Result: The comparison of MDRS scores of 2nd and 5th day show that delirium following anterior circulation stroke has a tendency towards spontaneous improvement. Whereas, delirium in patients with posterior circulation stroke did not show significant spontaneous improvement, rather, showed a worsening trend. One way ANOVA showed a p = 0.024 depicting significant difference of scores between two groups.

Conclusion: It is concluded that active intervention and treatment of post-stroke delirium following posterior circulation stroke is required as it does not have good prognosis and can lead to permanent residual brain damage and increased mortality.

Executive Function Characteristics and Clinical Symptoms in Drug-Naïve Children with Attention Deficit Hyperactivity Disorder (ADHD)

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Abstract

Objective: To evaluate and compare the performance of children with ADHD in executive functions (EF) tasks, and explore the relationship between executive function and clinical symptoms.

Methods: We evaluated 214 children, including 132 children with ADHD (divided in ADHD-I, ADHD-H, and ADHD-C subtype) and 82 controls. EF domains were assessed with Digital span test (DST)/backward digital span (DBS), Stroop Color- Word Test (SCWT), the Wisconsin Card Sorting Test (WCST), and the CANTAB Assessment Battery.

Results: There were significant differences between ADHD and controls in all of the EF measure scores ($p < 0.05$), and effect sizes showed clear deficits of ADHD children. SCWT, BDS and WCST scores did not differ between the girls and boys in ADHD groups ($p > 0.05$). Participants with ASD were impaired in planning and flexibility abilities. The ASD + group showed compared to the ASD - group more problems in inhibitory performance but not in the working memory task. Nevertheless, ADHD-C subtype performed more poorly in score of the SCWT, BDS and WCST ($p < 0.05$). Regression analysis indicated that the SCWT scores were relevant risk factors of hyperactive index of Conners parents' symptom questionnaire (PSQ).

Conclusion: Our findings replicate previous results reporting impairment of ADHD children in executive functions. Overall the ADHD group, the main difference for subtypes was significant, and the hyperactive behavior of children with ADHD was associated with their impaired response inhibition.

Effect of Image-based Vascular Age on 10-year Integrated Stroke/Cardiovascular Risk Calculator (AECRS 1.0)

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Abstract

Motivation: Vascular age (VA) is an important biological marker of cardiovascular disease (CVD). VA of a person is the chronological age (CA) at same predicted risk with all risk factors in normal ranges. Recently, VA was derived as a linear regression model function of carotid intima-media thickness (cIMT). Similarly, 10-year AECRS 1.0 integrated calculator was a recently proposed using CA. The objective of this study is to investigate the effect of inclusion of VA on AECRS10 for risk stratification and benchmark against AECRS 1.0 when using CA as input on a diabetic cohort from Japan.

Methods: The system is a two-step process: (i) VA computation using cIMT. (ii) This VA was then funneled into AECRS10

calculator to predict the risk of stroke/CVD and benchmarked against the risk when CA was adapted. The performance of AECRS10 is measured by plotting the area-under-the-curve, when cIMT is used as a gold standard. Three types of risk classes (low, medium and high) were used for risk stratification.

Results: Left and right common carotid arteries (CCA) of 202 Japanese patients were retrospectively examined to obtain 404 ultrasound scans. The mean CA of the cohort was 69 ± years. When using AECRS10 with CA as input, resulted in an AUC of 0.84 ($p < 0.001$), but when using VA as input, resulted in an AUC of 0.87 ($p < 0.001$).

Conclusion: Image-based AECRS10 stroke/CVD risk calculator is more effective when using vascular age compared to chronological age as risk factor and shows a 4% improvement.

Keywords: Cardiovascular disease, Stroke, risk assessment, Chronological age, Vascular age, Carotid intima-media thickness, AECRS10 risk calculator

Inhibition of Calcium/Calmodulin-Dependent Protein Kinase Kinase β is Detrimental in Hypoxia- Ischemia Neonatal Brain Injury

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Abstract

Neonatal hypoxia-ischemia (HI) is a major cause of death and disability in neonates. HI leads to a dramatic rise of intracellular calcium levels, which was originally thought to be detrimental in the brain damage. However, it has been increasingly recognized that calcium signaling may also play a protective role after injury, by triggering neuroprotective pathways. Calcium/calmodulin-dependent protein kinase kinase β (CaMKK β) is a major kinase activated by elevated levels of intracellular calcium. Here we evaluated the functional role of CaMKK β in neonatal mice after HI in both acute and chronic survival experiments. Postnatal day ten wild-type (WT) and CaMKK β knockout (KO) mouse male pups were subjected to hypoxia-ischemia injury. STO-609, a CaMKK inhibitor, was administered intraperitoneally after HI in WT mice. CaMKK β KO mice had lager infarct volume than WT mice and STO-609 increased the infarct volume in WT mice after HI. In chronic survival experiments, WT mice were treated with STO-609 showed increased tissue loss in the ipsilateral hemisphere three weeks after HI. Furthermore, when compared with vehicle treated mice, they showed poorer functional recovery, as measured by the wire hang test and corner test. Loss of blood-brain barrier proteins, a reduction in survival protein (Bcl-2), and an increase in pro-apoptotic protein Bax were also seen after HI with CaMKK β inhibition. In conclusion, inhibition of CaMKK β exacerbated neonatal hypoxia-ischemia injury in mice. Our data suggests that enhancing CaMKK signaling could be a potential target for the treatment of hypoxic-ischemic brain injury.

Effects of Acupuncture and PC Assisted Cognitive Training for Post Stroke Cognitive Disorders: Experiences from Multicenter Pilot Study in Middle Europe and China

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Abstract

Background: Stroke is one of the leading causes of death in Western countries as in China. It is also the most important cause of adult disability and dependency upon care. Stroke survivors therefore need specific and multidisciplinary rehabilitation services to recover independency in ADL and capability to participate in familiar, vocational, and social life.

Objectives: Improving relearning conditions of the lesioned brain is a very import fact that all the multidisciplinary approaches in stroke rehabilitation will succeed. Can acupuncture be an intervention to raise relearning potentials in the brain, either for cognitive functions and/or for motor and coordination functions?

Methods: In stroke patients with cognitive dysfunction, mainly attentional deficits, we performed a three-armed RCT (pilot study) using acupuncture, PC assisted cognitive training, or both in three centers (two in Middle Europe (Germany and Switzerland), one in China). All patients had been examined before and after 3 weeks of therapeutic interventions by TAP (Test for Attentional Performance) as primary outcome criterion, by TMT (Trail Marketing Test), NIHSS, MBI (Modified Barthel Index), and EQ-5D (EuroQol Questionnaire) as secondary outcomes. MoCA (Montreal Cognitive Assessment) sub modalities defined inclusion and exclusion criteria. All local academic Ethic Committees approved the study.

Results: 54 patients could be included. No drop out happened, All patients showed functional improvements, with no

significant difference between the three therapeutic modalities could be proven. But in subsample analysis, we saw some differences. The European patients had some better improvements in the PC-training and the combined groups. The Chinese patients showed more functional gain in the acupuncture and the combined subgroup. Best effects revealed in the combined group.

Conclusion: Acupuncture and PC-assisted training combined seemed to be the best condition for cognitive relearning. But, there might be a cultural predisposition for PC-assisted training in Western Europe patients, and for acupuncture in Chinese patients, when performing this therapeutic interventions alone. A similar study comparing mirror therapy and acupuncture has been started.

The Characteristic and Treatment of Variant Superior Sagittal Sinus Dural Arteriovenous Fistula

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Abstract

Variant superior sagittal sinus dural arteriovenous fistula (DAVF) is very rare and special entity. Aggressive symptoms (ICH and NHND) occurred in 70.4% cases. Cases with venous aneurysms (75%) have higher presentation of aggressive symptoms than those without (68%). Variant SSS DAVFs frequently locate in the middle third of SSS (61.5%) and drained eventually to SSS at a site with a distance from the fistula (70.6%). All variant SSS DAVFs should be treated with proper strategies. Except the supply arteries, these aggressive anatomic factors, such as direct CVD, normal vein drainage, deep vein drainage, possible presentation of venous aneurysm, and even outflow restriction, should also be taken into account to tailor a suitable treatment. Despite the aggressive characteristic of variant SSS DAVFs, a good outcome can be achieved in most cases if a proper treatment is selected. In addition, the disappearance of venous aneurysm of DAVFs after complete obliteration may happen dramatically.

T-lymphocyte Subsets as a Predictive Biomarker for Stroke-associated Pneumonia

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Abstract

The aim of this study was to facilitate the clinical treatment and prognosis of stroke-associated pneumonia (SAP) by examining changes in T-lymphocyte subsets. Stroke patients admitted in Suzhou Hospital between 2014 and 2016 participated in the study. Patients were divided into a pneumonia group (50 patients) and a non-pneumonia group (254 patients) based on a diagnosis of pneumonia. Information regarding risk factors for ischemic stroke was collected from all patients using a questionnaire. Compared with non-SAP patients, SAP patients were older, dysphagic, smokers, had higher NIH stroke scale (NIHSS) scores and neutrophil: lymphocyte ratio, had higher leukocyte, neutrophil, and CD8 levels, had lower CD3, CD4, and lymphocyte levels, and had a lower CD4:CD8 ratio. Patients with a higher NIHSS score had higher CD8 levels, lower CD3 and CD4 levels, and a lower CD4:CD8 ratio. No significant differences in T-lymphocyte subsets were found between the left and right cerebral hemispheres. After adjusting for other variables, smoking, dysphagia, NIHSS score, and CD4:CD8 ratio were positively associated with SAP. The areas under the receiver operating characteristic curve for dysphagia, NIHSS score, CD4:CD8 ratio, CD4:CD8 ratio + NIHSS score, and Dysphagia + CD4:CD8 ratio + NIHSS score were 0.583 (95% CI: 0.490-0.675), 0.791 (95% CI: 0.724-0.859), 0.676 (95% CI: 0.593-0.759), 0.846 (95% CI: 0.790-0.902), and 0.867 (95% CI: 0.815-0.918), respectively. A few T-lymphocyte subsets may increase susceptibility to pneumonia after acute ischemic stroke. Thus, the detection of T-lymphocyte subsets may predict the risk of SAP in such patients.

Keywords: T-lymphocyte, acute ischemic stroke, pneumonia, predictive biomarker

Mirror Therapy for Motor Function of the Upper Extremity in Patients with Stroke: A Meta-analysis

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Abstract

Objective: To evaluate the mean treatment effect of mirror therapy on motor function of the upper extremity in patients with stroke.

Method: Electronic databases, including the Cochrane Library, PubMed, MEDLINE, Embase and CNKI, were searched for relevant studies published in English between 1 January 2007 and 22 June 2017. Randomized controlled trials and pilot randomized controlled trials that compared mirror therapy/mirror box therapy with other rehabilitation approaches were selected. Two authors independently evaluated the searched studies based on the inclusion/exclusion criteria and appraised the quality of included studies according to the criteria of the updated version 5.1.0 of the Cochrane Handbook for Systematic Review of Interventions.

Results: Eleven trials, with a total of 347 patients, were included in the meta-analysis. A moderate effect of mirror therapy (standardized mean difference 0.51, 95% confidence interval (CI) 0.29, 0.73) on motor function of the upper extremity was found. However, a high degree of heterogeneity ($\chi 2$ = 25.65, P = 0.004; I2 = 61%) was observed. The heterogeneity decreased a great deal ($\chi 2$ = 6.26, P = 0.62; I2 = 0%) after 2 trials were excluded though sensitivity analysis.

Conclusion: Although the included studies had high heterogeneity, meta-analysis provided some evidence that mirror therapy may significantly improve motor function of the upper limb in patients with stroke. Further well-designed studies are needed.

Assessing the Quality of Life in Patients with Multiple Sclerosis in Kuwait: A Cross Sectional Study

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Abstract

Majority of individuals with multiple sclerosis (MS) experience disturbance in their life rhythm due to the disease progress. The main objective of this paper was to assess the level and the determinants of quality of life (QOL) amongst patients with multiple sclerosis (MS). A cross-sectional study was conducted among a convenience sample of 200 adult MS patients. Inclusion criteria: MS diagnosis for at least one year, and aged 21+ years. However, exclusion criteria were: having other neurological diseases, serious cardiovascular, orthopedic or other disability precluding participation. Self-administered questionnaire employed MSQOL-54 with two outcomes: Physical Health Composite (PHC) and mental health composite (MHC). Satisfaction with Daily Occupation scale was adopted through face to face interviews. The participants' mean age was almost 35.0 ± 9.8 years and 68% were females. The median of PHC score was 48.9/100, MHC score was 53.4/100, SDO performance was 10.0/14.0 and satisfaction scores was 51.0/70.0. Multivariate analysis revealed that unemployment was a principal determinant of poor: PHC (OR = 3.5,CI:1.36-8.95), performance (OR = 3.0,CI:1.51-5.83), and satisfaction (OR = 3.0,CI:1.44-6.25), while low family income was a predictor for poor MHC (OR = 3.6,CI:1.31-10.00). For the clinical features, low endurance was a significant determinant of poor: PHC (OR = 5.0,CI:1.07-23.34), MHC (OR = 11.0,CI: 2.17-55.53), and satisfaction (OR = 3.2,CI:1.15-9.01). Sensory, cognitive and visual problems were predictors of poor PHC, performance and satisfaction respectively. Level of patient satisfaction was indirectly associated with PHC and MHC. It was concluded that MS patients experienced a modest level of physical and mental components of QOL. Assessment of QOL is suggested to be comprised regularly in medical settings.

DNA Repair Genes and Trace Elements Associated with Oxidative Stress in Multiple Sclerosis

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Abstract

Multiple Sclerosis (MS) is a neurodegenerative disease that demyelinating, autoimmune, and inflammatory that can cause

neurological symptoms with disability. The pathogenesis of MS disease is not fully known. However, it was thought that environmental and genetic factors play a role together in the pathogenesis of the disease. Oxidative stress (OS), known as the main pathological cause of neurodegeneration, is caused by environmental factors. OS occurs as a result of imbalanced metabolism and excess reactive oxygen species (ROS). ROS toxicity occurs when macromolecules such as DNA, which contribute to inflammation and tissue injury are directly damaged. Cells are protected from OS by antioxidant defense and multiple DNA repair systems. OS is thought to play a role in the pathogenesis of MS disease. As a result of polymorphisms occurring in DNA repair genes, DNA repair capacity can be reduced. These single nucleotide gene polymorphisms can cause protective or harmful effects in neurodegenerative diseases and many other diseases. The trace elements believed to be associated with the OS are present at low concentrations in the body and these elements play important roles in various metabolic events, development of the nervous system, myelination of the nerve fibers, and neural stimulation In neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Amyotropic Lateral Sclerosis and MS, abnormalities has been reported in the body's trace elements. The purpose of this study is to examine the roles of DNA repair genes and trace elements that are thought to be related to OS in MS disease.

Investigation of the Relationship between Metalloproteinase-2 T1306C, Interleukin-18 (-607C/A) Gene Variations and Serum Trace Elements in Development of Parkinson's disease

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Abstract

Parkinson's disease is a common neurodegenerative disease characterized by resting tremor, bradykinesia, muscle stiffness, postural reflex disorders, psychiatric symptoms and aggregation of alpha-synuclein protein. Many genes are known to be effective in Parkinson's disease, where environmental and genetic factors play an important role. One of the genetic factors, metalloproteinases (MMPs) play an important role in the complex pathophysiology of Parkinson's disease. One of the variations in the MMP-2 T1306C gene results in a decrease in MMP-2 expression and enzymatic activity. Interleukin-18 (IL-18) gene that is another genetic factor is localized on chromosome 11q22.2-q22.3. It is thought that the IL-18 (-607C/A) gene variation occurred in this gene may be effective on binding of transcription factors and consequently may be modulate IL-18 mRNA expression. This gene variation is also characterized by cytosine/adenine base translocation in the -607.position of the gene. IL-18 (-607C/A) gene variation has been reported to be associated with neurodegenerative disorders such as Parkinson's and Alzheimer's disease. As another factor, iron from trace elements plays an important role in the pathophysiology of neurodegenerative diseases as a catalyst for free radical formation. An imbalance in copper homeostasis, which plays a functional role in many enzymes required for redox reactions, results in an increase in free radical production associated with neurodegenerative diseases. The aim of this study is to investigate the relationship between MMP-2 T1306C, IL-18 (-607C/A) gene variations and serum trace elements in the development of Parkinson's disease.

Keywords: Parkinson hastalığı, MMP-2 T1306C gene variation, IL-18 (-607C/A) gene variation, trace elements

CRISPR/Cas-9 Approach for the Treatment of Huntington's Disease in Mouse and Human Cell Lines

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Abstract

Huntington's disease (HD), an autosomal dominant disease, is a neurodegenerative disorder and is caused by a CAG repeat expansion in the gene encoding the polyglutamine-expanded mutant Huntington protein (mHTT). HD is a disorder characterized by loss of progressive GABAergic medium spiny neurons in the forebrain striatum. mHTT expression is common in the brain, progressive atrophy occurs as a result of affecting disproportionately of striatum. Transcription activator-like effector nuclease and CRISPR/cas 9 systems, such as zinc finger nucleases, are known as recent advances in genome editing technologies, and the establishment of isogenic control of human induced pluripotent stem cells (hiPSCs) is provided by

these developments. There are several studies that indicative the continuous correction of HD hiPSC cell lines in human and mouse through the use of these technologies. It has been proven that HD hiPSCs are corrected, using isogenic control hiPSCs, through a CRISPR/cas 9 system and a cut-and-paste mechanism, which a piggyBac (PB) transposon-based selection system, capable of efficiently switching between vectors and chromosomes. Evaluation of the corrected lines in the studies showed that in isogenic controls, that are rescued of phenotypic abnormalities and gene expression changes in HD hiPSC-derived neural cells. Trinucleotide repeat disorders, such as HD, are improved by restoring cas 9 specific gRNA and normal exogenous DNA. The aim of this study is to give general information about the mechanism of HD, which is a neurodegenerative disorder and to explain the role of CRISPR/cas 9 system in the treatment of HD.

Receptor Based Applications and Migraine: Customizing Treatment Using a Neuroplastic Approach

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Abstract

Migraine pathophysiology has been, and continues to be, a hotly debated topic that typically lands between neurological and vascular pathologies. Thanks to emerging research, we now know that migraine is neurological disorder with many concomitant physiological changes, including vascular ones. Combing the neurological understanding of migraine and the emerging field of neuroplasticity and receptor based therapies, we will discuss new way to think about migraine prevention and the way in which migraine is primarily addressed. Many new neurostimulation devices are hitting the market with varied, but promising, results. Fields such as nutrition, hormones, and musculoskeletal treatments are continuing to have mounting research as to their efficacy and usefulness for migraine. However, if all of these avenues show promise for helping with migraine, which ones do we decide to use as primary therapies? It is becoming more and more clear that it isn't what therapy or treatment is most effective for migraine, but what combinations of therapies are most appropriate for each individual patient, and how do we make that determination.

Migraine with Aura and Photosensitive Epilepsy: Common Cognitive Behavioral and Linked Neurophysiological Traits

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Abstract

Background: Migraine with aura (MWA) and Photosensitive Epilepsy (PSE) have been related due to their common visual hyperexcitability [1]. Although they are two different neurological diseases with different pathophysiology, a possible common underlying mechanism, still not fully understood, has been suggested [2]. Moreover a deficit of neural habituation to sensorial stimulation has been found in both diseases [3, 4]. On the other hand our previous studies highlighted a link between a specific cognitive behavior i.e. analytic cognitive style and both Migraine and Epilepsy [4, 5].

Analytic cognitive style has also been linked per se to lack of visual evoked potential habituation [4]. We aimed at evaluating information processing style in MWA patients in comparison to PSE subjects and healthy controls. We focused on the Visual/Auditory and the Global/Analytic dimensions of cognitive style.

Materials and Methods: We enrolled 25 MWA patients comparing them to 25 PSE subjects and healthy controls. All subjects underwent cognitive questionnaires for Analytic/Global and Visual/Auditory dimensions of cognitive style [5].

Results: Analytic scores were higher in both MWA and PSE groups compared to controls. Both auditory and visual scores were also significantly higher in patient groups respect to healthy subjects. Anova test: $p < 0.05$.

Conclusions: We highlight a common information processing style linked to deficit of habituation in MWA and PSE. This style i.e. visual and auditory analytic cognitive style and its associated neurophysiological correlate, i.e. lack of visual potential habituation [4], might suggest some pathophysiological relationship between these two disorders that deserves further investigations.

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A Double-blind Randomized Control Trial of Vagus Nerve Stimulation for Pediatric Patients with Intractable Epilepsy Between 3-6 Years of Age

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Abstract

Background: Preliminary evidence suggests that VNS treatment is effective for seizure reduction and mental development in young patients between 3-6 years of age that suffer from intractable epilepsy. However, robust clinical evidence for quantifying the difference of the efficacy and safety of VNS treatment in this specific patient population has yet to be reported.

Method: A two-armed, multi-center, randomized, double-blind, prospective trial (NCT03062514, clinicaltrials.gov) was carried out. Pediatric participants aged between 3-6 years old with intractable epilepsy were recruited and randomly assigned to experimental and control groups with a 1:1 allocation. Participants in the experimental group received electrical stimulation over 24 weeks under standard stimulation parameters. Participants in the control group didn't receive any stimulation during the 12-week double-blind period. The guardians of the participants were required to keep a detailed diary to record seizure activity. Outcome assessments including seizure frequency, Gesell mental developmental scores and adverse events were collected at baseline, 6, 12, 18 and/or 24 weeks after electrical stimulation is initiated.

Results: At the end of this trial, 44.2% participants are shown to be responsive for VNS (seizures/m decreased over 50%). Change rate of seizure frequency compared to preoperation in experimental group is lower than control group (-31.3 ± 56.8 vs -16.7 ± 56.7). Language improves in both two groups after VNS. No serious adverse event related to VNS is found. This trial supports the VNS treatment for 3 to 6 year old patients with intractable epilepsy.

Keywords: Pediatric intractable epilepsy, Vagus nerve stimulation, Efficacy, Safety

Poster Presentations

Decision Tree, Discriminant and Factor Analysis of Biogenic Amines in Diagnosis of Dystonia

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Abstract

Dystonia is the debilitating movement disorder of central nervous system, often inherited, appearing as involuntary movements, that occur due to deficiency or excess of neurotransmitters. The penetrance of dystonia is 30%, which means that inherited dystonia is manifested only in 30% of sibs carrying the mutating gene, while the rest suffer from latent forms, so called «forms frustes» of this disorder. Until now only few mutations responsible for dystonia have been unveiled, but we expect to exist up to 100 such mutations. Unless we uncover all mutations, responsible for dystonia, we require reliable test for diagnosis of latent forms of dystonia. The objective of this research was to elaborate discrimination of dystonia on the basis of biogenic amines exchange peculiarities. It was the observational case – control study. The control group was randomly chosen from those patients, who were checked for neuroglial tumors. We checked catecholamines and serotonin metabolites in plasma and urine of 12 dystonia patient's case group by means of chromatography method and compared the results obtained from these two groups. Then we carried comparison of these two groups by means of the decision tree method and discriminant analysis, and

we revealed their high and almost equal efficacy. The factor analysis also revealed its usefulness in the diagnosis of dystonia. The main conclusion is, that all these 3 statistical methods are effective, and comprising 5–hydroxytryptophan, turned to be the most sensitive indicator of either detecting diagnosis of dystonia or its exclusion.

The Role of Transient Receptor Potential Vanilloid Receptor 1 (TRPV1) and Peroxisome Proliferator-activated Receptors-alpha (pparα) in Mediating the Anti-nociceptive Effects of Palmitoylethanolamine in Rats

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Abstract

Objectives: Palmitoylethanolamine (PEA) is a ligand at peroxisome proliferator-activated receptors-alpha (PPARα), a nuclear receptor which has anti-inflammatory effects. Herein, Complete Freund's Adjuvant (CFA)-induced inflammatory pain model in rats and *in vitro* calcium imaging studies were used to evaluate the mechanisms that underlie the anti-nociceptive effects of PEA.

Methods: Adult male Sprague Dawley rats (180-250 g) received subcutaneous injections of CFA (0.1 ml) or saline into the plantar surface of the left hindpaw. Von Frey filaments were used to determine the paw withdrawal threshold (PWT). PEA (50 µg), WY14643 (50 µg, a selective PPARα agonist) were injected into the plantar surface of the left hindpaw at day 7 post-CFA injection, then the behavioral tests were repeated 6 hours post-drug administration. Rats were killed and whole dorsal root ganglia (DRG) were removed from all spinal levels. DRG neurons were dissected and prepared for calcium imaging. Neurons were loaded with the calcium sensitive ratiometric dye Fura 2AM. Changes in $[Ca^{2+}]i$ were measured as ratios of peak florescence at excitation wavelengths of 340 nm and 380 nm and expressed as a percentage of the KCl (60 mM) response.

Results: Both PEA and WY14643 significantly restored PWT in a PPARα-dependent fashion ($P < 0.01$). 15 nM capsaicin produced 63.9 ± 13.4 % of KCl response. Pre-incubation of DRG neurons with PEA 6 hours prior to stimulation with capsaicin, significantly reduce capsaicin-evoked calcium responses (42.9 ± 6.4 % of KCl response, $n = 54$, $P < 0.001$).

Conclusions: Modulating TRPV1 activity could provide the mechanism that underlies PEA anti-nociceptive effects observed *in vivo*.

Investigating the Role of Peripheral Mu-opioid Receptors in Pain Signaling Under Normal, Inflammatory, and Neuropathic States

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Abstract

As the mainstay of pain management, opioid-induced mechanisms remain a central focus for researchers and clinicians. Despite their profound ability to alleviate pain, clinical use of opioids is impeded by a myriad of side effects, secondary to their CNS actions. Adverse effects include respiratory depression, constipation, tolerance and addiction and are mediated by central opioid receptors (ORs). Although central mechanisms have been thoroughly examined, research pertaining to peripheral ORs is limited. Now, with the potential of targeted therapies, studies are pivoting toward the systematic characterization of peripheral opioid mechanisms. Studies performed at Johns Hopkins suggest opioids are effective in managing neuropathic pain. This finding was further developed with particular attention given to peripheral opioid receptors – specifically the Mu subtype (MORs). These reports suggest agonistic activation of peripheral MORs effectively attenuates neuropathic pain. Presently, investigation into the role and characterization of peripheral MORs is being conducted with the use of a conditional knockout (MOR-Flox-/- Pirt-cre +/-) model. Examination of pain signaling and associated responses of these cKO are being conducted under various pathological states, including spared nerve injury and chemotherapy-induced peripheral neuropathy (CIPN). Additional research indicates synergistic inhibition of neuropathic pain employs peripheral cannabinoid and mu ORs. Accordingly, the role of peripheral CB-1 receptors and a potential association with MORs is being investigated using a peripheral CB-1 conditional knockout. MOR agonists and dual targeting of peripheral opioid and cannabinoid systems may have potential as anovel therapeutic approach for attenuating neuropathic pain, without the occurrence of centrally mediated, deleterious effects.

Interventional First Person Video Game Training Reduces Fall Risk in Parkinson's Disease by Improving Gait, Contrast Sensitivity, Visual Acuity and Cognition

Beau Billings*, Sonia Koul, Shane Sterling, Shani Peter, William Taber, Richard Wu, Karina Pique and Charles Maitland

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Abstract

Parkinson's disease (PD) is a complex disease with motoric signs, gait disturbance, loss of contrast sensitivity visual acuity (CSA), and cognitive decline. Dopamine producing neurons in multiple brain sites are disrupted by the accumulation of α-synuclein protein. Degeneration of affected cells in these areas contribute to postural instability and increased fall risk. Despite pharmacologic interventions fall frequency increases as the disease progresses. Video gaming (VG) intervention seems to be effective in supplementing treatment of symptoms of neurodegenerative diseases. 23 PD patients, stage 2 to 4, H&Y randomized into three groups: first person active VG viewing (N = 8), third person passive VG, (N = 6), no intervention (N = 9). Pre and post intervention testing included: UPDRS, Montreal Cognitive Assessment tool, Freiberg CSA, GAITrite walking measuring functional ambulatory performance (FAP) score (compilation of walking functions that produce a fall-risk profile). The interventional VG was a first-person shooter that participants played three times a week for four weeks versus the passive VG. First-person VG players' FAP (0-100 scaling) scores improved by an average of 2.2 points compared to non-players ($p = 0.03$). Passive VG players also improved but not to a statistical significance. First-person players showed improved scores in UPDRS, CSA, and cognitive scoring but not to statistical significance. Our study suggests that reduced falls' risk following gaming is the result of multimodal improvements. It seems plausible that increased attention, combined with visual training results in better performance. Future studies are underway to determine the duration and sustainability of the effect of interventional VG therapy.

Argentine Tango Reduces Fall Risk in Parkinson's Patients

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Abstract

Objective: To objectively measure the effect of Argentine Tango on individuals with Parkinson's disease and investigate fall risk and quality of life as a result of enhanced motor performance.

Background: Parkinson's disease (PD) is a neurological disorder associated with motor-related signs: tremor, impaired balance, stiffness, bradykinesia. Previous studies have subjectively measured improvement in motor abilities using the Argentine Tango as a therapeutic intervention.

Design/Methods: 20 individuals were evaluated before and after Argentine Tango. 11 individuals (6 PD, 5 unaffected) participated in Tango lessons and 9 PD did not participate in lessons. PD individuals were scored using the United Rating Scale for Parkinson's (UPDRS) along with the Parkinson's disease Questionnaire (PDQ-39), a Freezing of Gait Questionnaire (FOGQ), and gait performance analyzed using GAITRite walking platform, which recorded a pre and post Functional Ambulation Performance (FAP) Score. Hierarchical Linear Modeling (HLM) was used to explore the statistical properties of the resulting FAP scores.

Results: A significant interaction was found between time (post) and intervention group ($t = 2.66$; $p < .001$), meaning that the intervention group had a significant reduction in fall risk when compared to the control group, which showed no statistical improvement (UPDRS, PDQ-39, and FOGQ scores overall showed no statistical significance).

Conclusions: Motor deficits in individuals with Parkinson's disease result in falls, freezing, and degraded quality of life. In this study, Argentine Tango improved gait performance and reduced fall risk. Issues of timing, frequency of intervention, and sustainability are currently under investigation with a larger sample size.

The Analysis of Disease-modifying Therapy Prescriptions in Different Type of Clinical Course of Multiple Sclerosis

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Abstract

Aggravation of Multiple sclerosis (MS) is lead to stable neurological deficits, so when focusing on preventive therapy we improve the quality of life and prognosis. The aim of our research was to investigate the frequency of disease-modifying therapy prescriptions by physician to evaluate their adherence to follow modern guidelines in MS management.

Material and Methods: It was randomized study of 50 case histories of MS patients. There were 9 (18 %) patients with MS onset, 33 (66 %) with relapsing-remitting type (RRMS), no one with primary-progressive type (PPMS), and 8 (16 %) with secondary progressive type (SPMS) of course.

Results: Among MS onset 8 (88.88 %) patients received the first line therapy (glucocorticoids, plasmapheresis or immune globulin), 2 (22.22 %) the second line therapy (alpha or beta-interferon, or Glatiramer acetate), and no one the third line therapy (Natalizumab, Fingolimod, Mitoxantrone), which is according to guidelines.

Patients with RRMS have been prescribed the first line therapy in 28 (84.85 %) cases, the second in 17 (51.51 %), and the third line in 1 (3.03 %) cases. We expected prescriptions of disease-modifying therapy – the first and the second group – for all the RRMS patients.

Patients with SPMS received the first line therapy in 7 (87.50 %) cases, the second in 7 (87.50 %), and the third line in 5 (62.50 %) cases. Thus, disease-modifying treatment has been prescribed in almost all the necessary SPMS cases.

Conclusion: The disease-modifying therapy is poorly prescribed to RRMS patients, but not for SPMS ones.

Readmission of Transient Ischemic Attacks in the United States

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Abstract

Transient ischemia is a temporary loss of neurological function lasting less than 24-hours, associated with obstruction of vasculature that perfuses the brain. Our study analyzes changes in hospital readmissions for patients diagnosed with transient ischemia between 2009-2014.

Using the Healthcare Cost and Utilization Project database, we performed a retrospective cohort study to determine the changes in 7-day and 30-day readmissions for transient ischemic attacks between 2009-2014.

We found that readmissions for patients diagnosed with transient ischemia decreased from 2009 to 2014 in the 7-day and 30-day categories ($p < .001$). Between 2009-2014, total readmissions decreased from 6,438 (4%) in 2009 to 4,476 (3.6%) in 2014 ($p < 0.001$) in the 7-day category. In the 30-day demographic, readmissions dropped from 16,787 (10.4%) in 2009 to 11,567 (9.3%) in 2014 ($p < 0.001$). We also determined that the overall trend of the cost of stay for readmission increased from 2009 to 2014 in both the 7-day and 30-day categories ($p < 001$). For 7-day readmissions, we saw an increase from $9,294 in 2009 to $10,852 in 2014. The mean cost of stay in 30-day readmissions increased from $10,264 in 2009 to $11,267 in 2014.

Readmission rates within 7 and 30 days of initial discharge for patients diagnosed with transient ischemia decreased from 2009 to 2014, while the mean cost of stay for readmission increased. Further research is warranted to continue the improvements made in transient ischemic attack readmission statistics and to better isolate the factors driving the rising cost of readmission treatment.

Dural Venous Sinus Thrombosis Presenting as Syncope

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Abstract

Introduction: Syncope is a frequently encountered complaint that normally resolves with supportive therapy. While neurocardiogenic syncope is the most common, neurologic syncope needs to be considered and ruled out early to determine if acute medical management is warranted.

Case Presentation: An 86-year-old woman with hypertension and Alzheimer's Dementia was admitted to inpatient hospital care following a sudden collapse with loss of consciousness after an episode of large volume diarrhea. Her vital signs were stable with an examination significant for orientation to self, mild aphasia, and 3/5 bilateral upper extremity strength. Her initial laboratory was positive for *Clostridium difficile*, but was otherwise normal. Her CT-head was non-significant while

a continuous EEG revealing slowing of the posterior dominant rhythm at 8Hz without no seizures. The patient was initially diagnosed with syncope from volume depletion and managed for her diarrhea. Following 1 day of non-improvement of her symptoms, a brain MRI was done revealing a filling defect in her left transverse sinus while a brain MRA confirmed a thrombosis of the left transverse sinus. The patient was immediately started on anticoagulation and levetiracetam for seizure prophylaxis before eventual discharge to rehabilitation and subsequent outpatient follow-up.

Discussion: Sinus venous thrombosis is an uncommon cause of syncope in the elderly with an annual incidence of 0.22-1.57 per 100,000. Syncope in this population is likely contributed by thrombosis causing decreased cerebral perfusion pressure and increased ICP. While an uncommon cause of syncope in adults, venous sinus thrombosis can be treated medically if detected and recognized early.

Analysis of the Efficiency of Antiepileptic Drugs in the Treatment of Infantille Spamas and Focal Epilepsy Associated with Tuberous Sclerosis Complex

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Abstract

Adequate selection of the first antiepileptic drug (AED) is an indispensable condition for the successful treatment of epilepsy. Objective: to make a comparative evaluation of the effectiveness of various AEDs in the treatment of epilepsy in patients with TC.

Materials and Methods: retrospective analysis of patients hospitalized with epilepsy and TSC for the last 2 years. Efficacy analysis was conducted in 134 patients (91/67, 9% with FS and 43/32, 1% with IS). Efficacy was estimated as the cessation of epileptic seizures for 6 months. Absence of seizures for 1 year or more and decrease in the number of seizures.

Results: Low efficiency of AEDs in starting monotherapy was noted -the cessation of seizures within 6 months on any AED was only 27.5% (25/91) with FS, with IC - 6/43 (13.9%). Remission on any first AED was observed only in 13.2% (12/91) and 3/43 (6.9%), respectively. VGB as the first monotherapy proved to be effective in 5/6 patients with FS and in 4/6 patients with IS. The introduction of the second drug added another 13.3% and 38.6% of patients with cessation of seizures, the third – 7.3% and 7.7% in FS and IS, respectively. The efficiency of VGB was reduced if it was used not as the first, but as the second and third. The percentage of unsuccessful treatment (including combined therapy) is estimated as 51.5% and 47.8% of patients with FS and IS, respectively.

Conclusion: Epilepsy associated with TSC is less sensitive to AEDs. VGB as the first monotherapy prov to be effective.

The Yellow Scale is Superior to the Gray Scale for Detecting Acute Ischemic Stroke on a Monitor Display in Computed Tomography

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Abstract

Purpose: The purpose of this study was to compare the efficacy of the color scale with regard to focal detection for CT in acute ischemic stroke.

Materials and Methods: Brain CT images of 19 patients diagnosed with acute stroke, based on magnetic resonance (MR) diffusion-weighted images obtained within an onset of 24 hours, and the images of five normal patients were displayed in each color look-up table (LUT) on a monitor. The detection of acute stroke was compared among 15 radiologists. The images were compared in gray, green, yellow, red, and blue scales of LUTs. The observers recorded acute ischemic stroke as "present" or "absent." They also located the position of the stroke lesion and described the degree of their conviction as to whether a lesion existed. Detection was evaluated by receiver operating characteristic (ROC) analysis. The area under the ROC curves (AUCs) was compared. In addition, reduced fatigue and the ease in image observation were compared.

Results: Compared to the other scales, the yellow scale had a significantly higher AUC, which indicated that this scale

allowed better detection of acute ischemic stroke. The gray scale produced the least fatigue in image observation.

Conclusion: The detection of acute ischemic stroke is improved by changing the display monitor from the gray scale to the yellow scale. From the perspective of color psychology, yellow is associated with higher arousal, cheerfulness, confidence, creativity, and excitement. Therefore, the yellow scale may be suitable for a medical imaging display.

Multiple Epidural Fibrin Glue Patches in a Patient with Spontaneous Intracranial Hypotension

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Abstract

Spontaneous intracranial hypotension (SIH) is a condition caused by spontaneous leakage of cerebrospinal fluid, with postural headache as the primary symptom. Orthostatic headache caused by SIH is often not resolved by conservative management. We performed 15 epidural blood patch treatments in a 43-year-old female patient; however, they were only transiently effective. To improve the patient's SIH and orthostatic headache, epidural fibrin glue patch treatment was attempted. Fibrin glue is a substance that can act as a bio-friendly adhesive by facilitating the coagulation cascade. In our case, 3 epidural fibrin glue patch treatments were performed and the symptoms completely resolved. In this report, we also discuss the possible use of epidural fibrin glue patches in the clinical setting.

Investigating Codon Bias and the Production and Processing of Dopamine in a Mouse Model of Familial Dysautonomia

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Abstract

Familial Dysautonomia (FD) is a severe neurological disease caused by mutation in ELP1, an essential subunit of the Elongator complex. FD is characterized by a dramatic reduction in the number of peripheral nerves. Perhaps the most disabling feature of FD is the severe nausea and vomiting attacks that occur during autonomic crises. These attacks are typically brought on by stress and are associated with a marked increase in circulating dopamine (DA) levels. The predominant view regarding the pathways that go awry to mediate this increase asserts that elevated levels of tyrosine hydroxylase (TH) in sympathetic nerve terminals overproduce DA during stress induced sympathetic activation to the extent that its production exceeds its conversion to norepinephrine (NE) with excess DA entering the blood stream. Elevated levels of TH are thought to arise as a compensatory mechanism for the depleted number of peripheral neurons in the disease. Given more recent studies demonstrating a function for ELP1 and Elongator in the translation of codon-biased genes, we wanted to revisit this question in the context of codon bias. Analyses of both sympathetic neurons and chromaffin cells in the adrenal medulla of Wnt1-Cre; Elp1 LoxP/LoxP fetuses demonstrate that TH levels are significantly elevated in the adrenal medulla and we posit that this increase is in part due to the AG-biased nature of the TH gene. Furthermore, we show that conversion of DA to NE may also be compromised in FD as a result of altered levels of soluble and membrane-bound forms of dopamine beta hydroxylase.

Generation of a High Throughput Screening System for Small Molecules that Can Rescue Axonopathy

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Abstract

Familial Dysautonomia (FD) is a neurological disease with both developmental and degenerative aspects including axonopathy of peripheral nerves. FD results from a point mutation in the ELP1 gene, causing reduced levels of the corresponding protein that functions in assembling a highly conserved, six-subunit complex known as Elongator. Elongator catalyzes the chemical modification of transfer RNAs needed for the translation of codon-biased transcripts that preferentially use AA- or AG-ending codons. Like FD, axonopathies are a common feature of many other neurological diseases including amyotrophic

lateral sclerosis (ALS), and Alzheimer's. Despite their prevalence in neurodegenerative diseases, the discovery of therapeutics for treating axonopathies has been impeded by the difficult and costly nature of culturing primary neurons. Therefore, an experimental model that can withstand the manipulation required for a high throughput small molecule screen is essential for drug discovery. *Candida albicans* shows a pronounced polarized growth phenotype that is distinct among other yeasts. To determine whether this phenotype is dependent on Elongator, as is polarized growth in neurons, we made a *C. albicans* Elp1 knockout. Importantly, this knockout exhibits a severely compromised growth habit. Our long-term goal is to use this knockout to develop a high throughput screen for small molecules that can rescue normal polarized growth. Molecules that rescue in our yeast model system, will then be tested *in vitro* for the ability to rescue axon elongation in Elp1 deficient neurons.

A Real Page "Turner": A Look at Parsonage Turner Syndrome and Its Rare Diagnosis

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Abstract

Introduction: Parsonage Turner Syndrome (PTS) is a rare neurological condition involving the brachial plexus that presents with an abrupt onset of unilateral shoulder pain. The challenging part about PTS is its variable presentation, often times presenting similarly to other conditions. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), one such syndrome, is a demyelinating condition affecting the extremities. Due to PTS' diverse symptomology and lack of diagnostic imaging, both diseases need to be considered when evaluating a patient with neuropathy.

Case Description: We present a 48-year-old male with upper extremity pain and weakness for one year. The patient began experiencing pain in his left shoulder before noticing associated weakness in his left and right forearm within a few days. All imaging was negative for any conclusive diagnoses at the time, and the patient was discharged with oral steroids. The patient consulted many neurologists, however, did not receive a definitive diagnosis between PTS and CIDP, and thus, he presented to our clinic.

On physical exam, the patient exhibited atrophy of left hand musculature, with associated diminished strength and sensation in the left upper extremity. Wall push-ups demonstrated bilateral winging of the scapula. Based on his history, physical exam, and lack of evidence of other neurological disorders present on imaging studies, the patient was diagnosed with PTS.

Discussion: There is importance in discussing different presentations of PTS cases that aid physicians in efficiently diagnosing their patients. Creating conversation about PTS may motivate researchers to find concrete diagnostic modalities that definitively diagnose this rare syndrome.

Solitary Cerebral Metastasis from Transitional Cell Carcinoma of the Bladder

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Abstract

Introduction: Cerebral metastasis is the most common neurological neoplasia triggered by primary tumors such as lung and breast. Transitional cell carcinoma (TCC) of the bladder accounts for less than 1% of brain metastasis and few cases have been reported in literature. Here we describe a rare case of TCC presenting with signs of neurological impairment.

Case Description: A 75-year-old male with history of TCC presented to the ED with right upper extremity hemiparesis and dysarthria of 5 hours duration. He had undergone cystoscopy with resection of tumor 3 years prior followed by gemcitabine chemotherapy and combination radiotherapy/immunotherapy. CT imaging revealed a hyperdense 3.3 cm mass in the left frontoparietal region with internal hemorrhage measuring 1.4 cm and surrounding vasogenic edema. He was treated immediately with high dose corticosteroids and antiepileptics which did not result in improvement of symptoms. Metastatic workup which included contrast enhanced CT of chest, abdomen and pelvis revealed no evidence of local or metastatic recurrence. Due to rapid worsening of his status, respiratory failure and encephalopathy, family did not want to pursue additional treatment and decided on inpatient hospice.

Discussion: According to literature, CNS involvement of disseminated TCC varies from 0.6% - 8%, and bladder carcinoma accounts for 0.5% of all intracranial metastases. Incidence of CNS involvement without evidence of recurrence or disseminated disease is extremely uncommon. Aggressive multitherapeutic regimens, which include gemcitabine, have been favored for its penetration of the blood-brain barrier but even with its use disease may present years later with an unfavorable prognosis.

The Impact of Failed Reperfusion on the Clinical Outcomes of Patients Presenting with Low NIHSS Large Vessel Occlusion Stroke

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Abstract

Objective: To compare clinical outcomes of patients with successful and failed reperfusions during endovascular mechanical thrombectomy for low NIHSS large vessel occlusion stroke.

Methods: We conducted a retrospective analysis on all patients who underwent thrombectomy between January 2012 to May 2017 at the Gates Vascular Institute in Buffalo, NY. Thirty-one patients with a large vessel occlusion and NIHSS ≤ 6 were identified. These patients were divided into two groups, those who received successful (TICI 2b/3) recanalization and those with failed (TICI 0/2a). Demographic, procedural and outcome data was collected. Occurrence of vasospasm, thromboembolic complications, symptomatic hemorrhage, discharge NIHSS, hospital stay and outcome at 90 days were compared between the two groups.

Results: Of the 31 thrombectomies, 26 were successful while 5 failed. Of the successful patients, there were 7 incidences of vasospasm (27%), 3 symptomatic intracranial hemorrhages (12%), 4 hospital deaths (15%) and 20 favorable outcomes (mRS 0-2 at 90 days) (77%). In contrast, there were 0 vasospasms, 2 symptomatic intracranial hemorrhages (40%), 2 hospital deaths (40%) and only 2 favorable outcomes in the failed group (40%). Neither group had any thromboembolic complications. Median (IQR) discharge NIHSS was 2 (1-4.75) in the successful group compared to 3 (3-40) in the failed group. Differences between the two groups were not statistically significant.

Conclusion: Mild stroke patients with TICI 2b/3 reperfusion had better outcomes across the board. Mechanical thrombectomy may confer benefits upon mild stroke patients with large vessel occlusion; however, additional research is needed to validate these benefits.

Inhaling Fumes: A Rare Case of Nitrous Oxide-Induced Lichtheim's Disease Causing Acute Paralysis

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Abstract

Lichtheim's disease, also known as subacute combined degeneration, is a rare complication of vitamin B12 deficiency, resulting in posterior and lateral spinal cord demyelination. Patients present with gradual weakness, unstable gait, and paresthesia. This vitamin deficiency occurs due to decreased dietary intake, pernicious anemia, or low gastric pH, although a possible link between Lichtheim's disease and nitrous oxide exists due to its ability to inactivate vitamin B12. We present the case of a 56-year-old male with a history of alcoholic hepatitis, who presented with an acute onset of sudden paralysis affecting his lower extremities. His methylmalonic acid level was noted to be dangerously high, and MRI of the spinal cord showed degeneration of the posterior cord (Figure 1), allowing for diagnosis of Lichtheim's Disease. The patient admitted to recently working on a racecar with nitrous oxide exposure, which likely is the culprit of his acute presentation. He was immediately started on B12 supplementation which has shown some improvement in his symptoms. However, he has also developed Lehermitte's sign and burning dysesthesias, therefore the continuing damage of nitrous oxide will be intently monitored. Indeed, Lichtheim's disease can be seen with various presentations; however, most cases present with a gradual onset of symptoms. The uniqueness of this case is its acute presentation. With only limited exposure to nitrous oxide, the patient experienced an abrupt paralysis in his extremities, unusual for patients with this condition. This case exposes the toxicity behind nitrous oxide and urges individuals to use them with caution.

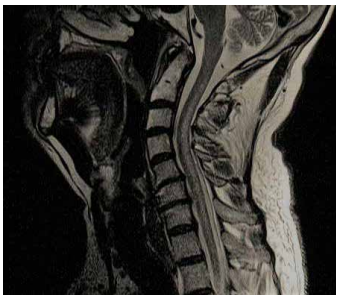

Figure 1: MRI changes signifying demyelination of the posterior cord.

Pre-procedural Factors Predictive of Outcome in Octogenarian Acute Ischemic Stroke Patients Receiving Mechanical Thrombectomy

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Abstract

Objective: Here we aimed to identify risk factors predictive of favorable outcomes in octogenarian stroke patients who received mechanical thrombectomy intervention.

Methods: A retrospective analysis was conducted on all consecutive patients who underwent Mechanical thrombectomy between January 2012 to May 2017. Eighty-eight octogenarian patients with large vessel occlusion were identified. These patients were divided into two groups, those with favorable outcome (mRS 0-2 at 90 days) and those with unfavorable outcome (mRS 3-6 at 90 days). Demographic, procedural, radiographic and outcome data was collected. Pre-procedural variables were compared between the two groups.

Results: Of the 88 octogenarian thrombectomies, 29 had favorable 90-day outcome (33%) whereas 59 had unfavorable outcome (67%). Factors that were significantly different between those with favorable and unfavorable outcome include: presence of infarct core before intervention and NIHSS score upon admission. Of the 29 favorable outcomes, 5 presented with infarct cores (17%) whereas 30 of the 59 unfavorable outcome patients presented with infarct cores (51%). The median (IQR) NIHSS upon admission for the favorable outcome interventions was 12 (9-15) in contrast to an 18 (14-21.5) for unfavorable outcome cases. Post procedure recanalization was not significantly different between the two groups.

Conclusion: Our study suggests infarct core and initial NIHSS score to be potential predictors of outcome in octogenarian stroke patients receiving mechanical thrombectomy. Interestingly, successful recanalization does not appear to be a predictor of outcome. Outcome appears to be more closely tied to pre-procedural variables than actual procedural success (recanalization).

The Effects of an Instrumental Cognitive Rehabilitation Program on Cognition and Depression in the Elderly with Mild Cognitive Impairment

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Abstract

Objective: The primary motor cortex is mostly related to hand function, and thus can effectively activate the brain region responsible for hand movements. Therefore, this study aimed to investigate the effects of an instrumental cognitive rehabilitation program that can induce hand movements on cognition and depression in patients with mild cognitive impairment who live in a community.

Methods: The subjects were 41 elderly people in a community who experienced mild cognitive impairment (experimental group: n = 21, control group: n = 20). A therapeutic intervention was conducted once a week and 90 minutes each time for a 12-week period. The experimental group underwent a cognitive rehabilitation program using an effective tool for hand movements, and the control group underwent a conventional cognitive rehabilitation program. As evaluation tools, the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K), the Global Deterioration Scale(GDS), and Geriatric Quality of Life – Dementia (GQOL-D) scale were employed with the same method before and after the intervention.

Results: The CERAD-K subscales of word list recall ($p < 0.01$), word list recognition ($p < 0.05$), and constructional praxis recall ($p < 0.05$) of the patients all showed significant improvements following the intervention. Significant improvements in the mean scores from the baseline to final assessment were observed in the GDS ($p < 0.01$), the GQOL-D ($p < 0.05$) at the end of week 12.

Conclusion: These positive results may provide a solution to prevent the social problem of rapidly increasing dementia. Dementia prevention programs offered by communities will contribute to lower the prevalence of dementia.

Impact of Breast Cancer Diagnosis and Lifestyle Factors on Depressive Symptoms

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Abstract

Breast cancer (BCA) is associated with risk of an array of psychoneurological symptoms (PNS) including disturbances in sleep, anxiety, and depression. Lifestyle factors with potential impact on PNS, remain largely unexplored.

Methods: A secondary exploratory analysis was conducted evaluating depressive symptoms in a cohort of women with stage I or II BCA during treatment for BCA and non-BCA controls (n = 58). Center for Epidemiologic Studies Depression Scale (CES-D) assessments were observed at 3 time points (baseline, month 4 and month 9). With generalized linear mixed model and estimating equation approach the impact of cancer diagnosis, age, alcohol consumption, race, smoking, and BMI was evaluated related to CES-D score.

Result: Breast cancer diagnosis (p = 0.0298), smoking (p = 0.0002), and mixed-race identity (>1 race, p = 0.0069) were significant predictors of CES-D score. Age, alcohol consumption and BMI were not significant.

Conclusion: Women undergoing active treatment for BCA were at elevated risk for depressive symptoms supporting a need for more extensive evaluation and interventions for depressive symptoms during treatment for BCA. Additionally, smoking and mixedrace identity, predictive of depressive symptoms, may compound risk in women with BCA. Further work is necessary evaluating the association of other factors including diet with BCA depressive symptomatology.

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Disfluency Characteristics and Inhibitory Control in School-aged Children with Stuttering and Children with Attention Deficit Hyperactivity Disorder

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Abstract

The purpose of this study was to investigate the characteristics of speech disfluency and inhibitory control in 15 school-aged CWS, grade-matched 15 children with concomitant stuttering and ADHD, and 15 children with ADHD.

Disfluencies in the speech samples were identified and classified as either other disfluencies (OD) or stuttering-like disfluencies (SLD). Reading, story retelling, and picture description tasks were used to elicit utterances from the participants. Stroop color-word task was used to tap the inhibition skills. Main findings of this study are the followings: (1) significant differences in OD were not observed among the types of the tasks and group. Also, CWS and children with concomitant stuttering and ADHD produced significantly more SLD when compared to the children with ADHD during all three tasks. (2) CWS and children with concomitant stuttering and ADHD produced more SLD during the story retelling task than the other two tasks. This finding suggests that CWS and children with concomitant stuttering and ADHD seem to be more vulnerable to a story telling task that places more meta-cognitive loads on speaker. (3) Stroop colorword T score distinguishes between CWS and ADHD groups. (4) There was a significant negative correlation between inhibitory control and OD in stuttering groups indicated that weak inhibition makes stuttering children produce more OD. In conclusion, it is necessary to include various speaking tasks to investigate the characteristics of speech disfluency in stuttering and ADHD children. Further, this study suggests the possible role of inhibition control on speech disfluency in the school-aged children.

Recovery of Brain Abscess-induced Stuttering after Neurosurgical Intervention

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Abstract

Stuttering occurs in approximately 5% of all children and 1% of adults. One type, neurogenic stuttering, is usually attributable to strokes or other structural damages to the brain areas that are responsible for language fluency. Here, we present the first case of neurogenic stuttering caused by a brain abscess. The patient was a 60-year-old man admitted for a seizure and administered an anticonvulsant, after which he began stuttering. Magnetic resonance imaging revealed a brain abscess in the left

frontal lobe that extended to the dorsolateral prefrontal cortex [BA (Brodmann area) 9 and 46], prefrontal eye field [BA 8], and premotor cortex and supplementary motor area [BA 6]. After neurosurgical drainage and antibiotic treatment, the symptoms had resolved. This case is unique in that the therapeutic effects and localization of the cause of stuttering were rapidly identified, allowing for a more accurate description of the neural circuitry related to stuttering.

Chronic, Passive Electrocorticography as a Cortical Stimulation Mapping Alternative: A Review

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Abstract

Electrocorticography (ECoG) in the form of cortical stimulation mapping (CSM) is the current clinical gold standard for neurosurgical preplanning in its capacity to both delineate eloquent cortex and record pathological regions of irregular neuronal activity, primarily for resective surgery in the refractory epilepsy population. Indicated by variable degrees of postsurgical success, there remains many significant improvements to be made regarding its methodological potential for misrepresentative results accompanied with elevated patient psychological, physiological, and economical costs. An alternative – chronic, passive brain mapping – is proposed herein to resolve these shortcomings by, instead, providing a wireless, non-stimulatory, temporarily implantable mapping approach to understanding epileptogenic cortex. By returning patient mobility, seizure behavior can be observed within naturalistic context for an increased duration without jeopardizing the safety of the patient through medication cessation, propagated discharges, intraoperative consciousness, or transcranial wiring increased infection risk associated with CSM techniques. Though unable to indicate eloquent cortex alone, up-and-coming noninvasive mapping approaches like functional magnetic resonance imaging (fMRI) represent promising substitutes with preexisting clinical infrastructure. Importantly, this form of implantable neural recording technology would not be limited in therapeutic benefit to the epileptic population, but to a myriad of neurological, degenerative, and even psychiatric disorders, most notably when paired with multimodal electrodes assessing multiple intracranial variables. This collection of a robust and dynamic variety of neuronal signaling across morbidities has opportunity to transform not only neurosurgical procedure, but neurological research, neurotherapies, and developing technologies like brain computer interfacing, yielding an unparalleled understanding of intracranial behavior and neuronal organization.

Effect of Neurogenic Compound NSI-189 on Indices of Cognition in 2 Mouse Models of Alzheimer's Disease

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Abstract

Background: NSI-189, a benzylpiperazine-aminopyridine, is a proprietary, orally active, new chemical entity that stimulates neurogenesis, synaptogenesis and increased hippocampal volume in mice. It has shown significant antidepressant and pro-cognitive effects in patients with major depressive disorder in a recent Phase II clinical trial.

Methods: We used two distinct mouse models of AD - 5XFAD and TAPP mice. After confirmation of cognitive impairment at 15-19 weeks of age, mice were treated orally for 12 weeks with NSI-189 at 30 mg/kg. After 6 and 12 weeks of treatment, learning and memory tests (Barnes maze and Object recognition tests) were performed along with repeated testing on the rotarod for assessing motor learning.

Results: Learning disabilities were significantly ameliorated by 12 weeks of oral administration of NSI-189 in both 5XFAD and TAPP mice. The twelve weeks of treatment with NSI-189 improved short-term memory capacity of 7month old 5xFAD and TAPP mice beyond the recognition capacity of control mice in the novel object recognition test. Long-term (6 weeks) memory loss was also ameliorated by the 12 weeks of treatment with NSI-189 in TAPP mice. Using the repeated rotarod test, motor performance as well as the motor learning ability of 5xFAD and TAPP mice receiving daily NSI-189 treatment were significantly improved compared to their baseline and their respective untreated transgenic counterpart to a level above control mice values.

Conclusions: Daily treatment with NSI-189 significantly reversed learning and memory deficits that were established in the 5XFAD and TAPP mouse model of AD.

Progressively Mysterious Leukoencephalopathy, a Curious Case of Seizures in an Untreated HIV Patient

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Abstract

Progressive Multifocal Encephalopathy (PML) is a fatal demyelinating CNS disorder that occurs exclusively in individuals with incompetent immune systems. Approximately 5% - 14% of patients with AIDS will develop PML during the course of their disease, with PML accounting for 0.7% of total deaths in this population. Twenty percent of HIV-1-infected patients with PML presented with new-onset seizures of various types, generalized or partial. Although the exact mechanism is unknown, PML causes damage to oligodendrocytes, with lesions in the subcortical white and gray matter areas of the basal ganglia and thalamus. We present a case of a 55-year-old Caucasian male brought in to the emergency department by EMS after his family witnessed him having new onset generalized seizures with jerky limb movement and urinary incontinence. His past medical history was significant for untreated HIV, polysubstance abuse (benzodiazepines and opioids) and Hepatitis C (s/p treatment).

Measures of Brain Function Provide Unique Insights into Behavioral Deficits in the Acute Stroke Setting

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Abstract

We hypothesized that in patients with acute stroke, a measure of brain function (EEG) explains acute behavioral deficits (NIHSS score), after controlling for effects of brain injury (infarct volume) and age. In 50 patients with acute stroke seen in the ED of our comprehensive stroke center, in addition to standard evaluation, EEG was performed using a wireless, 17-electrode, dry-lead system (Cognionics, Inc.). Acute stroke deficits (initial NIHSS scores) were examined in relation to age, brain injury, and brain function. The primary EEG measure used was whole brain (WB) DTABR, a commonly used composite measure of brain function defined as the ratio of EEG power in four frequency bands: (Delta*Theta)/(Alpha*Beta). Mean (SD) age was 65.6 (17.7). Median [IQR] NIHSS was 4. In bivariate analyses, infarct volume ($r = 0.66$, $p < 0.0001$) and WB DTABR ($r = 0.60$, $p < 0.0001$), but not age ($r = 0.24$, $p = 0.098$), were significantly related to NIHSS score. Because infarct volume and age do not completely explain NIHSS, we examined whether EEG (WB DTABR) is independently related to NIHSS. The partial correlation coefficient between NIHSS and WB DTABR, calculated controlling for infarct volume and age, was significant ($r = 0.46$, $p = 0.0009$); this remained true when examining brain function separately for each hemisphere: DTABR in only the ipsilesional hemisphere, $r = 0.38$, $p = 0.0075$; DTABR in only the contralesional hemisphere, $r = 0.53$, $p = 0.0001$; or when examining power in the delta or beta frequency bands alone. In conclusion, EEG measures of brain function provide insights into acute stroke behavioral deficits beyond what can be learned from infarct volume and age.

Inhibition of Calcium/Calmodulin-Dependent Protein Kinase Kinase (CaMKK) Exacerbates Impairment of Endothelial Cell and Blood Brain Barrier after Stroke

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Abstract

CaMKK (α and β) is a major kinase activated by elevated intracellular calcium. We have previously demonstrated CaMKK is neuroprotective in stroke. Brain microvascular endothelial cells play an essential role in maintaining BBB integrity, disruption of which aggravates ischemic injury. Interestingly, CaMKK has been shown to activate a key endothelium protectant Sirtuin1 (SIRT1). We hypothesized that CaMKK protects brain endothelial cells (EC) through activation of SIRT1 after ischemia. Oxygen-glucose deprivation (OGD, 18 hours) with reoxygenation (24 hours) was performed in human brain microvascular endothelial cells (HBEC- 5i). Middle cerebral artery occlusion (MCAO, 90 mins) was used to induce stroke in male mice

(20 to 25 g). Data are presented as mean ± SEM. STO-609 treatment reduced cell viability (%) after OGD (vehicle 71.45 ± 5.60 vs. STO-609 55.06 ± 5.02, n = 4, p < 0.05). CaMKK β Knockdown using siRNA increased cell death following OGD. Mechanistically, inhibition of CaMKK by STO-609 led to significant down-regulation of phosphorated SIRT1 (Ser-27) after OGD. Levels of total SIRT1 were also reduced by STO-609, consistent with the notion that phosphorylation prevents the degradation of this protein. Further, the effect of STO- 609 on cell viability after OGD was absent when SIRT1 was concurrently inhibited by EX-527. Finally, in a MCAO model, intracerebroventricular injection of STO-609 significantly worsened BBB integrity after 24-hour reperfusion (MCAO + DMSO 17.83 ± 6.34 versus MCAO + STO-609 55.74 ± 8.88, n = 5/6; P < 0.05). We demonstrate that CaMKK inhibition reduces EC viability after ischemia via SIRT 1. CaMKK may attenuate ischemic brain injury by protecting the microvascular system and preserving BBB integrity.

Case Study of Utilization of Digital Therapeutics (JOGO) for Post Right MCA Infarction

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Abstract

Introduction: Digital therapeutics (JOGO) involving surface electromyographic biofeedback (EMG BF) is an innovative treatment that uses sensory inputs to facilitate neuromuscular retraining. Compounding wireless tablets with conventional therapy (CT), JOGO improves the motor abilities of a patient with left hemiparesis post-right MCA infarction through neuroplasticity. JOGO's ease of use through features such as mobile gamification increases patient compliance relative to CT, augmenting clinical outcome.

Methods: We reviewed the patient's response to JOGO after undergoing right MCA infarction. The patient, left hemiparetic, facilitated tone and muscle complexity by weight bearing through the truncal and scapular complex over 3 weeks. JOGO EMG BF helped improve dorsiflexion and functional mobility through gait training. CT exercises such as stretching, pelvic bridging, etc. were performed in addition.

Results: MMT of ankle dorsiflexors improved from 1 + to 3 after JOGO EMG BF. Evaluations initial and 3 weeks post: Barthel (20/100) improved (87/100); Berg Balance improved (0/56) to (52/56); VMC upper limb improved from 1 to 4; VMC lower limb improved from 2 to 4. At time of discharge, the patient can walk with stick-supported circumduction gait, with little synergy present between upper and lower limb.

Conclusion: JOGO's proficiency in rewiring the patient's neural circuit induced the patient to adequately relearn the motor functions of her limbs. Embellished with portability and cost effectiveness, JOGO's user-orientated interface optimizes rehabilitation by allowing the patient to experience visual control over neuromuscular junctions. Further studies are in progress to evaluate efficacy in EMG BF integrated rehabilitation.

Folding and Stability of Intramolecular G-Quadruplex Structure by Myoinositol

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Abstract

Amyotrophic lateral sclerosis (ALS) and Frontotemporal dementia (FTD) are caused by abnormal expansion of hexanucleotide repeats (HRE) (G4C2)n in a non-coding region of the C9orf72 gene. Guanine-rich nucleic acid sequences can spontaneously assemble into G-quadruplexes and challenge the replication, transcription, and translation machinery. ALS and FTD linked (G4C2) n folds into two distinct G-quadruplexes. Recently, the structural and topological diversity of G-quadruplexes have attracted great attention. The characterization of G-quadruplexes and understanding the mechanism of their folding/unfolding will help to design potential small molecules to target it. Herein, we describe the topology of (G4C2)8 G-quadruplex structure and its folding in the presence of myoinositol which is a carboxylic sugar osmolyte abundant in brain. Circular dichroism (CD) spectroscopy was employed to study the change in the properties and configurations of (G4C2)8 in the presence of myoinositol. The parallel topology of (G4C2)8 were observed in higher concentrations of myinositol. The transition in the topology of (G4C2)8 was observed from anti-parallel to hybrid to parallel as the temperature and concentrations of

myinositol were increased. At high temperature even low concentration of myinositol favour the parallel topology. Myoinositol was playing significant role in stabilizing the structures of (G4C2)8 and allow to adopt the parallel topology. Our findings are important in order to understand the different folding of (G4C2)n and provided new insights about configurations of G-quadruplex which may be further used to design small molecules targeting neurological disorders.

Intrathecal Steroids for Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement

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Abstract

Background: Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a rare form of brainstem encephalitis centered in the pons that is responsive to immunosuppression with glucocorticosteroids (GCS). The chronicity of the disorder requires a maintenance immunosuppressive therapy, usually consisting of an oral GCS. Since chronic GCS therapy is necessary, these patients have many deleterious side effects of oral systemic GCS. It is hypothesized that the side effects of a short course of intrathecal steroids could treat CLIPPERS and avoid the systemic toxicities of chronic GCS therapy.

Methods: A literature search of publications was performed using PubMed database over times for the search term ""intrathecal" AND "steroids"", and ""intraspinal" AND "steroids"".

Results: Thirteen articles were found in the search. Six (46%) discussed the side effects, four (31%) discussed treating multiple sclerosis, two (15%) discussed treating diskogenic pain, and one (8%) discussed attempts to create a rat model to test the side effects. Side effects of intrathecal steroids included transient sensory loss, urinary incontinence, constrictive arachnoiditis, aseptic meningitis, subarachnoid hemorrhage, brain damage, spinal cord lesions, dense widespread pachymeningitis, and neurogenic bladder.

Conclusion: The serious complications of intrathecal steroids and systemic GCS have been well documented. In a rare and devastating disease like CLIPPERS, intrathecal steroids should be considered and its side effects weighed against those of chronic oral GCS.

Involvement of Merkel cell-neurite Complex in Mechanical Hypersensitivity Following Diabetic Peripheral Neuropathy: Role of Protein Kinase

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Abstract

Merkel cells (MCs) cluster in the basal layer of the epidermis and their associated primary afferents in the dermis form synapticlike structures, which is termed as Merkel cell-neurite complex, mediates touch sensation. However, probable mechanotransduction mechanisms in human type 1 diabetes mellitus (DM) remain elusive. In the present study, we used Sprague–Dawley rats to establish a rodent model of the human type 1 DM by a single intraperitoneal injection with streptozotocin (STZ) (60 mg/kg). Mechanical hypersensitivity, including hyperalgesia and allodynia, were evoked. Dermal denervation was revealed by the reductions of neurofilament 200-immunoreactivity (ir) subepidermal nerve fibers (SENFs). Conversely, the increases of phosphorylated protein kinase A (pPKA)-ir SENFs were observed. More importantly, the increases of phosphorylated protein kinase C alpha (pPKCα)-ir MCs were distinct gathered from the results of phosphorylated protein kinase C gamma (pPKCγ)-ir MCs. By an intraplantar injection with a PKA inhibitor (H89), hyperalgesia and allodynia were attenuated in a dose-responsive manner, which exhibited equivalent results as the efficacy of beta-2 adrenergic receptor antagonist (ICI 118,551). In addition, the classical PKCα inhibitor (Go6976) and a Piezo2 antagonist (Ruthenium red) both had dose-dependent analgesic effects on STZ-induced allodynia. Morphological evidence further confirmed that STZ-induced pPKA-ir SENFs and pPKCα-ir MCs were reduced after pharmacological interventions. From the results obtained in this study, it is suggested that Merkel cell-neurite complex may participate in the modulation of STZ-induced mechanical hypersensitivity through the specific PKC and PKA activation, which provides a potential therapeutic target and novel pharmacological strategies in human type 1 DM.

The Current State of Continuous Dopamine Delivery for the Management of Parkinson's Disease

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Abstract

Background: Parkinson's disease (PD) is a progressive neurodegenerative disease that is initially responsive to oral pharmacotherapy. During the natural course of PD, pharmacologic management becomes less effective where patients experience the "on-off" phenomena and regularly fluctuate between bradykinesia and dyskinesia. Continuous dopamine delivery (CDD) can provide a constant delivery of the dopaminergic drug resulting in a more stable treatment effect without the limitations of traditional oral therapy

Methods: A PubMed search was conducted using the following key words: "'Intrathecal Dopamine' AND 'Parkinson Disease'", "'Continuous Dopamine Delivery' AND 'Parkinson Disease'", "'Continuous Dopamine Stimulation' AND 'Parkinson Disease'", "'Intracerebroventricular Dopamine Infusion' AND 'Parkinson Disease'", and "'Cell Based Therapy' AND 'Parkinson Disease'". The search returned 586 total matches. Articles for this review were obtained from these matches or the articles referenced within them.

Results: Current CDD therapies include subcutaneous therapy, transdermal therapy, intrajejunal infusion, cell-based therapy, intracerebroventricular (ICV) therapy, and intrathecal infusion. The use of subcutaneous, transdermal and intrajejunal therapies are already in practice and have proven efficacy. Cell-based therapies have equivocal early results and their efficacy is questionable. Intrathecal and ICV infusions are unique in that they deliver dopamine directly into the CSF and have shown early promising results.

Conclusion: CDD was developed with the goal of constant and consistent release of dopamine into circulation throughout a 24-hour period, with the avoidance of the "on-off" fluctuations of traditional oral levodopa-carbidopa therapy. These experimental therapies show great potential and further investigation into their efficacy and therapy could extend the frontiers for management of PD.

A Common Mechanism of Proteasome Impairment by Neurodegenerative Disease-associated Oligomers

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Abstract

Protein accumulation and aggregation with a concomitant loss of proteostasis often contribute to neurodegenerative diseases, and the ubiquitin–proteasome system plays a major role in protein degradation and proteostasis. Here, we show that three different proteins from Alzheimer's, Parkinson's, and Huntington's disease that misfold and oligomerize into a shared three-dimensional structure potently impair the proteasome. This study indicates that the shared conformation allows these oligomers to bind and inhibit the proteasome with low nanomolar affinity, impairing ubiquitin-dependent and ubiquitin-independent proteasome function in brain lysates. Detailed mechanistic analysis demonstrates that these oligomers inhibit the 20S proteasome through allosteric impairment of the substrate gate in the 20S core particle, preventing the 19S regulatory particle from injecting substrates into the degradation chamber. These results provide a novel molecular model for oligomer-driven impairment of proteasome function that is relevant to a variety of neurodegenerative diseases, irrespective of the specific misfolded protein that is involved.

Is There a Key for Unlocking the Mechanisms of the Futurological Abilities of the Human Brain?

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Abstract

The methodology of Quantitative Functional Morphology (QFM) already allows to expose brain tissue to multifactorial systemic study to obtain one indicator reflecting the value of brain cognitive abilities. Now we suggest a significantly expanded mathematical model in two versions for the systemic assessment of the brain. The first option consists of 24 modules. The second version consists of four different equations, where each model contains 6 modules. The first small equation models the delivery of nutrients and oxygen to the brain arterioles. The second equation models the delivery of nutrients and oxygen from cerebral cortex capillaries to neurons. The third equation models the processes of electric potential generation on neurons. The fourth equation models the transfer of generated information into surrounding neuron environment. As a system-forming factor for mathematical model, we have adopted the conventional value of "information", which is produced in one second in $1mm^3$ volume of the cortex and is transmitted to the environment. Studies have been carried out on the brains of purebred white rats, on the brains of people who died from violent causes.

The developed method may be used:

- In clarifying the mechanisms of development of so-called brain functional disorders, in explaining the mechanisms of futurological abilities;

- In evolutionary assessment of the brain organization in animals and humans;

- For presenting data to tissue-engineering and organ-fabrication specialists to create a human brain with increased functional abilities. Hopefully, this will allow powerful human brains to oppose the coming technological singularity.

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