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Meeting Abstracts

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Keynote Presentations

Customized DNA (Precision Medicine) Directed Nutrition to Balance the Brain Reward Circuitry and Reduce Addictive Behaviors

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Abstract

Discovery of genetic influence on craving by Blum, and Noble allowed more research on genetic determinants of mental and physical health. It led to DNA Customization of nutraceutical products in humans. One such product KB220Z has been shown to reduce cravings by influencing gene expression. This and other products have made neuro-nutrigenomics an important field of scientific investigation. It offers promise of improving human health and wellbeing. Further, development of the Genetic Addiction Risk Score (GARS™), which analyzes genetic profile to predict likelihood of developing chemical or behavioral addiction (Reward Deficiency Syndrome [RDS]) could potentially help in the identification of vulnerable individuals prior to the development of addictive behaviors. While customization of neuronutrients, is still at its infancy, there are only three such studies from our laboratory in the literature for RDS behaviors, it promises to have a significant role in near future. Our research suggests that Gene Guided Precision Nutrition™ with specific polymorphic targeting may induce personalized treatment and or even relapse for RDS that includes both chemical and behavioral addiction.

Plasma Metabolomic Profiles and Cognitive Function

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Abstract

Our group has studied a longitudinal cohort of seniors, > 75 yo, to discover and internally validate peripheral blood measures that can accurate predict which cognitively normal subjects will progress to amnestic Mild Cognitive Impairment (aMCI) or Alzheimer disease (AD) within less than three years. We initially reported on plasma metabolites which are now more accurate as a diagnostic. We have extended this work on plasma metabolomics and have discovered and validated a panel of 24 analytes that predict phenoconversion to Alzheimer's disease with accuracy of > 96%. In addition to this discovery and internal validation work we have now externally validated both the initial 10 and follow-on 24 metabolomic panel. Finally, we describe a subpopulation within our cohort with superior neurocognitive function and discovery of a plasma metabolomic signature that distinguishes this group from normal. I will discuss the implications of this signature with regard to cognitive function and potential implications for dementia.

Advances in Neuroimaging and Its Applications: From PET/MRI Fusion Imaging to Super-Resolution Tractography

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Abstract

New imaging system, the Brain dedicated PET-MRI, using High resolution PET and Ultra High Field 7.0T Magnetic Resonance Imaging (MRI) and their applications to basic and clinical neuroscience, especially to the areas of neurological disorders such as Parkinson's disease will be discussed. With high field MRI, such as the 7.0T MRI, one can now visualize the details of the Substantion Nigra (SN) and Subthalamic Nueleus (STN) *in-vivo* as well as tractography hitherto unable to do with existing MRI systems. Together with molecular imaging using Positron Emission Tomography (PET), that is the brain dedicated PET-MRI fusion system developed recently, now, it is possible to visualize metabolic functional changes quantitatively in human brain *in-vivo* as well as connectivity through the tractography. Ultra-high field MRI also began to provide super-resolution tractographic images delineating the fine fiber structures such as the sub-components of the superior longitudinal fasciculus (SLF), among others, suggesting future potential applications neurological disorders.

Brain Plasticity and Brain Health

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Abstract

Studies conducted over the past decades have documented the neurological processes that govern life-long brain remodeling. Those studies have now shown how different patterns of brain engagement impact human performance and organic brain health. We have applied this science both to develop new 'biomarkers' that provide us with inexpensive, recursively usable indices of organic brain health, and to create a therapeutic toolset designed to strengthen and then sustain organic brain health also manifested by recovered neurobehavioral ability. Now validated in many controlled outcomes trials, a randomized controlled trial has now shown that this approach applied in 70s-80s elder population very significantly delays dementia onset. I shall describe these research and development efforts within the framework of your implementing strategies for your now managing your normal and at-risk adult patients' brain health.

If I Knew Then, What I Know Now
The Definitive Guide for Those Who do not have a Chronic Illness

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Abstract

My target audience is all medical personnel. The purpose of this Presentation is to encourage medical personnel who treat those diagnosed with a life-changing condition to go beyond the clinical role and provide a broader perspective on the effects of the illness. Here is what I wished I knew 15 years ago, when I was diagnosed with Parkinson's disease, drawn from what I learned over the last 15 years.

Dopaminergic Processing of Human Cognition and Behavior: What We Learned from the Data Acquired in the Live Human Brain in Real Time

Rajendra D. Badgaiyan

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Abstract

Most of the concepts on the influence of dopamine on human cognition and behavior are based on the data acquired in laboratory animals. These data however may not represent the processing in the human brain because animals lack highly developed cortical structures of the human brain. Additionally, animal data do not account for psychosocial factors associated with human cognitive and behavioral processing. Despite these issues, we use animal data because a reliable method for detection of task-induced release of dopamine in the live human brain was not available until recently. In the last few years we developed the Single-scan Dynamic Molecular Imaging Technique (SDMIT), which allows detection, mapping and measurement of dopamine released acutely in the live human brain. The technique exploits the competition between dopamine and its receptor ligand for occupancy of the receptor sites. In this technique, a radiolabeled dopamine receptor ligand is injected intravenously and volunteers are asked to perform a cognitive or behavioral task. During the task performance, ligand concentration is measured dynamically using positron emission tomography (PET) camera. Because of the competition, dopamine released by the task displaces the ligand from receptor sites, reducing its concentration. Dopamine released by the task is detected by measuring the ligand concentration in different parts of the brain using a specially formulated receptor kinetic model – the linear extension of simplified reference region model. Using this technique, we studied a number of cognitive and behavioral tasks to understand the role of dopamine in human cognitive and behavioral processing. The data acquired in these experiments highlights similarities and differences between the animal and human data on dopaminergic processing of cognition and behavior.

Elevated Plasma Homocysteine and Neurologic Disorders

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Abstract

Homocysteine (Hcy) is a sulfur-containing amino acid that is generated during methionine metabolism. It has a physiologic role in DNA metabolism via methylation, a process governed by the presentation of folate, and vitamins B6 and B12. Physiologic Hcy levels are determined primarily by dietary intake and vitamin status. Elevated plasma levels of Hcy (eHcy) can be caused by deficiency of either vitamin B12 or folate, or a combination thereof. Certain genetic factors also cause eHcy, such as C667T substitution of the gene encoding methylenetetrahydrofolate reductase. eHcy has been observed in several medical conditions, such as cardiovascular disorders, atherosclerosis, myocardial infarction, stroke, minimal cognitive impairment, dementia, Parkinson's disease, multiple sclerosis, epilepsy, eclampsia, and peripheral neuropathy. There is evidence from laboratory and clinical studies that Hcy, and especially eHcy, exerts direct toxic effects on both the vascular and nervous systems. My talk will be focused on the possible roles of eHcy relevant to various neurologic disorders.

Featured Presentations Early and Late Inflammation in the Alzheimer's Pathology

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Abstract

Inflammation is an important component of the Alzheimer's disease (AD) neuropathology which has provoked several randomized trials using NSAIDs and other anti-inflammatory treatments, with disappointing outcomes. As the AD pathology has been evolving silently for over two decades, we have postulated that the early CNS inflammation at preclinical stages might be a disease-aggravating process. In this presentation, I will introduce the concept and describe the characteristics of a "pre-plaque" inflammatory process, arising from the incipient AD-like amyloid pathology in transgenic rodent models. We propose that well-before the occurrence of amyloid plaques the intraneuronal accumulation of oligomeric Aβ peptides suffice for the presentation of "inflammatory neurons" and the recruitment of intermediate-activated microglial cells in a scenario of absence of phagocytosis and presence of a, "disease-aggravating," pro-inflammatory process. The early CNS inflammation in AD differs substantially from the classical, late, amyloid plaque-related process in which a role adaptive immune reaction predominates.

The differential nature of the early and late CNS inflammation in the continuum of the AD pathology would explain the positive effects of anti-inflammatory agents in diminishing the AD prevalence in individuals without cognitive impairments while the same compounds do not render beneficial effects when given to patients with AD clinical presentation.

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Novel Formulations of Pomegranate Seed Oil for the Treatment of Neurodegenerative Diseases

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Abstract

Administration of Nano-PSO (GranaGard), a nanodroplet formulation of pomegranate seed oil (PSO), to TgMHu2ME199K mice modeling for genetic prion disease delayed disease advance significantly. PSO comprises 80-90% of Punicic Acid, a conjugated linoleic acid considered one of the strongest natural antioxidants. In the present study, we administrated GranaGard as compared to a control Nano-Soya formulation to our Tg mice from their day of birth to their ethically approved terminal stage and followed them periodically for their clinical status. Mice were sacrificed at designated points, and their brains processed for pathological, biochemical and molecular analysis. We found that continuous administration of GranaGard resulted in increased survival of the TgMHu2ME199K mice by several months without any adverse effects. In addition, while GranaGard administration had no effect on disease related PrP accumulation levels, it induced a profound reduction in sulfated sugar amyloids, which feature in most neurodegenerative conditions. Most interestingly, GranaGard treated brains presented reduced levels of caspase III immunostaining and increased levels of Nestin expressing endogenous stem cells, indicating a massive neuroprotective effect. Biochemical experiments identified in GranaGard treated brains measurable levels of Conjugated Linoleic, a natural Punicic acid metabolite shown to have neuroprotective and anti- amyloid properties, indicating the brain targeting of these compounds We conclude that longterm administration of GranaGard is both safe and effective for the prevention/delay of progression of genetic CJD in mice. Its mechanism of action, neuroprotective and independent for PrP accumulation suggests this may be the case also in other neurodegenerative conditions.

Chronic Perturbation from Normal Expression. An Alternative Mechanism for the Role of *APP* in the Pathophysiology of Dementia

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Abstract

Since 1980s it has been known that numerous mutations in amyloid precursor protein (APP) gene mapped to human chromosome 21 lead to an early onset familial form of Alzheimer's disease (AD). However, the exact mechanism by which APP plays a role in the pathophysiology of cognitive dysfunction remains to be illuminated. Down syndrome (DS) is caused by the triplication of the entire or a portion of human chromosome 21. Importantly, all adults with DS develop AD neuropathology, from which a large proportion exhibit dementia of Alzheimer type. In addition, individuals with DS with no triplication of APP, develop no AD-related neuropathology. For these reasons, mouse models of DS could be used to unravel mechanisms by which APP overexpression participates in AD pathogenesis. Here we will show that over-expression of App during the critical period of development in the Ts65Dn mouse model of DS leads to reduced retrograde axonal transport of growth factors and degeneration of multiple brain circuits. Notably, removing the extra copy of App in Ts65Dn mice led to a significant improvement in the status of affected brain circuits. Our studies suggest that targeting App during early stages of development is an attractive therapeutic strategy for cognitive dysfunction in children with DS and reducing AD-related pathology in adults with trisomy 21.

Novel Pathway of Amyloid Proteins Aggregation. Assembly of Amyloids at Physiological Range of Protein Concentrations

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Abstract

The amyloid cascade hypothesis is currently considered as the main model for a vast number of neurodegenerative diseases including Alzheimer's, Parkinson's, and Huntington's diseases. Numerous studies have shown that amyloidogenic proteins are capable of spontaneous assembly into aggregates, and eventually form fibrillar structures found in amyloid or amyloid-like deposits. However, there is a serious complication with translating current knowledge on amyloid aggregation *in vitro* to understand the aggregation process *in vivo*. If the critical concentration for the spontaneous aggregation of Aβ peptide *in vitro* is in the micromolar range, physiological concentrations of Aβ are in the low nanomolar range making impossible amyloids to assemble. We have discovered a novel on-surface aggregation pathway that allows for spontaneous assembly of amyloid beta peptides at the physiological concentration range. Our combined experimental and computer modeling approaches demonstrate that the on-surface aggregation is a dynamic process, so the assembled aggregate can dissociate from the surface to the bulk solution. As a result, the dissociated oligomers can play roles of seeds for aggregation in the bulk solution, or start a neurotoxic effect such as phosphorylation of the tau protein to initiate its misfolding and aggregation. Both processes lead to neurodegeneration. Importantly, in the vast majority of cases, we found that aggregates formed on the surface are oligomers, which are considered to be the most neurotoxic amyloid aggregates. Therefore, we posit that on-surface aggregation is the mechanism by which neurotoxic amyloid aggregates are produced under physiological conditions. A change in membrane properties leading to an increase in affinity of amyloid proteins to the membrane surface facilitates the assembly of stable oligomers. The proposed model is a significant departure from the current model as it directs the development of treatments and preventions towards approaches that control the cell membranes composition to prevent the on-surface aggregation process.

In-vitro Imaging Based Screening of Alzheimer's Disease Serum Samples for Determining Abeta, Tau and Cholesterol Responses

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Abstract

Abnormal accumulation of amyloid plaques in cerebrovascular regions is associated with the development of neurodegenerative disorders including Alzheimer's disease. *In-vivo* imaging is being widely used for detection of amyloid plaques and also for examining AD-related pathologies in the brain. Besides, elevated levels of abeta and tau peptides detected in the peripheral blood circulation are implicated to AD pathology. The objective of the present study was to screen AD serum samples for evaluating response against abeta, tau and cholesterol using *in-vitro* imaging method.

Method: The plaque array method in combination with imaging flow cytometry was used for acquiring images of abeta, tau and cholesterol particles for morphological analysis.

Results: Initially, examining the interaction of wild type abeta-42 peptide and its genetic variants with cholesterol or phospholipid showed variations in the profiles of abeta particles formation. Similarly, binding analyses involving tau peptides carrying repeat domains-1, 2 and 3 with cholesterol and phospholipids indicated a higher-level effect of tau repeat domain-3 peptide on inducing amyloid particles formation. Besides, analyzing images of the amyloid particles revealed their morphology mostly as globular or random shapes. In a pilot study, screening of AD serum samples with severe, MCI and age-matched normal showed a higher, moderate and lower levels of responses for abeta-wt and tau domain-3 peptides, respectively.

Conclusion: The measurement of abeta, tau and cholesterol particles formation in AD serum samples indicated a good correlation with *in-vivo* imaging data suggesting the *in-vitro* imaging method may be a useful biochemical tool for both diagnosis and stratification of AD patients.

Multi-Modal Imaging in Pediatric TBI: A Longitudinal Study

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Abstract

There is considerable heterogeneity in post-TBI outcomes in children with moderate/severe traumatic brain injury (msTBI). Acute injury variables only account for some of this variance. In our study a measure of corpus callosum (CC) function, interhemispheric transfer time (IHTT), differentiated patients into two groups only a few months post-injury. We studied 21 children (16M/5F) with msTBI, assessed 2-5 months and 13-19 months post-injury, and 20 well-matched healthy control children. We assessed CC function through IHTT, measured using event-related potentials. We examined white matter (WM) microstructure using diffusion-weighted magnetic resonance imaging (dMRI) and regional brain volume using tensor-based morphometry (TBM). Half of the TBI patients had significantly slower IHTT at the first time-point (TBI-slow-IHTT, N = 11), and half were in the normal range (TBI-normal-IHTT, N = 10). The TBI-normal-IHTT group did not differ significantly from healthy controls in WM integrity. In contrast, the WM integrity of the TBI-slow-IHTT group was significantly lower than healthy controls across a large portion of the WM. Longitudinal analyses showed the TBI-slow-IHTT group experienced a progressive decline in WM integrity throughout the brain from 2-5 to 13-19 months post-msTBI. TBM analyses showed volume loss in the TBI-slow-IHTT group in the WM, while the TBI-normal-IHTT group appeared to return to a normal developmental trajectory. We have discovered a potential biomarker that identifies a subset of patients with impaired CC integrity in the first month's post-injury who experience widespread continuing and progressive degeneration. Identifying patients at risk for poorer outcomes will help clinicians know which patients might benefit from targeted treatment.

Magnetic Resonance is a Useful Modality for Evaluating Primary Muscle Diseases

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Abstract

Imaging techniques have assumed increasing importance in the diagnostic approach to patients with muscle disease. These techniques include computed tomography, ultrasound, and magnetic resonance imaging (MRI). MRI remains the gold standard for detecting changes in muscle tissue. T1-weighted images show the degree of fibro-fat degeneration in muscle, while high signal intensity on fat-suppressed T2-weighted and short T1 inversion recovery (STIR) muscle MR images indicate edema in muscle and it is found in inflammatory myositis and in different muscle dystrophies. Muscle MRI is very sensitive for localizing structural abnormalities in muscles; therefore, it allows the biopsy to be precisely targeted. Previous studies have shown that non-targeted single site biopsy may lead to the diagnosis being missed in approximately one-third of cases. MRI scan is useful in evaluating the severity of muscle wasting and its evolution in time. Clinical testing using the Medical Research Council scale is not sensitive enough to establish the pattern of muscle involvement in focal muscle diseases. Muscle MRI could assess the effect of drug treatment in inflammatory myositis. Muscle MRI, in combination with clinical evaluation, can contribute to the selection of appropriate genetic tests and more generally in the differential diagnosis of genetically distinct forms of neuromuscular disorders.

Patterns of Cerebral Ischemia in Children with Moyamoya

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Abstract

Introduction: Moyamoya disease is characterized by progressive cerebrovascular stenosis with recurrent cerebral ischemic events. Transient ischemic attacks are often associated with hyperventilation in children with moyamoya suggesting hypoperfusion rather than thrombotic vaso-occlusion as a prominent mechanism. The patterns of ischemia and severity of steno-occlusive disease in such children may elucidate these mechanisms.

Methods: Children, 1month to 18-years, with moyamoya, seen at our center over 11- years were assessed. A study neuroradiologist reviewed all pre-surgical neuroimaging. The ischemic injury was categorized into cortical, sub-cortical and watershed infarction. Angiographic findings were staged utilizing a standardized method.

Results: Twenty children, 15 females, median age 6.4 years, were included. All children had magnetic resonance imaging and angiography and in 16, conventional angiography was available. All 40 hemispheres, in 20 children, were evaluated. The initial clinical presentation included: neurological deficits 17, recurrent transient ischemic attacks 7, headache 8, seizures 8 and alteration in consciousness 4. Infarcts were bilateral in 13(65%) children (ischemia alone 14, ischemic stroke with hemorrhagic transformation 2, and primary hemorrhage 2). Infarcts were cortical/subcortical in 13(65%), both deep and cortical watershed in 11(55%) and cortical watershed alone in 5(25%) children. The predominant vascular territory involved was the middle cerebral artery. The internal carotid arterial system was involved in all, with stage IV being the most frequent angiographic stage.

Conclusion: Ischemic injury in deep watershed zones is common in childhood moyamoya and may reflect non-vaso-occlusive ischemic mechanisms. Location and severity of vascular involvement may correlate with various patterns of ischemic infarction in moyamoya disease and requires further study.

Progressive Muscular Atrophy in the Republic of Sakha (Yakutia)

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Abstract

Progressive muscular atrophy (PMA) is a rare disease characterized by the electoral defeat of the cells of the anterior horns of the spinal cord and is accompanied by progressive muscular weakness, hypotrophy, and fasciculations. In Yakutia, in the group of MND, the percentage of PMA is 11.5%. In our study, we compared disease duration between the groups of patients with sporadic and familial PMA. The average age at initial diagnosis in the group with the sporadic disease was 54.2 ± 11.8 years. In the second group with family cases, an average age at initial diagnosis reached 42.4 ± 9, 63 years. The average duration of disease in the first group of patients was 53.6 ± 30.3 months, while in the second group it was 140 ± of 37.8 months. This review will describe the clinical differences between sporadic PMA and family cases of PMA with autosomal dominant inheritance, with four sick members of the family in two generations. The work is done in the framework of the state assignment of the Ministry of Education and Science No 17.6344.2017/8.9 and No 17.7344.2017.

Embedding Human-Like Brains in Simulated Closed-Loop Experiments: The Neurorobotics Platform

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Abstract

Developing neuro-inspired computing paradigms that mimic nervous system functions is a well-established field of research that fosters our understanding of the human brain. Studying and validating models of brain function requires a proper embodiment of the brain model as well as a dynamic and rich sensory environment in which the agent–brain ensemble can be embedded and then be exposed to a realistic sensory-motor task. Since advanced brain models are too complex to be simulated in real time, it is now no longer possible to embed the brain into a real-world task. Rather, the embodiment needs to be simulated as well. The Neurorobotics Platform, developed in the framework of the Human Brain Project, is a new web-based environment that aims to fill this gap by offering scientists and technology developers a software infrastructure allowing them

to connect brain models to detailed simulations of bodies and environments and to use the resulting neurorobotic systems for in-silico experimentation. The platform can be used to test neuroscientific models of brain areas, or even reconstruction of these areas based on neurophysiological data. We illustrate the capabilities of the platform with some example experiments including the simulation of post-stroke rehabilitation experiments carried out on mice. This experiment aims at validating data-driven models of the mouse brain in order to examine the features of neuronal plasticity relevant for functional motor recovery.

Regulation of mitochondrial dysfunction in models of Parkinson's Disease

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Abstract

Mitochondria are organized in a highly dynamic tubular network that frequently undergoes fusion and fission. Defects in either fusion or fission, leading to mitochondrial fragmentation, limits mitochondrial motility, decreases energy production and increases oxidative stress, thereby promoting cell dysfunction and death. Recently, aberrant mitochondrial dynamics has been highlighted in the pathogenesis of a number of neurodegenerative diseases, such as Parkinson's disease. We have shown that Dynamin-related protein 1 (Drp1), a key regulator of mitochondrial fission, was activated and translocated to the mitochondria in dopaminergic neurons exposed to PD-associated neurotoxin, dopaminergic neurons differentiated from induced pluripotent stem cells (iPS) of PD patients carrying LRRK2 G2019S mutant, and the substantia nigra of mice subject to subacute MPTP exposure. Using a peptide inhibitor P110 that selectively suppresses Drp1 hyperactivation we have recently developed, we found that inhibition of Drp1 activation by P110 treatment reduced mitochondrial fragmentation and damage, corrected aberrant autophagy and reduced dopaminergic neuronal death in PD-related cell culture. Further, P110 treatment attenuated dopaminergic neuronal loss, dopaminergic nerve terminal damage and behavioral deficits in a MPTP-induced PD mouse model. Notably, P110 had no observed effects on mitochondrial function and cell survival under normal condition in culture and had no effects on animal behavioral status when treated in naïve mice. Together, we propose that inhibition of Drp1-mediated excessive mitochondrial fission might be a strategy for development of therapeutics towards treating PD.

Visuomotor Control in Patients with Parkinson's Disease

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Abstract

Previous studies have suggested that the deteriorated visuomotor control in patients with PD (Parkinson's disease) is due to deficits in sensory-motor processing rather than motor control. In this talk, I present our recent study that examined how PD and antiparkinsonian medication affect visuomotor control and the underlying sensory-motor system. We found that although antiparkinsonian medication improved visuomotor control in PD patients, they still showed significantly decreased control precision and response amplitude as well as increased response delay compared with healthy controls. Our model-driven analysis revealed that PD impairs the responsiveness and the predicting ability of the sensory-motor system as well as the stability of the neuromuscular system. Taking antiparkinsonian medication improves the responsiveness of the sensory-motor system. More importantly, it improves the ability of the sensory-motor system to make sensory predictions of the current control actions to anticipate the input error signals and generate control responses ahead of time up to the level of healthy controls. However, taking antiparkinsonian medication does not improve the stability of the neuromuscular system. Our study provides the first quantitative examination of the effects of PD and antiparkinsonian medication on the visual-stimulus-dependent sensory-motor and visual-stimulus-independent neuromuscular systems underlying visuomotor control. The findings have practical implications for developing sensitive assessment tools to evaluate the efficacy of different therapies for PD and preliminary screening and training tools for fitness-to-drive in PD patients.

Allogeneic/Xenogeneic Transplantation of Peptide-Labeled Mitochondria in Parkinson's Disease: Restoration of Mitochondria Functions and Attenuation of 6-Hydroxydopamine-Induced Neurotoxicity

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Abstract

Although restoration of mitochondrial function in mitochondrial diseases through peptide-mediated allogeneic mitochondrial delivery (PMD) has been demonstrated *in vitro*, the *in vivo* therapeutic efficacy of PMD in Parkinson's disease (PD) has yet to be determined. In this study, we compared the functionality of mitochondrial transfer with or without Pep-1 conjugation in neurotoxin (6-hydroxydopamine, 6-OHDA)- induced PC12 cells and PD rat models. We injected mitochondria into the medial forebrain bundle (MFB) of the PD rats after subjecting the nigrostriatal pathway to a unilateral 6-OHDA lesion for 21 days, and we verified the effectiveness of the mitochondrial graft in enhancing mitochondrial function in the soma of the substantia nigra (SN) neuron through mitochondrial transport dynamics in the nigrostriatal circuit. The result demonstrated that only PMD with allogeneic and xenogeneic sources significantly sustained mitochondrial function to resist the neurotoxin-induced oxidative stress and apoptotic death in the rat PC12 cells. The remaining cells exhibited a greater capability of neurite outgrowth. Furthermore, allogeneic and xenogeneic transplantation of peptide-labeled mitochondria after 3 months improved the locomotive activity in the PD rats. This increase was accompanied by a marked decrease in dopaminergic neuron loss in the substantia nigra pars compacta (SNc) and consistent enhancement of tyrosine hydroxylase– positive immunoreaction of dopaminergic neurons in the SNc and striatum. We also observed that in the SN dopaminergic neuron in the treated PD rats, mitochondrial complex I protein and mitochondrial dynamics were restored, thus ameliorating the oxidative DNA damage. Moreover, we determined signal translocation of graft allogeneic mitochondria from the MFB to the calbindin-positive SN neuron, which demonstrated the regulatory role of mitochondrial transport in alleviating 6-OHDA– induced degeneration of dopaminergic neurons.

Neuromuscular Effects of Vibration Therapy Regarding Motor Impairments

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Abstract

The complex interaction between sensory perception, motor integration in the central nervous system (CNS) and final output over the human locomotor system ensures flexible control to meet everyday movement requirements. Therefore, even small neurological impairments in the CNS lead to dysfunctional motor output. For instance, hyper-excitability of reflex pathways, such as in spasticity, might lead to modulated muscle stiffness control which can be observed in movement patterns. Recent techniques have been introduced in clinical and sportive settings to modulate the basis of motor control in the CNS such as vibration therapy. Based on high-frequency stimulation, vibration impacts sensory perception (muscle spindles) as well as central nervous control (supraspinal and spinal level). Therefore, in the CNS, enhanced intelligent input via the cortex (corticospinal) but reduced reflex-associated spinal excitability has been demonstrated after vibration. This might be associated with a greater central motor control. Especially patients suffering from reflex hyperexcitability affecting the locomotor system might benefit from those effects. The presentation gives an overview of the current state of the art regarding neuronal modulation and its motor effects following vibration. It focuses on the impact of vibration on a peripheral as well as spinal and supraspinal level assessed with complex electrophysiological approaches. With the modulation of motor control, the execution of voluntary movement might be improved. Possible applications of vibration in populations who could benefit from those effects are illustrated such as in patients with motor impairments due to neurological disorders.

Have We Over-Estimated the Role of Dopamine in Striatum as the Contributing Nigrostriatal Compartment to Locomotor Function? Evidence from the Aging Perspective

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Abstract

Major loss of dopamine in striatum coincides with the onset of motor impairment in Parkinson's disease (PD). Similar motor impairment can occur in aging adults. However, no study has yet reported striatal dopamine loss in aging at the 70-80% threshold associated with motor impairment in PD. Given the prevalence of aging-related motor impairment and rapidly increasing number of elderly, it is imperative to resolve the neurobiological basis for aging-related motor impairment and identify strategies to reduce risk or severity. Here, we present results from two independent studies that evaluate the relationship of striatal dopamine regulation with motor function. The first study evaluated the effect of 30% calorie restriction, beginning at middle-age, in rats on the motor decline over 6 months. The second study selectively reduced striatal dopamine content by tyrosine hydroxylase inhibition in young rats to evaluate the impact on locomotor activity. Calorie restriction significantly attenuated aging-related locomotor decline in association with an unexpected significant reduction in striatal dopamine content and tyrosine hydroxylase expression. However, in the substantia nigra, both dopamine and tyrosine hydroxylase increased. In the second study, selective inhibition of striatal tyrosine hydroxylase in young rats reduced dopamine content to ~30%, representing the decrease observed in calorie-restricted rats and the average loss reported in aging studies. Locomotor activity was unaffected by striatal dopamine reduction. Taken together, these results indicate locomotor activity may be dissociated from decreased striatal dopamine content or tyrosine hydroxylase function. Therefore, the neurobiological basis for the aging-related motor decline may be unrelated to dopamine neurotransmission in the striatum.

Osteoprotegerin Full Length Protein Mitigates Muscular Dystrophy in Fast-Twitch Skeletal Muscles

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Abstract

Background: Receptor activator of nuclear factor κB (RANK), its ligand RANKL and the soluble decoy receptor osteoprotegerin (OPG) are the key regulators of osteoclast differentiation and bone remodeling. We hypothesized that the dysregulation of the RANK/RANKL/OPG microenvironment is not limited to osteoporosis but is also very important in Duchenne muscular dystrophy (DMD).

Methods/Results: Full-length OPG-Fc treatment restores completely the force of fast-twitch dystrophic extensor digitorum longus (EDL) muscles (233% gain) and markedly protects against eccentric contraction-induced damage in MDX mice. On the other hand, selective depletion of muscle RANK with the Cre-lox conditional inactivation approach (MDX RANKmko) is less effective than full-length OPG-Fc treatment but significantly improves the force production of dystrophic EDL and Sol muscles by respectively 83% and 46%. Because full-length OPG-Fc serves as a decoy receptor for the tumor necrosis factor related apoptosis-inducing ligand (TRAIL) and RANKL, MDX mice were then treated with anti-TRAIL and anti-RANKL antibodies to decipher the dual function of OPG. The inhibition of RANKL and TRAIL for 10 days increased significantly the force of dystrophic EDL muscles by respectively 45% and 17%. To confirm the superiority of full-length OPG-Fc, MDX mice were treated with the truncated form of OPG-Fc that carries only the 4 domains of RANKL. As expected, the truncated OPG-Fc had similar effects than anti-RANKL, increasing the force production of EDL muscles by 43%.

Conclusion: Our results open novel treatments in which full length OPG-Fc may treat simultaneously osteoporosis and muscle degeneration in DMD patients.

Is Spinal Surgery Safe in Octogenarians?

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Abstract

Background: An aging population and advances in medical management often require spinal surgeons to increasingly operate on patients older than 80 years. The ability to predict complications and mortality rates would allow discrimination of which octogenarians are able to safely undergo spinal surgery. Therefore, the aims of this study were to determine whether comorbidities and extent of surgery were associated with complications in this age group, in addition to which comorbidity and physical status assessment scales were best associated with the development of complications following spinal surgery.

Methods: A retrospective cohort study was performed. Comorbidities and physical health status were analysed using the American Society of Anesthesiologists (ASA) physical ill- ness rating, Charlson Comorbidity Index (CCI) and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) score. Complications and extent of operation were sourced from patient records. The association between comorbidities/extent of operation and complications was analysed using negative binomial regression analysis.

Results: A total of 54 patients were included in our study (22 elective and 32 emergencies); 38 patients suffered at least one complication (14 elective and 24 emergencies, including six deaths). Increased CIRS-G and CCI scores were associated with increased incidence of total complications in the elective cohort. Increased number of operated spinal levels was also associated with complications.

Conclusion: Elective Spinal Surgery can be safely performed in well-selected patients over 80 years of age. However, the extent of surgery, CIRS-G, and CCI scores were associated with increased complications from spinal surgery in octogenarians.

Update on Effective Client-Focused Dementia Day Programmes in the Community: Improving the Quality of Life for People Living with Dementia and their Families

Annie Weir

Impact Research NZ and Honorary Academic, School of Critical Studies, Faculty of Education, University of Auckland, New Zealand

Abstract

Dementia Day programs play an important role in supporting the wellbeing of both older people living with dementia and their caregivers. To ensure day programs deliver on these aspirations, service providers regularly review services offered to older people. A study aimed at investigating the elements that make up an effective client-focused dementia day program and exploring the methods employed by organizations to measure the quality of outcomes of day programs was undertaken. A mixed methods approach was employed including an international literature review, document analysis, interviews, focus group, online survey, site observations, and a photovoice exercise. Participants included multiple stakeholders including service funders, those delivering the service, clients and their caregivers. The research revealed that effective day programs comprised five core elements, including activities aimed at improved client functioning; caregiver benefits; workforce capability; cultural responsiveness; and service processes. Reporting and auditing processes, as well as surveys, are reportedly used as methods to measure the quality of outcomes of day programs. I will provide an update on the original research to demonstrate the current relevance of the five core elements.

Immediate Biomechanical Changes in Response to Functional Electrical Stimulation of Peripheral Nerves in Patients

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Abstract

Individuals that suffer from neurological deficits often experience foot drop and knee instability during gait, related to a lack of active control of lower extremity muscles. These impairments combined, significantly hinder gait activity and may place the individual at an increased risk for falls. In order to compensate, individuals will often develop compensatory movements that

often produce a greater energy cost.

Common solutions for foot clearance and knee instability are the use of an ankle-foot orthosis (AFO) and/or functional electrical stimulation (FES) on lower extremity musculature. Advancements in technology have produced FES systems for the lower extremity that can produce a functional gait cycle. This descriptive study evaluates the BioNesss L-300 Plus® system effectiveness for individuals with neurological gait deficits.

Two participants with neurological impairments, using a repeated measures within-subject design, took part in one session of motion analysis data collection measuring joint angles at the hip, knee, and ankle. The resulting joint angles were compared during 4 phases of the gait cycle in three different environments: without FES, with BioNesss L-300® (calf only), and with BioNesss L-300 Plus® (calf and thigh).

Study results indicate improved joint angles and more activity in hip musculature with the using the BioNesss L-300 Plus® system for both participants as well as immediate improvements in gait speed. These findings indicate a possible improved and more efficient gait pattern, as well as more appropriate joint angles in all phases of the gait cycle by utilizing both the BioNesss L-300 Plus® system.

Communication-Principle-Based EMG-Bridge for Motor Function Rebuilding of Paralyzed Limbs

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Abstract

Introduction: The existing functional electrical stimulation (FES) for motor function rehabilitation uses artificial and mostly periodic pulse trains to stimulate the paralyzed muscles. Such a system can only achieve limited and coarse movements. To make the FES more effective and more natural, we have conceptualized the technique called electromyographic bridge (EMGB).

Methods: An EMGB system consists of a group of surface recording electrodes, a row of EMG-signal amplifiers and subsequent signal processors, a wired or wireless signal transmission system, a row of FES-signal generators, and a group of surfaces stimulating electrodes. The EMGB effectively forms pathways from the brain to the paralyzed limb via the spinal cord, the peripheral nerve, and the muscle of the controlling limb. Thus, a communication system is built up between the brain controlling the healthy limb and the paralyzed limb to be controlled, and the paralyzed limb can follow movements of the healthy limb.

Results: A prototype of 2-channel EMGB has been designed and tested for product registration inspection and used in clinical experiments in several hospitals. Paretic limbs and fingers of more than 60 hemiplegic patients have been treated. The rating scales have quantitatively shown that the EMGB device has significantly better rehabilitation effects than the existing FES devices.

Conclusion: The concept of an EMGB that can regenerate EMG-signals and rebuild motor function in paralyzed limbs has been presented with its system construction and functionality. The effects of the system have been demonstrated by clinical experiments using a prototype 2-channel EMGB device.

Intracranial Dural Arteriovenous Fistulas: Natural History and Rationale for Treatment with Stereotactic Radiosurgery

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Abstract

Dural arteriovenous fistulas (DAVFs) are acquired vascular lesions that abnormal dural arteries shunt blood directly into

the venous sinuses. Their natural course may be slowly progressive and the symptoms depend on their locations and patterns of the venous drainage. Cavernous sinus (CS) DAVFs often present with ocular manifestations, while patients with transverse/sigmoid (T/S) sinus DAVFs frequently experience a headache and pulsating tinnitus. In the late stage of the DAVF, patients may suffer from venous hypertension, increased intracranial pressure and fatal cerebral hemorrhages. The annual bleeding risks are estimated around 1.5-8.1%. DAVFs with antegrade sinus or cortical venous drainage (CVD) have been clinically regarded as benign, whereas DAVFs with retrograde CVD are considered aggressive. The treatment methods for DAVFs include surgical resection, embolization, and radiosurgery. For DAVFs with benign clinical symptoms, radiosurgery may be indicated as an initial treatment. For aggressive DAVFs with extensive venous reflux, or immediate risks of hemorrhage, initial treatment with endovascular procedure including embolization and angioplasty or with surgery is suggested. In this report, we present a 17-year experience using Gamma Knife radiosurgery for the treatment of 321 patients with DAVFs in various locations. The strategy of treatment, radiosurgical method and outcome of the patients are described. Our prescribed mean margin dose during radiosurgery was 17.2Gy. In our series, 98% patients had a stable or improved condition after radiosurgery. Stereotactic radiosurgery using the Gamma Knife is a safe and effective alternative for the management of DAVFs.

Less is More Redux: An Alternative, Empirically-Based Strategy for the Administration of Antipsychotic Medication in Order to Improve Outcome

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Abstract

The mechanism of action of antipsychotic medication as well as how often they should be given remains largely unknown. In spite of these uncertainties, the administration of antipsychotic medication, in appropriate amounts, remains the cornerstone for the management of patients with schizophrenia and is frequently the criterion by which successful treatment l is assessed. But the reduction in positive symptoms of psychosis is not the same as recovery. Emerging data has demonstrated that prolonged dopamine blockade, the suggested mode of action of antipsychotic agents, is cytotoxic producing atrophic changes in the brain. The sine qua non of schizophrenia, originally named by Kraepelin dementia praecox, is cognitive deterioration. We argue that current practice of medicating patients with schizophrenia is contributing to the intrinsic dementia leading to even more withdrawal and suffering.

A recent, long-term study concluded that patients receiving less accumulated antipsychotic medications had more fulfilling and productive lives than the control group receiving daily medication according to accepted practices. We propose a strategy of scheduled intermittent dosing to both control psychotic symptoms while minimizing the risks of excessive and perhaps unnecessary iatrogenic long-term effects of these drugs. Additionally, less medication would be expected to reduce other undesirable effects of antipsychotic agents such as metabolic side effects which contribute to reduced lifespans of these patients. Finally, scheduled intermittent dosing would significantly reduce the massive expenses of the drugs themselves as well as the costs of their medical sequelae.

Organization of the Primary Motor Cortex in Individuals with Spinal Cord Injury; Implications for Rehabilitation

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Abstract

Movement training for improving upper limb control is an essential component of rehabilitation for individuals with spinal cord injury (SCI). Understanding the cortical representation of arm muscles in SCI is fundamental to designing more effective movement training regimes. In uninjured individuals, the primary motor cortex (M1) contains overlapping muscle representations, an organization that reflects muscle synergies. This organizational feature has yet to be studied in SCI yet is considered a key element that defines the coordinated action of multiple muscles during human movement. Using Transcranial magnetic stimulation (TMS), we investigated the bilateral representation and overlapping distribution of muscles of the upper limb in chronic cervical SCI and aged-matched controls (n = 8, each group). Muscles studied included the abductor pollicus brevis (APB), flexor carpi radialis (FCR) and biceps brachii (BB) and the cortical territory (cm^2), overlapping territory (cm^2) of the target muscles, and center of gravity was computed. Results indicate a reduction in the cortical territory dedicated to all

three muscles in SCI (i.e. reduced complete overlap) compared to uninjured controls. Further, SCI had greater cortical territory dedicated to a single or dual muscle representation. These data indicate that overlapping organization is preserved in the motor cortex of SCI, however, the overlapping representation does not extend to all three muscles. The implication from these data is that movement training emphasizing synergies that incorporate all three muscles (APB, FCR, BB) may promote greater representational overlap (similar to uninjured controls) and provide functional gains in motor control.

Percutaneous Endoscopic Trans Pedicle Approach for Herniated Nucleus Pulposus in the Lumbar Hidden Zone

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Abstract

Although endoscopic procedures for lumbar disc diseases have improved greatly, treating migrated disc herniation is still a challenging task. Because of anatomic limitations, a rigid endoscope cannot effectively reach the herniated nucleus pulposus (HNP) in the hidden zone. The purpose of this study was to describe the trans pedicle approach for HNP in the hidden zone using the percutaneous endoscopic lumbar discectomy system and to demonstrate the clinical results. Materials and Surgical Technique: Under fluoroscopy, the percutaneous endoscopic lumbar discectomy cannula is placed on the superior articular process, and a trephine with a diameter of 7.3 mm is used to make a bone hole. Through the bone hole, an HNP in the hidden zone can be detected with a rongeur for percutaneous endoscopic lumbar discectomy, the HNP can be removed, and then the decompressed nerve root is verified. We have treated two cases of hidden-zone HNP using the trans pedicle approach. In all cases, the HNP was successfully removed, as confirmed by postoperative MRI. Clinical outcomes were acceptable.

Need for Palliative Care for Neurological Diseases

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Abstract

The role of Palliative Care (PC) was long underestimated among the neurologists as their main focus was on diagnostic procedures and specific pharmacological therapies. However, during the last years, the growing amount of literature on PC for people with progressive neurological diseases has pointed out the importance of this issue. It is now imperative that neurologists understand and learn to apply the principles of palliative medicine. In particular, when dealing with neurodegenerative disorders, neurologist must exhibit a good combination of high clinical experience, skills in communication and attention to bioethical general principles application. At variance with the traditional model of PC usually only applied to end of life stage, a new concept of PC promotes its application since the early course of progressive and disabling conditions, addressing all symptoms that worsen patient's quality of life over the entire course of the disease.

In our speech the heterogeneity and complexity of neurological nosography, the long duration of the advanced stages of many neurological diseases as well as the difficulty of identifying the end stage, will be examined. We'll focus on the peculiar features common to the most important neurologic disorders and particularly on MND, movement disorders, multiple sclerosis and dementia. As ad hoc training is far from being satisfactory in our country, our current purpose is to foster the culture of PC among neurologists and to implement training in the specific skills that have to be acquired.

Nociceptor PKC Isoforms Differentially Mediate Paclitaxel-Induced Spontaneous and Evoked Pain

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Abstract

As one of the most effective and frequently used chemotherapeutic agents, paclitaxel produces neuropathic pain that may persist after therapy. The mechanisms underlying this dose-limiting side effect remain unclear. Given the fundamental role of protein kinase C (PKC) in various pain conditions, this study aimed to investigate the functional involvement of PKC isoforms in the persistent pain induced by paclitaxel. Using multiple complementary methods, we found that upon the treatment of paclitaxel, a subset of PKC isoforms, namely βII, δ and ε, were rapidly activated in primary afferent sensory neurons. Persistent activation of PKC βII, δ & ε was also observed in spinal cord and dorsal root ganglion after paclitaxel treatment. Isoform-selective inhibitors of PKCβII, δ and ε (i.t.) effectively attenuated paclitaxel-induced mechanical allodynia and heat hyperalgesia. Strikingly, only PKCβII and δ, but not PKCε, were identified as mediators for the spontaneous pain induced by paclitaxel. Nociceptor hyperexcitability induced by paclitaxel correlated with the behavioral manifestations of pain seen *in vivo*. Our data demonstrate the involvement of three spinal PKC isoforms in different components of the pain phenotype generated by paclitaxel, offering novel targets for pharmacologically blocking paclitaxel-induced spontaneous and evoked pain.

I Can Literally Do This Blindfolded: The Blindfolded Code Training Simulation Exercise

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Abstract

Background: Communication errors are the leading cause of preventable patient harm in medicine. The purpose of this study is to describe a relatively well-established, yet not well-described, teaching technique that blindfolds the team leader.

Methods: A resident physician is provided a blindfold and positioned facing away from the resuscitation team. The team members surrounding the patient announce their names and role. They can only execute orders directed to them by name. The team leader can ask questions about the monitor; however, the team member must describe the appearance of the rhythm in layman's terms. The team leader must remember to switch out chest compressors, ask a team member to start bagging, have another team member insert an advanced airway, and interpret the potentially changing rhythm.

Results: A 15-item survey was administered to blindfolded code team leaders (N = 27) after the completion of their code resuscitation. Our results show 100% of residents agree/strongly agree that this knowledge could be transferred to the clinical setting. The majority of residents (81.5%) strongly agreed the blindfolded code training exercise was more challenging than typical code training exercises. Most residents (81.5%) strongly agreed the blindfolded code training allowed them to use the critical thinking skills acquired throughout residency. Nearly all residents (88.9%) strongly agreed that blindfold code training made them better utilize closed loop communication in comparison to typical code training to ensure task performance and/or completion.

Conclusion: Learners overwhelmingly found the blindfolded code training as a challenging and beneficial exercise to improve communication during resuscitations.

Towards a Curative Treatment for Multiple Sclerosis: A modified View of Transfer RNA

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Abstract

Multiple sclerosis is an immune driven neurological disorder that is characterised by the rapid expansion of T cells that are directed to self-antigens in the brain. Recently, we demonstrated that it is possible to control immune cell attack on the brain during ongoing disease using the mouse model of Multiple Sclerosis, Experimental Autoimmune Encephalomyelitis (EAE). Our strategy involves replacing a naturally occurring modification on transfer RNA, known as queuosine, with an artificial nucleobase, which we termed NPPDAG; a de novo designed small molecule (Boland et al. 2011; Fergus et al. 2015; Vargheese et al. 2017). We observed that NPPDAG treatment could result in an unprecedented reversal of clinical symptoms to baseline after only five daily doses, even when the EAE diseased animals had already succumbed to visible hind-limb

paralysis. As such, we are hopeful this therapeutic approach may be applicable to patients that are experiencing disease relapse or suffering progressive disease symptoms. Underpinning the complete remission of clinical symptoms was a dramatic reduction of markers associated with immune hyperactivation and the restoration of neuronal gene expression associated with neuronal repair, even after a single dose. Our data indicate that NPPDAG can selectively limit the expansion of activated T-cells, sparing the naïve T-cell population. This selectivity for activated immune cells is partly ensured by the fact that only transfer RNA of rapidly-proliferating, non-differentiated cells are under-modified with queuosine and are therefore receptive for NPPDAG incorporation. A deeper understanding of how RNA modifications influence the translation process could offer an exciting opportunity to eventually put a halt to this debilitating, lifelong illness.

Cognitive and Neurologic Outcome after Hypothermia Treatment for Perinatal Asphyxia

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Abstract

Introduction: Perinatal asfyxia can cause severe cognitive, behavioural and neurologic problems in children. To diminish cerebral damage neonates born with asfyxia: Apgar score at 5 minutes < 7, arterial umbilical cord pH < 7.10, prolonged reanimation or convulsions, are treated with hypothermia during 72-hours.

Methods: All children born between January 2008 and August 2011 who received hypothermia were included in the study. Neurologic examination, continous aEEG and an MRI-cerebrum after hypothermia treatment were performed. The Bayley Scales of Infant Development (BSID-III) were applied at the age of 24 months to determine cognitive and psychomotor development. At 5.5 years of age the movement-ABC-II, Child Behaviour Checklist (CBCL) and the Wechsler Preschool and Primary Scales of Intelligence (WPPSI-III-NL) were applied. At both ages a neurologic examination and a Gross Motor Function Classification System (GMFCS) score were given.

Results: Eighty infants were treated with hypothermia of whom 26 died in the first week after birth (32%). Of the 54 survivors 51 children were seen at the follow-up policlinic at the age of 24 months (94%). Forty-nine children were seen at the age of 5,5 years (91%) Three children (6%) appeared to have a cognitive outcome less than 85 (-1 SD). Two children (4%) had cerebral palsy (CP): 1 dyskinetic CP and 1 unilateral spastic CP, GMFCS-II respectively I.

Conclusion: Therapeutic hypothermia improves outcome in children with perinatal asphyxia. It reduces mortality without increasing disability. However, mortality and morbidity remains high so perinatal care has to be further improved.

Improving Cardiovascular Health in an Individual with Spinal Cord Injury in a Clinical Setting

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Abstract

Introduction: Individuals with spinal cord injury (SCI) face health disparities and a number of challenges in maintaining cardiovascular health compared to the able-bodied population. The causes are multifactorial including susceptibility to numerous medical conditions that impart a health hazard; illness behaviors leading to a disproportionate percentage of deaths as a result of preventable causes, and changes in the ability to exercise to maintain heart health. Therefore, establishing and providing effective interventions for individuals with SCI is vital, however, the majority of rehabilitation research has been performed in research laboratories.

Purpose: To identify the possible physiological adaptations gained from utilizing a functional electrical stimulation (FES) bike for aerobic conditioning to address the increased prevalence of cardiovascular risk factors exhibited by the chronic SCI population, ASIA A-D in an outpatient clinic setting.

Sample: Single-subject case study involving an individual with tetraplegia, enrolled in an outpatient wellness program.

Methods: Participant engaged in a cardiovascular endurance exercise program using an FES bike 30 minutes, 3 times a week for 6 months in a clinical setting, supervised by a physical therapist. The following variables were measured at baseline and at the end of the 6-month intervention: hemoglobin A1c, cholesterol (total, HDL/LDL ratio), and serum triglycerides.

Findings: Participant's A1c, LDL cholesterol, and triglycerides decreased, and HDL cholesterol increased after 6 months of intervention.

Conclusion: Cardiovascular conditioning with an FES bike conducted in an outpatient setting, can reduce cardiovascular risk factors and facilitate health in individuals with chronic SCI.

Alzheimer's Disease and the Inverse Warburg Hypothesis

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Abstract

Epidemiological and biochemical studies show that the sporadic form of Alzheimer's disease (AD) is characterized by the following hallmarks: an exponential increase with age, a prolonged prodromal phase, and an inverse comorbidity with cancer.

I will show that these hallmarks, which are now known to conflict with the Amyloid Cascade Model, are consistent with the Inverse Warburg Hypothesis. This hypothesis is a bioenergetic model of AD which postulates that the sporadic form of the disease is the result of *mitochondrial dysregulation* – an age-induced energy deficit in the mitochondrial activity of neurons, and the following cascade of events:

(1) *Metabolic reprogramming* – the up-regulation of oxidative phosphorylation in order to maintain adequate energy production and thereby ensure neuronal viability (the Inverse Warburg effect).

(2) *Natural selection* – competition for oxidative substrates between intact neurons with normal Oxphos activity, and impaired neurons defined by compensatory increases in oxidative phosphorylation.

(3) *Disease propagation* – the spread of metabolic abnormalities within the brain due to the selective advantage of reprogrammed neurons.

I will describe the empirical support for the Inverse Warburg Hypothesis and propose a new class of therapeutic strategies for AD, based on metabolic interventions.

Exploring the Microbiome and Alzheimer's Disease

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Abstract

This presentation aims to show how our microbiome may influence health and the way we age. We provide a background describing the links between oral bacteria and sporadic Alzheimer's disease (AD) and present our data from Next Generation Sequencing (NGS) comparing bacterial reads from AD and cognitively normal temporal cortex. Immuno-senescence alters the way our bodies respond to bacteria. Targeted immune responses wane with age as the less efficient and proinflammatory innate immune system predominates, resulting in a generalized rise in cytokines such as TNFα and increased bacterial load. One source of bacteria is the mouth and increased periodontal pocket depth promotes the proliferation of anaerobes capable of eliciting a particularly robust TNFα response from the oral epithelium; perhaps providing one route for bacterial ingress into the brain as raised TNFα compromises the integrity of the blood-brain-barrier (BBB). Sensitive techniques such as bacterial 16S ribosomal RNA gene PCR, combined with NGS, are now capable of detecting classically "asymptomatic" levels of bacteria. Though largely "immune-tolerated", bacteria escaping the mouth or gut can subvert otherwise benign biofilms to promote inflammation and inflammation has long been associated with AD. We suggest that for a subset of AD patients, aging favors the overgrowth of oral anaerobes, promoting inflammation, facilitating the ingress of bacteria into the brain and quietly influencing the pathogenesis of AD. Our findings emphasize the need for a better understanding of the host/microbiome interplay in neurological disease, which may provide a missing piece of the puzzle towards identifying new therapies and preventive strategies.

Everolimus Rescues the Early Learning and Memory Deficits and Ameliorates the AD-like Pathology in the 3×Tg-AD Mice

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Abstract

Overwhelming evidence shows a primary role for the mammalian target of rapamycin (mTOR) signaling in the pathogenesis of Alzheimer's disease (AD).

To investigate the relation between Aβ and mTOR, we injected the synthetic analogue of rapamycin, everolimus, into the cerebroventricular space of a triple transgenic mouse model of AD (3×Tg-AD), which develops age-dependent amyloid-β peptide (Aβ) and tau accumulation associated with cognitive decline. In particular, 6-month-old 3×Tg-AD mice and age-matched wild-type littermates (Non-Tg) were used. At this age, the 3×Tg-AD mice show early intraneuronal Aβ accumulation and tau mislocalization, which correlate with the onset of cognitive decline. The mTOR enzymatic activity and the levels of phosphorylated p70S6K, a downstream target of mTOR, was significantly increased in the 3×Tg-AD mice compared to control mice; centrally administered everolimus significantly reduced the phosphorylation of p70S6K and decreased the levels of APP and Aβ. The Aβ reduction was confirmed by immunohistochemical analysis.

We next sought to investigate the effect of everolimus on the learning and memory of 3×Tg-AD mice, using three independent behavioral paradigms: the novel object recognition test, a behavioral task mainly dependent on multiple cortical areas, the inhibitory avoidance, which is highly dependent on the hippocampus and amygdala, and the spatial version of the Morris water maze, a hippocampal-dependent task. Overall, our data indicate that everolimus infusion rescued the early learning and memory deficits in the 3×Tg-AD mice.

In conclusion, we show that autophagy induction via everolimus may represent a valid therapeutic strategy in AD when administered early in the disease progression.

The Green Tea Amino Acid Theanine for Cognitive Declines

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Abstract

Theanine is an amino acid present in the green tea leaves by 2-3% with a structural analogy to glutamine rather than glutamic acid. We have been studying on pharmacological profiling of this green tea amino acid in neural progenitor cells endowed to proliferate for self-renewal and to differentiate into neuronal, astroglial and oligodendroglial lineages in embryonic, developing and adult rodent brains. In cultured neural progenitor cells from embryonic rat and mouse neocortex, theanine promoted both proliferation and subsequent neuronal differentiation. In cultured progenitors from the dentate gyrus of adult nestin-GFP mice, theanine increased the size of neurospheres composed of clustered proliferating cells. In murine embryonic carcinoma P19 cells, similar facilitation was seen in proliferation and neuronal differentiation after exposure to theanine. Exposure to theanine up-regulated the glutamine transporter *Slc38a1* transcript in rat and mouse progenitors, whereas theanine failed to further promote both proliferation and neuronal differentiation abilities already facilitated in P19 cells stably overexpressing *Slc38a1*. Significant deterioration was found in cognition impairment scores measured by double-blinded physicians in healthy elderly age-matched people given normal green tea capsules compared to those with capsules of green tea enriched of theanine after daily oral intake for 7 to 12 consecutive months. We are now in progress to make several dietary supplement products enriched of theanine supposed to be beneficial for the prophylaxis of particular cognition impairments.

Risk Factors for Cognitive Impairment in Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS)

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Abstract

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disease with motor, psychiatric, and cognitive manifestations that occurs in carriers of the fragile X mental retardation 1 (*FMR1*) gene premutations. This was a retrospective chart review of 196 individuals (127 men, 69 women) with FXTAS. Forty-six (23%) participants were cognitively impaired, of whom 19 (10%) had dementia. Risk factors for dementia were examined (CGG repeat size; alcohol, benzodiazepine, and opioid use; diabetes; hyperlipidemia; hypertension; hypothyroidism; obesity; sleep apnea; surgeries with general anesthesia; depression; family history of dementia). Thirteen individuals with FXTAS and dementia were then compared with thirteen cognitively intact individuals matched on age, gender, and FXTAS stage. CGG repeat size was significantly higher (mean 98.5, SD = 22.2) in the dementia group, compared to the cognitively intact group (mean = 81.6, SD = 11.5; $p = 0.0256$). These results show that CGG repeat size is a risk factor for FXTAS dementia.

Gender-Specific Hippocampal Dysrhythmia and Aberrant Hippocampal and Cortical Excitability in the APPswePS1dE9 Model of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder resulting in progressive cognitive decline, memory loss and death. In this study, we analyzed the effect of AD on hippocampal and cortical frequency characteristics. Computerized 3D stereotaxic electrode positioning and implantable video-EEG radiotelemetry were used in APPswePS1dE9 AD mouse model. Long-term surface and deep intracerebral EEG recordings were performed from the primary motor cortex M1 and the hippocampal CA1 region in both genders. EEG recordings were analyzed for motor activity, electroencephalographic seizure activity and frequency characteristics using a FFT based approach.

Male but not female APPswePS1dE9 mice displayed increased motor activity during the dark cycle. Automatic seizure detection unraveled severe electroencephalographic seizure activity in both M1 and CA1 deflection in APPswePS1dE9 mice that turned out to be gender-specific. Seizure activity in APPswePS1dE9 was highly variable as has been reported for other AD mouse models. Frequency analysis of M1 and CA1 EEG recordings elicited complex age, gender, circadian and activity dependent alterations in the theta and gamma range. Females displayed an antithetic decrease in theta and increase in gamma power at 18-19 weeks of age whereas related changes in males occurred earlier at 14 weeks of age.

Our results demonstrate a systematic gender-specific evaluation of cortical M1 and hippocampal CA1 hyperexcitability/seizure and frequency analysis of APPswePS1dE9 mice and controls using implantable video-EEG radiotelemetry without restraint. The observed gender-specific network alterations in APPswePS1dE9 are likely to be related to cognitive and behavioral deficits and might serve as early biomarkers/EEG fingerprints for AD in the future.

Preventing Autism? Primary care on the front-lines

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Abstract

Autism spectrum disorder (ASD) is on the rise. Numerous causative factors have been proposed over the years, from parenting styles, environmental exposures, to genetic factors. The primary care physician has been often unwittingly caught in the debate, witnessing the rise of the anti-vaccine movement with deleterious public health results. Among the myriad of dissonant voices, however, we are beginning to see a unified picture of ASD trickle down from the fields of neurodevelopment and developmental psychology. Increasingly consistent theories of development have a potential to introduce evidence-based preventative measures in primary care. These efforts aim at the mother-infant dyad at a critical time of infant brain development. We are increasingly witnessing a change in focus in ASD to the mutual nurture-based interactions of the parent and infant, and our traditional concept of "early intervention" may simply not be early enough. Autism, after all, is a disorder in which multiple environmental and developmental factors converge on that joyful bond that unites mother and infant. It is in the context of this bond that primary care physicians encounter their young patients during well-infant visits, post-partum visits, and maternity floor rounds. Starting out from such encounters, the presenter draws on the most recent trends in neurodevelopment to explore new options in preventative care in infant mental health. Current nationwide efforts in advocacy in this filed are discussed, with the hopes for clinicians to actively foster the development of the brains of their little patients and prevent ASD.

Motor Proficiency and Level of Physical Activity in Preschool Children with Autism Spectrum Disorders

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Abstract

Although DSM-V does not cover a motor failure criterion to diagnose for autism spectrum disorders (ASD), growing body of the literature shows that children with ASD display lower motor proficiency than children without ASD (Jasmin et al. 2009; Lloyd et al. 2011; Lui & Breslin, 2013). Social-communicative issues, sensorial differences, failures in eye contact and limited experiences and lower participation in daily living and play skills could affect these issues in motor skills and level of physical activity (Block, Block & Halliday, 2006; Reid, 2005). In addition, the sedentary behavior and overweight/obesity trend is observed in children with ASD, who have possible secondary conditions such as using medicine (Curtin et al. 2010; Srinivasan et al. 2016). The purpose of this study was to explore a relationship among the gross and fine motor skills, autism severity, and level of physical activity in preschool children with ASD. 27 children, between 4-6 years old were assessed with Gilliam Autistic Rating Scale-2 Turkish Version (GARS-2-TV) for autism severity, Bruininks-Oseretsky Test of Motor Proficiency-2 (BOT-2) for level of gross and fine motor skills, and accelerometer (McRoberts, NL) for level of physical activity (steps, standing/locomotion time, total energy expenditure (TEE), relative TEE (%), and TEE in locomotion) in this study. The data was analyzed via SPSS 21. Autism severity, total score of the motor skills, average steps/24 hrs and active time (h/min) of the participants was determined as 95.37 ± 12.84, 5.30 ± 9.32, 8868 ± 4303, 5.47 ± 1.96, respectively. Results showed that children with ASD displayed lower motor proficiency based on norm scores. Although the number of daily step of the participants was not reflecting a sedentary condition, sedentary time (14.81/24 h) was higher than active time (5.47/24 h). Moreover, there was negative correlation between autism severity and motor profile scores of the participants ($r = -0.66$, $p < 0.005$). Findings reflect that a motor program should be implemented into their daily educational curriculums during the preschool period in children with ASD.

Clinicians with Dyslexia: Their Experiences and Coping Strategies

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Abstract

Dyslexia is a common Specific Learning Difficulty (SpLD) with a worldwide prevalence of 10%. Within the medical profession, dyslexia are also common. At one UK medical school, 10% of their students have a SpLD. This paper forms part of a series of research into medical students and junior doctors with dyslexia.

This is a qualitative study. An interpretive phenomenological approach was used, within an interpretivist research paradigm. Eight UK junior doctors were interviewed. Interviews were transcribed verbatim and transcripts analysed thematically by SS and JA in an iterative process.

An unexpected meta-theme was that of fear and isolation. This led to participants holding mixed views of their dyslexia and its impact upon them. Negative experiences with medical schools and postgraduate supportive/educational bodies were also reported. Participants survived the academic and emotional hardships of their medical studies in a variety of ways. These included a heavy reliance on their colleagues at undergraduate level. These social bonds were lacking and subsequently desired in working life. They would have liked to know how their colleagues with dyslexia were feeling and coping with the stresses of working life in a busy hospital – but they felt isolated and unable to share with others.

Our findings within this study are varied, and some are troubling. That said, these qualitative results may not be generalizable. For this reason, we are currently undertaking a survey to explore the impact of dyslexia on junior doctors in the UK, to quantify the findings presented here.

Nutrition from an Epigenetic Perspective to Optimize Birth and Child Health Outcomes

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Abstract

Background: The purpose of this review is to evaluate the dietary and environmental risk factors associated with poor birth outcomes as a result of epigenetic changes and determine the most effective nutrition educational interventions that can be taken to improve birth outcomes and child health. Articles exploring gene-environment interactions related to poor birth outcomes, family influence on maternal diet and web-based nutrition education aimed at college students, expectant parents or parents were reviewed.

Results: The literature review identified the following concepts and/or materials that need to be incorporated into the curriculum for effective nutrition interventions: importance of parent modeling of healthy food intake, home availability of healthy foods, restricting availability of junk and processed foods likely to contain pesticide or heavy metal residues, tables listing foods high in methyl donating and other nutrients important for key gene function, and tools for understanding food ingredient labels to determine which ingredients have allowable heavy metal concentrations.

Conclusion: Community and/or web-based interventions emphasizing the role of food ingredients and toxic substances in gene modulation and the development of diseases can result in significant dietary improvements and reductions in risk factors associated with poor birth outcomes such as gestational diabetes or autism. A healthier diet can be promoted among families through web-based nutrition instruction or diet support groups. Heavy metal levels (e.g. lead, arsenic, and inorganic mercury) in blood may be influenced by dietary intake of processed foods, and lower levels are associated with lower fasting glucose levels and symptoms of autism.

Diagnostic, Treatment and Prevention of Autism – A Continuation

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Abstract

In the conventional theory ASD (or Autism in short) is defined as neurological development disorder. So, most of research is geared toward the understanding and treatment of the central nervous system. But in Chinese medicine there is not a single meridian associated with the brain. There are at least six yang meridians that reach the brain. So ASD cannot be due to problem in the brain alone. There must be other problems in the child beside the brain. We have used infrared imaging system to take picture of the body of a child with ASD. There is always inflammation in the head and inflammation in some of the other seven areas: 1. Area on the head, each ASD child has different behavior problem and has different area of inflammation on the head. 2. Thyroid development is abnormal. 3. Immune system is overactive. 4. There are problems associated with large intestine and small intestine, 5. Bowel movement and urine has problems which shows up in inflammation in the Bladder meridian. –6. Some has inflammation associated with stomach meridian-7 Inflammation in the reproductive system. 8. Cold feet.

Measurement of Ocular Motor Abnormalities in Autistic Children Using Line-of-Sight Detection with Pixel Number Variation

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Abstract

In Japan, the prevalence rate of autism, a condition that affects communication and social development, is ten times higher than it was in the past. We aimed to establish an objective diagnostic criterion for children with autism spectrum disorder.

To this end, we conducted eye-tracking tests on children with autism and neurotypical children. Utilizing a technique, which uses afterimages to determine eye blinking, we obtained the pixel number variation (numerical value) in gaze direction based on the center of mass of pixels associated with the pupil. The results revealed that the autistic subjects failed to track the moving object. This finding demonstrates that this technique of measuring abnormality in pixel number is effective for distinguishing persons with autism from persons with typical development, and thus can serve as an objective criterion in the diagnosis of autism.

This analysis yielded a decision boundary clearly demarcating the autism and neurotypical distributions, and thus confirming the reliability of our method. Our assessment method allows the capture of eye movement based on afterimages without the need for any special equipment; only a camera-mounted PC is required. In other words, the technology provides a clear and simple method of detection. As such, it can serve as a supplementary assessment tool for child psychiatrists in diagnosing autism in children. Moreover, it can also assess learning efficacy and treatment efficacy among persons with autism in education settings.

The Addition of MRI to CT Based Stroke and TIA Evaluation does not Impact One Year Outcomes

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Abstract

Background: The 2010 American Academy of Neurology guideline for the diagnosis of acute ischemic stroke recommends MRI with diffusion weighted imaging (DWI) over noncontrast head CT. No studies have evaluated the influence of imaging choice on patient outcome. We sought to evaluate the variables that influenced one-year outcomes of stroke and TIA patients, including the type of imaging utilized.

Methods: Patients were identified from a prospectively collected stroke and TIA database at a single primary stroke center during a one-year period. Data were abstracted from patient electronic medical records. The primary outcome measure was death, myocardial infarction, or recurrent stroke within the following year. Secondary outcome measures included predictors of getting an MRI study.

Results: 727 consecutive patients with a discharge diagnosis of stroke or TIA were identified (616 and 111 respectively); 536 had CT and MRI, 161 had CT alone, 29 had MRI alone, and one had no neuroimaging. On multiple logistic regression analysis, there were no differences in primary or secondary outcome measures among different imaging strategies. Predictors of the primary outcome measure included age and NIHSS, while performance of a CT angiogram (CTA) predicted a decreased odd of death, stroke, or MI. The strongest predictor of having an MRI was admission to a stroke unit.

Conclusions: These results suggest that long-term (one-year) patient outcomes may not be influenced by imaging strategy. Performance of a CTA was protective in this cohort. A randomized trial of different imaging modalities should be considered.

Effect of Task Specific Training and Wrist-Fingers Extension Splint on Hand Joints Range of Motion and Function after Stroke

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Abstract

Background: Most stroke patients experience hand impairments that can result in persistent limitations in daily activities.

Objective: This study aimed at estimating the immediate and retention effects of task specific training and wrist/fingers extension splint on hand joints range of motion and function after stroke.

Methods: Twenty-four right handed patients with first ever stroke represented the sample of the study. The participants were randomly assigned into two equal groups. The study group received task specific exercises five times a week for an hour concurrently with wrist/fingers extension splint which was used two hours for each three hour (day and night) excluding exercises and sleeping hours for 16 weeks. The control group received traditional passive stretch and range of motion exercises. Manual dexterity and upper limb function were assessed by nine holes peg test and Fugl-Meyer upper extremity and hand. Goniometry was used for measuring wrist, metacarpophalangeal, thumb carpometacarpal joints active range of motion.

Results: Significant improvements were observed in nine holes peg test, Fugl-Meyer upper extremity and hand scores and ranges of motion at post-intervention and follow-up compared to pre-intervention at $P \leq 0.05$.

Conclusions: The results of this study provide an evidence that task specific training and wrist/fingers extension splint are effective in improving fingers dexterity, upper extremity function and wrist/hand range of motion.

A Pilot Randomized Control Trial of a Comprehensive Reminder System to Improve Health Behaviors in Stroke Patients

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Abstract

Background and Purpose: The health behaviors of hypertensive stroke patients in China are not satisfactory. This study was designed to test the effect of a Comprehensive Reminder System constructed from the Health Belief Model on health behaviors and blood pressure control in this population.

Methods: A randomized, parallel-group, assessor-blinded experimental design yielded participation of one hundred and seventy-four hospitalized hypertensive ischemic stroke patients. The intervention consisted of face-to-face and telephone health belief education, a patient calendar handbook, and weekly automated short-message services. Data was collected at baseline and 3 months after discharge.

Results: Three months after discharge, both groups showed improved health behaviors, yet compared with the control group, the intervention group showed significantly better health behaviors, including physical activity, nutrition, low-salt diet, and medication adherence. The intervention group had significantly decreased systolic blood pressure and increased blood pressure control rate. There were no significant changes in the behaviors of smoking or alcohol use.

Conclusion: At 3-months, use of the Comprehensive Reminder System based on the Health Belief Model, suggests improvement in most health behaviors and blood pressure control in hypertensive ischemic stroke patients. Modifications in the system would target smoking and alcohol use behaviors.

Neurovascular Protection by Ischemic Preconditioning

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Abstract

Neurovascular units (NVU) are the structural and functional elements of the brain and are susceptible to stroke. Ischemic preconditioning (IPC) induces ischemic tolerance against subsequent ischemic injury to the NVU and brain, but the protective mechanisms are unclear. We hypothesize that IPC activates transcription factor Nrf2 and upregulates downstream cytoprotective enzymes to protect the NVU and brain. MCAO was induced in male wildtype and Nrf2 KO mice, 12 min for IPC, and 60 min for stroke. Neurological function, infarct, and BBB integrity were examined. *In vitro*, cultures of rat primary neurons and mouse brain microvascular endothelial cells (MBMEC) were used to induce IPC and OGD. LDH release and permeability assays were performed. Nrf2 activation was evaluated. Our results showed that IPC reduced neurological dysfunction and infarct volume compared to control group; this protection was abolished in Nrf2 KO mice. IPC increased Nrf2 nuclear translocation and DNA binding activity, and upregulated HO-1. HO-1 was expressed in microvessels, astrocytes and neurons, the major NVU components. IPC also reduced Evan's blue extravasation after stroke, and upregulated claudin 5 and cadherin 5. *In vitro*, IPC robustly activated Nrf2 and induced HO-1, and protected neurons against ODG. Nrf2 knockdown with shRNA abolished the protection. IPC also reduced BBB leakage and LDH release after OGD in MBMEC cultures or astrocyte-MBMEC co-cultures. Moreover, treating MBMEC cells with Nrf2 activator attenuates BBB damage after OGD. Therefore, neurovascular protection underlies the mechanisms of ischemic tolerance via Nrf2 activation, making Nrf2 a promising target for stroke intervention.

Automated Carotid Artery Plaque Burden and Stenosis Severity Measurements: A Web-based Tool for Multicenter Clinical Trial

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Abstract

Objective: This study presents AtheroCloud (AC) - a novel, smart, telemedicine-cloud-based vascular screening, analysis and clinical report generation software package that computes: (i) carotid intima-media thickness (cIMT) and its variability; (ii) lumen diameter (LD) and its variability; (iii) Stenosis Severity Index (SSI) for stroke/cardiovascular risk screening using B-mode ultrasound.

Method: Arterial ultrasound scans from multiple clinical centers can be uploaded from their local server into the secure cloud and multiple users can compute the cIMT/LD/SSI using AC at the same time. cIMT and LD are computed using advanced detection methods, while SSI was computed using NASCET criteria. We benchmarked AC against the manual reading and validated against the commercial AtheroEdge™ (AtheroPoint, Roseville, CA, USA).

Results: 100 patients (73M/17F, mean age: 68 ± 11 years), IRB approved, Toho University, Japan, consisted of L/R CCA artery (200 ultrasound scans, Toshiba, Japan) were collected using a 7.5-MHz transducer. Mean cIMT readings for L/R carotids were (in mm): AC: (0.87 ± 0.20, 0.77 ± 0.20) and correspondingly for manual: (0.97 ± 0.26, 0.89 ± 0.29), respectively. Mean LD readings for L/R carotids were (in mm): AC: (6.49 ± 1.77, 6.66 ± 1.70) and correspondingly for manual: (6.29 ± 1.79, 6.45 ± 1.63), respectively. Combined L/R CC between AtheroCloud and manual for cIMT and LD readings were: 0.96 ($P < 0.0001$) and 0.99 ($P < 0.0001$), respectively. While considering an error threshold of 10% between AC and manual, our observations showed that 91.15% of cIMTs and 95.86% of LDs were under this threshold. For cIMT and LD readings using the cutoff risk thresholds (0.9 mm and 6 mm, respectively), the AUC for the ROC was 0.99 and 1.0, respectively. Benchmarking

results between AtheroCloud and AtheroEdge™ showed the mean cIMT difference was 2.27% and 3.75% for the left and right carotids. The corresponding mean LD difference for left and right carotids were: 1.95% and 2.26%, respectively. Our statistical tests that included Z-test, Chi-Square test, Mann-Whitney test, and Kolmogorov-Smirnov (KR) test demonstrated consistency, reliability, and accuracy.

Conclusions: The proposed AtheroCloud system is completely automated, fast, reliable, accurate, reproducible, anytime-anywhere, and smart tool for multi-center clinical trials and routine vascular screening.

Transient Ischemic Attack as the Unusual Initial Manifestation of Acute Promyelocytic Leukemia

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Abstract

Patients with acute promyelocytic leukemia (APL) are prone to both bleeding and thrombosis. Both of these have a significant impact on the morbidity and mortality of patients with this disease. Here we report a case of a 41-year-old male, who presented with transient ischemic attack (TIA) and early neurological deterioration (END) as initial menifestations prior to an ultimate diagnosis of acute promyelocytic leukemia (APL). This patient had no cerebrovascular risk factors or familial cerebrovascular disease. The patient experienced an acute ischemic stroke, verified by magnetic resonance imaging (MRI) in less than 24 h after his second hospital admission. Some APL patients suffer from cerebral ischemia as initial manifestation or during induction therapy, and patients presenting this condition may continue to deteriorate until their death during hospitalization. Thus, APL should be considered as a possible underlying disease in patients with TIA without cerebrovascular risk factors. Delayed diagnosis and treatment of APL can be fatal.

Dodecafluoropentane Improves Neurological Function Following Anterior Ischemic Stroke

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Abstract

Introduction: Dodecafluoropentane emulsion (DDFPe), an advanced oxygen transport drug, given IV Q90 min maintains viability in the penumbra during cerebral ischemia in the standard rabbit anterior stroke model (STND). This study investigated shortened dosage schedules of DDFPe in nonstandard posterior (NSTND) strokes following occlusions of the posterior cerebral arteries.

Hypothesis: DDFPe given at shortened schedules of 30 or 60 min intervals will reduce neurological deficits, percent stroke volume (%SV), and serum glutamate levels in NSTND ischemic strokes.

Methods: New Zealand White rabbits (N = 26) were randomly placed into three groups: A (n = 9) Q60 min saline injection controls, B (n = 9) 2% DDFPe given IV Q30 min, and C (n = 8) DDFPe Q60 min. DDFPe treatment was begun 1 hour after embolization. These groups were subdivided into STND and NSTND based on angiographically verified embolization of cerebral arteries. Neurological assessments and blood samples were done at 0.5-1 hour intervals. Rabbits were euthanized at 7 hours following embolization. Stained brain slices were measured for %SV.

Results: The 30 and 60 min subgroups did not differ and were combined as DDFPe-STND or DDFPe-NSTND groups. In the DDFPe-STND stroke group, the %SV, NAS, and serum glutamate were decreased vs. STND controls ($p = 0.0016$, 0.008, and 0.016 respectively). In the DDFPe-NSTND stroke group %SV, NAS, and serum glutamate did not differ statistically compared to NSTND controls ($p = 0.82$, 0.097, and 0.06, respectively).

Conclusion: More frequent dosage schedules provided no additional improvement. In anterior strokes DDFPe improves recovery but not in the more severe NSTND strokes.

Successful Medical Treatment of Bivalvular Infective Endocarditis Complicated with Young Stroke

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Abstract

Staphylococcus aureus bacteremia (SAB) associated with infective endocarditis (IE) is common. Ischemic infarction is the frequent neurological complication of IE. However, young stroke resulted from IE is rare. We herein report a case of acute mitral valve and aortic valve infective endocarditis complicated with young stroke 8 days after left foot debridement due to methicillin-sensitive Staphylococcus Aureus (MSSA) related cellulitis. The patient discharged successfully after 6 weeks of antibiotics with oxacillin in spite of valve replacement surgery due to hemorrhagic transformation of right frontoparietal lobes.

Mode of Action of Granulocyte Colony-Stimulating Factor (G-CSF) and/or S-Methyl-N, N-Diethylthiocarbamate Sulfoxide (DETC-MeSO) as a Novel Therapy for Stroke

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Abstract

In this study, we investigated the neuroprotective effect of G-CSF and/or DETC-MeSO in the rat middle cerebral artery occlusion (MCAO) stroke model. Focal cerebral ischemia was induced by occlusion of the left middle cerebral artery for 2 hours. Cortical blood flow and body temperature were continuously monitored by laser-Doppler flowmetry (LDF) and electric heating pad with rectal probe, respectively. DETC-MeSO was administered subcutaneously (5.6 mg/kg) for 4 and 8 days with the first injection occurring 24 hour after reperfusion. The infarct size in the left hemisphere was measured by 2, 3, 5-triphenyltetrazolium chloride (TTC) staining. The level of pro-apoptotic proteins, such as Bax, Bak, BAD and BIM declined, while BCL-2, anti-apoptotic marker, was markedly increased by DETC-MeSO. DETC-MeSO decreased Caspase-3 activation by preventing release of Cytochrome-C from mitochondria. Levels of the Endoplasmic Reticulum (ER) stress protein markers p-PERK, p-eif2α, ATF4, JNK, XBP-1 and GADD34 were markedly increased in MCAO models, and significantly declined after DETC-MeSO administration. Moreover, DETC-MeSO could downregulate CHOP, an induced apoptotic marker by ER stress. Similar results were also observed with the application of G-CSF. In conclusion, our results show that DETC-MeSO and/or G-CSF elicits neuroprotection not only through the suppression of ER stress but also through reduction of apoptosis. (Supported in part by James & Esther King Biomedical Program, Department of Health, State of Florida, Grant # 6JK08).

Improved Stroke Risk Stratification by Fusion of Two Machine Learning Systems Derived from Multiple Sources of Carotid Artery

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Abstract

Objective: Plaque growth in medial wall is bidirectional causing stenosis, unlike cIMT which is measured on one side (far) of the wall. Lumen diameter (LD) is used as biomarker for stroke-based risk stratification, while cIMT is used as biomarker for cardiovascular risk stratification. Each of these biomarkers leads to the design of its own machine learning (ML) systems for

high/low risk stratification. This study presents a greedy approach to combine two ML systems using the LD and cIMT as dual sources leading to the hypothesis that the performance of the combined system is better. We call this as an ensemble ML system.

Methods: The architecture of the system consists of running the two conventional ML systems based on the biomarkers cIMT and LD. Both ML systems use SVM classifier during training and testing protocols using linear and Gaussian kernel functions while adapting three kinds of cross-validation protocols (K = 2,5, and 10). The posterior high/low risk class probability is estimated for each the patient while using the two ML systems. Two strategies are adapted for the design of the ensemble ML: (i) by taking the average of the posterior class probability derived from the two individual ML systems; (ii) by fusing the two ML systems using a greedy approach, so the ensemble system is always better than either of the two individual ML systems.

Results: The database consisted of 407 patients acquired using Toshiba machine (Toho University, Japan). The mean accuracies and AUC of LD model is 97.71% (0.977), cIMT model is 98.89% (0.988), ensemble averaging model is 98.72% (0.988) and ensemble greedy model is 98.89% (0.990) for K = 10 partition protocol for Gaussian RBF classifier.

Conclusion: The risk estimation accuracy is better in ensemble-based approaches.

Neurological Complications of Sickle Cell Anemia

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Abstract

Sickle cell anemia (SCA) is a hereditary disorder of hemoglobin (Hb) where the sickle gene is inherited homozygously. The sickle mutation results in the formation of sickle Hb. Deoxygenated sickle Hb polymerizes and deforms RBCs into the sickle shape which, in turn, block micro- and macro-blood vessels. Clinically, sickle cell disease in general and SCA in particular is a triumvirate of: hemolytic anemia, pain syndromes and multi-organ damage. The acute painful vaso-occlusive crisis is the hallmark of SCA. Neurological complications of SCA are among the most serious and potentially fatal aspects of the disese. Before the advent of transcranial Doppler ultrasonography in the 1990s, the prevalence of stroke in children with SCA younger than 19 years was 11% and 24% in adults by the age of 45 years. Stroke could be ischemic, hemorrhagic, overt or silent. Ischemic stroke is more frequent in children, whereas intracerebral hemorrhage is more prevalent in adults. Approximately two thirds of children with cerebral infarction may develop further ischemic events within 3 years if not treated. Other neurological complications include transient ischemic attacks, seizures, meningitis and spinal cord infarction. The Stroke Prevention Trials in SCA showed that blood transfusion prevents the occurrence of primary and secondary strokes in children. The problem arises when children are transitioned to adult care where transfusions may be discontinued. One third of patients who discontinued transfusion after transition died within 3 years. Blood transfusion could be simple or exchange where the patient's RBC are removed and replaced with normal RBC.

Central Nervous System Symptoms and Stroke in Thyroid Storm

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Abstract

Thyroid storm is an endocrine emergency characterized by multiple organ failure due to thyrotoxicosis. It is known to have central nervous system (CNS) manifestations, such as agitation, restlessness, delirium, mental aberration/psychosis, somnolence/lethargy, convulsion and coma. The diagnostic criteria for thyroid storm (TS) used worldwide were established by Burch and Wartofsky, which however may misdiagnose thyrotoxic patients with severe nonthyroid illness. Therefore, the Japan Thyroid Association and Japan Endocrine Society established their diagnostic criteria for thyroid storm in 2012. Their criteria place more weight on CNS manifestation, which is characteristic to TS. Their guideline for management of TS was published in July 2016. It is also known that some TS patients have thromboembolism. The characteristic manifestations such as atrial fibrillation, hyperthermia, and DIC may cause hypercoagulability. We encountered severe case of stroke after TS despite anticoagulation with warfarin. Here we discuss about CNS symptoms and stroke in TS, demonstrating our significant experience with our own patients.

Need for Improvement of Residents Education in Order to Minimize Rediologic Errors in Detection of Cerebral Venous Thrombosis

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Abstract

Introduction: Thrombosis of the cerebral veins and sinuses is an emergency condition associated with intracranial venous congestion and consequent regional ischemia and cortical infarcts, most frequently hemorrhagic. The aim of this study is to evaluate the presence of radiologic errorin reporting cerebral venous thrombosis (CVT).

Methods: Computerized tomography (CT) and/or magnetic resonance imaging (MRI) of the brain were reevaluated in 10 patients with CVT, affecting cerebral sinuses, deep intracranial veins or cortical veins. Known predisposing conditions in these patients were coagulopathy, malignancy and petrous apicitis.

Results: Correct diagnosis was established immediately in only 40% of patients with CVT, while the mistake in the final report was evident in 30% of patients. In 10% of reports inconclusive finding was noted, while in 20% of patients with CVT initial report was wrong, associated with the correction in the final report. The disease was associated with two lethal outcomes while permanent neurological deficit was noted in one patient. Application of MRI with susceptibility-weighted imaging or T2 gradient-echo sequence was the most important in detection of the cortical veins thrombosis.

Conclusion: Education of both radiology and neurology residents in detecting both direct and indirect signs of cerebral venous thrombosis is extremely needed in order to decrease the rate of fatal outcome. Inclusion of susceptibility-weighted imaging or T2 gradient-echo sequence as obligate part of protocol, especially in patients with acute or subacute headaches may significantly improve the detection of thrombus within the cortical veins.

Lysosomal Damage and Inhibition of Autophagy Contribute to Secondary Injury in Neurotrauma

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Abstract

Autophagy, a lysosome dependent intracellular degradation process, plays an important role in maintaining cellular homeostasis, particularly in post-mitotic cells like neurons. Autophagic dysregulation has been implicated as one of the major contributors to neuronal cell death in neurodegenerative diseases but its role in response to acute traumatic brain injury (TBI) and spinal cord injury (SCI) has remained unknown. Our recent data demonstrate that autophagy flux (the progress of cargo through the autophagy system from sequestration into autophagosomes to delivery and degradation in lysosomes) is inhibited immediately after TBI and SCI. This inhibition is caused by compromised lysosomal membrane integrity and consequent decrease in lysosomal activity, leading to accumulation of dysfunctional autophagosomes. Our data specifically implicate phospholipase cPLA2 as a mediator of the damage to the lysosomal membranes after brain trauma and demonstrate that its inhibition can augment autophagy flux and improve functional outcomes after TBI. Additionally, we have demonstrated that at early time points (24h) after TBI and SCI inhibition of autophagy flux is restricted to neuronal cells and is associated with both apoptotic and non-apoptotic neuronal cell death. At later time points (3 days after injury) autophagy flux is inhibited specifically in the most activated phagocytic microglia and macrophages. Thus, inhibition of autophagy may contribute to development of secondary injury after neurotrauma by both increasing neuronal cell stress and death and by promoting neuroinflammation. We postulate that restoration and enhancing autophagy flux may represent future treatment strategies for TBI and SCI patients.

The Emerging Spotlight on Chronic Traumatic Encephalopathy

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Abstract

Although chronic traumatic encephalopathy (CTE) was first described over 90 years ago, it has re-emerged as a possibly more prominent late-life complication of athletes who have suffered repetitive concussion, repetitive head contact exposure, or both. CTE appears to be a distinct neuro-degenerative tauopathy characterized by perivasuclar foci of p-tau immunoreactive astrocytic tangles and neurofibrillary tangles in the neocortex and at the depths of the cerebral sulci. Behavior changes range from depression, suicidality and poor impulse control to progressive dementia, with or without parkinsonian features. CTE can only be diagnosed post-mortem, and most cases have been described from a single center that houses a large brain bank of former American football players. This talk will focus on why this syndrome re-emerged ¬-- both scientifically and politically -- coupled with an analysis of possible risk factors for development of this condition. Finally, policy implications in sport will be explored.

Outcome Monitoring in a Cognitive Rehabilitation Training with Virtual Reality not Immersive in Severe Brain Injury

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Abstract

This study has as its objective, the correlation of neuroimaging data under auditory stimulation, with the quantitative results of neuropsychological tests and the data recorded by VR. The experimental group, consisting of 4 patients with severe vascular acquired brain injury, aged between 19 years and 50 years, after an intensive period of 12 weeks of training on a daily basis for 90 minutes / day, underwent at T0 and T3 in RMNf and the administration of neuropsychological tests (ENB2). The cognitive training protocol foresees the exploration of the following skills: memory, attention, executive functions, calculation, understanding, telerecettivi systems and coordination. During the execution of the RMNf we had activated, through auditory input, the same skills that we activated with the administration of the test ENB2 and with the training, with the well-known exclusion limits of visual and motor sensory channel. The application of virtual reality in rehabilitation, is a recent application method. Throughout the use of RV Non-Immersive (Desktop VR) with ad hoc programs, we get the simulations mediated by the computer, which allow the patient undergoing training, to interact with an artificial environment similar to the real one and to evaluate with accurate precision, the functional parameters, expression of the improvement of the neuromotor and cognitive conditions. The presence of a playful background, stimulates the patient to participate the training. The existence of immediate visual and auditory feedback, implements awareness, motivation and mood.

A Novel Role for Neural Stem Cells in Post-Injury Astrogliosis

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Abstract

Reactive astrocytes are a heterogeneous population of cells that play key roles in the response to damage. It has been suggested that reactive astrocytes can "de-differentiate" into multipotent self-renewing neural stem cells (NSCs), as measured by their ability to form neurospheres *in vitro*. This led to the hypothesis that these de-differentiated reactive astrocytes could serve as a local source of multipotent cells for brain repair. Using genetic tagging and the neurosphere assay, we confirmed the

presence of stem cells at the injury site, but unexpectedly, we found that these cells originated in the subventricular zone (SVZ). We found that NSCs exit the niche and migrate to sites of injury, akin to progenitor cells. Furthermore, we demonstrated that this NSC migration is not limited to a single injury paradigm or brain location, Once in the damaged area, NSCs give rise to a novel subpopulation of reactive astrocytes that contributes to astrocyte scar formation. These findings highlight a novel role for the SVZ in post-injury gliosis.

Isolated Internuclear Ophthalmoplegia after Massive Supratentorial Epidural Hematoma: A Case Report and Review of Literature

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Abstract

Background: Isolated Internuclear ophthalmoplegia (INO) following traumatic brain injury (TBI) is rare, with the majority of reported patients suffering from minor head injuries. We report a patient with INO after a massive supratentorial epidural hematoma. We review the literature published since 1966, to summarize the mechanisms of injury and clinical outcomes of INO after TBI.

Case Description and Literature Review: A 54-year-old woman suffered from isolated INO 10 hours after emergent evacuation of a massive supratentorial epidural hematoma. The brainstem displacement caused by downward herniation led to a deficient blood supply. Magnetic resonance imaging showed an infarct at the right dorsal-medial pons. Her symptoms partially improved by 1.5 months postoperatively.

A total of 27 patients, including ours, with INO after TBI have been reported over the past 50 years. Young male patients (mean age, 30.8 years; male, 67%) are more common, and INO tends to be bilateral (67%). Infarction, hemorrhage, and fiber injury are nearly equally responsible for causing INO (35%, 35%, 30%, respectively). Most patients recover spontaneously; 65% gain full recovery at a median time of 3 months, and 91% have at least partial recovery at 4.5 months. The median time for full recovery after infarct, hemorrhage, and fiber injury is 12, 90, and 150 days, respectively.

Conclusions: INO should be in the differential diagnosis of TBI patients with an adduction deficit, despite the condition's rarity. Isolated INO is a relatively benign sequela of TBI, with all but 1 reported patient achieving at least partial recovery over 12 months.

Propylparaben as a New Pharmacological Strategy to Reduce the Short- and Long-Term Consequences of Status Epilepticus

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Abstract

The antimicrobial agent propylparaben (PPB) has been widely used as a preservative in drugs, cosmetics and food for more than 60 years. Studies indicate that PPB induces cardioprotection after ischemia-reperfusion injury by inhibiting voltage-dependent Na+ channels. *In vitro* experiments carried out in our laboratory revealed that PPB reduced the neuronal activity of hippocampus, an effect that is mediated by blockage of Na^+ channels. Because Na^+ channels participate in the generation of nerve impulses that trigger the release of neurotransmitters such as glutamate, their blockage by PPB may induce inhibitory and neuroprotective effects in the brain. Experiments focused on investigating whether the i.p. application of PPB after pilocarpine-induced status epilepticus (SE) reduces the acute and long-term consequences of seizure activity. Initially, we investigated the effects of a single administration of PPB after SE. Our results indicated that compared to the administration of diazepam (DZP) alone, a single dose of PPB after DZP injection diminished the seizures-induced high extracellular levels of glutamate in the hippocampus. This effect was associated with less neuronal damage in this brain area. We also found that the subchronic administration of PPB during the post-SE period is able to prevent the long-term consequences of seizure activity such as high hippocampal excitability and interictal glutamate release, astrogliosis and cell damage in hippocampus. Finally, we confirmed that the subchronic administration of PPB used in our experiments does not induce toxic effects. Our data indicate that PPB represents a new therapeutic strategy to reduce the consequences of seizure activity.

Migraine with Aura in the Preclinical Phase of Parkinson's Disease: Focus on Shared Lack of Habituation and Linked Cognitive Behavior

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Abstract

Objective: Several studies addressed the relationship between Parkinson's Disease (PD) and migraine, motivated by the established dopaminergic alterations in both diseases. Migraine with aura (MWA) has been reported in preclinical phase of PD (1, 2). Both disorders share a neurophysiological alteration i.e. lack habituation (3) that has been shown to be to be correlated with analytic cognitive behavior (4). The latter has been linked to migraine (5). We aimed at further investigating the relationship between PD and migraine and whether a link exists between analytic cognitive style of information processing and PD.

Methods: 30 idiopathic PD patients at early stage of disease, were randomly enrolled and matched with migraineurs with and without aura and healthy volunteers. All subjects underwent cognitive behavioral tests and migraine diagnosis according to IHCD II criteria.

Results: We highlighted significant higher scores in analytic style of information processing (Sternberg) in both patient's groups compared to controls. Scores in analytic information processing of auditory stimulations were higher in PD and in MWA compared to other groups (Anova: p values < 0,005). Lack of association with migraine was observed in PD patients, whereas 45% of them reported having had MWA attacks before the onset of disease.

Conclusions: We are highlighting association between MWA and preclinical phase of PD and improvement of MWA attack after the onset of PD. Moreover, we show an auditory analytic behavior linked to lack of habituation common to both diseases, warranting further research. On the basis of our results, we speculate a possible compensatory mechanism of migraine attack.

Migraine Diagnosis: Mimickers & Confounders

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Abstract

Migraine actively afflicts approximately 10% of the general population and is the most common primary headache disorder encountered by healthcare providers. Ironically, migraine's high prevalence can predispose to diagnostic inaccuracy. Not every headache suffered by a migraineur should be reflexively attributed to migraine; a history of migraine offers no protection against aneurysmal subarachnoid hemorrhage, meningitis, ischemic stroke or a host of other conditions that vary in clinical significance from inconsequential to life-threatening. On the other hand, non-migraineurs can have headache identical to migraine that are generated by another and potentially far more serious neurologic process. Around 20-25% of migraineurs experience aura, and aura symptoms often are mistakenly attributed to cerebrovascular disease or another paroxysmal disorder; such lack of diagnostic specificity may result in clinical management that is both expensive and clinically detrimental to the patient. Conversely, symptoms typical of aura may be generated by pathophysiology wholly unrelated to migraine, and in such cases insufficient diagnostic sensitivity may produce a catastrophic clinical outcome. Achieving optimal levels of diagnostic sensitivity and specificity is integral to the management of any medical disorder that is highly prevalent. This presentation is intended to assist clinicians in understanding better how to accomplish that goal in respect to migraine.

Selective Targeting of Nuclear Factor-kB p65 in Neurodegeneration

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Abstract

The increasing incidence and paucity of efficient therapy for neurodegenerative pathologies including Alzheimer's disease (AD) is an emerging health concern globally. Dysregulated activation of nuclear factor kappa B (NF- κβ) and inflammation is integral to the pathogenesis of neurodegeneration. Recently efforts are directed towards developing biological therapies to restore healthy balance by targeting specific molecules that promote imbalanced responses. We developed an innovative strategy to selectively target activated p65, the NF- κβ subunit associated with perpetuating neuroinflammation and neurodegeneration. Glucocorticoid induced leucine zipper (GILZ), is a NF- κβ interacting protein that suppresses p65 induced transactivation of pathological mediators. Mutational and binding analyses suggested that GILZ binds the transactivation domain of p65 (p65-TAD) exposed only in activated cells. Adopting homology modeling and docking analyses we designed peptide analogs of the polyproline type II helical p65 binding motif of GILZ. Referred to as Provaidya GILZ analogs (PGA), *in-silico* characterization was used to rank PGA based on structural similarity, near native docking and similarity in binding kinetics with p65-TAD as wild type GILZ. Functional evaluation showed that top five PGA are well tolerated and exhibit minimal lethal dose (LD_{50}) values comparable to known peptide drugs. Select two PGA peptides protected human brain cells against Aβ induced toxicity *in-vitro*. Significantly the two PGA suppressed microglial activation and inflammation in lipopolysaccharide induced murine model of AD. Together these data suggest that select PGA exhibit significant inhibitory potential to suppress neuroinflammation mediated neurodegeneration, the benefits of which can be extended to multiple diseases including AD and Parkinson's disease.

Thermography Examination of Abdominal Area Skin Temperatures in Individuals with and without Focal Onset Epilepsy

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Abstract

Early osteopathic theory and practice and the work of the medical intuitive Edgar Cayce suggested that the abdominal areas of individuals with epilepsy would manifest "cold spots." The etiology for this phenomenon was thought to be abdominal adhesions caused by inflammation and viscero-somatic reflexes caused by adhesions or injury to visceral or musculoskeletal system structures. Indeed, until that advent of electroencephalography in the 1930s-medical practice regarding epilepsy focused on abdominal neural and visceral structures. Two hypotheses were formulated to evaluate any abdominal temperature phenomena: 1. An abdominal quadrant division analysis would find one or more quadrants "colder" in the focal onset epilepsy group (ICD9-CM 345.4 and 345.5) compared to controls. 2. Total abdominal areas of individuals with focal onset epilepsy wound be colder than a control group. In the quadrant analysis, there were significant differences in that more epileptic patients had colder left upper abdominal quadrant temperatures than the control group (66.8% vs 44.9%; P = 0.030). In the total abdominal analysis, however, there were no significant differences. The results support the hypothesis that individuals with focal onset epilepsy have colder abdominal areas. In addition to presentation of this published study, further research and description of the contribution of osteopathic manipulative medicine to the neurosciences including seizure disorders and vertigo will be presented also included is description of ongoing research at UCSD on traumatic brain injury and Parkinson's disease patients.

Transcriptome Profiling of Neural Tissue in Vitamin E Deficient Animal Models

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Abstract

A key link between α-tocopherol (α-TOH) and neural health and disease was illuminated by the discovery of genetic mutations in the α-TOH transfer protein gene (*TTPA*) in ataxia with vitamin E deficiency (AVED). However, much remains unknown about the molecular pathogenesis of α-TOH deficient neurodegeneration. Experimental murine ($Ttpa^{-/-}$) and spontaneous equine α-TOH deficient models are impacted by tissue α-TOH levels and have striking histopathologic similarities to AVED. Using RNA-sequencing, we investigated the temporal interactions of genotype and diet on spinal cord gene expression in $Ttpa^{-/-}$ and $Ttpa^{+/+}$ mice and investigated downstream differential gene expression effects in equine

α-TOH deficiency. Strand-specific RNA libraries were sequenced at ~25M reads/sample, quality score trimming and raw read quantification performed and differential gene expression evaluated using limma-voom (murine) and the Exact Test in EdgeR (equine) and pathways analyses performed using PANTHER-pathway. In *Ttpa*$^{-/-}$ mice, up-regulation of the immune response, cytokine activity and defense pathways was observed between weaning and 6 months of age; an effect that was potentiated when mice were maintained on a vitamin E deficient diet. In equine neuroaxonal dystrophy, up-regulation of liver X receptor target genes were identified. These findings suggest a role of α-TOH in modulating the inflammatory response within the spinal cord during post-natal development and the potential downstream effects of a α-TOH deficiency through activation of nuclear receptors by lipid peroxidation.

The RNA/DNA-Binding Factor TDP-43 as a Player in Neurodisorders

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Abstract

Amyotrophic lateral sclerosis (ALS) is a fatal, adult-onset degenerative disorder of the motor neurons. The diseased spinal cord motor neurons of more than 95% of ALS patients are characterized with mis-metabolism of the RNA-DAN-binding protein TDP-43. More than 40 different single amino acid substitution mutations of TDP-43 have been identified in sporadic (sALS) and/or familial ALS (fALS). Thus far, all animal models for the basic or transcriptional studies of ALS are based on transgenic overexpression of the TDP-43 protein. We have generated mouse lines with homologous knock-in of a fALS-associated mutation and a sALS-associated mutation, respectively. Interesting, only the latter mice would develop a full spectrum of age-dependent ALS-like pathologies. Comparative analysis of the mutant mice and spinal cord motor neurons (MW) derived from their embryonic stem cells (ESC) suggests that different ALS-associated TDP-43 mutations have differential capability in causing ALS, likely dependent on the genetic background and environmental factors. If time allows, the possible role of TDP-43 as a link between neurodegenerative diseases and neuro-developmental disorders will be discussed.

A New Concept of Amyotrophic Lateral Sclerosis (ALS) and Parkinsonism-Dementia Complex (PDC) of the Kii Peninsula of Japan (Muro Disease)

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Abstract

A new concept of amyotrophic lateral sclerosis/ parkinsonism-dementia complex in the Kii peninsula, Japan (Kii ALS/PDC) has been proposed. Muro disease (syndrome) has been thought to be an endemic neurodegenerative disease in the southern part of the Kii peninsula. Recent intensive and comprehensive research has revealed it to be a complex, genetically heterogeneous disease. 1) Clinical features of Kii ALS/PDC are ALS, parkinsonism and/or dementia 2) Neuropathological features of Kii ALS/PDC are multiproteinopathy including tauopathy, α-synuclein and TDP-43 opathy, mainly tauopathy. 3) At present, there are four subtypes of the Muro disease: sporadic amyotrophic lateral sclerosis (ALS), ALS with C9orf72 gene mutation, ALS with optineurin gene mutation and Kii ALS/PDC with tauopathy. 4) Heterogeneity of geographical distribution. 5) Classical ALS dramatically decreased and ALS/PDC still continues. From these viewpoints, clinical and neuropathological criteria have been established for Kii ALS/PDC with tauopathy. Kii ALS/PDC with tauopathy is almost identical to ALS/PDC in Guam.

Physician-Assisted Death in Washington and Oregon Patients with Amyotrophic Lateral Sclerosis

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Abstract

Background: The Death with Dignity (DWD) Act went into effect in 1997 in Oregon and 2009 in Washington. Since then, 1876 terminally-ill patients have sought medications to end their lives in Oregon and Washington. Of these patients with

neurological disease, most had amyotrophic lateral sclerosis (ALS).

Methods: We compared institutional-level data specifically for ALS patients across three tertiary medical centers in the Seattle to publicly available data from the states of Washington and Oregon.

Results: In a retrospective case series, we describe 131 cases in Washington and Oregon who sought prescriptions under DWD. We identified 39 Washington ALS patients who requested DWD from our three institutions starting in 2009. The median age of death was 65 years (range 46-86); 77% used the prescribed medication. In Oregon, 92 patients sought prescriptions with 77% using the medication; median age of death was 67 years (range 34-86). In both states, the major patient reasons for requesting DWD reported by physicians were loss of autonomy and dignity and decrease in enjoyable activities. Inadequate pain control, financial cost, and loss of bodily control were less commonly reported. In both states, compared to the all-cause DWD population, more patients with ALS were non-Hispanic white, married, educated, enrolled in hospice, and died at home.

Conclusions: Participation in the DWD Act in Oregon and Washington is rare and safely achieves patient objectives of preserving autonomy. Our series illustrates some of the unique challenges that ALS patients encounter in the DWD process.

Pu-erh Tea Protects the Nervous System by Inhibiting the Expression of Metabotropic Glutamate Receptor 5

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Abstract

Pu-erh tea, a kind of post fermented tea, produced mainly in the Yunnan province of China. Pu-erh tea is a specialty pure natural green tea of Yunnan, with lipid-lowering, antihypertensive, antiarteriosclerosis, anticancer, hypoglycemic effect etc, although, the major constituents putatively responsible for these beneficial effects remain unknown. This study is based luciferase activity detection method by constructing a luciferase plasmid. In the research of Pu-erh tea, we found Pu-erh tea can inhibit the metabotropic glutamate receptor 5 (mGluR5) promoter activity. Based on these findings, the aim of the invention is to provide the application of drugs Pu-erh tea in preparing antiepilepsy or health care products, and provide a new means of treatment of epilepsy.

Dual Pathology Model of Temporal Lobe Epilepsy

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Abstract

Insults to the nervous system in infants may affect the integrity and function of selected neuronal circuits and may be the cause of several neurological disorder, including epilepsy. In an animal model of dual pathology of temporal lobe epilepsy with focal dysplastic lesion, induced by a focal cortical freeze lesion at birth, and hyperthermia induced seizures at postnatal day 10, chronic limbic seizures together with deficits in learning and memory and hippocampal atrophy at adulthood were reported. Electrophysiological study using this model reported change in intrinsic membrane properties of CA1 pyramidal cells and interneurons. In addition, an increase of both GABA-egic inhibition and glutamate-ergic excitation was noticed. The changes observed is not limited to somato-dendritic region but also affect axonal excitability. The advantage of this model is the late development of recurrent seizures, allowing the study of the changes induced by the dual pathology, and determine the one inducing seizures in adulthood and the one protecting against seizures induction in early weeks after the insults. This approach will allow for targeting specific systems for the development of therapeutic strategies in at-risk children and patients with temporal lobe epilepsy who suffered febrile seizures.

Quantitative Evaluation of the Enhancing/Depressing Characteristics of Extrinsic Factors on the Electroactivity of Neuronal Networks and Brain Organisms Based on VTMM

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Abstract

Introduction: In order to quantitatively evaluate the enhancing/depressing characteristics of extrinsic factors such as drugs, drinks, environment condition etc. on the electroactivity of neuronal networks, a method based on microelectrode arrays (MEA) and called voltage threshold measuring method (VTMM) is introduced. Its effectiveness is validated by using three types of extrinsic factors which act on two kinds of neuronal networks as examples.

Methods: The VTMM-based system mainly consists of a voltage pulse signal generator, an MEA device, a multi-channel neural signal amplifier, and an oscilloscope. Two kinds of neuronal networks were used as examples. The first kind is of neuronal networks formed on the MEA device by cultured hippocampal neuron cells separated from fetal rats of voltage thresholds (V_{Th}) of neuronal networks were determined by applying voltage pulses with increasing amplitude at one electrode of the MEA and monitoring recording from other electrodes until one typical neural spike was observed on the oscilloscope consistently. As the example of the electroactivity-enhancing factor, acetylcholine (Ach) was chosen, and as the example of the electroactivity-depressing factor, ethanol (alcohol). As one example of environment conditions and complex-functional factors, the body temperature was chosen. Besides six series of data about the voltage thresholds of two kinds of neuronal networks versus changed degrees of three influence factors on the threshold voltages, six fitted curves and four mathematic formulas were obtained.

Results: From the control experiments which were made under normal culturing conditions, i.e. with standard culturing medium temperature (T_M) of 37 °C, the baseline threshold voltages of 56 mV and 31 mV have been obtained for hippocampal neuronal networks cultured on the MEA and brain slices, respectively.

From further experiments following results have been obtained:

1) V_{Th} was inversely proportional to the ACh concentration (C_{ACh}), the mathematic formulas are 60-10.848 mV*mL/μg and 31.7-8.550 mV*ml/μg for hippocampal neuronal networks and hippocampus brain slices, respectively, and action potentials (APs) could be invoked without electrical stimulation when C_{ACh} increased to 33 μmol/L. The enhancing characteristic of Ach on two kinds of neuronal networks has been quantitatively demonstrated.

2) In the ethanol concentration (C_{EtOH}) range of $0 \le C_{EtOH} < 110$ mmol/L, the V_{Th}–values of hippocampal neuronal networks have an exponential dependency to C_{EtOH}, the threshold voltage dependency can be given by $V_{th} = 72.677e^{0.022CEtOH}$, and no APs could be invoked when C_{EtOH} exceeded 110 mmol/L, and in the range of $0 \le C_{EtOH} < 120$ mmol/L, the V_{Th}–values of hippocampal brain slices have a similar exponential dependency to C_{EtOH}, the threshold voltage dependency can be given by $V_{th} = 34.407e^{0.029CEtOH}$, and no APs could be invoked when C_{EtOH} exceeded 120 mmol/L. The depressing characteristic of ethanol on two kinds of neuronal networks has been quantitatively demonstrated.

3) For both hippocampal neuronal networks cultured on the MEA and brain slices, the V_{th}-vs.-T_m curves are of U-pattern. When T_M dropped from 37 °C, the V_{th}–values increased. When T_m rose just a little higher than 37 °C, the V_{Th}–values fall to only several mV. The hippocampal neuronal networks lost their electroactivity when T_m dropped below 34 °C or rose above 42 °C, and the hippocampal brain slices lost their excitability when Tm dropped below 33 °C or rose above 43 °C. The enhancing/depressing dual characteristic of medium temperature on two kinds of neuronal networks has been quantitatively demonstrated.

Conclusion: The MEA-based VTMM is quantitative and effective for evaluating the electroactivity of neuronal networks. The Ach, ethanol, and temperature sensitivity experiments demonstrated the validity of the proposed VTMM. Quantitative results have been obtained for the evaluation of the electroactivity of hippocampal neuronal networks cultured on the MEA and hippocampal brain slices which under the influence of the enhancing factor acetylcholine (Ach), depressing factor ethanol (alcohol), and enhancing/depressing factor medium temperature.

Anti NMDAR Encephalitis: What to do When Clinical Presentation Goes Atypical?

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Abstract

There are non-psychiatric illnesses that, nevertheless, show prominent psychiatric symptoms. Neuroimmunological disorders have a special position in this group. For instance, multiple sclerosis is not a psychiatric disease, but it may include important mood disturbances and psychosis. An emerging group of autoimmune encephalitis has risen in the past decade. Though not considered as classical psychiatric disorders, they frequently show psychotic symptoms and affective dysregulation. They were initially called "limbic encephalitis" in the late sixties, but after Joseph Dalmau and colleagues published ten years ago a pivotal paper about anti-NMDAR encephalitis as a paraneoplastic syndrome, it has become a growing research field, and there is increasing evidence regarding the underlying mechanisms of what we nowadays call autoimmune encephalitis. Anti-NMDAR encephalitis has a well described clinical progression with five stages, but there are also milder or incomplete presentations, so-called *formes frustes*. I recently published a case report about an atypical expression of the disease in which antibodies were confirmed in cerebrospinal fluid, and ataxia was the cardinal symptom after a short period of psychosis. Some clinical features were crucial to suspect autoimmune encephalitis in that patient, and I consider they should be part of the psychiatrist´s strategies for diagnosing. Here I present a clinical tool to approach this kind of patients by an acronym: "*INVISIBLE*", for *IN*-sidious onset and progression, *BI*-zarre psychosis, *SI*-lent fever, and *BLE*-nd of symptoms and diagnoses. The "B" instead of "V" indicates the atypical presentation..

Cord Blood Mononuclear Cell Therapy by Side-Cisternal Puncture for Delayed Encephalopathy after Carbon Monoxide Poisoning (DEACMP) with Positive Outcomes

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Abstract

Background: Delayed encephalopathy after acute carbon monoxide poisoning (DEACMP) is a disease with poor prognosis. In cases with late neurological sequelae, if no significant improvement is seen with hyperbaric oxygenation therapy or other routine methods, stem cell transplantation may become necessary for the treatment.

Methods: A, Cord Blood Mononuclear Cell Therapy by side-cisternal puncture(Gong Dianrong's method) B, The Mini-Mental State Examination score (MMSE score) (12) and Activities of Daily Living score (ADL) were calculated before and after Mononuclear Cell treatment (Gong Dianrong's method) for one year.

Results: In this report we describe the clinical outcomes of 15 patients who were treated with mononuclear cell therapy by side-cisternal puncture(Gong Dianrong's method) for delayed encephalopathy after carbon monoxide poisoning. After three months' Mononuclear Cell therapy the MMSE scores and ADL scores were statistically better than pre-treatment scores.

Conclusions: The mononuclear cell therapy by side-cisternal puncture(Gong Dianrong's method) may be an innovative treatment with positive outcomes, which is practiced in the clinic, simple and safe. The immediate availability cord blood Mononuclear Cell in cerebrospinal fluid (CSF) may be a particular advantage for patients who require row Mononuclear Cell transplantation for treatments of their central nerve diseases.

The Cuprizone-Induced Changes in 1H-MRS Metabolites and Oxidative Parameters in C57BL/6 Mouse Brain: Effects of Quetiapine

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Abstract

Cuprizone is a copper-chelating agent and able to induce oligodendrocyte loss and demyelination in C57BL/6 mouse. Recent studies have used the cuprizone-fed mouse as an animal model of schizophrenia to examine putative roles of altered

oligodendrocytes in this mental disorder. The present study reported the effects of cuprizone on brain metabolites and oxidative parameters with the aim of providing neurochemical evidence for the application of the cuprizone mouse as an animal model of schizophrenia. In addition, we examined effects of quetiapine on the cuprizone-induced changes in brain metabolites and oxidative parameters; this atypical antipsychotic was shown to ameliorate the cuprizone-induced demyelination and behavioral changes in previous studies. C57BL/6 mice were fed a standard rodent chow without or with cuprizone (0.2% w/w) for four weeks during which period they were given sterilized saline or quetiapine in saline. The results of the proton magnetic resonance spectroscopy (1H-MRS) showed that cuprizone-feeding decreased 1H-MRS signals of N-acetyl-L-aspartate (NAA), total NAA (NAA + NAAG), and choline-containing compounds (phosphorylcholine and glycero- phosphorylcholine), suggestive of mitochondrial dysfunction in brain neurons. Biochemical analyses showed lower activities of catalase and glutathione peroxidase, but higher levels of malondialdehyde and H_2O_2 in the brain tissue of cuprizone-fed mice, indicative of anoxidative stress. These cuprizone-induced changes were effectively relieved in the mice co-administered with cuprizone and quetiapine, although the antipsychotic alone showed no effect. These findings suggest the toxic effects of cuprizone on mitochondria and an antioxidant capacity of quetiapine, by which this antipsychotic relieves the cuprizone-induced mitochondrial dysfunction in brain cells.

Anti-Oligoglycosyl Ceramide Antibodies-Mediated Neurological Disorder: A Subtype of Multiple Sclerosis?

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Abstract

Multiple Sclerosis is mainly involved in central nervous system (CNS) but not peripheral nervous system (PNS). On the other hand, chronic inflammatory demyelinating polyradiculopathy (CIDP) is mainly involved in PNS but not CNS. Recently, however, new clinical phenotypes where both CNS and PNS are impaired are emerging such encephalomyeloradiculoneuropathy (EMRN) and combined central and peripheral demyelination (CCPD). In 2014, we discovered new type autoantibodies against oligoglycosyl ceramide in sera and cerebrospinal fluid (CSF) from these patients and the titers of these autoantibodies were well correlated with disease status (*Neurology 2014*), where we proposed that these autoantibodies can be the surrogate marker for EMRN. Since then, we have collected more than 15 similar cases from Japan, China, and US. The clinical phenotypes seem rather broad; some developed CNS impairment first and followed by PNS involvements, others vice versa. However, most of EMRN cases well responded to immunomodulatory therapies employing large dosage of immunoglobulin supplement and steroid pulse therapy. Among autoantibodies against oligoglycosyl ceramide, anti-lactosylceramide antibodies (α-LacCer) were most frequently present in these patients. Previous studies have shown that α-LacCer act on neutrophils and activate its inflammatory responses. We will report the results of biochemical and immunological investigation on neuronal cells as well as detailed clinical pictures of EMRN patients.

Poster Presentations

The Use of CranioSacral Therapy for Autism Spectrum Disorders: Benefits from the Viewpoints of Parents, Clients, and Therapists

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Abstract

Objective: The objective of this preliminary study was to explore: the use of CranioSacral Therapy for persons with Autism Spectrum Disorder, the demographics of participants, and the retrospective interpretation of reported changes related to the intervention. Participants included therapists, parents, and clients.

Methods: Recruitment of participants was conducted through electronic networks and online questionnaires surveys were provided. Demographic questions posed to gain preliminary understanding of the rationales for such treatment and surveys were unique to each subject group. All participants were given a 20-item functional behavior checklist as a means to measure their perception of change attributed to this intervention. Open-ended comments were also encouraged to explore perspectives

from their experiential treatments. The qualitative data collected was analyzed via Inductive Content Analysis. The data was stored on excel and analyzed manually and independently by all 3 authors.

Results: A total of 405 people responded to the recruitments and of the participants who completed surveys, 264 were therapists and 124 parents. Only a small sampling of clients responded. The demographics of professionals using CST for ASD, their level of CST training, and their qualifications to work with ASD were reflected. Demographics and referral sources of parents, and other details of their experiences, were surveyed. Perceived changes to the use of CST were explored through analysis of responses to both the Likert scale as well as the open comments. This study found that there was a positive response by all 3 targeted groups leading to the authors concluding that further study into precise mechanisms of how CST benefits Autism Spectrum Disorders (ASD).

Conclusions: This preliminary study introduces the concept of CranioSacral Therapy as a treatment option of symptoms associated with ASD. Its clinical use has been available for three decades but little empirical studies exist. The results of the survey suggest that CST is already being professionally recommended as a treatment. The participants' experiences reported or observed changes, suggest that CST for ASD holds value to pursue future clinical study.

A Phenomenological Analysis of Autism and Empathy

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Abstract

Phenomenology's first tenet is that consciousness is intentional: always "of" something or someone. Phenomenology registers all behaviors, even autistic behaviors, as acts of meaning-making, although inchoate until consciousness can grasp that which is other than itself. According to the discoverer of phenomenological method, Edmund Husserl (1859-1938), the stages of development from unborn to neonate to child result from the young one's growth towards empathy. Empathy (not the I in the other's place which remains I), however, is exactly the recognition of otherness that those on the autistic spectrum never develop. This paper will navigate the sequence of meanings required for empathy to bring to light certain lacunae in autistic achievements. The neurotypical fetus enacts a constitutive a priori in movements that it makes in the womb. Thumb-sucking, kicking, turning, the unborn's consciousness begins to locate itself in its space. In the succession of its acts, it achieves its first inklings of its temporality. From these beginnings, the neonate is born into a world which already awaits it. Movement is necessary to grasp the sensations that make up a perceptual world. The healthy infant moves towards what attracts it or turns from that which repeals it. In either case, the infant reacts to sensory possibilities in keeping with its own virtualities, intending associations across sensory fields as stable objects. It can see what it touches. The infant incapable of such synthesis does not constitute others as bodily objects who can be known as other subjects the I can feel with.

DNA Damage, DNA Susceptibility to Oxidation and Glutathione Redox Status in Patients with Alzheimer's Disease

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Abstract

Purpose: The current study was carried out to determine oxidative DNA damage, H_2O_2-induced DNA damage which reflects DNA susceptibility to oxidation, and the ratio of GSH/GSSG which plays an important role in protection of target molecules from oxidation in patients with Alzheimer's disease (AD).

Method: A total of 67 patients with AD were involved in the study. DNA strand breaks and H_2O_2-induced DNA damage were determined in lymphocyte DNA by the comet assay. The GSH and GSSG levels in the erythrocyte lysates were measured with a commercial spectrophotometric kit and then the ratio of GSH/GSSG was calculated.

Results: DNA strand breaks and H_2O_2-induced DNA damage were higher, the ratio of GSH/GSSG was lower in the AD group than those in the control group. There was no relation between Mini-Mental State Examination score of the patients and

strand breaks, H_2O_2-induced DNA damage and GSH/GSSG ratio.

Conclusion: Oxidative DNA damage in the terms of DNA strand breaks is higher in peripheral lymphocytes of patients with AD. High level of DNA damage may be derived from increased DNA susceptibility to oxidative stress. As a matter of fact, level of DNA strand breaks after *in vitro* incubation of lymphocytes with H_2O_2 is higher in the patients with AD than those in the controls. Taken together, both increased systemic DNA damage and DNA susceptibility to oxidation may be derived from decreased GSH/GSSG ratio in AD patients. This finding shows the importance of antioxidant support in AD management.

Immediate Effect of Neuromuscular Bandage Applied on Trunk to Reduce Spasticity in Upper and Lower Limbs in Children with Cerebral Palsy

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Abstract

Spasticity is the most common clinical form of cerebral palsy. In the bibliography are studies on the effects of Kinesio Taping® (KT) on the nervous system and mainly on the management of muscle tone.

Objective: To evaluate the immediate effect of the application of KT on trunk to reduce spasticity in upper and lower limbs in children with cerebral palsy GMFS V.

Method: We performed a prospective comparative study, clinical testing approach, quasi-experimental with measures pre-test-post-test, where 21 patients with cerebral palsy GMFS V were studied. Spasticity was assessed with the modified Ashworth scale for upper and lower limbs, bilateral adductor tone scale hips and goniometric measurements in the four limbs, all of the above made by the specialist physician in pediatric rehabilitation. For statistical analysis, nonparametric Wilcoxon test was used for paired samples, after verification of the distribution of the data using SPSS version 17.0, considering a P value ≤ .05 as statistically significant.

Results: The obtained reduction in spasticity in all four limbs, decreased muscle tone hip adductors and increased ranges of flexion, extension and abduction of the hips and shoulders, bending, knee extension and ankle was statistically significant, $P < .05$ and clinically relevant in an application session of neuromuscular bandage.

Conclusions: The neuromuscular bandage applied on the trunk is an effective method to reduce spasticity. The positive results of this initial study could be presented as a promising field of action for future research in the area, an improvement in the quality of life of patients with this type of chronic complications.

Dehydroepiandrosterone- A Silent Observer or Powerful Modulator of Glutamatergic Neurotransmission after Transient Ischemic Attack?

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Abstract

Excessive stimulation of N-methyl-D-aspartate receptor (NMDAR), specifically its 2B subunit (NMDAR2B) represents one of the essential factors involved in molecular cascade that accompanies brain damage during ischemia. Several modulators of its activity and expression have been proposed, such as dehydroepiandrosterone (DHEA). Although effects of DHEA have been extensively investigated over the years, its influence on hippocampal glutamatergic neurotransmission, specifically on the expression of vesicular glutamate transporter 1 (vGlut1), NMDAR2B and postsynaptic density protein 95 (PSD-95) in transient ischemic attack still remains questionable. Hence, for the purpose of the experiment, adult male Wistar rats were treated either with vehicle or DHEA (20 mg/kg *i.p.*) 4 h following sham operation or 15 min bilateral common carotid artery occlusion (I/R). Hippocampal synaptosomal fraction was isolated 24 h after the surgery while protein levels of NMDAR2B, vGlut1 and PSD-95 were determined using Western blot technique. In current experimental setup, ischemic insult remarkably increased NMDAR2B and vGlut1 protein levels compared to vehicle treated sham group, while their decrease by subsequent DHEA treatment, although noticeable, was not statistically significant. Significant decrease of PSD-95 protein level was observed in

all experimental groups compared to vehicle treated sham. According to obtained data I/R may over- activate glutamatergic neurotransmission in rat hippocampus and highlights DHEA as its potential modulator. Since PSD-95 is involved in anchoring synaptic proteins, among others NMDAR2B, and plays an important role in NMDAR-mediated excitotoxicity that promotes neuronal death following transient ischemic attack, further studies that would elucidate these opposites but interesting findings are necessary.

The Defeat of the Peripheral Motor Neuron in Spinocerebellar Ataxia Type 1 in the Republic of Sakha (Yakutia)

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Abstract

Among the indigenous population of North-Eastern Siberia - the Yakut population celebrated an extremely high-level accumulation of the mutant SCA1 gene, responsible for the development of spinocerebellar ataxia type 1 (СЦА1). Soreness СЦА1 makes up 36.6 per 100 thousand among the Yakut population. The age of onset of manifestation of the signs of the disease is in inverse exponential relation to the number of CAG repeats in the mutant gene. Severe symptoms and rapid progression of the pathological signs observed in cases of the disease at a young age. Analysis of lifetime cases СЦА1 showed that this indicator, except for the level of expansion of CAG repeats depends on a number of accelerating and slow down the progression of the disease factors. One of the accelerating factors leading to fatal outcome is the development of respiratory insufficiency due to lesions of the peripheral cervical motor neuron in the anterior horns of the spinal cord.

The aim of the study was to identify the neuronal disorders of the peripheral motor neuron in the SCA 1, as a factor accelerating the development of the disease for the development of methods of secondary prevention.

Materials and Methods: In total, the study included 40 people, including 22 of the carriers of the mutant gene СЦА1 and 18 healthy individuals formed the control group. Patients СЦА1 ataxia scale (ICARS) were divided into three groups, depending on the severity of ataxia. When conducting electroneuromyographic investigated the following parameters: residual latency, the amplitude of M-response amplitude of sensory response conduction velocity in motor and sensory fibers. For signs of motoneuronal of the lesion was assessed by parameters of F-waves and potentials of fibrillati.

Conclusion: Clinical, genetic and electrofunctional studies have shown that the clinical picture of SCA 1, in addition to cerebellar-pyramidal syndrome, perhaps the defeat of the peripheral motor neuron in the region of the bulbar nuclei groups of the brain stem and motor neurons of the cervical spinal cord. This indicates a Multisystem neurodegenerative process at the SCA 1 and aggravates the disease.

Recognition of Emotional Situation in AD Patients

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Abstract

Objective: Patients with Alzheimer's disease show deficit in emotion processing. Aim of this study was to explore the ability of Alzheimer's patients (AD) in recognizing the emotional significance of events.

Methods: Twenty-eight AD patients (experimental group age range 60-78 yo, education 5-13) were compared to 28 healthy subjects (Health Control Group - HG) matched to AD. All participants were submitted to a neuropsychological battery and to three experimental tasks: 1) Recognition of Emotional Setting Task, composed by 60 black and white drawings depicting emotional situations to be associate to picture of the appropriate facial expression, 2) Emotion Naming Task, 20 pictures of facial emotion expression to be named 3). Emotion Recognition Task: 20 items each presenting pictures of two different facial emotion expressions to be distinguished.

Results: The percentages of correct answers were analysed. Analysis of Variance showed a significant effect on groups, tasks and group by tasks. The experimental group was divided in two subgroups on MMSE: AD: 16 < MMSE < 20 and MCI: 20 < MMSE < 24. Both subgroups had significantly worst performance than HG. MCI had better performance than AD group in all three experimental tasks. MCI group had worse performance than HC group both in the Emotion Naming Task and in the

Emotion Discrimination Task, but in the Recognition of Emotional Setting Task.

Conclusion: Our findings suggest that the experimental group was less efficient than HC group in processing emotion; furthermore, within the experimental group, MCI were better than AD subgroup.

The Mechanisms of Actions of Beta-Amyloid Peptide and Donepezil on Long-Term Potentiation in Rat Hippocampus

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Abstract

Beta-amyloid peptide (Aβ) is believed to contribute to memory disturbances in neurodegenerative diseases. Long-term potentiation (LTP) in hippocampus is widely recognized as a cellular model of learning and memory. Literature data show that Aβ suppresses long-term potentiation (LTP), and mechanisms of suppression vary depending on experimental conditions. We suppose the following explanation of the inhibitory effect of Aβ on LTP observed in our experiments (20 min treatment of rat hippocampal slice with 200 nM Aβ). Aβ interacts with mGluR5 (antagonists – MPEP and SIB-1757) on outer surface of neuronal membrane and triggers a cascade: activation of phospholipase, IP_3 production, IP_3 receptor activation (antagonist - 2APB), release of Ca^{2+} from the endoplasmic reticulum, the activation of calcineurin (antagonist –FK 506), the intensification of the process of dephosphorylation of proteins. Donepezil is both an agonist of sigma1 receptor and a potent acetylcholinesterase inhibitor, and it is widely used for the treatment of neurodegenerative diseases. It has been shown in our experiments that donepezil rescues hippocampal LTP impaired by Aβ. We suppose that the effect of donepezil develops with the involvement of sigma1 receptors. This assumption is supported by the following results: agonist of sigma1 receptor PRE-084 simulates the effect of donepezil, and antagonist of sigma1 receptor haloperidol removes the effect of donepezil. We believe that the agonists of sigma1 receptor are able to attenuate the pathological effects of Aβ due to interaction of sigma1 receptors and IP_3 receptors on endoplasmic reticulum and blockade of calcium signal caused by Aβ.

Thalamocortical Sensorimotor Circuit Damage Associated with Disorders of Consciousness for Diffuse Axonal Injury Patients

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Abstract

The relationship of structural and functional brain damage and disorders of consciousness (DOC) for diffuse axonal injury (DAI) is still not fully explored. We employed diffusion tensor imaging (DTI) and resting-state fMRI (RS-fMRI) to examine the changes of resting activations and white matter (WM) integrity for DAI with DOC. WM damages were observed in the body and genu of the corpus callosum, right external capsule (EC) and superior corona radiate (SCR), left superior cerebellar peduncle (SCP) and posterior thalamic radiation (PTR). The RS-fMRI revealed augmented amplitude of low-frequency fluctuation (ALFF) in the anterior cingulate cortex, hippocampus, insula, amygdala and putamen, and reduced ALFF in the precuneus, thalamus, pre-central and post-central gyri. Correlation analysis identified positive associations between the Glasgow Coma Scale (GCS) and activation of the precuneus and between GCS and DTI measurements in the left PTR and SCP, but a negative correlation was found between GCS and activation of the thalamus. Cross modality association analyses indicated that activations of the amygdala and postcentral gyrus were correlated with DTI measurements of the right EC and left PTR respectively. These results implicate that the WM damages in thalamocortical sensorimotor circuit and aberrant brain activity responding to self-awareness and sensation are critical factors to DOC, which expand the current understanding of the neural mechanisms underlying DAI.

Dysgenesis of the Corpus Callosum Presenting as First-Onset Seizures in an Apparently Normal 32-year Old Female

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Abstract

Dysgenesis of the Corpus Callosum is a brain abnormality involving the large nerve fibers connecting the two hemispheres of the brain. The corpus callosum connects the left and right cerebral hemispheres and facilitates interhemispheric communication. It is the largest white matter structure in the brain, consisting of 200–250 million contralateral axonal projections. The corpus callosum is important in integrating motor, sensory and cognitive functions. When it is malformed, these functions might be affected. This case report documents a patient with a malformed corpus callosum. She came in for first-onset generalized tonic clonic seizures. As part of a routine workup for patients with first-onset seizures, a computed tomography (CT) scan of the brain was done. It revealed dysgenesis of the corpus callosum. She was started on valproic acid and was discharged improved. Callosal disorders usually present with some degree of neurologic impairment. The index case however has no detectable neurologic deficits and is apparently normal. The rarity of a dysgenetic corpus callosum mandates more epidemiological studies to further elucidate this disease.

Keywords: Dysgenesis; Corpus Callosum; Seizure; Normal

Developmental Outcomes in Children with Malnutrition

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Abstract

Background: Developmental challenges and malnutrition are two major childhood health problems in the developing world and malnutrition is a major risk factor for poor development, which can, ultimately, lead to developmental challenges with life-long implications, affecting the individual, the family and the society at-large.

Methodology: We searched PUBMED & COCHRANE REVIEW databases, published documents from WHO, UNICEF, UNDP and the World Bank and citations thereof, for relevant literature on brain development and malnutrition, dietary supplementation and brain development.

Results: Effect of nutrition on the developing brain has been thoroughly studied and established. Under-nutrition, particularly during fetal and 1st two years of post-natal life, is a major risk factor for poor neuro-development, leading to motor, cognitive and speech delay, as well as behavioral problems and learning disabilities. Macro and micro-nutrients, like proteins, Iron, Iodine, Zinc, vitamin-B, C and D, choline and essential fatty acids are essential for proper brain development. Supplementation of pregnant and lactating mothers, infants and toddlers with multiple micro-nutrient, specially Iron, Iodine, Vitamins B12 and Folate and choline has been found beneficial, particularly among the vulnerable population.

Conclusion: Dietary supplementation for pregnant and lactating mothers, infants and toddlers along with a congenial socio-emotional environment and cognitive stimulation from an early age can go a long way to help the child at-risk attain his developmental potential.

Different Basal Forebrain Nuclei Display Distinct Projecting Pathways and Functional Circuits to Sensory Cortices in the Mouse

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Abstract

Neuronal groups within basal forebrain (BF) provide cholinergic innervation to sensory, motor and prefrontal cortices. Previous results suggest anatomo-functional organization of BF corticofugal projection system that may control cortical sensory processing. Acetylcholine transmission is mainly guaranteed by disperse cholinergic neuron groups within BF: medial septum, horizontal/vertical (HDB/VDB) limbs of diagonal band of Broca and nucleus basalis magnocellularis (B) providing most cholinergic innervation to sensory, motor and prefrontal cortices. Early anatomical descriptions of BF cholinergic projections were consistent with the notion of diffuse ipsilateral pathways to the cortex; however, previous results suggest a refined anatomical and functional topographical organization of BF-cortical projection system that may control cortical sensory processing in a specific manner.

To elucidate if there are common or separate pathways linking BF with sensory cortices retrograde fluorescent tracers and optogenetic stimulation were performed in B6. Cg-Tg(Chat-COP$_4$*H$_{134}$R/EYFP, Slc$_1$8a$_3$)5$^{Gfng/J}$ mice (European Community Council Directive 2010/63/UE). Fluoro-Gold (FG) and Fast-Blue (FB) were injected into somatosensory (FG) and auditory/visual cortices (FB). For optogenetic stimulation single-unit recordings were performed with tungsten microelectrodes on BF; cortical field potential was recorded through tungsten macroelectrodes.

Anatomical results revealed FlGo and FB labeled-neurons in BF: 62% in VDB/HDB were double-labeled while 38% were single-labeled (65% FlGo, 35% FB); double-labeled neurons in B averaged 32%, while single-labeled neurons by either tracer were roughly 50%. We also observed that there were ipsi- and contralateral projecting neurons which projecting pathway depends on the BF nuclei studied. Optogenetic results indicate that light stimuli applied on BF neurons induced spike firing, cortical desynchronization and an increase of auditory and tactile cortical responses. Stimulation of VDB/HDB mainly induces an increase of tactile responses in S1 cortex while stimulation of B area increased both auditory and tactile responses in A1 and S1 cortices. Our studies suggest that cholinergic projections to the cortex are organized into segregated and overlapping pools of neurons that may modulate specific cortical areas.

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Comparison of Executive Functioning Skills in Individuals with Parkinson Disease and Individuals with Traumatic Brain Injury

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Abstract

The aim of the current study is to examine executive functioning (EF) skills in individuals with Parkinson disease (PD), individuals with traumatic brain injury (TBI), and age-and-gender matched neurologically healthy adults across clinical and real-life based tasks. Executive functioning (EF) skills include range of cognitive skills including task inhibition, task management, planning, self-monitoring, coding, and manipulation of information (Funashahi, 2001). These skills are extremely important for efficient daily life functioning. Both PD and TBI are neurological conditions which are associated with cognitive deficits including attention problems, memory deficits, and EF deficits (Cipresso et al. 2014). Few existing studies have investigated the effects of these two neurological conditions (PD and TBI) during real-life functioning such as a shopping task. There is a critical need to develop and examine ecologically valid measures which accurately reflect the EF performance of individuals with neurogenic disorders including PD and TBI (Jacoby et al. 2013). Therefore, the present study aims to examine EF performance across different (clinical and real-life) tasks. Specifically, the three groups are compared on lab-based cognitive and EF tests (including Stroop test, Design Fluency Test, Montreal Cognitive Screening), self-reported measures for EF performance, and during a real-life shopping task. Preliminary results indicate trends of EF deficits among individuals with PD and individuals with TBI when compared to the control group. Findings from the study will thus provide information regarding how participants in the three groups perform in different settings as well as the relationship between self-awareness and real functioning among these participating groups.

Anatomical Specificity of Matrix Metallo-proteinase-9 Expression in Glioblastomas: A Voxel-Based Mapping Analysis

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Abstract

Purpose: Matrix metalloproteinase-9 (MMP-9) is an important factor involved in tumor cell invasion, tumor growth, and angiogenesis. The aim of the current study was to investigate the anatomical specificity of MMP-9 expression in glioblastomas by using voxel-based neuroimaging analysis.

Methods: Clinical information and preoperative magnetic resonance images of 133 patients with glioblastomas were reviewed. Evaluation of MMP-9 expression was performed by using immunohistochemistry. Tumor lesions were manually

segmented and based on the structural image of each patient and then registered to a standard brain atlas. Voxel-based regression analysis was subsequently performed to identify the specific brain regions that were associated with MMP-9 expression levels.

Results: A significantly larger lesion volume of T2-hyperintensity was demonstrated in tumors with low MMP-9 expression compared to those with high MMP-9 expression ($p = 0.010$). No significant difference was found in the lesion volumes of the contrast enhancement areas between the two groups ($p = 0.452$). The major correlated cluster with high MMP-9 expression was identified in the right frontal lobe, while a cluster located at the posterior region of the right lateral ventricle was correlated with low MMP-9 expression.

Conclusion: Voxel-based statistical analysis revealed the anatomic specificity of MMP-9 expression levels in glioblastoma. The identified correlation between molecular biomarkers and anatomical distribution may increase our understanding of the biological characteristics of glioblastoma and provide new insight into the molecular subtypes of glioblastoma.

The Green Tea Amino Acid Theanine Promotes mTOR Signaling in Neural Progenitors

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Abstract

Chewable tablets enriched of theanine, which is a green tea amino acid analogous to glutamine rather than glutamate, is now on sale in Japan as a dietary supplement expected to be beneficial for the prophylaxis of cognitive declines on the basis of our previous findings using neural progenitor cells. In this study, we evaluated the phosphorylation of intracellular proteins relevant to the mammalian target of rapamycin (mTOR) pathway, which is responsible for the cell growth in a manner sensitive to intracellular glutamine levels, in neural progenitor cells. Exposure to theanine not only up-regulated transcript expression of the glutamine transporter Slc38a1, but also facilitated the phosphorylation of mTOR and downstream proteins, in neurospheres composed of clustered proliferating progenitors from embryonic mouse neocortex. Although stable overexpression of Slc38a1 also promoted the phosphorylation of mTOR-relevant proteins in undifferentiated embryonal carcinoma P19 cells, theanine failed to further accelerate the stimulated phosphorylation in these stable Slc38a1 transfectants. In embryonic murine neurospheres previously exposed to theanine, a significant increase was seen in the number of cells immunoreactive for the neuronal marker protein MAP2 after spontaneous differentiation in the absence of theanine. These results suggest that theanine promotes the mTOR signaling pathway required for self-renewal along with accelerated neurogenesis in murine undifferentiated neural progenitor cells.

Dust Storm and Neurological Disorders

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Abstract

The main purpose of the study was to explore the potential hazard of dust storm on the occurrence of neurological disorders inpatient care in Taiwan. Data were drawn from inpatient care, meteorological records, air pollutant data, and dust storm records to analyze the associations of dust storm episodes with the daily number of stroke admissions. ARIMA method (Auto-Regressive Integrated Moving Average) was used to examine the associations between dust storm episodes and the logarithm of the daily number of stroke inpatient care, after adjusting for the time-trend effect, ambient temperature, season, and air pollutants. The results showed that dust storm to be significantly associated with an acute higher risk for overall stroke inpatient care in Taiwan. The magnitude of the ratio for excessive stroke inpatient care to the mean number of daily stroke inpatient care was about 7.7%, 22.0% and 12.0 % for the dust-storm day, post-dust storm day 1, and post-dust storm day 2, respectively. After adjusting for the time trend effect, the ambient temperature, and season, the increased risk for stroke inpatient care was still significant during post-dust storm days 1, 2, and 3. From the public health point of view, an alarm system indicating dust storm events and their potential hazards should be incorporated into local medical services. The patients who have existing risks for neurological disorders should be advised to prevent their personal exposure to dust storm events and wear adequate protective equipment.

Neurological Disorders and Stock Markets

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Abstract

The primary aim of this study is to examine the impact of wealth on neurological disorders in Taiwan. To explore whether the way people manage their wealth affects the risk of neurological disorders occurrence, we analyze the relationship between the change in margin trading amount and inpatient care for strokes. We obtain data from the Taiwan National Health Insurance Research Database (NHIRD) and Taiwan Stock Exchange (TWSE) to examine the possible relationship between inpatient care for strokes and the margin trading of securities. Autoregressive moving average with exogenous variable (ARMAX) regression is used to examine the relationship. The result shows that leveraged investment is associated with an increase in stroke inpatient care. *Our analyses reveal that an increase in the daily change of margin trading positions leads to more stroke inpatient care in the following days, especially the third and sixth days after the increase.* We also find that the effect of margin trading is significant for males and people between 45 and 74 years old, while it is not significant for females, for people above 74, and for people below 45. In summary, borrowing money through margin trading to buy stocks is quite risky to health, especially if the prices of those stocks fall past a certain level or if there is a sudden and severe drop in the stock market.

Directed Screening of Anti-Oligomeric Aβ42 Antibodies

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Abstract

Although many risk factors have been found so far to be responsible for Alzheimer's Disease, the beta-amyloid peptide has always been considered the culprit of this dementia. We have reported two anti-oligomeric Aβ42 single-chain variable fragment (scFv) antibodies, named AS and MO6, obtained from the human antibody library of AD patients or a healthy donor. Both them not only specifically recognize the oligomeric Aβ42, but also attenuated Aβ42-induced cytotoxicity.

Based on these results, here some novel anti-oligomeric Aβ42 scFv antibodies were obtained from the directed-evolution library of AS and MO6. A few of these mutant antibodies had a similar antigen-recognizing specificity to AS or MO6, but their function could be regulated by some other small molecule medicines. For example, some small molecule medicines were found to be able to enhance the protective effects of these mutant antibodies against Aβ42 cytotoxicity on the model cells *in vitro* (Figure 1), but did not affect the protective functions of other similar antibodies.

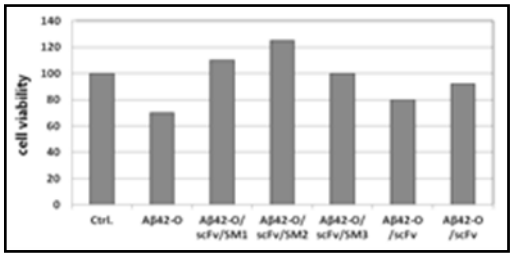

Figure 1: The protective effects of mutant scFvs and small molecule medicines (SM)

Obviously, the functional characteristic of these mutant scFv antibodies were related to their structures or conformations. The functional mechanism and the relationship of these mutant anti-Aβ42 scFv antibodies with the small molecule nootropics is worthy of further study.

Medications and Pollution during Pregnancy – Do They Contribute to Neuro-developmental Diseases?

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Abstract

There is a growing concern that medications and pollution may contribute to the increasing incidence of neurodevelopmental diseases in children. For example, treatment with glucocorticoids, which are administered to women in threat of preterm labor to accelerate lung maturation in the premature infant, associates with adverse mental health in childhood. Several reports of paracetamol use during pregnancy show it may be associated with both ADHD and autism. SSRI usage during pregnancy is linked to early life depression. Pollutants are also linked to neurodevelopmental diseases in children. Since it may be difficult to correct for confounding factors in human studies, it is desirable to develop animal models and downstream molecular markers of neurodevelopment. The potential of the developing chicken embryo as a model system for nonclinical safety studies of pharmaceuticals (and environmental toxins) has been reviewed by members of our research team. Glucocorticoid dexamethasone transiently increased the expression of Pax6, a transcription factor necessary for the differentiation and migration of neurons, followed by a decrease and morphological alterations in the chicken cerebellum. In contrast, paracetamol treatment resulted in a delayed elevation of Pax6 expression. Interestingly, another transcription factor co-expressed with Pax6, NGFI-B, is necessary for apoptosis in this nerve cell population. SSRI increased several miRNAs known from cancer research, in the developing chicken cerebellum, a finding that could be further explored in human blood. Finally, we have shown that bisphenol A, an environmental toxin, induced both increased Pax6 expression as well as morphological alterations in the mouse and chicken embryo cerebellum.

Understanding the Educational Needs of Clinicians Who Manage Patients with Huntington's Disease: A National Survey Analyzing Both Clinician and Patient Perspectives

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Abstract

Background: Huntington's Disease (HD) has a complex presentation that varies widely between individual patients and presents a significant challenge to multidisciplinary care teams. Continuing education programs offer an effective means of improving clinician performance, but to be most effective, these programs must be targeted to the greatest areas of need. Currently there is little data available on clinician HD practice patterns, or HD patient perspectives.

Design/Methods: This ongoing study is using a case-vignette survey to quantify HD-related practice patterns, attitudes, and barriers of 125 US-practicing neurologists at HD Centers of Excellence and in the community setting. The survey investigates key aspects of management including diagnosis, treatment approach and goals, communication with other clinicians, and barriers encountered when managing patients. Interviews are being conducted to understand the roles of 12 genetic counselors, nurses, and physical therapists at HD Centers of Excellence. One hundred responses are being collected for a patient survey which focuses on patient barriers to care, their goals for treatment, perceptions of shared decision-making, and most needed topics for future education.

Results: Qualitative and quantitative survey data will be presented to establish the educational needs of the HD care community, and recommendations for targeted programs with the greatest chance to improve patient outcomes will be provided.

Conclusions: The results of this study will enable the development of optimally-targeted educational programs for clinicians, as well as patient-directed interventions. These programs will provide clinicians and patients the tools they need to achieve the best possible quality of care.

Mobility and Balance Differences in Patients with Mild to Moderate PD Compared to Age Matched Controls: A Descriptive Study

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Abstract

Parkinsons Disease (PD) is a common neurodegenerative disease in older people. The diagnosis is made by clinical observations of mobility, balance, resting tremor, and patient self-reported non-motor symptoms. The objective of treatment is to maximize function and minimize functional dependency. Standard treatment includes medication management with patients encouraged to follow a healthy lifestyle and stay active. The question is whether medically managed patients with mild to moderate PD can restore similar mobility and balance as age matched controls. In this descriptive, cross sectional study, 15 patients with medically managed mild-moderate PD and 15 age matched controls were compared on outcomes of clinically standardized tests of mobility and balance and self-reported medical histories summarizing health problems, exercise intensity, medications and depression. The two groups were similar in age and gender, however, age matched controls reported significantly more health problems, more prescription drugs and reduced exercise regimes compared to patients with PD. There were no significant differences in gait speed, balance, turning time or functional reach. However, the quality of gait (hesitancy in initiation) was significantly lower for patients with PD indicated a higher level of depression. Adding dual tasking to the TUG significantly increased time performance in a subsample of patients with PD with compared to a subsample of age matched controls. Medically managed patients with mild-moderate PD, who are exercising more than average, have similar mobility and balance compared to age matched controls. Further research is needed to determine if exercise is critical to maximizing mobility and balance for patients with PD and if dual task balance testing could provide more sensitive discrimination between medically managed patients with mild-moderate PD and age matched controls (275).

Descriptive Characteristics of Children with Autism at Autism Treatment Center, KSA

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Abstract

Autism characteristics in sixty children (aged from 2 to 8) were assed. Their behavioral symptoms were evaluated using the Autism Treatment Evaluation Checklist (ATEC). ATEC has four main domains of autistic disorders (Speech/Language/Communication, Sociability, Sensory/Cognitive Awareness, and Health/Physical/Behavior) in children with clinical diagnosis by Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and Childhood Autism Rating Scale (CARS) of autism spectrum disorder (ASD). Utilizing ATEC checklist, our study describes significant behavioral observations between autistic children which could effectively contribute to better under- standing and treatment during their early intervention stage.

Development of Multiplexing Bio-image Sensor to Detect the Activities of ATP and Hydrogen Ion

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Abstract

Multiplexing bio-image sensor based on a charge coupled device (CCD)-type pH image sensor has been developed to visualize the activities of adenosine triphosphate (ATP) and hydrogen (H^+) ion in real-time. All pixels of the proposed bio-image sensor are working like a pH sensor with a sensitivity of 35.8 mV/pH. Furthermore, only the enzyme immobilized pixels measure the electrical potential caused by the produced H^+ ions by enzymatic reaction between the immobilized apyrase and ATP solution. The measured data by each pixel is reconstructed into two-dimensional images. Therefore, the sensor can provide visual information into the spatial-temporal distribution of the targeted element. In my study, an immobilization technique of enzymes on the pH image sensor has been developed to fabricate ATP and H^+ ion image sensor. The apyrase-immobilized

pixels of the fabricated sensor were able to detect ATP with a sensitivity of 37.8 mV/mM and detection limit (LOD) of 1.3 μM. Also, it was confirmed that pixels without an enzymatic membrane can measure the diffused H^+ ion from nearby membranes. From these results, a reasonable measurement timing was calculated under 10 seconds. In the next study, an ATP, acetylcholine and pH image sensor with improved resolution for patterning the enzymatic membrane will be attempted. The proposed multiplexing bio-image sensor is expected to analyze activities of co-released neurotransmitters in the nervous system, because the shape and order of enzymatic patterns and the targeted elements can be customized simply by the kinds of immobilized enzymes.

Deficient Neural Responses to Reward Processing in Problematic Internet Use Adolescents

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Abstract

Problematic Internet Use (PIU) is the inability to control the desire of Internet use and is related to dysfunction of various risk-taking behaviors. Although a few neuroimaging studies have examined the brain activities of risky reward processing in PIU adults, few neurophysiological evidences are available, especially for the PIU adolescents. The current study aims to examine risky reward processing in PIU adolescents as compared to healthy controls while they subjectively experience monetary gain and loss during a simple gambling task by using event-related potentials (ERPs) as well as behavioral measures of impulsivity and risk-taking. Behaviorally, compared with controls, PIU adolescents exhibited risk-seeking pattern. ERP results showed that the feedback-related negativity was enhanced for the PIU adolescents versus controls, which appeared for gain context but not for loss context. The difference waves of feedback-related negativity between losses and gains was enhanced in response to the high-risk versus low-risk outcomes, which appeared for the PIU adolescents and controls. Further, the PIU adolescents as compared to controls exhibited a diminished P300 to both gains and losses. These findings suggest that deficient outcome/reward processing and increased risk-taking observed in PIU teenagers may be at least partly due to positive reward deficiency and/or dysfunctional positive reward circuitry in the brain, suggesting that problematic Internet use can be considered as part of the cluster of the reward deficiency syndrome (RDS).

Astroglia in the Neuroinflammatory Process: Prion Disease as Model

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Abstract

Brain disorders such as Alzheimer's, Parkinson's and Huntington's are called prion-like diseases on the basis that they are all proteinopathies where aberrant proteins spread throughout the brain during disease progression. Consequently, studies elucidating pathogenic mechanisms of prion disease may be relevant to these other neurodegenerative disorders. All these brain pathologies are currently accepted to share a neuroinflammatory process. Neuroinflammation is a dynamic process aimed to maintain brain tissue integrity where production of pro-inflammatory cytokines by glial cells plays a relevant role. Inflammation might also mediate a positive feedback loop exacerbating neurological damage. The overall aim of this study is to go depth into molecular mechanisms related with astroglia in their function to repair brain after insult. They will be assessed in natural prion disease and extended to prion-like diseases. In depth studies about their plastic behavior and/or immune mechanisms where they are directly involved are necessary to clarify neuroinflammatory pathway. Research into factors involved in the brain inflammatory response would lead to establish potential strategies against neurodegeneration characteristic of these disabling disorders.

Neuromotor Control Strategies During Walking in Children with Cerebral Palsy: Preliminary Results

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Abstract

Decreased dynamic postural control diminishes functional mobility in individuals with Cerebral Palsy (CP), but the neural control strategies underlying their walking patterns have not been addressed. In this study, we investigate balance control strategies due to sensory perturbation during walking in children with CP. A child with spastic diplegic CP who is able to walk without assistance was participated. The subject walked on a self-paced instrumented treadmill surrounded by a virtual environment. The visual perturbation consisted of a visual scene rotation every 10-13 steps around the sagittal axis of the ground to the right or left at a constant acceleration of 60 °/sec^2. The vestibular perturbation consisted of a 0.5 mA current Galvanic Vestibular Stimulus (GVS). Each perturbation initiated on heel strike. Results showed that step response shift was shown in perturbation direction after the sensory perturbation. Similar step response pattern was shown on left and right side. With vestibular perturbation, the step response is relatively larger and earlier during the 1st single swing than with visual perturbation, especially on right swing limb. In addition, Center of Pressure (CoP) shift was shown in perturbation direction clearly on only right stance limb during the 1st single stance. With vestibular perturbation, the CoP response is larger relatively than with visual perturbation, especially on right side. Sensory stimuli elicit balance responses using both the foot placement mechanism and the lateral ankle strategy. These approaches and findings may support a multi-dimensional clinical approach to potentiate typically motor-centric strategies for improving mobility in children with CP.

An Open, Randomized Exploratory Study for Non-Motor Symptoms of Idiopathic Parkinson 's Disease with an Oil Based, Enema-Like Ayurveda Therapy (Anuvasana Basti)

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Abstract

Background: The prevalent treatment goals for Idiopathic Parkinson's Disease in mainstream care have been to increase striatal dopamine levels. Though predominantly perceived as a motor disease, Parkinson's disease (PD) is now being understood as a complex multi-system, neurodegenerative disease originating in the gut years before it affects the basal ganglia. Its manifestations include debilitating non-motor features like constipation, sleep disorders, fatigue, anxiety, painful sensations. These are frequently missed, unaddressed and significantly affect the quality of life.

Methods: Based on this understanding and an Ayurvedic rationale, we chose a specialised therapy (Anuvasana Basti) which delivers an oil through an enema route for 16 consecutive days. 15 patients of Idiopathic Parkinson's Disease identified by Queen's Brain Bank criteria[4] were selected and divided into two groups. Group A (n = 8) received Mashadi Taila Basti (Sesame oil prepared with black lentils and herbs like Withania somnifera and Mucuna pruriens) and Group B (n = 7) received Murchhita Tila Taila (non-medicated Sesame oil). Assessment was done using a 70-point scale – Movement Disorder Society Task Force (MDS – UPDRS)5 – currently used for clinical research. It has four components: Non-Motor (NMEDL) and Motor Experiences of Daily Living (MEDL), Motor Examination (ME) and Motor Complications (MC).

Results: By the student's paired t test, Group A showed a significant response in the total MDS UPDRS score ($p < 0.002$), NMEDL ($p < 0.003$), MEDL $p < 0.01$. Clinical features that responded most significantly were constipation, anxiety, sleep disturbances, fatigue, painful sensations. Motor symptoms of global spontaneity of movement and tremor experience also improved significantly. Group B responses were not significant in any of the four major components, except individual symptoms like constipation and fatigue ($p \approx 0.05$).

Conclusions: These early encouraging results provide a possible addition to the therapeutic armamentarium against IPD, if confirmed by larger studies. Through Ayurveda, there is scope neuroprotection with *Withania somnifera*[6] levodopa substitution with potentially reduced dyskinesias and other benefits with *Mucuna pruriens* and whole system Ayurvedic therapies which may

all enhance clinical avenues for management if systematically followed up, including Ayurvedic logic in the study design.

Acknowledgements: We thank the Parkinson's Disease and Movement Disorder Society of India, KG Mittal Ayurveda Hospital, Dr. Pettarusp Wadia, MD, DNB, for their support and guidance.

Amyloid Precursor Protein Modulates Niemann-Pick Type C Pathology and Lifespan through GPCR and Cytokine Signaling Pathways

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Abstract

Niemann-Pick Type C disease (NPC) is an inherited pediatric neurodegenerative disease caused by mutations in NPC1 (95%) or NPC2 (5%) genes, either mutation resulting in a clinically identical disease. Currently, the functions of NPC1 and NPC2 remain unknown along with the specific mechanistic etiology of NPC pathogenesis. There are multiple hypotheses linking various cellular and pathological findings to the pathogenic process of NPC, including accumulation of cholesterol and sphingolipids, impaired calcium signaling, and mitochondrial dysfunction. Significant neuroinflammation and amyloid-beta and tau aggregation have also been reported in NPC brains. Previously, we have reported that the function of amyloid Precursor Protein (APP)—famously known for its potential pathogenic role in Alzheimer's disease—affects the pathological outcome of NPC in an established mouse model (BALB/cNctr-*Npc1*^{m1N}/J). Genetic knockout of the *App* gene resulted in decreased lifespan and neuromuscular function. At the cellular level, neuronal death and neuroinflammation was significantly increased. Our results are congruent with increasing recent evidence in support of APP's role as a stress modulator in the brain. To further expand our findings, we performed a genome-wide transcriptome analysis of the wildtype, *App*$^{-/-}$, *Npc1*$^{-/-}$, and *App*$^{-/-}$/*Npc1*$^{-/-}$ mice in BALB/c background. Gene Set Enrichment and Ingenuity Pathway Analysis with causal network highlight various signaling pathways. Particularly, genes associated with GPCR and cytokine signaling are significantly enriched, providing mechanistic support for the view of APP as a cellular stress responder and support for the search of anti-inflammatory targets as a viable therapeutic approach in NPC management.

New N-Arylsulfonyl-(D)-Leucinamides as Multi-targeted g-Secretase Modulators

Ming-Kuan Hu[1*], Yung-Feng Liao[2], Yu-Chia Hsu[1], Yeu-Cherng Tang[1], Ming-Yun Chang[2] and Bo-Jeng Wang[2]

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Abstract

The amyloid hypothesis has been known as the major targets for Alzheimer's disease (AD) therapies and inhibition of γ-secretase is one of therapeutic approaches to treat the underlying pathology of the disease. Various types of N-arylsulfonamides have been reported to decrease Aβ concentration by modulating γ-secretase activity and as candidates for the treatment of AD. In this study, we described the design and synthesis of a type of new *N-arylsulfonyl-(D)-leucinamides* based on the lead compound, N-(4-chlorophenylsulfonyl)-N-(2-fluorobenzyl)-leucinamide (4). The results indicated that N-(3-fluorobenzyl)-leucinamides 16b and 17b exhibited strong γ-secretase inhibition but displayed indistinct substrate selectivity for cleavage between APP and Notch. Nevertheless, both leucinamides provided amyloid-g recognition and showed inhibitory effects on the amyloid aggregations. Further, the exceptional suppression of ERK-mediated activation suggested that these potent g-secretase modulators may adapt an alternative pathway to prominently induce the differential inhibition of C99 cleavage by g-secretase.

Congenital Transmission of Chagas with Control Dropouts and Spraying

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Abstract

Vector-borne diseases are the leading causes of death amongst all disease. They remain as highest risk for lives of millions of people in many countries of the world. Scientific and economic impacts of vector-borne disease are significant. Chagas is one of the vector-borne diseases found in Latin American countries with its large impact. Studies indicate that vector control is the most convergent way to control vector-borne diseases. To control vectors, spraying insecticide is the easiest and safest way, but sometimes it is cost worthy for long period of spraying. Also, for most of the Vector-borne diseases treatments are available, but because of unawareness they spread at high frequency. People may start to opt the treatment but the side effects or cost of treatment, force them to leave treatment in between and that create larger dropouts. Vertical transmission of disease also plays vital role in spreading disease as it increases infected population. As costs are incorporated with spraying and dropout both and our aim is to minimize the total cost associated by controlling both spraying and drop-out in a way spraying should be maximum and dropout should be minimum for disease control.

Treatment of Chronic Pain using Combination of Sub-Anesthetic Ketamine Infusions, Yoga and Mindfulness-Based Cognitive Therapy for Pain (Y-MBCTpain)

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Abstract

Chronic pain is not just a physical sensation; rather it is an enduring experience and involves many complex aspects including persistent pain perceptions and pain memories, along with co-morbid anxiety, depression, difficulty moving, muscle weakness, and reduced quality of life—requiring further healthcare resources. Fear of pain often leads to avoidance of important activities such as exercise, creating a vicious cycle of avoidance, disability, depression, and more enduring pain. Persistent activation of nociceptive pathways up-regulates the activity of spinal dorsal horn glutamate (N-Methyl-D-Aspartate receptors (NMDAR), causing hyperalgesia by central sensitization and also by amplifying the ascending nociceptive pathways to the brain through synaptic neuroplasticity mechanisms that include long-term potentiation and long-term depression, two main processes involved in pain memory formation that modulate pain perception/experience. Ketamine is an analgesic and dissociative anesthetic inhibiting NMDAR, and benefits not only chronic pain but also depression and PTSD, and may provide lasting improvement for months following infusions of 1-6 sub-anesthetic doses.4, This abstract proposes the use of an integrated approach for chronic pain that combines sub-anesthetic (1 mg/kg) ketamine infusions with Y-MBCTpain psychotherapy. Y-MBCTpain is a modification of Pradhan's TIMBER (Trauma Interventions using Mindfulness Based Extinction and Reconsolidation) psychotherapy used for chronic refractory PTSD that has been effectively applied alone or in combination with ketamine infusions. Y-MBCTpain includes a combination of Yoga and standardized mindfulness methods that modify the pain experience using the five-factor inventory of pain experience and brief cognitive behavioral therapy (CBT) techniques in user friendly formats.

Neuroimaging Complication of Neonatal Meningitis in Full and Near Terms Newborn: A retrospective Study of One Center

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Abstract

This was a retrospective cohort study of newborn full and near full term with diagnosis of meningitis due to streptococcus group B. We included newborns (0-28 days) and not less than 35 weeks, having been admitted to the Robert Debre Hospital between 1984 to 2014, and the diagnosis of meningococcal B streptococcus has been proven by CSF culture. Twenty-five cases of neonatal meningitis B streptococcus between 1985 and 2010 have been reported. Two were excluded because they had congenital anomalies; 14 records have not been found in the archives. In total, only 9 cases have been analyzed. Eight children had either a CT scan or MRI and head ultra sound (HUSS). All eight had an abnormal imaging: 5 cases 62.5% had a stroke, one case of ventricular leukomalacia perished was highlighted, as described above. Other abnormalities were asymmetric peri cerebral edema, a right temporal cortical subcortical lesion; 1 echogenicity and ventricular dilatation. All children admitted were symptomatic: neurological symptoms were present in 66.66% of cases, breathing in all cases, or hemodynamic in 33% of cases. In our study, the main acute neuro-imaging complication is stroke; with 25 per 100 of neurologic disabilities at four-year-old.

Research on Mitochondrial DNA Mutations in Patients with SCA3/MJD

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Abstract

Spinocerebellar ataxia type 3(SCA3) is a degenerative neurological disorders caused by trinucleotide repeat expansion within the ataxin-3 gene. It is characterized by multi-system involvement and diverse clinical phenotypes, which cannot be fully explained the length of the CAG repeats. One possible explanation for the phenotypic heterogeneity could be the presence of mitochondrial DNA mutations that modify disease severity. To explore the role of Mitochondrial DNA(mtDNA) variations in SCA3 pathogenesis, we analyzed polymorphisms of six mitochondrial genes, MT-LT1, MT-ND1, MT-CO2, MT-TK, MT-ATP8 and MT-ATP6, in 102 unrelated SCA3/MJD patients and 100 healthy controls. The results showed that there were 24 variations of those mtDNA genes in the SCA3 patients and only 10 in the unrelated healthy controls. There was no difference of the relative mtDNA copy number variation between the SCA3 patients and healthy controls (93.20 vs. 89.66, P > 0.05). In the group of SCA3 patients, the relative mtDNA copy number showed a negative correlation between the number of CAG repeats (r = -0.210, P < 0.05), but did not correlate with the age at diagnosis, the age of onset, disease duration, ICARS scores and SARA scores. Our research demonstrated that the frequency of mutated mtDNA in SCA3 patients was higher than that in the healthy group. The mtDNA relative copy number in SCA3 patients was not significantly different compared to the healthy group. Thus, the copy number might not be treated as a biomedical indicator when measuring the severity of illness in SCA3 patients.

Lateralized Damage to the Structures Involved in Reward Processing in Depressed Patients

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Abstract

Impairment of the brain reward system is an important deficit in clinical depression. Reduced motivation to seek rewarding experiences and blunted sensitivity to reward elicits symptoms of depression in these patients. In this experiment we used magnetic resonance imaging (MRI) to study volumes of the structures involved in reward processing. We examined volumetric MRI data of 21 clinically depressed geriatric patients meeting diagnostic criteria for major depression (DSM-IV). Additionally, the volumes were correlated with volunteers' Geriatric Depression Score (GDS). We observed that the left NAc volume was significantly smaller (p = 0.001) than the right. The left amygdala was also smaller but the difference was not statistically significant (p = 0.70). The correlation between the GDS and left amygdala volume was highly significant (r = 0.55, R2 = 0.30; p = 0.01) but it was not significant with the volume of right amygdala (r = 0.34; R2 = 0.12; p = 0.13). There was a weak positive correlation between the left (r = 0.33; R2 = 0.11; p = 0.14) and right (r = 0.40; R2 = 0.16; p = 0.08) NAc volumes and GDS. The results suggest that the reduced volumes of left NAc, and left amygdala could be associated with impaired processing of the reward system in patients with clinical depression.

Activation of C-Jun Amino-Terminal Kinase is required for Valproic Acid-Induced Neuronal Differentiation of Mouse Embryonic NSCs and Neurite Outgrowth of NSC-Derived Neurons

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Abstract

Valproic acid (VPA), a drug prescribed for bipolar disorder and epilepsy, has the potent ability to induce neuronal differentiation, promote neurite extension and exert a neuroprotective effect in neurodegenerative diseases and central nervous system (CNS) injuries; however, comparatively little is presently known regarding the molecular mechanism underlying its action. Recent studies have suggested that c-Jun N-terminal kinase (JNK) is involved in neuronal differentiation and neurite outgrowth during neuronal development. In the present study, we cultured mouse embryonic NSCs and treated these with 1 mM VPA for up to 7 days. Our results show that VPA promotes the neuronal differentiation of mouse embryonic NSCs and neurite outgrowth of NSC-derived neurons, moreover, VPA induces the phosphorylation of JNK-c-Jun. In contrast, JNK inhibitor SP600125 blocked the VPA-stimulated neuronal differentiation of mouse embryonic NSCs and neurite outgrowth of NSC-derived neurons. Taken together, these results indicate that the activation of JNK plays a pivotal role in VPA-stimulated neuronal differentiation of mouse embryonic NSCs and neurite outgrowth of NSC-derived neurons.

Effect of Ocimum Basilicum Extract Treatment on Functional Recovery against Ischemia Reperfusion Induced Cerebral Injury in Mice

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Abstract

Stroke is one of the leading causes of disability and death worldwide. Free radicals play crucial role in disease progression and neuronal injury in stroke. As a consequence, treatment with antioxidants is an important strategy for the management of stroke. *Ocimum basilicum* L. has been used traditionally in CNS disorders. Antioxidant potential of *O. basilicum* is well documented. Thus, the present investigation was designed to evaluate the effect of *O. basilicum* extract (OBE) administration on functional recovery in a mouse model of ischemia reperfusion (I-R) induced brain damage. The ischemic injury was induced by bilateral common carotid artery occlusion (BCCAO, 15 min) followed by 24 h reperfusion. Mice were treated with OBE (200 and 400 mg/kg) for 7 days once daily after BCCAO. Functional recovery in terms of memory and motor coordination was assessed using Morris Water Maze, Elevated Plus Maze tests and neurological severity score, respectively. Infarct size was determined using TTC staining. Brain biochemical parameters (lipid peroxidation, glutathione, SOD) were also evaluated. Treatment with OBE significantly attenuated the memory impairment and motor incoordination induced by I-R in mice. Also, brain infarct size was significantly reduced and endogenous antioxidant levels were restored in mice treated with OBE in comparison to BCCAO control mice. Chromatographic evaluation (HPLC) of OBE revealed the presence of phenolic acids. The neuroprotection by OBE may be attributed to phenolic acids present in the extract. Based on these results, it may be concluded that OBE may be developed as a neuroprotective drug.

The Relationship between Dementia/Alzheimer's Disease and Volunteering

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Abstract

Today there are more than 47 million people who suffer from dementia across countries, and Alzheimer's disease is the common cause of dementia. The productive aging literature suggests that volunteering has health benefits including better physical and mental health outcomes. Yet, the impact of both formal and informal volunteering on dementia and Alzheimer's diseases are scarce. Guided by the activity theory and role theory, this study used logistic regression model focusing on older Americans aged 69 and older from the Health and Retirement Study (2010), to examine the impact of volunteering on dementia and Alzheimer's diseases. The results indicate that formal and informal volunteers have lower odds of having dementia or Alzheimer's diseases than non-volunteers. Older age and a greater number of chronic health conditions were are associated with greater odds of having dementia or Alzheimer's diseases and being a member of a racial minority group are risk factors for Alzheimer's diseases. Greater exercise is associated with lower odds of the presence of dementia or Alzheimer's diseases. The results not only confirm the concept of activity theory and role theory but also inform policymakers and health practitioners to encourage older adults to engage in volunteering to prevent cognitive impairment in old age.

The Impact of Early Childhood Experience on Self-rated Memory in Late-life

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Abstract

Memory decline is an extremely stressful experience for both older adults and their family members that can create a great emotional and economic burden. Despite the negative consequences of memory decline, studies in cognitive health have often focused on the medical aspects of its determinants. Guided by the life course perspective, the current study examines the early childhood risk and protective factors of memory. Using data from the 2011 wave of the National Health and Aging Trends Study, we used multiple logistic regression to examine the association between self-rated memory and four early-life factors: childhood health; childhood financial situation; whether or not the participant was born in the U.S.; and whether or not the participant lived with both parents. The analytic sample included 2,954 Medicare beneficiaries aged 65 and older (59% male; 75% white; 48% young-old [65-74]). Compared to adults who were not born in the U.S., older adults who were born in the U.S. had 0.59 times the odds of self-rated memory decline ($p < .0001$); compared to those who had poor childhood health, people with better childhood health had 0.78 times the odds of self-rated memory decline ($p < .0001$); compared to those who had poor childhood financial situations, people with better childhood financial situations had 0.79 times the odds of self-rated memory decline ($p < .0001$). Applying the life course perspective, policy makers can focus on long-term improvement in health and living conditions starting from a young age to reduce negative cognitive consequences in late-life.

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