Journal of Neurology & Experimental Neuroscience

https://doi.org/10.17756/jnen.2018-suppl1

Meeting Abstracts

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Proceedings of the 4th Neurological Disorders Summit (NDS-2018)

Keynote Presentations

Brain Dynamics of Normal and Abnormal Learning, Memory, and Cognition with Applications to Alzheimer's Disease, Amnesia, Autism, and Neglect

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Abstract

Adaptive Resonance Theory, or ART, is a neural model that explains how normal and abnormal brains may learn to categorize and recognize objects and events in a changing world, and how learned categories may be stably remembered. ART unifies the explanation of diverse data about normal and abnormal modulation of learning and memory by acetylcholine (ACh). In ART, vigilance control determines whether learned categories will be general and abstract, or specific and concrete. ART models how vigilance may be regulated by ACh release in layer 5 neocortical cells by influencing after-hyperpolarization currents. This phasic ACh release is mediated by cells in the nucleus basalis of Meynert that are activated by unexpected events. ACh also controls tonic control of vigilance. A breakdown in both phasic and tonic vigilance control due to structural degeneration during Alzheimer's disease provides a dynamical explanation of Alzheimer's symptoms. ART also explains how breakdowns of tonic control may occur in mental disorders such as autism, where vigilance remains high, and medial temporal amnesia, where vigilance remains low. Tonic control also occurs during sleep-wake cycles. Properties of up and down states during slow wave sleep arise in ACh-modulated laminar cortical ART circuits that carry out important perceptual and cognitive processes in awake individuals. This insight allows a unified description of brain dynamics during wakefulness and sleep. Sleep disruptions before and during Alzheimer's disease, and how they contribute to a vicious cycle of plaque formation in layers 3 and 5, are also clarified from this perspective.

Manipulation of the Brain's Serotonergic System by Diet and Companionship

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Abstract

Sickle cell disease (SCD) is a common genetic disorder affecting millions of people globally. It is characterized by neurobehavioral alterations including depression, anxiety, cognitive impairment and pain. Altered brain connectivity and central sensitization of nociceptive system co-exist in human subjects and transgenic mice with SCD. These neurobehavioral conditions are inter-dependent and influenced by the affective state through emotional and environmental circumstances. Therefore, we examined if improving the diet and creating a happier environment would reduce pain as an outcome measure in transgenic mice expressing human sickle hemoglobin recapitulating the clinical and pathological features of SCD. We found that enriched diet and housing male sickle mice with females stimulated the serotonergic top-down pathways in the brain leading to a significant reduction in pain in male mice. Treatment of both male and female sickle mice with serotonin enhancing strategies using duloxetine reduced pain, suggesting a critical role of serotonergic mechanisms in neurobehavioral symptoms in SCD. Our

data show the mechanism of action of serotonin norepinephrine reuptake inhibitors (SNRI) in ameliorating pain via top down mechanisms in the brain. These findings have translational potential for using SNRIs and/or alternative strategies by improving diet and creating a happy environment to ameliorate neurobehavioral symptoms of SCD.

Guaranteed to Show You How to Successfully Re-invent Yourself

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Abstract

If you have decided that you desperately and passionately commit to transform yourself no matter how much effort, time and sacrifice that it will take, keep reading, this information is for you. As the well-known expression goes, "The definition of insanity is doing the same thing over and over again and expect that you are going to get a different result." Many of us have never learned this lesson. We hold on to familiar approaches to life issues when deep down inside we know that we will get the same result, although unhealthy, one that we are actually comfortable with. Doing something different takes either a very brave person or very desperate person. I recommend that you take the bravery route and not wait for you to become desperate, some call it "hit rock bottom." Being exposed to someone who is brave enough to transform, or is in the process of transforming, his or herself, a mentor, makes a tremendous difference because you realize that it is possible to succeed, "If they can do it, so can I." Seek out a mentor. I have broken this down into two parts using an old adage adapted to fit my needs. First, "out with the bad." Then, "in with the John good.

Mitochondrial Myopathy

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Abstract

Mitochondria are intracellular organelles where more than 90 percent of cellular ATP is produced. Mitochondrial failure causes cell dysfunction and/or cell death. Mitochondrial disease presence varies differently from individual to individual, depending on what cells or organ are involved. In this talk, I will discuss mitochondrial dysfunction involving muscles causing mitochondrial myopathy.

Repositioned Drug to Restore Mitochondrial Biogenesis

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Abstract

Bioenergetic compromise is a feature of several neurodegenerative diseases, including Alzheimer's and Parkinson's disease (PD). We sought to determine the network underlying bioenergetic failure in PD. Analysis of patient midbrain tissue and laser captured substantia nigra dopamine neurons revealed a dysregulation of PGC-1alpha and a subset of nuclear encoded respiratory chain subunit genes. We confirmed in PD tissue that PGC-1alpha was reduced at the protein level. To understand how to upregulate PGC-1alpha we screened a library of FDA approved drugs that could increase the gene levels in a cellular assay. A small number of PGC-1alpha upregulators (PU-xx) were identified, one of which, PU-91 has been advanced. PU-91 increases PGC-1alpha in a dose-dependent manner, extinguishes pro-inflammatory gene expression, upregulates anti-oxidant genes, and increases mitochondrial content. In cellular assays and PD models, PU-91 is highly neuroprotective. Pharmacokinetic (PK) indicate that PU-91 entry into the CNS could be improved. To this end, we identified the mechanism that limits CNS bioavailability and a natural product (K), acting to block this mechanism, that augments CNS bioavailability. PK of the combination of PU-91 plus K increase CNS bioavailability of PU-91 more than 4-fold. Preclinical PD studies show that PU-91K has additional benefit. The implications of this work will be discussed in the context of planning for clinical development.

Neurotransmitter Imaging

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Abstract

Neuroimaging techniques lack a sensitive method for detecting acute changes in neurochemical milleau of the brain. Since neurochemicals are important determinants of the brain function, a method that allows detection of acute changes in the neurochemistry would allow us to understand the brain function better. We recently developed a technique to detect, map and measure dopamine released acutely during cognitive or behavioral processing. The technique is called single scan dynamic molecular imaging technique (SDMIT). It exploits the competition between a neurotransmitter and its receptor ligand for occupancy of the same receptor site. In this technique after patients are positioned in the positron emission tomography (PET) camera, a radio-labeled neurotransmitter ligand is injected intravenously and the PET data acquisition started. These data are used by a receptor kinetic model to detect, map and measure neurotransmitter released dynamically in different brain areas. Patients are asked to perform a cognitive task while in the scanner and the amount of neurotransmitter released in different brain areas measured. By comparing it with the data acquired in healthy volunteers during performance of a similar task, it is possible to determine whether a neurotransmitter release is dysregulated in the patients and whether the dysregulation is responsible for clinical symptoms. Since this technique measures neurotransmitter released under conditions of cognitive stress, it can detect changes at a very early stage, when dysregulation of is not expressed at rest but manifests under conditions of cognitive overload.

Introducing Precision Behavioral Management (PAM™) of Reward Deficiency Syndrome, the Construct that Underpins All Addictive Behaviors

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Abstract

Worldwide, daily there are several millions of people increasingly unable to combat their frustrating and even fatal romance with getting high; for some 'high' may be just experiencing "normal" feelings of well-being. The National Institutes on Alcohol Abuse and Alcoholism and on Drug Abuse (among others) conduct and fund outstanding research using sophisticated neuroimaging and molecular genetic applied technology to improve understanding of the intricate functions of brain reward circuitry and resting sate functional connectivity, that is purportedly playing a key role in the addiction symptomatology. There is controversy as to the ultimate definition of addiction involving ASAM, ISAM, on one hand and other psychological and World Health organizations on the other hand. From a neuroscience perspective, while it is widely accepted that dopamine is a major neurotransmitter implicated in behavioral and chemical addictions, there remains controversy about how to modulate dopamine clinically in order to treat and prevent various types of addictive disorders. While for the most part Medication Assisted Treatments (MATS) promote dopamine blockade or unintentional dopamine down –regulation in the long term, adherence and relapse prevention has been poor. This is especially true even for even for buprenorphine –naloxone combinations. It appears, though, that a prudent approach may be a biphasic short-term blockade followed by long-term dopaminergic upregulation, with the goal of enhancing the functional connectivity within the brains reward circuitry, possibly targeting the reward deficiency and the stress-like anti- reward symptomatology arising in the context of addiction. Such phenotypes can be characterized using the Genetic Addiction Risk Score (GARS)™. Utilizing GARS upon entry to a pain clinic may reduce the guessing about who would become addicted to powerful pain medications and thus offer a more plausible objective way of

identifying addiction liability through genotyping with GARS. Dopamine homeostasis may thus be achieved via customization of neuronutrient supplementation (putative pro-dopamine regulation) based on the GARS test result along with a behavioral intervention developed by our group, dubbed "Precision Behavioral Management" (PBM)™.

Speaker Presentations

Brain-Machine Interface – The Turning Point for the Future Medicine

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Abstract

In the future brain-machine interface (BMI) shall be the major assistive device and therapeutic methods, and the role of medical person should change. So the understanding of the current technology of BMI and the therapeutic points is important. The therapeutic approach of BMI for the stroke, not as the assistive devices, will be discussed as an example.

Closed feedback is currently associated with the treatment outcomes of randomized controlled trials of BMI rehabilitation. A man is not the simple machine, so the initiative has the significant role in the behaviors of patients with stroke. Positive feedback especially immediately given can make many people engage in the therapeutic activity more voluntarily.

Recording of the brain response pattern can be further analyzed for the more beneficial pattern of the brain. The computing power of current big data era will more be improved, and the further analysis can be more and more improved.

Patients and caregivers will pay for the promising methods such as BMI. For the future clinical optimization, clinicians and engineers should make the clear protocol, not only for the practical use but also for the continuous development of the BMI. The protocol should comprise the monitoring of technical failure and the adjustment methods for the clinicians during the application to the patients.

In the future patient and the payer centered communication and reimbursement system shall exist and the common terminology and protocols for the BMI are needed. The BMI can be the therapeutic turning points in the near future.

The Dementia Care in Hospitals Program

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Abstract

The Dementia Care in Hospitals Program (DCHP) is an all-of-hospital cognitive impairment (CI) awareness and communication program supported by cognitive screening of all patients aged 65 years and over, a training program for staff and a bedside alert, the Cognitive Impairment Identifier (CII). This program aims to change the hospital care paradigm from one where all adults in hospital are expected to manage the complex demands of hospital care, to one where it is recognised that additional support and a change to the hospital processes and environment is needed for those with CI, which on study baseline data is 34% of patients 65+.

The program was developed in 2004 by Ballarat Health Services (BHS), in Victoria, Australia with extensive consumer support. It has been taken up by 25 Victorian hospitals. The CII is an abstract graphic, trademarked to BHS, and endorsed as a national symbol for CI in hospitals by Alzheimer's Australia National.

Patients 65+ admitted to 4 hospitals in different jurisdictions were screened for CI using validated tools. Those who screen positive have the CII placed over the bed, their families are actively engaged in care and all staff (clinical and non-clinical) use the learned communication strategies during any patient interaction.

The DCHP has been evaluated nationally to measure its impact on hospital-acquired complications, carer satisfaction, patient quality-of-life and staff satisfaction and practice change.

This abstract will report on the preliminary outcomes of the evaluation with respect to staff satisfaction, patient quality of life and hospital acquired complications.

Screening for Schizophrenia in Recruits, Active Duty Soldiers and Veterans: Can We do a Better Job?

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Abstract

From World War I, the United States military medical services have continually worked to improve their ability to identify prodromal or mild schizophrenia symptoms at enlistment and early during training in order to limit personnel disruptions during active duty and deployment to combat theaters. The longer a recruit progresses through training to active duty, the greater the disruption for the military command when schizophrenia is diagnosed. In particular, the diagnosis of schizophrenia in a soldier may cause key military unit members being withdrawn from their combat team. This results in short-term and long-term problems for the military command and its mission. The economic burden to the United States military and the United States Government continues for the lifetime of the soldier who has been diagnosed with schizophrenia at any point during their training creating a lifetime service connected disability. I will briefly discuss the history of the United States armed forces medical services' efforts to minimize the number of recruits entering the military and becoming active duty before being diagnosed with schizophrenia. A more aggressive screening protocol for schizophrenia based on existing tests and technology will be presented.

Evidence of Similar Symptoms in ABA Recipients and PTSD Patients

Henny Kupferstein

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Abstract

Is There Long-Term Harm of Applied Behavior Analysis (ABA) Autism Childhood Intervention? Two groups of respondents, caregivers of autistic children and autistic adults, were separately surveyed about their experiences as a consumer of widely-used interventions. This data was intended for future interventions to consider the input of autistic individuals who experienced the intervention firsthand and their caregivers' perceptions. Further investigating the association between sociodemographic factors of developmental disabilities interventions is a public health concern of autistic adults in the United States.

Neurological Disease Tracking and Fingerprinting through Fine-Motor Keyboard Typing Rhythms

Roy Maxion

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Abstract

Typing is a fine-motor activity whose rhythms appear to be unique to individuals – like fingerprints. Using keyboard timings, a typist's identity can be determined, within ten keystrokes, with an accuracy of 99.9%. Typing rhythms can also reveal a typist's affective state (e.g., stress/anxiety), and perhaps provide early indicators of cognitive decline (e.g., Dementia), cognitive impairment (e.g., head trauma, concussion), and other neurological conditions (e.g., Parkinson's, Alzheimer's). This talk will describe the results of a study in which the typing rhythms of 116 subjects were used to differentiate between neutral and stressed affective states. Using a single-subject ABA experimental design, stress was induced using a combination of speeded workload and social evaluation. We will explain the computer-based tool and methodology for stress induction and objective affect evaluation. Discrimination accuracy between neutral and stressed states was 100%. We will also present the results of a pilot study in which Parkinson's symptoms were tracked over the course of a year, showing the signatures of good and bad PD days, changes in medications, and progression of the disease. Patients can be monitored non-invasively over the Internet, and outcomes conveyed automatically to physicians.

Ambient Artificial Illumination: Neurological Disorders Friend or Foe?

Deborah Burnett* and Karolina Zielinska-Dabkowska

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Abstract

Entrained to the constantly changing daylight and darkness spectral qualities of natural light, all earth-bound lifeforms have evolved under varying light wavelengths delivered throughout a predictable 24-hour cycle. Increasingly, modern man has abandoned natural daylight and dark photoperiods in favor of 24/7 artificial light provided by compact fluorescent (CFL) and light emitting diodes (LED) technologies. These modern light sources differ considerably from the spectral qualities of bright natural daylight and evening darkness now recognized as essential zeitgebers for species-specific chronobiological function, genetic expression, and neuroendocrine response. As presented by Dr. Karolina Zielinska-Dabkowska in a recent Nature article "Make Lighting Healthier: artificial illumination can stop us sleeping and make us ill" 1 this session will examine both the potential benefit and human health problems now linked to these energy efficient light sources. In terms of application to neuroscientific research and medical practice, additional comment will be presented as to emerging bench to bedside and observational studies investigating circadian supportive ambient light interventions for improving neurodegenerative patient sleep efficacies, enhancing workplace alertness for shift workers, and protecting neonatal neurosensory development in preterm infants.

A Comparative Study of Potential Ligands to the Homology Model of Human Alpha2 Adrenoceptor

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Abstract

The regulatory systems participate in different pathologic states development and adrenergic system is the one that increasingly gains attention, in the context of its involvement in cardiovascular dysfunction, vasoconstriction, memory formation, neurogenesis, alcohol addiction, etc. Among others α2-adrenergic receptors (α2-Ars) serve as important drug targets. Subtype specific drugs for β1 and α1 receptors are available, but data for α2-Ars are absent due to the lack of respective receptor model.

Our docking studies based on turkey β1-adrenergic receptor as a template to model subtype of human α2-Ars. Five well known and two newly synthesized ligands Mesedin and Beditin were docked to resulting adrenoceptor 3D model to detect probable binding site cavity with corresponding aminoacids residues and estimate binding affinity based on free energies. We found out that new potential ligands, α2–adrenoblockers Mesedin and Beditin, which possess high anti-hypoxic effect in experiments, revealed significant protective effect in experimental animals in acute and chronic stress conditions as well as in neural cell cultures in hypoxic conditions, interacted with α2-Ar model in different sites. The obtained data were criss - cross compared between well-known and unknown agonists and antagonists. It was mentioned that Mesedin and Norepinephrine formed more common binding poses with human α2-Ar homology model. It was also detected some hydrogen bond formation with binding sites for studied ligands, which may be responsible for stabilizing ligand-protein complex.

Phenomenology of Misophonia, a Conditioned Aversive Reflex Disorder

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Abstract

Misophonia is an understudied but relatively common respondent behavior condition, the effects of which range from annoying to debilitating. Misophonia is known as a condition where commonly occurring innocuous stimuli (e.g. chewing sounds) elicit anger and accompanying physiological responses. An fMRI study identified higher activity in anterior insula which is driven by vmPFC as a basis for misophonia. Recent basic research on misophonia as a behavioral phenomenon has identified an immediate physical response (typically a muscle flinch) elicited by misophonic stimuli, which is unique for each

person. Although there are common misophonic stimuli, each person has a unique set of stimuli, which often includes both auditory and visual stimuli, but can be any sensory modality. We conducted two basic research studies on the phenomenology of misophonia to document the initial physical response to misophonic stimuli previously reported in cases studies. One study exposed participants to weak auditory and visual misophonic stimuli, and participants reported immediate physical sensations and emotions. The second study used electromyography (EMG) and direct observation of the immediate physical response to misophonic stimuli in three participants. Results show that misophonic auditory and visual trigger stimuli elicit physical responses in addition to emotional responses. The highly varied initial physical response (and cases studies) support stimulus-response classical conditioning as a neural mechanism contributing to the development and maintenance of misophonia. It may be more appropriate to view misophonia as a conditioned aversive reflex disorder, rather than an emotional response disorder.

Growth, Physical and Pubertal Development of Children with Stimulant Treated Attention Deficit Hyperactivity Disorder (ADHD)

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Abstract

An important goal of studying neurological disorders is to develop treatments that can improve the functioning of affected individuals. For ADHD we are fortunate to have stimulant medication which is extremely effective for improving the executive functions of the brain. However, as a common and often lifelong condition, it is important to consider the adverse effects of treatment.

Stimulant treatment is associated with initial weight loss. DXA scanning has shown this to be fat loss, particularly central fat, together with a reduction in the rate of lean tissue accrual. Biochemical tests indicate a reduction in bone turnover, with the loss of fat correlating with a reduction in leptin. A typical pre-pubertal child also experiences 1cm less growth per year for the first 3 years. With these treatment-related alterations in physical development and hormone levels in mind, we compared the growth and pubertal development of adolescent boys with ADHD who had been stimulant treated for at least 3 years with that of community controls. Boys aged 12.00-13.99 years were relatively lighter but showed no delay. Boys aged 14.00-15.99 years were smaller, lighter and less advanced in their puberty, with an inverse relationship between the dose of medication and the height velocity. These findings suggest that stimulant medication delays the rate of maturation during puberty, including the timing of the peak height velocity, but not the onset of puberty.

These treatment-related changes may be secondary to the changes in appetite regulation and could have psychosocial consequences during adolescence, or long-term physical consequences.

X-ray Phase Contrast Tomography Reveals Early Vascular Alterations and Neuronal Loss in Neurological Disorders

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Abstract

Techniques previously used to investigate damage to vascular and neuronal networks in neurological disorders suffer from several limitations. In particular, 2D imaging restricts spatial coverage, entails destructive sample preparation, and may lead to data misinterpretation due to lack of information on the third dimension. In contrast, recent ex-vivo study in mice demonstrated that imaging by X-ray Phase-Contrast Tomography (XPCT) enables the study of the 3D distribution of both vasculature and neuronal networks, without sample sectioning or specific preparation. We have generated and quantified multiscale XPCT to evaluate alterations in vascular and neuronal networks at relevant disease phases of the animal model for multiple sclerosis, experimental autoimmune encephalomyelitis (EAE), in affected mice and to understand how treatment with mesenchymal stem cells (MSC) modifies them. A direct 3D morphological description of EAE lesions is provided at both vascular and neuronal levels at two different length scales. Such a multi-scale direct analysis has never been performed to understand EAE pathology and address the effect of an innovative therapeutic strategy. The results strongly indicate a trend in alteration of the micron vessels and possible occlusions in the capillaries, an observation never obtained in tissue without the use of a contrast agent. Simultaneous 3D XPCT imaging of neuronal alterations supports the findings of a massive loss of lower motor neurons. Such vascular and neuronal alterations were considerably reduced in MSC-treated mice.

We have also applied XPCT to the investigation of other neurodegenerative disorders, i.e. Alzheimer and ALS, and data will be presented.

The Role of Neuropeptide Y Family in Inflammatory Bowel Disease

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Abstract

Inflammatory bowel disease (IBD) is a chronic recurrent condition and it includes three main disorders: ulcerative colitis, Crohn's disease, and microscopic colitis. These three diseases differ in clinical manifestation, courses, and prognosis. Interactions between the gut neurohormones and the immune system are thought to play a pivot role in inflammation, especially in IBD. These neurohormones are believed to include members of the neuropeptide YY (NPY) family, which comprises NPY, peptide YY (PYY), and pancreatic polypeptide (PP). Understanding the role of these peptides may shed light on the pathophysiology of IBD and potentially yield an effective treatment tool. Intestinal NPY, PYY, and PP are abnormal in both patients with IBD and animal models of human IBD. The abnormality in NPY appears to be primarily caused by an interaction between immune cells and the NPY neurons in the enteric nervous system; the abnormalities in PYY and PP appear to be secondary to the changes caused by the abnormalities in other gut neurohormonal peptides/amines that occur during inflammation. NPY is the member of the NPY family that can be potentially useful candidate targets for treatment of IBD.

Masseter Botulinum Toxin Injection Complications-Recognition and Prevention

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Abstract

The Asian face often exhibits a square-shaped lower face due to masseter muscle prominence or hypertrophy. The application of botulinum toxin on the masseter muscle is very popular in Asian countries. This treatment effectively reshapes the lower face and facial contour. Although toxin treatments are very effective and safe, the risk of a variety of side effects or complications remain. Complications can be divided into four etiological group: non-muscular; toxin effect related; dose/level related; and injection site related. In this session, I will present the recognition, causes, and prevention methods for neurotoxin complications in masseter injections.

Electrical Stimulation Enhances the Efficacy of Cell Transplantation Therapies for Neurodegenerative Retinal Diseases

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Abstract

Although retinal degenerations are unique in mechanisms, they invariably involve the irreversible loss of retinal neurons, neuronal connections, and activation of glial cells in the micro environment. For example, photoreceptor loss is common during retinitis pigmentosa (RP), while age-related macular degeneration (AMD) involves degeneration of both photoreceptor cell and the retinal pigment epithelium (RPE) death. Glaucoma, on the other hand, involves the selective loss of retinal ganglion cells (RGCs). To date, there are currently no single reliable clinical treatment options to completely prevent or reverse the loss of retinal neuron. Recently, several novel techniques are currently being evaluated for their potential therapeutic use in the treatment of retinal degeneration, including gene therapy, optogenetics, electrical stimulation (ES), cell transplantation (CT), etc. Although CT is one of the most attractive treatment options, the application of CT methods in the retina comes with several limitations. Thus, we hypothesize that a dual therapeutic approach should be adopted utilizing ES to augment CT to treat retinal degeneration. While this theory has never been tested in the retina, it is supported by various studies in other tissues highlighting the additive benefits of the two techniques, whereby CT can be used to replace lost cells and/or provide trophic support, while ES can be utilized to stimulate and protect the remaining endogenous cells in addition to facilitating function in the transplanted cells.

A Non-Contact Sleep Monitoring System

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Abstract

Sleep monitoring is very important as we see sleep quality as a good indicator of quality of life. Disordered sleep can be implicated with many diseases such as insomnia, obstructive sleep apnea (OSA), and parasomnia. Polysomnography (PSG) is the most essential method for sleep assessment and has long been regarded as the golden standard. It is, however, cumbersome and inconvenient for daily use as well as has limitations in time, cost, and duplicability. Over the last two decades, technological advancements in wearable hardware and computing algorithms have made sleep assessment publicly more accessible, but almost all of wearable devices are using contact electrodes and show limitations in accuracy and convenience.

In this talk, we introduce a non-contact sleep monitoring system based on the impulse radio ultra-wideband (IR-UWB) radar sensor technology. The radar sensor continuously emits a sequence of narrow impulse signals, and receives signals reflected from the human body. By installing the radar sensor at a distance of approximately 1m from the bed, we were able to measure the sleep and respiratory variables such as total sleep time, sleep efficiency, and apnea-hypopnea index (AHI). For 17 patients, the performances of the IR-UWB radar sensor were statistically compared with the gold standard (PSG data) provided by the Sleep Center at Hanyang University Hospital, Seoul, Korea. The intraclass correlation coefficient (ICC) analysis between the radar sensor and the PSG data shows that the correlation coefficient r = 0.90, 0.81, and 0.89 for the total sleep time, sleep efficiency, and AHI, respectively.

The Phenotype of Idiopathic Parkinson's Disease in Populations of African Origin

Marcelle Smith[*] and Girish Modi

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Abstract

As the life expectancy of African population's increases, degenerative diseases like Idiopathic Parkinson's Disease are gaining more notice and have inspired an increase in Parkinson's disease research in Africa. Most studies have been prevalence studies, revealing a lower prevalence of PD in African patients and those of African origin, compared to their Caucasian counterparts. Researches have begun to investigate the differences in disease phenotype between patients of different ethnic groups. In this talk we will discuss the most important historical studies on Parkinson's disease in African Patients, as well as the recent investigations into disease phenotype. We will also address the way forward, in terms of clinical PD research.

Parkinson's Disease and 22q11.2 Deletion Syndrome: Video Case Report, Recent Developments and Diagnostic Challenges

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Abstract

22q11.2 deletion syndrome (22q11.2DS), also known as velocardiofacial or DiGeorge syndrome, is the most common human microdeletion, affecting at least 1 in 4000 live births. Many patients with this deletion remain undiagnosed until adulthood due to the absence of 'major' phenotypic hallmarks, which usually present during early childhood. These adult onset problems are increasingly described in the literature and implicate different medical subspecialties. The association of Parkinson's Disease (PD) with 22q11.2DS has acquired increasingly robust evidence and the hemizygous 22q11.2 deletion has been recently proposed has a new genetic risk factor, accounting for approximately 0.5% of patients with early-onset PD.

A challenging case report with video documentation of a patient with Early-Onset Parkinson disease and typical features of 22q11.2DS leading to genetic screening and confirmation of the deletion will be presented. Comorbidities demanding a high degree of suspicion for this entity and PD phenotype in the presence of 22q11.2DS and response to standard treatments will be discussed.

A Novel Pharmacological Approach to Treating Tinnitus-Inducing Neuropathy

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Abstract

Tinnitus, the phantom perception of sound, is a frequent neuropathological consequence of noise- or blast-induced cochlear injury. As a result, tinnitus is a particularly pervasive problem in the U.S. military and greatly affects quality of life and military readiness. This disorder appears to involve maladaptive increases in spontaneous neural activity in the central auditory system that develops in response to reduced signaling from peripheral cochlear neurons secondary to injury by noise or blast. Consistent with this rationale, objective characteristics of tinnitus include reduced afferent ribbon synapse densities among sound-transducing inner hair cells (HCs) in the cochlea, altered auditory brainstem response (ABR) wave amplitude patterns, and pathological changes in the expression levels of key signal gating factors in auditory centers of the brain.

In our work with a novel compound, NHPN-1010, as a therapeutic for preventing hearing loss, we discovered that its administration also significantly reduced behavioral evidence of tinnitus in rat models of noise- and blast-induced cochlear injury. This therapeutic attribute coincided with reduced neuropathological evidence of tinnitus, including normalized ABR wave amplitude ratios and normalized expression patterns of Arc/Arg3.1 and other gating factors associated with altered inhibition and excitation in the central auditory pathway. Although, NHPN-1010 was known to reduce cochlear HC loss, our recent work has revealed that its administration also induces post-traumatic cochlear synaptogenesis, promoting re-innervation of de-afferented inner HCs even after a significant delay in intervention. Based on these key therapeutic properties, NHPN-1010 represents an exciting candidate for mitigating, and potentially reversing, noise- or blast-induced tinnitus.

Specific Effects of Cardiovascular, Respiratory and Neurocognitive Disorders and Anti-Hypertensive Treatment in Truly Elderly

Jadwiga Attier-Żmudka[1,2*], Beatrice Berteaux[1], Jean-Marie Sérot[1], Youcef Douadi[3], Claire Sorel[4], S Dao[5], Ingrid Gyselinck[1], Anne-Sophie Macaret[6] and Olivier Balédent[3]

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Abstract

The elderly population is rarely included in research. Arterial hypertension, cardiac arrhythmia, and sleep apnea syndrome are common in elderly patients, especially in those with dementia. The brain and its vascular system cannot be considered separately from the heart and the lungs, which provide energy and oxygen supply. The presence of vascular risk factors may increase the risk of Alzheimer's disease. The relation between blood pressure and dementia has been the subject of numerous epidemiological studies, midlife hypertension is a risk factor for dementia and Alzheimer's disease but the association between hypertension and risk of dementia is lower in the older population.

Basing on a clinical examination, geriatric and neuropsychological assessment, blood tests, structural magnetic resonance imaging, 24-hour ambulatory blood pressure measurement, and electrocardiogram in 95 patients, aged 75 years and older, suffering from neurodegenerative diseases, we analyzed the relation between the cognitive, cardiac, and respiratory parameters.

Polysomnography revealed sleep apnea syndrome in 68% participants. The hypertension occurred by night and was not so prevalent. All correlations between polysomnography parameters and cognitive status variables were significant. A case of an older for whom cognitive improvement and reduced risk of falls were noticed after mild blood pressure elevation is reported. A fair modulation of an antihypertensive treatment, based on the cognitive status of the elderly, can avoid multiple complications.

This study highlights the discrepancy between the available epidemiological data and our results.

Efficacy and Mechanism of Cord Blood Cell Therapy for Children with Cerebral Palsy

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Abstract

Umbilical cord blood (UCB) cells have been suggested to exert therapeutic effect for cerebral palsy (CP). By conducting double-blind randomized controlled trials, we could observe the safety and efficacy of allogeneic UCB infusion in CP subjects. Physical and mental function evaluations using standardized measures including Gross Motor Performance Measure, Gross Motor Function Measure, and Bayley Scales of Infant Development-II Mental and Motor scales, and muscle strengths of extremities, showed therapeutic efficacy of UCB cells. To assess therapeutic mechanism of UCB in CP, ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET/CT) and diffusion tensor images were also used. ^{18}F-FDG-PET/CT showed activation of basal ganglia and thalami and anti-inflammatory findings in periventricular white matter after UCB administration. Diffusion tensor images suggested improvement in white matter integrity which correlated with motor performance. According to molecular works using blood samples of the CP subjects, we found possible role of innate immune response triggered by UCB infusion. Elevations of pentraxin 3 and interleukin-8 levels in plasma and toll-like receptor 4 expression in blood cells were observed up to 12 days after UCB treatment and those correlated with the motor improvements observed up to 6-month post-injection.

In this presentation, the efficacy related factors and therapeutic mechanism of cord blood cell treatment that were found through the trials will be discussed.

Effects of Musical Training on Cortical Plasticity within Cognitive Rehabilitation of Patients with Traumatic Brain Injury

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Abstract

Musical training is a highly multi modal complex stimuli for the brain. Reading and playing an instrument simultaneously receives and transmits visual (music literacy), auditory (listening), and kineasthetic (motor) information to a specialized brain network. Music making over time has shown to effectively change the structure and enhance function of many brain areas. Musical training has become a useful framework to study brain plasticity and to be a possible tool in neurologic rehabilitation. Here, for the first time we demonstrated structural and functional brain changes after 8 weeks of musical training on traumatic brain injury (TBI) patients with cognitive deficits. 3 groups were recruited for the study, one TBI group (n = 7), two groups

of healthy participants (n = 11), one with music training and one baseline group (n = 11) without music. fMRI neuroimaging scans pre-post revealed functional changes in brain areas regulating executive functions, as attention, memorization and social interaction in the two music groups. Neuropsychological tests pre-post correlated with fMRI results, enhancement of cognitive performance in both music-training groups. Interviews pre-post in the TBI group documented that six out of seven participants were able to return to their jobs after the music intervention period. Structural changes were found in Basal Ganglia in the control group with music, and in Lingual gyrus in the patient group. The key findings of this study are the clear evidence for a causal relationship between musical training and reorganization of neural networks promoting enhanced cognitive performance. This study adds a novel music-supported intervention within rehabilitation of TBI patients with cognitive deficits.

Road Accident Prevention

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Abstract

Introduction: Road accidents are the main cause of death and disability in Italy under the age of 40 and are a matter of absolute priority. Italy, thanks to preventive measures, has recorded in 2012, a reduction in mortality from road accidents of 48.5% compared to 2001, which are in line with the European average value.

Outcome: The objective of our experimentation focused, certainly, on highlighting all the prevention tools, but above all, on the feedback that this information/training produced in the students undergoing training through:

1. Empathic activation,
2. Acquisition of the value of life and
3. Understanding of the prevention message.

From January 2015 to June 2017 our experiment was lead in three different middle schools located in different districts in Rome, for a total of 580 students. Each experiment session lasted for 2 days: the first day was performed by our Neurorehabilitation team in each school, while in the second day the students were invited to our rehabilitation center.

Tools and Methodologies: The tools used to achieve the objectives were:

- Traffic accident prevention film in England, France and Italy;
- Presentation of the Adelphi Center,
- Illustration of the functioning mechanisms of the brain,
- Visit to the Center, compilation of questionnaires for learning feedback, appreciation and emotional involvement.

Conclusion: The approval rate reached the highest mark in 95% of the cases. 100% of the students felt that the prevention message passed fully. While for what concerns the value of life and the importance of the helping relationship, the recorded values are respectively 66% and 78%.

In summary, the authors are satisfied by the results collected in terms of the emotional impact and sensitization. And overall, authors are also satisfied with the emotional impact and sensitization.

Role of the Microtubule-Associated TPPP/p25 in Parkinson's and Related Diseases and Its Therapeutic Potential

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Abstract

Over many decades symptomic treatment of Parkinson's disease (PD), the second most common neurodegenerative disorder, has been optimized using L-dopa, deep brain stimulation, physio- and pharmacotherapy. The discovery and development of therapeutic strategies for PD and other synucleinopathies are limited by a lack of understanding of the exact pathomechanisms. The hallmarks of these diseases are frequently multifunctional disordered proteins displaying moonlighting and/or chameleon features, which are challenging drug targets. A representative of these proteins, in addition to α-synuclein, is the disordered Tubulin Polymerization Promoting Protein (TPPP/p25). It regulates the dynamics and stability of the microtubule network through its bundling and acetylation promoting activities. TPPP/p25 is expressed specifically in oligodendrocytes (OLGs) in normal brain. Its non-physiological level is tightly related to CNS diseases such as multiple sclerosis (TPPP/p25-positive OLG destruction in myelin sheath), glioma (loss of TPPP/p25 expression) and synucleinopathies (TPPP/p25 and α-synuclein co-enrichment in

neuronal and OLG inclusions in the cases of PD and Multiple System Atrophy, respectively). The established anti-proliferative potency of TPPP/p25 may raise its influence in cancer development. The recognition that whereas overexpression of TPPP/p25 could kill neurons in PD, while its loss keeps cells alive in oligodendroglioma could contribute to our understanding of the interrelationship of 'TPPP/p25 diseases'. These observations underline the key roles of TPPP/p25 in physiological and diverse pathological processes. Consequently, its validation as drug target needs a new innovative strategy, namely, the interface of its pathological complex, which is distinct from the physiological one, has been suggested as a specific anti-Parkinson drug target.

Multiple-Target Stimulation in Hemidystonia for Greater Outcome

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Abstract

Pallidal stimulation has been the usual surgical treatment for dystonia in the last decades. The continuous investigation of the physiopathology and the motor pathways involved leads to the search for complementary targets to improve results. We present the case of a 37-year old female, with idiopathic hemidystonia for 11 years exhibiting hyperkinetic and hypokinetic movements, who was treated with deep brain stimulation. The globus pallidus internus and the ventral intermediate/ventral oral posterior complex of the thalamus were stimulated separately and simultaneously for three months and compared using the Fahn Marsden Scale and the Global Dystonia Severity Rating Scale with a follow-up of 3.5 years. Combined stimulation had better results compared to single-target modulation, the synergism of multiple-target resulted in complete improvement of the mixed dystonic symptoms. The use of a single target may not entirely treat the symptoms and a complementary target should be considered for greater outcome.

Dance and Equine-Assisted Therapy in Autism Spectrum Disorder: A Blinded Randomized Clinical Trial

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Abstract

Autism spectrum disorder (ASD) is a serious neurodevelopmental disorder related to various neurological and psychiatric adversities. One of the most restrictive symptoms of ASD is the difficulty of relationship. Perhaps this difficulty is involved with functional impairments in ASD. The aim of the study was investigate the influence of dance, and Equine-Assisted Therapy (EAT) in children with Autism Spectrum Disorder (ASD). All participants were allocated into three intervention groups (Dance, EAT, Dance&EAT), randomly distributed and going through twenty-four sessions (one-hour, twice a week) in each group. All interventions were divided into four sets: warm-up, flexibility training, balance and relaxation training. The following measures were used before and after the interventions: Functional Independence Measure (FIM), World Health Organization Disability Assessment Schedule (WHODAS) 2.0 version, and Childhood Autism Rating Scale (CARS). It was a cross over clinical trial. Fifteen participants were allocated in each group. Dance improved functional independence ($p = 0.03$), communication ($p = 0.01$), and psychosocial adjustments ($p = 0.02$). In relation to functioning, Dance improved after intervention ($p = 0.04$). Intergroup analysis evidenced significantly greater improvements in classification of functioning in Dance&EAT ($p = 0.0001$). It was evidenced changes related to ASD graduation ($p = 0.01$) in Dance, ($p = 0.03$) in EAT, and ($p = 0.02$) in Dance&EAT. The proposals contributed for communication, social participation and functional independence in ASD participants.

Retinal Lesions in Genetic Neuromuscular Diseases (DM1, FSHD, and DMD): Review and Potential Experimental/Clinical Applications

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Abstract

After summarizing retinal abnormalities in three neuromuscular diseases with systemic manifestations, we propose strategies for improving knowledge about their molecular mechanisms. These diseases include: facioscapulohumeral dystrophy (FSHD; OMIM609032), myotonic dystrophy (DM1; OMIM160900), the two most frequent genetic neuromuscular diseases in adults, and Duchenne muscular dystrophy (DMD; OMIM310200) in boys. Few visual complaints related to retinal alteration have been reported by patients, as retinal lesions rarely affect the macula. Only systematic examination of the fundus and electrophysiological testing detected abnormalities. In DM1 patients, pattern dystrophy was reported A study indicated that 56.7% of DM1 patients had epiretinal membranes in at least one eye. In FSHD, most patients developed mild to moderate abnormalities of the retinal vasculature, with no clear relation with severity of the myopathy. In DMD patients, inner retinal dysfunction documented by electroretinogram recording and color vision defects have been reported.

To date, for DM1 and FSHD, there is no experimental research for the eye, but only for muscle and brain of animal models. In some DMD mouse models, retina and brain lesions were observed, which might constitute early biomarkers of disease severity and genotype-phenotype relationships. Patient registries with clinical and genetic data are being developed around the world, but with limited ophthalmic data.

The longer life expectancy of patients justify multidisciplinary, collaborative and translational research plans between research/clinical teams on muscle, brain and eye, as said by London A. "The retina as a window to the brain — from eye research to CNS disorders.

Neurophysiological Features of Restless Leg Syndrome in Parkinson's Disease

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State Institution, Republican Scientific and Practical Center of Neurology and Neurosurgery, Belarus

Abstract

The pathogenetic mechanisms underlying the restless legs syndrome (RLS) closely related to dopaminergic insufficiency and iron metabolism disturbances in the structure of the extrapyramidal system. Hypofunction of diencephalic-spinal dopaminergic tracts changes in the functional state of the subcortical-brainstem-spinal systems with development of the sensory-motor disorders. This fact likely explains why RLS in patients with PD occurs more frequently than in general population.

We investigated the neurophysiological features of RLS in PD. To assess the functional status of the somatosensory system and sensory-motor integration we used the somatosensory evoked potentials (SEPs), blink reflex (BR) and sympathetic skin response (SSR). 75 patients with PD were examined: 36 with RLS (1st group), 39-without RLS (2nd group) and 30 healthy individuals.

SEPs study revealed that in the 1st group, the interpeak intervals (IPI) N9–N13, N11–N13 were significantly shorter and the IPI N13-N20 was longer as compared with the 2nd group. A significant increase in the amplitudes N20-P23 and N13-P18 was in the 1st group, which reflects sensitization processes in patients with RLS. A trend to hyperexcitability responses of BR was observed, which can reflect insufficiency of the inhibitory mechanisms at the segmental level and deficiency of supraspinal descending control in PD patients with RLS. SSR study revealed prolonged latency and an increase in the positive component amplitude in the 1st group and positive correlation between the severity of RLS and SSR latency.

Identified somatosensory disturbances and changes in the brainstem and spinal reflexes probably determine the clinical features of RLS in PD.

NGF-Dependent Axon Growth and Regeneration are Altered in Sympathetic Neurons of Dystrophic *mdx* Mice

Maria Egle De Stefano*, Loredana Lombardi and Irene Persiconi

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Abstract

Duchenne muscular dystrophy (DMD) is a lethal disease, determined by lack of dystrophin (Dp427), a muscular cytoskeletal protein also expressed by selected neuronal populations. Consequently, besides muscular wasting, both human patients and DMD animal models suffer several neural disorders. Our previous studies on the superior cervical ganglion (SCG) of wild type and dystrophic *mdx* mice, strongly suggested that Dp427 could play some role in NGF-dependent axonal growth, both during development and adulthood. To address this issue, we performed a series of *in vitro* and *in vivo* experiments. At first, we analyzed axon regeneration potentials of SCG neurons of both genotypes after axotomy *in vivo*. While noradrenergic

innervation of *mdx* mouse submandibular gland, main source of nerve growth factor (NGF), recovered similarly to wild type, iris innervation (muscular target) never did. We, therefore, evaluated whether dystrophic SCG neurons were poorly responsive to NGF, especially at low concentration. Following *in vitro* axotomy in the presence of either 10 or 50 ng/ml NGF, the number of regenerated axons in *mdx* mouse neuron cultures was indeed reduced, compared to wild type, at the lower concentration. Neurite growth parameters (i.e. number, length), growth cone dynamics (live imaging experiments) and NGF/TrkA receptor signaling in differentiating neurons were also significantly reduced. In conclusion, we propose a role for Dp427 in NGF-dependent cytoskeletal dynamics associated to growth cone advancement, possibly through indirect stabilization of TrkA receptors. Considering NGF activity in nervous system development and remodeling, this aspect could concur in some of the described DMD-associated neural dysfunctions.

MicroRNA and Transcription Factors: Key Players in Dopamine Neuron Network

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Abstract

Recent achievements in dopamine neuron miRNA, a large class of non-coding RNAs are very exciting. A wide array of techniques involving forward genetics, molecular cloning, bioinformatics analysis and the latest technology, deep sequencing have greatly advanced miRNA discovery. Most of the miRNA targets are transcription factors (TF's) which have paramount importance in regulating the dopamine neuron differentiation and survival. Studies of transcription factors, such as Nurr1, Foxa1, Engrailed-1/2, Lmx1a/b and Pitx3, have not only revealed importance of these genes during development, but also roles in the long-term survival and maintenance of these neurons. The expression of these factors has been associated with resistance to neurodegeneration. The available data and knowledge in the field is not sufficient to understand the mechanism of miRNA and TF's in dopamine neuron death. We used three different algorithms; DIANA *Micro*-CDS, TargetScan, and miRanda and predicted miRNAs for *Nurr1, Foxa1, Lmx1a/b, En1/2*. Further we profiled the expression of the predicted miRNA in regulation of *Nurr1, Foxa1, Engrailed-1/2,* and *Lmx1a/b* that occurs at normal and stress environment. These results provide potentially new information to obtain novel markers which help in early detection of dopamine neuron degeneration.

Effects of Health Qigong Exercises on Reducing Symptoms of Parkinson's Disease

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Abstract

The purpose of this study was to investigate the effects of Health Qigong on the treatment and reducing symptoms of Parkinson's Disease (PD). Fifty-four moderate PD patients (N = 54) were randomly divided into experimental and control groups; Twenty-eight PD patients were placed in the experimental group which the prescribed medication plus Health Qigong exercise will be used as intervention. The other 26 PD patients as the control group were treated only with regular medication. Ten-week intervention had been conducted for the study, and participants completed the scheduled exercises 5 times per week and 60 minutes each time (10 minutes for warm-up, 40 minutes for the exercise, and 10 minutes for cool-down). Muscle hardness, one-legged blind balance, physical coordination, and stability were collected before, during, and after the intervention. Comparisons were made between the experimental and control group through the Repeated Measures ANOVA. The results showed that PD patients demonstrate a significant improvement on muscle hardness, the timed 'up and go', balance, and hand-eye coordination (the turn-over-jars test). There were no significant differences between the two groups on gender, age, and course of differences ($P < 0.05$). The study concluded that Health Qigong exercises could reduce the symptoms of Parkinson's disease, and improve the body functions of PD patients in both the mild and moderate stages.

Towards Terrain-Enabled Gait Therapy using Immersive VR with Physical Terrain Display for Parkinson's Disease

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Abstract

This research describes development of terrain-enabled Virtual Reality (VR) based gait therapy where challenging terrain features are graphically rendered and physically created for the user, such that the user trains with more realistic conditions. Parkinson's Disease (PD) studies have already demonstrated improved gait characteristics with VR based gait therapy, but these lack real world challenges since haptic terrain rendering is challenging and limited in existing VR systems. This research focuses on using the Smart Shoe to physically render terrain features. An immersive CAVE VR system is used to graphically display terrain features on the ground and walls, which move as the user locomotes. A motion capture system is used to track foot placement relative to the VR display and the Smart Shoe physically renders features mimicking the terrain where the user steps.

IRB approved subject studies using the system compare gait characteristics and evaluate survey data to determine efficacy of the technique. PD subjects and healthy peers are included in the study while using the Smart Shoes with rendering, Smart Shoes without rendering, and regular shoes to compare statistical difference between the three scenarios. Kinematic and spatiotemporal results derived from motion capture data indicate the Smart Shoe is capable of creating gait perturbations for future PD therapy. Questionnaire data shows increased realism and desired gait challenges using the system. Thus, the terrain-enabled VR-based gait therapy using the Smart Shoe is promising as a PD gait training tool, which is the subject of ongoing work.

Deep Learning Based Risk Assessment and Stenosis Measurement in Common Carotid Artery

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Abstract

Background and Objective: Diagnosis of cerebrovascular diseases with the help of carotid ultrasound has started to become a routine. The measurement of image-based common carotid artery lumen diameter (CCA-LD) is a promising approach for quantification of the degree of stenosis. The human delineation of LD is error-prone, unreliable, subjective and slow. The curvature associated with the vessels along with non-uniformity in the plaque growth poses further challenges.

Methods: This study proposes Deep Learning based automated stenosis measurement and risk prediction for cerebrovascular diseases. In this approach, a Fully Convolution Network (FCN) is used for identification of far wall and near wall of common carotid artery. 407 B-mode ultrasound images were retrospectively analyzed for the entire process.

Results: The validation of our algorithm was done against the three manual expert tracings. The coefficient of correlation between the three manual tracings for LD was 0.93, 0.94 and 0.93, respectively. The precision of merit between the manual expert tracings and the automated system was 96.7%, 96.1% and 96.4%, respectively.

Conclusion: The experimental analysis demonstrated superior performance of the proposed method over conventional approaches. Several statistical tests demonstrated the stability and reliability of the automated system.

Neuromender: A Serious Game Designed Upper Limb Rehabilitation in the Home

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Perron Institute, Australia

Abstract

The Neuromender system is a serious game designed to assist with the upper limb rehabilitation of stroke survivors. Unlike

conventional rehabilitation methods, the system can be set up in a stroke survivor's home, allowing them to engage with the system several times daily in an easy to access and convenient environment. The system enables remote configuration and monitoring of survivors by their clinicians. Emphasis is also being placed on the convenience afforded by the system and the cost effectiveness of the system, utilizing inexpensive off-the-shelf desktop PCs and peripherals.

The system amplifies a survivor's elbow movement, allowing them to control a character onscreen. The performance of the survivor is measured by the amount of mindful control of the character. As the player improves their score, the sensitivity is decreased in order to challenge the participant to move their arm more.

The system is currently being trialed by stroke survivors in their homes in collaboration with a public hospital, in order to determine its current efficacy in rehabilitating upper limb movement. In addition, stroke survivor feedback is being collected in order to determine how the system can be made more engaging for them. The presentation will give the trial results.

Granulocyte Colony Stimulating Factor (GCSF) Gene Therapy in Stroke and Alzheimer's Disease Model

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Abstract

Granulocyte colony stimulating factor (GCSF) is an FDA-approved drug that stimulates growth and differentiation of myeloid precursors. We have designed and constructed gene therapy vectors consisting of self-complementary AAVs driving expression of GCSF with either a neuron specific synapsin 1 promoter plus a hypoxia regulated domain (HRE), or the synapsin 1 promoter alone, or the ubiquitously active CMV promoter. In PC 12 cell cultures, we found that AAV vectors containing GCSF gene significantly increased cell viability from 50% to 80% compared to the control group, namely, transfected with AAV-GFP vector under three experimental conditions including glutamate -, hypoxia – and Aβ - induced toxicity. In the bilateral carotid artery occlusion (BCAO) global ischemic stroke model, we also found that AAV-GCSF gene therapy greatly increased the survival rate, decreased the infarct size, reduced the stress markers for mitochondria, e.g., DRP1, endoplasmic reticulum, e.g., GRP78, pIRE1, autophagy, e.g., Beclin1 and increased mitochondrial enhancing protein, OPA1 and anti-apoptotic proteins e.g., Bcl-2 as well as improving the behavioral outcome. These results suggest that GCSF gene therapy could provide a new and novel approach for therapeutic intervention in stroke and Alzheimer's disease (Supported in part by grant from James and Esther King Biomedical Program, State of Florida, Grant # 6JK08; Grant from Aeura Company).

Individualized Noninvasive Neuromodulation in Cognitive Rehabilitation after Stroke

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Abstract

Human cognition requires, and is to a large extent based on, our ability of selectively focusing on certain aspects of our surroundings. This ability of spatial attention control is often severely impaired after stroke and traumatic brain injury. Investigating the neurobiological mechanism underlying these cognitive abilities is paramount for understanding the relationship between brain and cognition as a prerequisite to develop new means to initiate, guide, and support enhancement and rehabilitation. Magneto-/electroencephalography research demonstrated that attention control is related to oscillatory mechanisms in specific lower frequency-bands (4-20 Hertz), especially the alpha frequency (10Hz). Directing attention to one visual hemifield lateralizes alpha power in parietal cortices. We applied transcranial alternating current stimulation (tACS) to modulate alpha lateralization as measured by EEG and then assessed how such a tACS-induced change in alpha power lateralization leads to respective changes in behavioral task performances in healthy volunteers. Based on these studies, we then applied this tACS alpha lateralization protocol also in patients suffering from lateralized spatial attention deficits (hemineglect) in an attempt to specifically support their cognitive rehabilitation.

Effects of Stroke Unit Care in Acute Ischemic Stroke Patient Ineligible for Thrombolytic Treatment

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Abstract

Background: Several trials have verified the benefits of stroke unit (SU) in acute stroke care worldwide.

Objective: Compare clinical outcomes and costs of care in acute ischemic stroke patients who were ineligible for thrombolytic treatment (recombinant tissue plasminogen activator-rt PA) in a primary stroke center.

Material and Method: A prospective study was conducted in acute ischemic stroke patients, aged 15 years old and above, presenting within 72 hours of onset. At discharge, neurological and medical complications, mortality rate, National Institutes of Health Stroke Scale (NIHSS), Barthel Activities of Daily Living (Barthel ADLs Index), and modified Rankin Scale (mRS) for Disability were measured, as well as the length of stay, and cost of hospital care.

Results: There were 1,110 acute ischemic stroke patients, 472 subjects (42.52%) in general medical ward (GMW), and 638 subjects (57.48%) in stroke unit (SU). The number of neurological (brain edema, hemorrhagic transformation, or recurrent stroke), and medical complications (gastrointestinal hemorrhage, pneumonia, or pressure sore) in GMW had highly statistical significance ($p < 0.001$, $p < 0.001$) more than those in SU, with adjusted OR (aOR) (95% CI) of 84.53 (31.14 to 229.46), 4.03 (1.99 to 8.17), respectively. Whereas, the death rate, NIHSS, and disability (Barthel Index of ADLs, and mRS) were statistically significant lower among SU cases ($p = 0.05$, $p < 0.001$, $p < 0.001$) respectively. The median length of stay was three days in both groups, while the median cost of in hospital care was 10,206 Thai Bahts in SU, which was 15.23% higher ($p < 0.001$).

Deep Learning Algorithm for Establishing Relationship Between cIMT and Age in Diabetic Cohort for Stroke Risk Assessment

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Abstract

Introduction: An important biomarker for stroke risk prediction among CVD affected patients is carotid intima media thickness (cIMT), computed as the mean distance between lumen-intima (LI) interface and media-adventitia (MA) interface in the wall of the carotid artery. Manual quantification of cIMT is slow, erroneous and subjective process. Automated techniques for delineation are faster and less prone to error. Earlier automated methods used various image features such as greyscale median and white calcium area to predict risk of assessment. The inclusion of intelligence-based learning methods such as deep learning (DL) provides an interesting alternative to the previous methods. The study presents the relationship between DL-based cIMT and age.

Methods: Ultrasound (US) images were obtained from 202 diabetic patients from Toho University Ohashi Medical Center, Tokyo, Japan for clinical purposes. Two tracings (GT1 and GT2) from two different radiologists with varied experience levels formed the gold standard or ground truth. DL system consisted of two stages: In stage-I, a 13-layer convolution neural network was used to extract high level features in US images, leading to estimation of LI and MA interfaces using the ground truth (GT). These were then refined using a calibration system in stage-II. The cIMT was measured on the refined LI/MA interfaces by computing the standardized polyline distance method. Two DL-based intelligent systems (DL1 and DL2) were designed using GT1 and GT2, respectively.

Results: The cohort consisted of 202 patients (155 M/47 F); mean age 69 ± 15.9 years; Mean HbA1c, LDL, HDL and Cholesterol of patients were 6.28 ± 1.1 mg/dl, 101.27 ± 31.6 mg/dl, 50.26 ± 14.8 mg/dl and 175.04 ± 38 mg/dl, respectively. Using our two DL methods (DL1 and DL2), the CC between cIMT and age were: 0.41 and 0.42, respectively. Our validation CC between cIMT and age for two manual readings (GT1 and GT2) were: 0.40 and 0.41, respectively. The percentage error for two DL systems were: 2.5% and 2.5%, respectively.

Conclusion: Our automated DL system shows high-moderate correlation between cIMT and age, and was validated against manual readings, and consistent with previously published literature. The DL-based strategy for border delineation is accurate and clinically useful.

Sensory E-Textiles and Playful Objects: Designing for Advanced Dementia Care

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Abstract

In the UK many people living with advanced dementia live in specialist units in residential healthcare where they often experience little cognitive or sensory stimulation and receive few visitors. Research has shown that boredom and lack of activity contributes to depression, resulting in the use of medication that can lead to deeper withdrawal and loss of interest in life. The aim of this research is to develop highly personalized sensory textiles and playful hand-held objects that can offer an effective non-pharmacological approach to advanced dementia care, improve quality of life and increase positive emotion.

Outcomes from two international research projects: LAUGH and Sensor e-Textiles are described. Qualitative ethnographic methodologies, underpinned by Compassionate Design and grounded practical theory have been used to inform the design of playful objects and sensory e-textiles that are presented. Compassionate Design focuses attention on three themes considered vital in designing for this demographic. These include: sensory stimulation, personalization and designing for moments of connection. The integration of embedded technology enables highly personalized designs to be created that can be used to soothe, comfort, stimulate and engage people living with the advanced stages of the disease. A series of co-design workshops including people living with dementia, family members, carers, health professionals and technologists have informed this design research.

A rich immersive evaluation process, via a series of live labs, has revealed ways in which these playful hand-held objects can contribute significant benefits to individual wellbeing and offer an alternative approach to advanced dementia care.

n-3 PUFA Combined with an Antioxidant in Prevention of Cognitive Decline

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Abstract

Prevalence of neurodegenerative diseases is increasing with aging population. The later therapy introduced, the less improvement can be achieved, due to progressing neuronal loss. In addition, clinical manifestation of cognitive decline appears long time after first brain functional and structural changes occur. Therefore, preventive measures implemented in early stage of developing dementia could be valuable. Observations suggest that fish consumption, rich in essential polyunsaturated fatty acids (PUFA), may hamper risk of dementia. Contrary, widely prevalent dietary n-3 PUFA deficiency increases that risk. Docosahexaenoic (DHA) and eicosapentaenoic acid (EPA) exert strong activity in modulation of many processes, leading to neuronal death. DHA and its metabolites diminish toxicity of insoluble beta-amyloid plaques. Stimulation of brain derived neurotrophic factor (BDNF) and shifting balance in favor of anti-apoptotic genes are examples of DHA importance. EPA has strong anti-inflammatory properties, which may act in synergy with specialized pro-resolving molecules (e.g. protectins, maresins). Clinical benefits of n-3 PUFA were not demonstrated in Alzheimer's disease, but significant improvement in mild cognitive impairment (MCI) was proven in many randomized trials. Both DHA and EPA are vulnerable to oxidation, and high oxygen consumption fuels oxidative stress in brain tissues. Therefore, n-3 PUFA combined with an antioxidant, e.g. alpha-lipoic acid, has been proposed by researchers. Food supplementation with DHA and EPA combined with an antioxidant (e.g. Liponerv, Qpharma) appears to be an interesting, safe and inexpensive proposition for patients with early cognitive decline symptoms, as a part of long-term neuroprotective strategy, including care for general health, physical and mental activity.

In the Search of Universal Cognitive Algorithms

Alexander Serov
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Abstract

A number of modern experimental studies in the field of neurophysiology testify to the possibility of the existence of universal algorithms. These algorithms, being implemented in appropriate neurostructures, are able to describe the processes that accompany cognitive activity. Our research related to the search for these algorithms is based on the idea of leading role of perception in the process of cognitive activity.

In our previous work, we proposed a new type of cognitive architecture: the Dynamic Artificial Neural Network (DANN). Distinctive feature of this architecture is the dependence of the structure of neural network on time. The structure and nature of the connections of neuro-elements in this model are determined by the direct experience of perception and cognitive activity.

One of the most difficult tasks in the study of cognitive functions is the task of investigating the processes of generation of a system of mental patterns. Successful solution of this problem would allow creating artificial systems capable of autonomous cognitive activity. Based on proposed DANN architecture, we developed numerical model that describes processing of sensory data and links results of this processing to the processes of changing the neurostructure. In this paper, we illustrate features of proposed models by results of numerical experiments on modeling the evolution of the structure of neural system.

Translational Profiling Identifies Candidate Molecular Pathways Underlying Cholinergic Neuron Impairment in a Mouse Model of Alzheimer's Disease

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Abstract

Cholinergic neuron impairment occurs early and progresses throughout Alzheimer's disease (AD). Late in AD, extensive death of these cholinergic neurons is common. Since the molecular underpinnings of this cholinergic dysfunction and neuronal death remain poorly understood, we combined translating ribosome affinity purification (TRAP) with RNA sequencing (TRAP-Seq) to identify the actively translating mRNAs in degenerating cholinergic neurons of the TgCRND8 mouse model of AD. We first crossed TgCRND8 mice with bacterial artificial chromosome-based TRAP (BAC-TRAP) mice which express an EGFP-tagged ribosomal fusion protein, called EGFP-L10a, driven by the cholinergic neuron-specific choline acetyltransferase (Chat) promoter (generated through the GENSAT project). EGPF-L10a incorporates into polysomes in Chat-expressing neurons allowing the molecular phenotyping of cholinergic cells *in vivo*. TRAP-Seq followed by a differential transcript expression analysis revealed down-regulation in the active translation of established cholinergic transcripts such as neurotrophin and cholinergic receptors. Additional down-regulation of genes in pathways related to AD, oxidative phosphorylation, and the ribosome were noted. The cholinergic translatome also demonstrated up-regulation of genes enriched in pathways such as glutamatergic receptors, long-term potentiation, axon guidance, and calcium signaling. In contrast, the total anterior forebrain transcriptome predominantly showed up-regulation of transcripts and pathways that related to cytokine signaling, complement and coagulation cascade, and the immune system. These total transcriptome alterations are consistent with previously identified whole tissue gene expression changes in AD. Taken together this study differentiated the anterior forebrain cholinergic neuron translatome from the total transcriptome in TgCRND8 mice, identifying candidate pathways underlying cholinergic neuron susceptibility in the AD pathogenic process.

Ubisol Q10: A Water Soluble Nano-Micellar Formulation of CoQ10 Halts Progression of Neurodegenerative Diseases and Cellular Aging

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Abstract

There has been an exponential increase in the number patients diagnosed with Alzheimer's and Parkinson's disease as number of elderly increases. Although the etiological factors triggering AD and PD are very different, they ultimately bring about neuronal death which is, most likely, executed by a common mechanism(s) including oxidative stress, mitochondrial dysfunction and stress, accumulation of misfolded proteins and defective organelles and impaired proteasome and autophagy mechanism. Currently, there are no effective treatments to halt the progression of these diseases. Recently we have reported unprecedented efficacy of Ubisol-Q10 (Next Remedies Inc.) in protecting neurons in *in vitro* and *in vivo* models of neurodegenerative diseases. The formulation contains CoQ10 and PEG-α-tocopherol forming jointly water- soluble nanomicelles. We have confirmed bioavailability of this formulation in brain. A comprehensive behavioral analysis of transgenic animals (PD and AD mice models) fed with this formulation indicated significant improvement in motor activity in PD and long term memory and emotional reactivity in AD models compared to untreated animals. These results were complemented with histochemical analysis that indicated significant protection of neurons in substantia nigra region in PD models, lower amyloid beta burden (plaques) and increased autophagy in AD mice. This treatment leads to the stabilization mitochondrial functions, decrease of oxidative stress in neuronal cells, increased autophagy and induction of pro-survival astroglial cells. Thus Ubisol Q10 could offer a treatment that could halt the progression of disease in AD and PD patients.

Modulation of Brain Homeostasis by Transcription Factor NRF2 and Impact in Alzheimer's Disease

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Abstract

Failure to translate successful neuroprotective preclinical data to a clinical setting in Alzheimer's disease (AD) indicates that amyloidopathy and tauopathy alone provide an incomplete view of disease. Here, we will attempt to summarize the most relevant findings about the relevance of additional homeostatic deviations that result from loss of activity of NRF2, a transcription factor whose activity declines with ageing. NRF2 has been classically considered as the master regulator of the antioxidant cell response, although it is currently emerging as a key component of the machinery to control neuroinflammation and proteostasis. Accordingly, our transcriptomic analysis demonstrated that NRF2-KO mouse brains reproduce dysregulated pathways of human ageing and AD brains. Then, we generated a mouse that combines amyloidopathy and tauopathy with either wild type (AT-NRF2-WT) or NRF2-deficiency (AT-NRF2-KO). AT-NRF2-KO brains presented increased markers of oxidative stress, neuroinflammation as well as worsen of APP ad TAU pathology. Young adult AT-NRF2-KO mice exhibited deficits in spatial learning and memory and reduced long term potentiation in the perforant pathway. This study demonstrates the relevance of normal homeostatic responses that decline with ageing, such as NRF2 activity, in the protection against proteotoxic, inflammatory and oxidative stress and provide a new strategy to fight AD.

Embodiment in Reading Comprehension

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Abstract

Assistive Augmentation is an emerging field where assistive technologies mix with interaction design, cognitive science, and neuroscience. The augmentation provides enhanced embodied experiences that seamlessly assimilate with the user's mind

and body. The key elements are the substitution and enhancement of incoming sensorial information. Here "augmented sensors" are used to introduce and speculate about remapping information from one sensory modality to another, creating new cognitive modalities.

Perception is a mix of incoming sensorial information, processed through different channels, each creating separate representations of the same event. Moreover, human cognition has specialized in dealing simultaneously with verbal and non-verbal information to extract meaning of events and human communication. In reading, these separate cognitive subsystems are used to increase comprehension supplementing the text with non-verbal information, like illustrations. However, both representations are of incoming visual information that competes for focus and attention. An embodied reading experience adds sonic and haptic non-verbal information to the text, incrementing channels of incoming information, and thus also increasing the construction of mental models in top-down processing. For this embodied reading to work as an assistive augmentation, smart eyeglasses (augmented sensors) were designed to measure the reader's mental workload. The glasses monitor the nose temperature to identify if the reader is in a state of flow or frustration; if frustrated, the embodied information is triggered.

Oligomer β-Amyloid Suppresses Hippocampal γ-Oscillations through Activation of the mTOR/S6K1 Pathway

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Abstract

In early Alzheimer's disease (AD) oligomer β-amyloid (Aβ) is prominent in the brain, while Aβ plaques and neurofibrillary tangles are limited. Neuronal synchronization at gamma frequency (30-100 Hz: γ-oscillations), a timing matrix required for optimal functioning of information processing, learning and memory, is impaired in early-stage AD patients. We explored the mechanism by which Aβ affects γ-oscillations evoked by kainate in mouse hippocampal slices and synaptic currents underlying γ-oscillations. Oligomer $Aβ_{1-42}$ caused a concentration-dependent, irreversible reduction of γ-oscillation strength and regularity, while increasing its frequency. The mTOR1 inhibitor rapamycin prevented the $Aβ_{1-42}$-induced suppression of γ-oscillations and the activation of mTOR, whereas the mTOR activator leucine mimicked the $Aβ_{1-42}$-induced suppression. Activation of the downstream kinase S6K1, but not inhibition of eIF4E, was required for the $Aβ_{1-42}$-induced suppression. The involvement of the mTOR/S6K1 signaling in the $Aβ_{1-42}$-induced suppression was confirmed in Aβ-overexpressing APP/PS1 mice, where inhibiting mTOR or S6K1 restored degraded γ-oscillations. To assess the network changes that may underlie the mTOR/S6K1 mediated γ-oscillation impairment in AD, we tested the effect of $Aβ_{1-42}$ on IPSCs and EPSCs recorded in pyramidal neurons. $Aβ_{1-42}$ reduced EPSC amplitude and frequency and reduced IPSC frequency, which could be prevented by inhibition of mTOR or S6K1. These experiments indicate that in early AD, oligomer $Aβ_{1-42}$ impairs γ-oscillations through a reduction of inhibitory interneuron activity, by activation of the mTOR/S6K1 signaling pathway, which may contribute to early cognitive decline and provides new therapeutic targets.

Poly-Deprescribing to Treat Polypharmacy - Countering the First Iatrogenic Epidemic

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[2]ISRAEL Founder IGRIMUP -International Group for Reducing Inappropriate Medication Use & Polypharmacy, Israel

Abstract

Improved medical technology has resulted in rapidly increasing subpopulations of Very Old, Comorbidity, Dementia, Frailty/disability, and Limited life-EXpectancy (VOCODFLEX) for whom no evidence based medicine (EBM) really exists. However, having more specialists implementing more "single disease model" guidelines/medications result in Inappropriate Medication Use & polypharmacy (IMUP). The Garfinkel method advocates rethinking/reevaluation for each drug in older people based on ethics, EBM (when present), clinical judgment and patient/family preferences. It was proven effective and safe in nursing homes, significantly decreasing drug load, mortality and hospitalizations. In the community, Poly-de-prescribing of $\geqslant$ 3 drugs was achieved by 122 participants (PDPs); $\leqslant$ 2 drugs stopped by 55 'non-responders' (NRs); average age 83.4 ± 5.3 vs. 80.8 ± 6.3 ($p = 0.0045$), follow up 43.6 ± 14 vs. 39.5 ± 16.6 months ($p = 0.09$) in PDPs and NR, respectively; comparable prevalence of most diseases/symptoms. The main barrier to de-prescribing was family doctor's unwillingness to adopt PDP

recommendations ($p < 0.0001$). The baseline median number of medications taken by both groups was 10 ($p = 0.55$). On last follow up, drug count was 11 (IQR 8 to 12) in NRs, but only 4 (IQR 2 to 5) in PDPs ($p = 0.0001$). PDPs showed significantly less deterioration (sometimes improvement) in functional/mental/cognitive status, sleep quality, appetite, sphincter control, and fewer major complications, as compared to older people who followed all guidelines of all specialists ($p < 0.002$ in all). The rate of hospitalizations/mortality was comparable. Health improvement occurred within 3 months after de-prescribing in 83%, persisted for $\geqslant$ 2 years in 68%*. Obviously, the socio-economic win-win is huge.

Design Intervention for Enhanced Appetite among Pre-Dementia and Memory Center Elders

Valencia Browning-Keen*, Laura Burleson and Christian Martinez

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Abstract

Influenced by Dr. Berg of Sweden's Memory and Aging Project multidisciplinary study provided insights into subtle brain changes and disease-onset markers rating clinical dementia in dementia residents and Dr. Brian Wansick's studies on environmental factors that increase food consumption, this four-stage process assisted in the development of an appropriate foodservice environmental checklist when feeding or encouraging eating episodes of pre-dementia free-living Elders. During stage one, information was collected to develop the environmental checklist and dietary intake. By manipulating the environmental factors that increase food consumption, dementia and Alzheimer's residents may experience less confusion and anxiety and may have improved intake to support a positive nutritional assessment. The focus group interview of experts in the area of interior design and foodservice operations assisted in the survey development that was used in stage two at 31 facilities in extended care communities. In stage three, the plate waste study analyzed three variations of design intervention in a free-living pre-dementia senior and active life-style center to determine enhanced appetite. The last stage of the intervention will include using these three variations in memory centers to determine enhanced eating episodes and the improved nutritional status among dementia residents. Workshops to teach how to evaluate facility adequacy in environmental design and how to evaluate nutrition services to enhance food intake and promote nutrition assessment are being developed and the development of Best Practice Universal Protocols. Best practice protocols for residents diagnosed with dementia are still not uniform worldwide.

Diagnosis and Prevention of Autism at Birth

Gary Steinman

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Abstract

It has been documented that the mean level of insulin-like growth factor-1 (IGF) in the cerebrospinal fluid of young children is commonly found to be depressed in autistic children between 1 and 4 years, when compared to unaffected youngsters. This appears to be closely associated with the deficient layers of axonal myelin in brain biopsies of autistic children. This could explain the brain dysconnectivity related to aberrant behavior in such affected individuals. Gene polymorphism and maternal viral infections are known to depress IGF production. Prevention of demyelination in autism could be achieved by feeding breast milk exclusively, which is high in IGF, or the combination of glatirmater and 1-3(des)IGF injections beginning at birth to deficient infants and continuing for at least one year. A similar combination might be used in reducing demyelination in multiple sclerosis.

Personalized Machine Learning for Future Autism Therapy

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Abstract

Recent developments in AI and Machine Learning are revolutionizing many fields of medicine by bringing novel diagnostic and therapeutic tools for individuals with neurodevelopmental conditions such as autism. Specifically, due to the large heterogeneity of this population, the traditional one-size-fits-all paradigm is suboptimal. This calls for novel personalized assistive technologies. In this talk, I will outline the most recent advances in robotic technology for assisting the therapy

for children with autism, with the goal of measuring their engagement during the therapy. To this end, I will introduce a personalized machine learning (ML) framework for automatic perception of the children's affective states and engagement during robot-assisted autism therapy. This framework is evaluated using a dataset of multi-modal audio, video and autonomic physiology data of 35 children with autism (age 3-13) and from 2 cultures (Asia and Europe), participating in a 25-minute child-robot interaction. The proposed framework has potential to improve existing therapies for autism by offering more efficient monitoring and summarization of the therapy progress.

Sensory Processing in Neurodevelopmental Disorders – An Opportunity for a Translational Approach?

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Anatomy & Cell Biology, Schulich School of Medicine and Dentistry, The University of Western Ontario, Canada

Abstract

The auditory system undergoes tremendous development and plasticity during early life, however, typical maturation is perturbed in individuals with neurodevelopmental disorders. The ability to accurately process sound is key for the proper development of the auditory and multi-sensory systems, for the development of speech, and for interaction with the environment. Sensory pathways are well described and highly preserved between species, they therefore offer a unique opportunity to use animal models for understanding the neural underpinnings of sensory processing disruptions as well as the consequences on other cognitive functions.

CNTNAP2 loss-of-function mutations have been identified as one of the rare single gene causes for autism. Here, we will report our findings in the CNTNAP2 knock-out rat, an animal model with high construct and face validity for a spectrum of neurodevelopmental disorders, including autism, and developmental language disorder. These animals show sensory and cognitive deficits reminiscent of neurodevelopmental disorders in humans. Electrophysiological recording reveal specific disruptions in auditory processing early in development and across auditory processing stages that to some extend normalize in the adult. Many associated changes in auditory-evoked behavior still manifest in adult stages, though. These findings will help to understand mechanistic causes for sensory processing abnormalities, and can the model can serve for developing treatments.

Targeting Aberrant Cl- Homeostasis and $GABA_A$-ergic Transmission in Down Syndrome to Design Innovative Therapeutic Approaches

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Abstract

Down syndrome (DS) is the most frequent genetic cause of intellectual disability. A large body of literature demonstrated that altered $GABA_A$-ergic transmission through Cl-- permeable $GABA_A$ receptors ($GABA_A$Rs) considerably contributes to learning and memory deficits in DS mouse models. However, the efficacy of $GABA_A$ergic transmission had never been directly assessed in DS. We have shown that $GABA_A$R signaling is excitatory rather than inhibitory, in the hippocampi of adult DS mice. Accordingly, hippocampal expression of the cation Cl– cotransporter NKCC1 is increased in both trisomic mice and individuals with DS. Notably, NKCC1 inhibition by the FDA-approved diuretic bumetanide restores inhibitory $GABA_A$ergic signaling, synaptic plasticity and hippocampus-dependent memory in adult DS mice. Based on these findings, a pilot clinical trial will soon start on adult individuals with DS patients. Yet, although repurposing bumetanide for DS is a straightforward therapeutic approach, this may be hindered by bumetanide's diuretic effect. In this talk, I will summarize all findings from our laboratory on DS and impaired Cl- homeostasis, and show preliminary results recently collected on alternative therapeutic approaches to avoid bumetanide's unfavorable diuretic side effect.

The Differential Diagnostic of Idiopathic Toe Walking

H.C. David Pomarino

Praxis Pomarino, Germany

Abstract

Idiopathic toe walking (ITW) is the persistence of the tip-toe walking pattern after two years of age. The diagnosis is made by ruling out any neurological or orthopedic condition which causes this walking anomaly. There are other medical conditions in which the weight bearing occurs on the forefoot which can lead to misdiagnosis and misguided treatment. The main goal of this publication is to provide a concise review of idiopathic toe walking and its classification according to clinical characteristics found among children with a tip-toe walking pattern. In addition, we will point out some physical characteristics that may help to differentiate toe walking from other medical conditions in which the gait pattern occurs on the forefoot as well. Typical conditions which are commonly known to cause a pathological forefoot gait, like autism and tethered cord are intentionally excluded from this article. This review highlights the importance of the observation of the foot features, gastrocnemius shape and gait analysis during the clinical examination to distinguish idiopathic toe walking from other conditions.

Identification of Autism Spectrum Disorders in Day-Care Centers

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Abstract

Early symptoms of ASD develop through the second year of life, making a stable ASD diagnosis possible at 24 months of age. However, in general, children with ASD have their diagnosis at an older age. This retrospective study, including 30 children with ASD and 30 control children aged 3–6 years, explored the possibility of developing a short observation list to be used in day care settings for children 12–24 months of age. From 73 symptoms selected from published screeners and observation tools, we were able to construct a list of six symptoms that retrospectively differentiated children with ASD from typically developing children at 12–24 months of age when recalled by day-care personnel.

Efficiency of High-dose I/V Immunoglobulin Therapy in Children with Autism Spectrum Disorders Associated with Genetic Deficiency of Folate Cycle Enzymes

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Abstract

Background: Previously, it have been repeatedly reported on the effectiveness of i/v immunoglobulin therapy in some children with autism spectrum disorders without specifying selection criteria of potential responders to immunotherapy.

Objective: to evaluate high-dose immunoglobulin therapy efficacy and safety in children with autism spectrum disorders and genetic deficiency of folate cycle.

Materials and Methods: The studied group consisted of 78 children aged 2 to 10 years who have been on i/v immunoglobulin at a dose of 2 g/kg per month for 6 months. The control group included children of similar age and gender distribution, which received only non-drug rehabilitation support. Such polimorphisms as MTHFR 677 C > T, MTHFR 1298 A > C, MTRR 66 A > G and MTR 2756 A > G were detected in various combinations by PCR test with restriction. The dynamics of psychiatric symptoms were assessed using the Aberrant Behavior Checklist scale. Statistical analysis was performed with Studet's T-criteria and non-paremetrical number of sings Z by Urbah.

Results and Discussion: Complete elimination of the phenotype of autism spectrum disorders has been obtained in 21 patients and a marked improvement in 33 children of study group ($p < 0.05$; $Z < Z_{0.05}$). In parallel, we evaluated positive dynamic of other clinical manifestations of folate cycle deficiency phenotype: PANDAS (19 of 21), epilepsy (29 of 36) and gastrointestinal (in 49 out of 68 children) syndromes ($p < 0.05$; $Z < Z_{0.05}$). There was no positive dynamics of the pyramidal tract lesion symptoms ($p > 0.0$; $Z > Z_{0.05}$). Decrease of the total opportunistic serum viral load and increasing the previously low number of natural killer cells in the blood were achieved ($p < 0.05$; $Z < Z_{0.05}$). Almost complete elimination leukoencephalopathy MR-symptoms was observed in 29 patients, and positive dynamics - in 24 cases in the study group ($p < 0.05$; $Z < Z_{0.05}$).

Conclusions: I/V immunoglobulin has a complex positive impact on the manifestation of a genetic deficiency of folate

cycle in children, including autism spectrum disorders, extrapyramidal disturbances, bowel syndrome, epileptiform brain activity, opportunistic infections and immune deficiency, and leukoencephalopathy.

Responses to Bilingualism of Vietnamese Children with Autism Spectrum Disorders

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Abstract

Direct research into how speaking or hearing more than one language effects the development of children with autism is scarce. This means that families have little information to help them when deciding whether or not to raise their child with autism bilingually – a pressing question for the increasing number of families in Vietnam. More evidence that asks whether this "bilingual exposure" (i.e. hearing more than one language) might be harmful or beneficial to children on the spectrum is needed. As a foundation for this, we recently conducted a study at a specializing school for children with autism in Ho Chi Minh City, Vietnam by making the children expose to both English and Vietnamese. Based on some initial results of this study, there are some potential advantages and disadvantages of bilingualism for children with autism.

Depressive Symptoms and their Correlates in Parents of Children with Autism Spectrum Disorders

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Abstract

This study aims to investigate the relationship between parental self-reported depression, parent personality, the severity of children's autism spectrum disorders (ASD) symptoms and parenting stress. A case-control study including 361 autistic children and 345 typically developing children and their parents, respectively was conducted from 2009 to 2012 in Shanghai. Parents (n = 722) of autistic outpatients in Shanghai Mental Health Center completed: One in-house questionnaire; Autism Behavior Checklist (ABC); Self-Rating Depression Scale (SDS); Parenting Stress Index (PSI); Eysenck personality questionnaire (EPQ). The mean SDS scores of fathers (t = 5.837, P = 0.000) and mothers (t = 10.653, P = 0.000) were higher in the case group than in controls. Parents of ASD children showed much more parenting stress and different personality profiles compared to control group parents (t = 20.836, P = 0.000). Relative analysis showed that parental emotional symptoms were significantly related to parental education level (father: r = -0.304, mother: r = -0.252), parenting stress (father: r = 0.337, mother: r = .462), and parental personality traits like Neuroticism (father: r = 0.387, mother: r = 0.518) and psychoticism (father: r = 0.228, mother: r = 0.301). In the subsequent stepwise multiple regression analysis, emotional stability (Neuroticism subscale of EPQ) was most significantly correlated to paternal depression (adjusted R2 = 0.153) and Parenting burden (Parent domain of PSI) was most significantly correlated to maternal depression (adjusted R2 = 0.284). ASD symptom severity was not related to parental depression. Parental personality traits and parenting stress may be the most salient factors impacting parental depressive symptoms. Understanding how parental personality traits impact on parental emotional states may be an important consideration in the treatment of ASD.

Intracellular Injection of Brain Extracts from AD Patients into *Xenopus* Oocytes Evokes Ca^{2+} Release from Intracellular Stores

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Abstract

Previous studies have shown that the elevated levels of intracellular soluble beta amyloid (Ab) oligomers in brain extracts from AD patients are well correlated with cognitive decline, suggesting their pathogenic role in AD. Examination of brain extract from AD patients revealed elevated content of this soluble oligomers, detected by the conformation-dependent OC-antibody. These OC-positive oligomers are considered among the most toxic species of A^2, capable of inducing intracellular molecular changes, such as disruption of Ca^{2+} homeostasis. We have shown that synthetic $A\beta_{42}$ OC-positive oligomers trigger formation of toxic Ca^{2+}-permeable membrane pores and intracellular Ca^{2+}release from the endoplasmic reticulum stores. In the

present study, selected samples of brain extracts from control and AD patients have been used to investigate their toxicity by imaging intracellular Ca^{2+} responses following their intracellular injections into *Xenopus* oocytes. Injection of brain extracts from a control patient elicited little changes in intracellular Ca^{2+}, comparable to the effects observed after injection of PBS buffer alone. On the contrary, injection of extracts from AD brains triggered local Ca^{2+} transient and global Ca^{2+} waves within few seconds that persisted for several seconds and closely resemble the Ca^{2+} signals previously observed after intracellular injection of synthetic $A\beta_{42}$ oligomers. The Ca^{2+} transients were strongly inhibited by pre-incubation of brain extracts with OC antibody for 24 hours. These results further support the notion that intracellular Aβ aggregates may play a key role in the pathology of AD by disrupting intracellular IP_3 Ca^{2+} signaling.

Guanabenz Does Not Affect the Survival of SOD1 G93A Mice When Administered After the Onset of Disease

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Abstract

Objective: In the present study, we investigated whether guanabenz is protective when it is administrated after the onset of disease.

Background: Amyotrophic lateral sclerosis (ALS) is a progressive, lethal neurodegenerative disease, for which so far there is no effective treatment. Although mechanisms underlying ALS remain elusive, increasing evidence suggests that endoplasmic reticulum (ER) stress play an important role in the pathogenesis of ALS. Our previous study demonstrated that pre-symptomatic administration of guanabenz, an inhibitor of ER stress, significantly delayed the onset of disease, extended the lifespan, improved motor performance and attenuated motor neuron loss in female SOD1 G93A mice, and the underlying mechanisms might be associated with the prolongation of eukaryotic initiation factor 2α (eIF2α) phosphorylation.

Design/Methods: In the present study, we investigated whether guanabenz is protective when it is administrated after the onset of disease.

Results: Our results showed that post symptomatic treatment with guanabenz could decrease the exogenous mutant SOD1 levels, without affecting the levels of endogenous SOD1 in mouse model of ALS. The expression of microtubule-associated protein 1 light chain 3 (LC3) II, a marker of autophagy, and autophagic vesicle (AVs) were not affected by guanabenz treatment in motor neurons of the ALS mice in our study, which indicated that the decrease of exogenous mutant SOD1 was not related to the autophagy.

Conclusions: Unlike the protective effects observed when it was administered pre-symptomatically, guanabenz initiated after the onset of disease didn't affect lifespan, motor performance and motor neuron loss in SOD1 G93A mice.

Screening Hand-Eye Coordination Deficit Using a Video Game

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Abstract

There are evidences indicating the existence of motor coordination deficits in many children with mental or physical disabilities such as children with Autism Spectrum disorders (ASD) and children with Down syndrome. Individuals with motor coordination disorder may have trouble with tasks requiring hand-eye-coordination. In this paper, we propose a game-based method to distinguish between children with ASD, Down syndrome, and typically developed children. Thus, we have developed an interactive game which requires hand-eye-coordination capabilities. The game can be played on touch screen platforms, such as tablets or smartphones which are widely available. Consequently, the game can be played at anytime and anywhere in the world and the data can be gathered and processed simultaneously. This video game has been tested on several subjects who have been in one of these three groups of children, i.e. children with autism, children with Down syndrome, and typically developed children. Then machine learning methods are used to analyze the data and determine features that can be used to distinguish between these three groups of children. The extracted features showed different motor pattern behaviors between these three groups. In other words, this game can be used as a screening tool for detection of Autism Spectrum Disorder and Down

syndrome children. The screening capability of this tool becomes important especially in the developing countries which have limited medical resources. Also, the natural setup, of this game, for evaluating the hand-eye coordination capabilities makes it suitable for everyone, even countries with strong medical support. Furthermore, the promising results show that the game can be used as a complementary rehabilitation tool in obtaining hand-eye-coordination skill. Finally, the game has the capabilities to be used as an assessment tool for hand-eye-coordination. In the future, we tend to use the game for determining other types of mental or physical disorders, such as children with ADHD or people with Parkinson.

Developing Mobile Applications for Assisting Children with Autism: Innovative Solutions for Users, Families and Clinical Staff Project Under the Sponsorship of TIM (Telecom Italia Group) Foundation

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Abstract

Several researchers along with technicians have been developing software and hardware to support and/or replace the standard method of teaching for children with autism spectrum disorders (ASDs) and/or other developmental disabilities. Moreover, computer-based intervention and electronic tablets have shown benefits for people with special needs increasing their independence, academic and cognitive skills, social communication, and leisure time. Simultaneously, m-health solutions including online-learning platforms and real-time databases regarding performances of children's therapies offer innovative solutions for assisting the families of children with autism and their teachers. Therefore, the aim of the current study is to evaluate the effectiveness of tablet applications created to enhance specific abilities of children with ASD, who followed Applied Behavior Analysis treatment (ABA) compared with the internal control group (CG). Trainings lasted 4 weeks for children selected in a randomized way, while the CG followed only the behavioral therapy. To sum up, we want to respond to three questions: (1) whether the experimental group (EG) using the applications obtains greater progress within standard therapy, (2) whether the real skills of children examined at baseline have an impact on the application scores, and (3) whether the graphic features of the applications influence the motivation of children. Likewise, we want to assess the efficacy of training and supervision at distance through online programs including real-time data recording of therapies. To conclude, the selection of a specific electronic device for users should be essentially personalized by clinical staff in order to achieve the perfect combination between virtual and standard learning.

Pupillometry as a Method for Examining Phenotype in ASD: Latency to Constriction Discriminates ASD from Typically Developing Adolescents

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Abstract

Pupillometry and eye-tracking technology have gained increased attention in recent years as non-invasive research tools for examining the clinical phenotype in ASD. A distinct measurement method in comparison to eye-tracking, pupillometry assesses reflexive brain function emanating from the locus coeruleus norepinephrine system and can be conducted within a neurological exam of CN II and CN III. Our work has extended research done examining the pupillary light reflex (PLR), to include a subtype of ASD representing high-functioning skills, often difficult to confidently diagnose. Behavioral assessments and the PLR were used to document differences and characterize a relatively homogenous group of individuals with high-functioning ASD from typically developing adolescents. This work demonstrated a research method for examining the atypical PLR in ASD within the context of the clinical neurological exam. Latency thresholds for discriminating ASD from typical development were shown in a pilot sample. Further evidence for the use of PLR and hand-held technology are needed to document its potential viability for clinical use in screening for neurodevelopmental delay and ASD. Study replication is underway in a broader sample of children.

Surgical Considerations of Intractable Mesial Temporal Lobe Epilepsy

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Abstract

The best opportunity for seizure freedom in patients with medically intractable temporal lobe epilepsy is surgical removal or disconnection of the temporal seizure focus. Mesial temporal lobe epilepsy (MTLE) is a distinct syndrome of temporal lobe epilepsy that recognizes the paramount importance of the mesial temporal structures in the majority of patients with temporal lobe epilepsy. For those individuals with medically intractable MTLE, selective amygdalohippocampectomy surgery provides an excellent opportunity for seizure freedom that limits the resection to the temporal lobe structures primarily involved in seizure genesis. This presentation describes the historical evolution of the selective amygdalohippocampectomy for intractable MTLE, the neuroanatomical basis for removal and disconnection of the mesial structures of the temporal lobe for intractable MTLE, selection of appropriate patients for this surgical approach, and analysis of outcomes of surgical patients.

Migraine Headache and Bipolar Disorder Comorbidity: A Systematic Review of the Literature and Clinical Implications

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Abstract

Aims: Psychiatric disorders are often comorbid with, and can complicate the treatment of, patients with migraine headache. Antidepressants, which are often invoked in migraine prophylaxis as well as the treatment of depression, may precipitate significant mood changes among bipolar disorder patients. A systematic review of the literature addressing the co-occurrence of bipolar disorder and migraine was conducted. The treatment of dually affected patients is also discussed.

Methods: A comprehensive search of MEDLINE, EMBASE, PubMed, PsycINFO, Web of Science, and CINAHL was conducted using terms related to migraine and bipolar disorder. Weighted means of the prevalence rates were calculated to compare with general epidemiological prevalence trends for migraine and bipolar disorder, respectively.

Results: Eleven studies met inclusion criteria. Studies demonstrated a high rate of comorbidity. The weighted mean prevalence rate for migraine headache among bipolar disorder patients was 30.7%; for bipolar disorder among migraineurs, the weighted mean prevalence rates were 9% and 5.9% in clinic-based and epidemiological studies, respectively. The association was most notable among women and patients with the bipolar II disorder subtype.

Conclusions: High rates of comorbidity exist between migraine and bipolar disorder, exceeding estimated prevalence rates in the general population. Comorbidity may portend a more serious clinical course for dually afflicted individuals.

Implications: Clinicians need to structure treatment approaches to address concurrent migraine and bipolar disorder in dually afflicted individuals. Anticonvulsants (e.g., valproate, lamotrigine and topiramate); atypical antipsychotics (e.g., olanzapine or quetiapine); and calcium channel blockers (e.g., verapamil) may be considered for optimal treatment.

The Relationships of Social Provisions and Social Support to Promoting Physical Activity among People with Multiple Sclerosis

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Abstract

The presentation will present an overview of social provisions and social support in promoting physical activity among people with MS, based on the presenter's recent quantitative and qualitative studies. The presentation will include practice implications.

The Crystal Structure of PARK14/PLA2G6 Suggests Mechanisms of Protein Regulation and the Role of Neurodegenerative Mutations

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Abstract

Calcium-independent phospholipase PLA2G6A (or iPLA2b) is a signaling enzyme which hydrolyzes phospholipids to generate potent lipid messengers in response to stress or injury. The enzyme is a product of the PARK14 gene with strong genetic link to a spectrum of neurodegenerative disorders including Parkinsons disease (PD). Various mutations in PLA2G6 gene have been reported in different PLA2G6-associated neurodegeneration (PLAN), including infantile neuroaxonal dystrophy (INAD), neurodegeneration with brain iron accumulation (NBIA), Karak syndrome, and young-onset dystonia-parkinsonism syndrome with recessive inheritance. It is also linked to idiopathic PD and represents one of the major phospholipase activities in the brain. The enzyme regulates several signaling cascades including agonist-induced arachidonic acid release, insulin secretion, vascular constriction/relaxation, store-operated calcium-entry, cellular proliferation, migration and autophagy. However, the mechanisms of its activation and tissue-specific functions remain poorly understood. We have solved a crystal structure of the PLA2G6 and investigated mechanisms of the protein activity and interaction with calmodulin. The first crystal structure revealed an unexpected oligomeric structure and the conformation of catalytic and auxiliary protein-interaction domains. Together with biochemical studies, the structure suggests mechanisms of the phospholipase activity, of the inhibition and activation as well as of the tissue specific cellular localization. It provides a well-defined framework to investigate the role of neurodegenerative mutations and the function of PLA2G6 in the brain as well as its role in other diseases.

Experiences Related to Need for Support and Information when a Parent is Diagnosed with Multiple Sclerosis – A Family Perspective

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Abstract

Background: Multiple sclerosis (MS) affects the whole family and has a substantial impact on the children. Health care professional have traditionally focused solely on the patient. When a parent is diagnosed with MS there is a need to widen the perspective and be aware also of a child's needs. Knowledge on what kind of support and suitable interventions for these children and their parents need are limited.

Aim: To gain an understanding of how health-care services can support the empowerment of children when a parent is diagnosed as having Multiple Sclerosis (MS). The study explores needs and desires when a parent is diagnosed with MS from a triple perspective; the ill parent, the healthy parent and the children.

Materials & Method: Focus group interviews were conducted with adolescents, parents with diagnosed MS, and partners representing members of ten families. A qualitative study design using content analysis was used. Questions were raised about issues to acknowledge and act upon to make it easier for a child to cope.

Results: Participants indicated that family members need to be recognized, as one family member's illness affects the entire family, both initially and onwards in their everyday lives. Both ill and healthy parents wished for support from health care professionals in addressing their children's needs. As they assumed that health care was only for the patient, they rarely asked for such support. Participants stressed their need to be informed about the disease and that information should be individualized and offered throughout the disease course.

Spinal Epidural Hematoma Related to Intracranial Hypotension

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Abstract

A 45-year-old female visited the hospital with sudden severe headache and posterior neck pain. The headache occurred whenever the patient was in a sitting or standing position, but not in a supine position. The patient did not have any traumatic history or abnormal neurologic finding. Next day, she developed sudden quadriplegia and sensory loss. Cervical spine MRI scan was taken, and the compatible findings to acute epidural hematoma (EDH) were shown at C2-7.

The emergency operation was performed. The venous engorgement and hyperemia were found. During the surgery, there was no trace of damage to the dura mater. After the operation, the patient recovered all motor and senses. However, cerebrospinal fluid (CSF) leakage occurred. Then lumbar drainage was thus performed. The opening pressure upon lumbar puncture was not measured as it was very low. CSF leakage was not controlled and the surgical repair was performed. There was no leakage at the dorsal part of the dura but there was some leakage at the C5-6 ventral part that was not found at the first operation. After the operation, the patient had been discharged without any neurologic deficits.

CSF leakage is a cause of intracranial hypotension, which can result in postural headache. It is difficult to state that an intracranial hypotension due to CSF leakage leads to spinal EDH. However, in regards to this case, it is sensible to suspect intracranial hypotension as a possible cause of spinal EDH.

Botox® in Chronic Headache by a "United" Anatomical Regional Targeted (ART) Technique: Case-Based Introduction

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Abstract

Introduction: Migraine headaches are a common and disabling condition that affects 18% of female and 6% of males worldwide. Food and Drug Administration (FDA) in America support Botox® for treatment in both migraine and chronic headache as a phase III research from 2007, even if the mechanism is unclear. Taiwan FDA also support this indication from this year (2017). The landmark Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) is the most popular method that most doctors used. However, the method is not anatomical localization. Anatomical regional targeted (ART) technique was suggested by some plastic surgeons but the effect was still under evaluation. However, both methods don't consider the pattern of trigeminal neuralgia in buccal region. Here we will introduce the combination of ART technique and the evaluation of trigeminal neuralgia to treat a patient with migraine and chronic headache.

Materials and Methods: By six patients with different patterns of chronic headache and migraine, Botox® injection was performed according to special anatomical locations.

Results: Evaluation was completed by two plastic surgeons two weeks after the procedures. Temporal migraine, occipital migraine, frontal migraine, and trigeminal neuralgia were identified. Boosting was made on two patients due to trigeminal neuralgia. All patients were free from the headache around 3-7 days after the procedure.

Conclusions: Combined with the concept of anatomy and headache pattern, we could use less dosage of Botox® to treat migraine but achieved the same effect. Headache by a more anatomical and effective method.

Stereotactic Bilateral Transfrontal Minimal Radiofrequency Thermocoagulation of Amygdalohippocampal Complex for Bilateral Medial Temporal Lobe Epilepsy: A Retrospective Study of Twelve Patients

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Abstract

Background: Some patients with temporal lobe epilepsy have bilateral discharges and a few of them have bilateral medial

temporal sclerosis. Stereotactic bilateral radiofrequency thermocoagulation (RFTC) of amygdalohippocampal complex can terminate seizures or reduce seizure severity in patients with bilateral medial temporal lobe epilepsy (BMTLE).

Purpose: To explore the safety and efficacy of bilateral transfrontal minimal RFTC of amygdalohippocampal complex for the treatment of BMTLE.

Methods: A total of 12 BMTLE patients were treated with bilateral transfrontal minimal RFTC of amygdalohippocampal complex under limited coagulations. The volumes of coagulated lesions were less than 0.6 cm^3 Clinical outcomes were evaluated with Engel's classification, Liverpool Seizure Severity Scale (LSSS) 2.0, Wechsler Adult Intelligence Scale-Revised (WAIS-R) and Wechsler Memory Scale-Revised (WMS-R). The Quality of Life (QOL) was evaluated with 36-item Short Form Health Survey (SF-36).

Results: Of the 12 patients, 5 (42%) were assessed as Engel I during 12–62 months' follow-up. LSSS scores declined sharply compared with baseline of the patients not under seizure-free category. Functions of memory and intelligence declined transiently without statistical significance ($P > 0.05$) immediately after surgery but improved significantly ($P < 0.05$) 6 months later. The qualities of life were improved except Vitality.

Conclusion: Bilateral transfrontal minimal RFTC of amygdalohippocampal complex is capable to terminate seizures or reduce seizure severity in patients with BMTLE. Under limited coagulations, neuropsychological function was not affected but improved along with seizure control.

Pregnancy with Meningioma: Report of Two Rare Cases

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Abstract

Background: Meningioma in pregnancy is a rare occurrence. Whenever it is accompanied with pregnancy, it is mostly symptomatic with complaints like headache, vomiting, visual disturbance, seizures or altered sensorium. The management is challenging as the fetal well-being is also affected along with complications of raised intracranial pressure during labour.

Case Report: Here we discuss two such cases of meningioma in third trimester. One was frontal meningioma with intact neurological functions. On the other hand, second patient had a left sphenoid meningioma with left optic atrophy and right hemiparesis. Both of them underwent cesarean delivery under general anesthesia. However, the neurosurgical excision of meningioma was accompanied with the delivery in the second case as the situation demanded the same.

Conclusion: These cases always warrant a multimodality approach involving obstetrician, neonatologist, anesthetist and neurosurgeon. The timing of delivery or neurosurgery depends on the clinical situation i.e.; fetal maturity, neurological condition, progress of symptoms and patients' wishes.

How the Brain Keeps Seizures at Bay

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Abstract

Human neocortex tissue is capable of activating an endogenous anticonvulsant mechanism, which is absent in rats. Excessive neuronal activity leads to elevated intracellular Na^+, which causes the neuronal GABA transporter (GAT) to reverse and co-transport two Na^+ and one Cl- with each GABA zwitterion. Both the increase in cytoplasmic Na^+ and the depolarization during high frequency activity cause GAT reversal. This reversed GAT leads to increased GABA release. Thus, elevated intracellular Na^+ can evoke GAT-mediated release of GABA which, as the main inhibitory neurotransmitter, could counteract excessive neuronal activity.

A marked decrease in extracellular Ca^{2+} happens before and during paroxysmal neuronal activity. While lowered Ca^{2+} usually reduces vesicular transmitter release because of a lack of Ca^{2+} necessary for exocytosis, there is an inverse correlation between extracellular Ca^{2+} and GABA release, evoked by elevated intracellular Na^+. Uniquely, the additional increase in GABA release because of calcium-withdrawal dwindles during the course of illness in Rasmussen encephalitis.

The Na^+/Ca^{2+} exchanger (NCX) is an important electrogenic transporter for maintaining Na^+ and Ca^{2+} homeostasis. Reduction of extracellular Ca^{2+} amplifies the NCX activity, leading to elevated cytoplasmic Na^+, which, together with the

intracellular Na^+ increment, due to excessive neuronal activity, enhances GABA transporter reversal. NCX inhibition lowers transporter-mediated GABA release. NCX activators, however, may augment GAT-mediated GABA release. Thus, these activators should represent potential new anticonvulsants, since, in epilepsy, the endogenous anti-seizure mechanism may not be sufficient.

Dopamine Antagonists in Autism Spectrum Disorders: Review and Focus on BDNF Stimulators Loxapine and Amitriptyline

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Abstract

Background: Drug development and repurposing are urgently needed for individuals with autism spectrum disorders (ASD) and serious behavior problems including impulsive aggression and self-injury.

Method: We review dopamine antagonists, as well as amitriptyline which has weak dopamine-blocking activity but more potent inhibition of serotonin and norepinephrine reuptake. The older antipsychotic loxapine which has atypical antipsychotic features in low dose will be reviewed for preliminary evidence in ASD. We discuss emerging data on amitriptyline in ASD, together with promising effects of both drugs on BDNF and brain health.

Results: Dopamine antagonists are a mainstay of treatment in ASD, for irritability, aggression and self-injury. Although risperidone and aripiprazole have been most studied in ASD, serious side effects limit their use, notably weight gain and associated medical illnesses. Importantly, low dose loxapine appears more weight neutral, and preliminary studies suggest efficacy and safety in adolescents and adults with ASD. Amitriptyline appears effective in ASD for insomnia, irritability, anxiety, impulsive aggression, hyperactivity, and enuresis, but more studies are needed. Concerns of overdose toxicity with amitriptyline are reduced in ASD since most individuals with ASD do not self-administer medications. Both loxapine and amitriptyline may stimulate BDNF, improving neural health.

Conclusions: For severe aggression and self-injury in ASD, low dose loxapine may be useful in adolescents and adults, often together with stimulant and/or non-stimulant ADHD medications. Amitriptyline appears effective in low doses in children, adolescents and adults with ASD for impulsive aggression and self-injury, as well as several other related symptoms. Further studies are warranted.

Spectrum of Drug Resistant Epilepsy Patients in Eastern Indian Sub-continent in 2018

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Abstract

The Magnitude of drug resistant epilepsy patients in Indian Sub-continent is gradually revealing itself as several reports, including ours, are published in recent years. We are studying drug resistant epilepsy patients since 2014 in Intractable Epilepsy Clinic of Nilratan Sircar Medical College & Hospital, Kolkata, India. The clinical, electro-physiological, neuro-imaging and drug -responsiveness spectrum is diversified among drug resistant epilepsy patients. We found 285 (11.5%) drug resistant cases among our total epilepsy cohort of 2478 till the end of first half of 2017. As new patients are getting added to our original cohort, despite finding new patterns, several old pattern remained, like, male were higher in percentage and the first decade was the most common age of presentation. Several sub-types of seizures had gender predilection. EEG findings varied, even normal EEG could be found in drug resistant epilepsy patients. Idiopathic etiology was most common. Females were mostly drug non-compliant. Most of the patients had deficient schooling which is multifactorial.

Nasal Oxytocin for the Treatment of Chronic Migraine Headache

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Abstract

The effects of nasal application of oxytocin has been investigated for effects in numerous, mainly neuropsychiatric, indications. However, there is now substantial evidence to support the idea that nasal oxytocin may be useful in alleviating craniofacial pain, including migraine headache. We will present results which demonstrate the neuroscience underlying these effects as well as pilot clinical results which show that nasal oxytocin can not only relieve headache pain, but also reduce the frequency of headaches in high frequency migraineurs. Oxytocin receptors are present on trigeminal ganglia neurons that co-express the pain neurotransmitter calcitonin gene related peptide (CGRP) as well as on sphenopalatine ganglia neurons that express the parasympathetic neurotransmitter pituitary adenylate cyclase-activating polypeptide (PACAP) both of which play key roles in the pathogenesis of migraine. Oxytocin can block the release of both peptides *in vitro*. Furthermore nasally applied oxytocin concentrates in the trigeminal system and inhibits the excitability of trigeminal ganglia and nucleus neurons. Thus, there is a clear scientific basis for the inhibition of craniofacial pain by nasal oxytocin and so, we performed pilot clinical studies in chronic migraineurs. These studies suggested that nasally applied oxytocin can not only attenuate migraine pain, but also decrease the frequency of headache attacks. Additional studies indicated that the effects of oxytocin can be potentiated by magnesium as magnesium ions act as allosteric modulators at oxytocin receptors. These results provide strong evidence that nasally applied oxytocin should be pursued as a novel therapy for craniofacial pain and particularly chronic migraine headache.

Common Primary and Secondary Causes of Headache in the Elderly

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Abstract

Headache in the elderly, defined as individuals aged 65 and older, can present as a diagnostic challenge, given the increase in potentially fatal diseases within this population. These individuals require a complete history, neurological examination, and assessment of potential secondary causes of headaches. Secondary causes include temporal or giant cell arteritis, subdural hematomas, central nervous system (CNS) tumors, strokes, and CNS infections. Once secondary conditions are ruled out, then primary causes of headache are considered such as tension-type headache, migraine, cluster headache, or hypnic headache. Medication treatment often requires diligent assessment of comorbid conditions, reduced medication tolerance, and potential medication overuse. This presentation will review the distinguishing characteristics of the most common types of headache in the elderly along with potential diagnostic tests and treatment.

The Effect and Safety of Different Surgical Approaches for the Treatment of Medial Temporal Lobe Epilepsy

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Abstract

Objective: To observe the outcomes of seizure control and the impairments of cognitive and memorial function of three different surgical approaches, such as hippocampal transection, anterior temporal lobectomy and selective amygdalo-hippocampectomy, for the treatment of intractable medial temporal epilepsy.

Methods: Eight cases of hippocampal transection, 10 cases of anterior temporal lobectomy and 11 cases of selective amygdalo-hippocampectomy performed by the author of this article were collected for statistical analysis of seizure control and neuropsychological examinations (including VIQ: verbal intelligence quotient, PIQ: performance intelligence quotient, FIQ: full intelligence quotient and MQ: memory quotient) before and after operation.

Results: The effective rates of seizure control were all high than 80% and seizure free rate were around 60% in the three groups without significant differences. All the neuropsychological examinations' score before and after operation have no significant difference in the hippocampal transection group ($P > 0.05$). However, in the anterior temporal lobectomy group, all scores were significant declined ($P < 0.05$) and in the selective amygdalo-hippocampectomy group, the scores of PIQ, FIQ and MQ were significant declined ($P < 0.05$). According to the span D-value of the score before and after operation, only the MQ were found with significant difference in the three groups ($P < 0.05$).

Conclusions: Hippocampal transection will not cause significant damage in intelligence and memory function. Compared with both anterior temporal lobectomy and selective amygdalo-hippocampectomy, hippocampal transection can preserve the memory function in the meanwhile of seizure control. So it is worth to be advocated and wide used for intractable medial temporal epilepsy.

The Effects of Mat Pilates and Reformer Pilates in Patients with Multiple Sclerosis: A Randomized Controlled Study

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Abstract

Background: Pilates is an exercise method which increases strength and endurance of core muscles and improves flexibility, dynamic postural control and balance.

Objective: To analyze and compare the effects of Mat and Reformer Pilates methods in Patients with Multiple Sclerosis (MS).

Methods: Thirty-eight patients with MS were included in the study. Participants were randomly divided into 3 groups as Mat Pilates, Reformer Pilates and control groups. The subjects in the Pilates groups did Mat or Reformer Pilates for 8 weeks, 2 days a week. The control group did breathing and relaxation exercises at home. Balance, functional mobility, core stability, fatigue severity and quality of life were evaluated.

Results: Balance, functional mobility, core stability, fatigue severity and quality of life improved after Pilates in Mat and Reformer Pilates groups ($p < 0.05$). On the other hand, we could not find any changing in the control group ($p > 0.05$). When the gain obtained in the Pilates groups is compared, it has been observed that progress has been more in trunk flexor muscle strength in the Reformer Pilates group ($p < 0.05$) and that the gain has been similar in the other parameters ($p > 0.05$).

Conclusions: As a result, patients with MS have seen similar benefits in Reformer Pilates and Mat Pilates

Through Cerebral Spinal Fluid Brainstem Stimulation for Vegetative State Patients

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Abstract

Objective: To work out the method which provides diffuse stimulation of brain stem reticular formation (RF) in vegetative state (VS) patients without additional damage of brainstem and thalamic structures by implanted electrodes.

Methods: Nine patients with VS for more than 3 months were treated by the method of through cerebral spinal fluid brainstem electrical stimulation (TCSFBS) for a period of 1 year. Two monopolar electrodes were implanted for TCSFBS implementation. The first electrode was inserted in the lateral ventricle of spared hemisphere. The second one was implanted in the cistern Magna or epiduraly between low margin of occipital bone and posterior arch of C 1 vertebra. Clinical effects, electro-encephalogram (EEG) and auditory brainstem response (ABR) were researched in all patients during TCSFBS therapy.

Results: Such well known markers of RF activation as arousal response (AR) and desynchronization reaction (DR) were detected in all VS patients during TCSFBS. Six out of the 9 cases emerged from VS. Two out of these 6 cases regain consciousness. The other 4 patients were in MCS. The remaining 3 cases failed to emerged from VS.

Conclusion: Efficiency of RF stimulation for VS patient's treatment is shown in researches of class II evidence. Method of deep brain stimulation (DBS) with implantation of bipolar electrode in thalamic or brainstem structures provides RF activation in some VS patients. A part of VS patients do not display signs of RF activation during DBS may be due to brainstem and thalamic lesion foci which are mandatory for post traumatic VS patients. The TCSFBS can provides activation of RF in VS patients without additional damage of thalamic and brainstem tissue in the trajectory of implanted electrodes.

Minimum 5 Year Follow-up of Multi-Segmental Lumbar Degenerative Disease Treated with Discectomy and the Wallis Interspinous Device

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Abstract

We evaluate the clinical effects and radiological findings of the Wallis interspinous device (Zimmer, Warsaw, IN, USA) for the treatment of multi-segmental lumbar degenerative disease after a minimum 5 year follow-up period. A total of 26 adult patients underwent a primary discectomy followed by fixation of the segment with the Wallis interspinous device between December 2007 and August 2008. Twelve men and 14 women with an age range of 43 to 56 years (average: 47.6) were included. The visual analogue scale (VAS) for low back and leg pain, Oswestry Disability Index (ODI), foraminal height (FH), anterior disc height (aDH) and posterior disc height (pDH), range of motion (ROM) and Pfirrmann grades were obtained and compared before and after surgery. The VAS and ODI significantly decreased postoperatively ($p < 0.05$). The postoperative FH and pDH values increased significantly compared with the preoperative levels ($p < 0.01$) and the increase in the FH and pDH values remained statistically significant during the follow-up period. There were no statistically significant changes in the aDH values before and after surgery ($p > 0.05$). Also, there were no statistically significant changes in the ROM and Pfirrmann grade at the instrumented level and at the cephalad-adjacent segment ($p > 0.05$). In our study, no patient underwent further surgery because of a re-prolapse or progression of index level degeneration or adjacent segment disease. The Wallis interspinous device was a useful alternative for treating multisegmental lumbar degenerative disease and it offered a significant minimum 5 year symptom control.

Evaluation of the Expanded Disability Status Scale and the Multiple Sclerosis Functional Composite as Clinical Endpoints in Multiple Sclerosis Clinical Trials: Quantitative Meta-Analyses

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Abstract

Objectives: This study compared the sensitivity of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) as clinical endpoints in multiple sclerosis (MS) clinical trials.

Methods: MEDLINE and Embase databases searches were conducted using keywords and Medical Subject Heading (MeSH) terms related to MS, EDSS, and MSFC. All statistical analyses were conducted using comprehensive meta-analysis (CMA). The percentages of the overall changes in EDSS and MSFC were compared. The relative risks were calculated in randomized clinical trials (RCTs).

Results: A total of 123 studies were identified. There were nine studies (6 case series and 3 RCTs) included in the analysis. In the case series, the EDSS change rate in MS patients was 33.5% (95% CI = 12.9–63.2%) and the MSFC change rate was 30.3% (95% CI: 9.2–65.2%). In RCTs, patients who take the drug would be 22.9 times as likely as patients who did not take the drug to experience a change in the EDSS scale (RR = 22.9, 95% CI = 0.996–1.517, p = 0.055). Patients who take the drug would be 48.9 times as likely as patients who did not take the drug to experience a change in the MSFC scale (RR = 48.9, 95% CI = 0.916–2.419, p = 0.108).

Conclusions: There is controversy about the sensitivity of the EDSS and MSFC in detecting the progression of MS disease. The EDSS and MSFC are effective tools to assess the clinical severity and progression of MS disease. MSFC is more sensitive than EDSS in detecting the progression of MS disease.

Treatment of Multiple Sclerosis Patients with Expanded *ex vivo* Autologous Regulatory T Cells $CD4^+CD25^+FoxP3^+CD127^{low}$

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Abstract

Introduction: Regulatory T cells (Tregs) $CD4^+CD25^+FoxP3^+CD127^{low}$ provide among others regulation of inflammatory reactions by suppressing effector cells. The function and the numbers of Tregs are compromised in patients with Remitting Relapsing Multiple Sclerosis (RRMS). We aimed to determine whether adoptive transfer of expanded ex vivo autologous Tregs (eTregs) into patients with RRMS are safe and tolerable, and if they can restore the patients Treg deficit leading to disease-modifying effects.

Methods: In our study we traced differentiation of eTregs $CD4^+CD25^+FoxP3^+CD127^{low}$ after short-term cultivation of initial $CD4^+$ T cells of 37 RRMS patients. Fourteen patients were injected once with 300 – 450 x 10^6 eTregs and followed for 24 weeks.

Results: The resulting cell population consisted of 96, 2-98, 5% Tregs with increased capacity to suppress proliferation of effector target cells. The RRMS patients injected with Tregs reported minor and only temporary side effects. Two weeks after the cell injection the Treg level in the patients' peripheral blood samples was elevated with a tendency to slowly decline during the following 2-3 months. The number of relapses was reduced by 76% in the RRMS patients. The expanded Tregs were seen to be twice as active in respect to up-regulation of FOXP3 and Helios genes expression compared to the patients Tregs at time of harvesting.

Conclusion: Infusion of eTregs is safe and feasible leading to a significant reduction in relapse and leading to EDSS stabilization indicating that the method could hold the potential to become a new treatment option for RRMS patients.

Poster Presentations

Maternal Mortality in Women with Epilepsy

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Abstract

It is estimated that there are 10,000 women with epilepsy of childbearing potential in Ireland (population 4.77 million). We determined the maternal mortality rate for women with epilepsy attending the Rotunda Hospital between 2004 -2013 (Total births 92259). Of 793 women who attended the specialist Epilepsy Clinic, 379 were currently or recently on medication for control of epilepsy. There were 3 maternal deaths in women with epilepsy during this time, which represents a mortality rate of 0.8%.

In those women who died, there were concerns in relation to risks to the fetus by taking Anti-Epileptic Drugs (AED) and also issues with access to neurology services before pregnancy, acceptance of specialist support and lack of consistency in advice from health care professionals outside of Ireland.

Implementing the nationally agreed care plan for women with epilepsy will improve the quality of care given and potentially we will see a reduction in maternal mortality in these women.

Evaluation and Optimisation of *In Silico* Designed Sphingosine-1- Phosphate (S1P) Receptor Modulators for the Management of Multiple Sclerosis

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Abstract

Multiple Sclerosis (MS) is a chronic autoimmune disorder affecting the Central Nervous System through inflammation, demyelination and neurodegeneration. Sphingosine-1- phosphate receptor (S1PR 1) modulators have been approved for the management of MS. Phosphorylated Fingolimod mimics endogenous sphingosine-1-phosphate (S1P), a bioactive lipid that regulates remyelination and cell injury. Amiselimod is a successor of Fingolimod and undergoing clinical trials. In this study, de novo and *in silico* drug design will execute the ligand binding pocket and binding modalities of Fingolimod and Amiselimod in an attempt to optimize and impart selectivity to the cognate receptor with a better side effect profile and inducing to a lesser extent bradycardia.

Pharmacological Evaluation of Apocynin for Its Anti-Alzheimer's Activity

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Abstract

Alzheimer's disease (AD) is the most common form of dementia, affecting over 50 million of people worldwide with the global patient population doubling over 20 years. The disease is incurable having deteriorating effect due to progressive degeneration. The current therapies offer only symptomatic relief, suggesting the need for newer approaches and improved therapies.

Apocynin (4-hydroxy-3-methoxyacetophenone), a plant-derived antioxidant showed profound neuroprotective effects in a pre-clinical animal model of Parkinson's disease (PD) by attenuating oxidative damage and neuroinflammatory responses. Hence owing to its neuroprotective effect in PD, apocynin was primarily screened in scopolamine induced memory impairment by inhibitory avoidance task in AD model of zebrafish. In this task, fishes were initially trained to enter the dark compartment from white through sliding door. Once in dark compartment; a physical shock- like a marble was dropped ahead of the fish. This was repeated twice more. Post 1 hour of the trial session, fish were exposed to 100 ml of 200 µM scopolamine solution for one hour to induce memory deficits. After which fish was exposed to apocynin and test session performed. Apocynin was able to reverse scopolamine induced memory deficits in zebrafish by increasing latency to enter the dark compartment.

Apocynin was further evaluated in an $A\beta_{1-42}$ induced AD rat model. Here $A\beta_{1-42}$ peptide was stereotactically injected in hippocampus of rats. Biochemical parameters like superoxide dismutase, Catalase, reduced glutathione and lipid peroxidation were evaluated and showed promising results.

Hence preliminary screening reveals that apocynin attenuates the oxidative damage induced by $A\beta_{1-42}$ in AD rat model.

Evaluation of Neuroprotective Effect of Ursolic Acid in Rotenone Induced Parkinson's Disease in Rats

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Abstract

Parkinson's disease (PD) is a slowly progressive, neurodegenerative disease primarily due to degeneration of dopaminergic neurons in the substantia nigra (SN). Numerous studies suggest that mitochondrial alterations, oxidative stress, impaired clearance of misfolded proteins are implicated in PD pathogenesis. Ursolic acid (UA), a natural pentacyclic triterpenoid carboxylic acid, is known to possess anti-oxidant, anti-inflammatory effects along with other biological activities. Thus the objective of the present study was to evaluate the neuroprotective effect of UA against the pathological alterations induced by rotenone in rat brains. In the present study rats were injected bilaterally with rotenone (12 µg) in SN. The rats were further orally treated with UA (5 and 10 mg/kg) for 30 days. Behavioural studies like Rota-rod, open field and Barnes maze test were conducted during the course of the study. At the end of study mid-brain homogenates were evaluated for antioxidant (Reduced glutathione, superoxide dismutase, catalase and lipid peroxidation), proinflammatory (TNF α), immunohistology of TH positive neurons and mitochondrial (complex I and mitochondrial biogenesis) parameters. UA significantly improved the locomotor and the muscular activity as compared to the negative control group. A significant attenuation in the cognitive dysfunction by UA was observed in barnes maze test. The oxidative stress and inflammation caused due to rotenone toxicity was significantly reduced by UA treatment. UA also significantly prevented the mitochondrial complex I inhibition by rotenone. The preliminary results strongly demonstrate the neuroprotective potential of UA against rotenone induced neurotoxicity in rats, which is being confirmed using immunohistochemistry and mitochondrial biogenesis parameters.

Nonconvulsive Status Epilepticus (NCSE) Presenting as Dissociative Fugue

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Abstract

Background: Nonconvulsive status epilepticus (NCSE) is a critical neurological condition that is commonly under recognized due to its atypical clinical presentation. High-risk groups include known epileptic patients, elderly, and critically ill population. Diagnosis is easily made through continuous EEG monitoring. Its treatment follows the status epilepticus protocol, with intravenous benzodiazepines as first line therapy.

Clinical Case: This case is about a 38-year-old female with distant history of absence epilepsy, off medications for prolonged period of time, who was brought to the ED after being found acutely confused, wandering at a train station. Neurologically, she was alert, completely disoriented, and otherwise intact. Initial extensive workup, including an infused brainMRI, was normal. No electrolytes abnormalities, toxic agents, nor potential infectious sources were identified. A continuous EEG was started and immediately demonstrated generalized continuous polyspike-wave discharges, compatible with status epilepticus. Two rounds of intravenous benzodiazepines (lorazepam 4 mg) were promptly administered with complete clinical resolution and slow return to an electrographic quiet background rhythm of 8-9 Hz. She was observed for 24 hours and discharged the following day on antiepileptic coverage.

Conclusions: Acute confusional state, even in absence of focal neurological findings, must raise the question of NCSE. EEG is a rapid diagnostic tool that should be performed in all suspected cases. Early diagnosis and prompt treatment prevent further clinical deterioration, refractory disease, and irreversible neurological damages.

Treatment Outcomes in Children Diagnosed with Tic Disorders: A Retrospective Comparison Between Behavioral Intervention and Pharmacotherapy

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Abstract

In the world of modern pediatric medicine, practitioners have a plethora of treatment options available to help control childhood Tic Disorders (TD). While just over 3% percent of the pediatric population present with some form of TD, only about 1% are diagnosed with a tic disorder called Tourette Disorder (TD). In many cases TD does not present by itself, but rather with various co-morbidities. It is these associated disorders, such as obsessive-compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD) are primary concerns for the treating physician. In review of the current literature, it can be concluded that separately, both pharmacotherapies and Comprehensive Behavioral Intervention for Tics (CBIT) have been effective in treating tics and its various co-morbidities. However, what the existing literature lacks is an in-depth comparison of both treatments and the patient profile that each treatment may be most beneficial for. The goal of this study was to answer those questions and provide information about effective treatment planning for practitioners.

This study included 24 pediatric patients who participated in CBIT and 25 patients who underwent treatment by pharmacotherapy. Demographic and TD-associated information was collected using a retrospective chart analysis. The results demonstrated that 100% of CBIT participants demonstrated decreased tic severity whereas patients who participated in pharmacotherapy experienced 60% decreased severity, 24% unchanged status, and 16% increased severity. These results indicate that participation in CBIT has proven to be more useful in the reduction of tic severity, thus supporting its clinical use in medical settings.

The Influence of the Subcortical White Matter Hyperintensities to the Cognitive Patterns and their Changes in Normal Hospital Visited Elderly

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Abstract

In normal aging we performed a short term longitudinal study of the cognitive changes related to the white matter

hyperintensities (WMH) in South Korea. Participants were consecutively recruited. On magnetic resonance imaging (MRI), deep white matter hyperintensities (DWMH) were classified into D1 (the longest diameter of DWMH < 10 mm), D2 (10 mm≤DWMH≤24 mm), and D3 (25 mm < DWMH). Likewise perventricular white matter hyperintensities (PWMH) were classified into P1 (caps or rim < 5 mm), P2 (between P1 and P2) and P3 (10 mm < caps or rim). The WMH were divided into three groups according to combinations of DWMH and PWMH: Group I (minimal: D1P1, D1P2, D2P1), Group III (severe: D3P3), and Group II of remaining combinations. The three groups were matched in age, education and general cognition. The follow-up neuropsychological tests were analyzed in the three groups.

A total of 95 Participants were recruited (76 in minimal, 15 in moderate and 4 in severe). Mean age were 62.0 ± 11.7 and female was predominant. Mean score of Korean version of mini-mental status examination was 27.1 ± 2.7 and that of clinical dementia rating sum of boxes (CDR-SOB) was 0.9 ± 0.8. Follow-up neuropsychological tests complex cognitive abilities such as multiplication and division of calculation were affected by the increasing of WMH. Rey-Osterreith complex figure test (RCFT) recognition test of true positive (p = 0.014) and Korean color word stroop test (K-CWST) word reading correct (p = 0.012) were also affected according to the hyperintensities burden. CDR-SOB score suggest the possibilities of the useful clinical tool in the longitudinal study of the normal cognitive function (p = 0.009).

Glycosides of Cistanche Regulate the Expression of ARP3 and NF-κB in the Rat Model of Vascular Dementia

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Abstract

Glycosides of cistanche (GCs) are unique to Chinese herbal medicines, and have been clinically used in some ethnic communities in China. In addition, GCs have been reported to improve cognitive impairments in patients with VD. In the current study, we used a 2-VO method to establish a VD rat model. Using the MWM test, we found that GCs could improve cognitive ability among VD rats. However, the precise mechanisms of this effect remained unclear. Our previous experiments revealed that GC intervention caused changes of protein expression profiles in the hippocampus of VD rats, including some postsynaptic proteins related to the structure of dendritic spines, such as ARP3.

Association Between Vitamin D Insufficiency and Metabolic Syndrome in Patients with Psychotic Disorders

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Abstract

This study examined the association between vitamin D and metabolic syndrome in patients with psychotic disorders. The study enrolled 302 community-dwelling patients with psychotic disorders. Sociodemographic and clinical characteristics, including blood pressure, physical activity, and dietary habit were gathered. Laboratory examinations included vitamin D, lipid profile, fasting plasma glucose, HbA1c, liver function, and renal function. Vitamin D insufficiency was defined as < 20 ng/ml. Clinical characteristics associated with vitamin D insufficiency were identified. Among the 302 participants, 236 patients (78.1%) had a vitamin D insufficiency and 97 (32.1%) had metabolic syndrome. Vitamin D insufficiency was significantly associated with the presence of metabolic syndrome (p = 0.006) and hypertension (p = 0.017). Significant increases in triglycerides and alanine transaminase were observed in the group with a vitamin D insufficiency (p = 0.002 and 0.011, respectively). After adjusting for physical activity and dietary habit scores, vitamin D insufficiency remained significantly associated with metabolic syndrome and hypertension. Vitamin D insufficiency was associated with metabolic syndrome and was particularly associated with high blood pressure, although the nature, direction and implications of this association are unclear.

Lentiviral Gene Transfer Altering Brain GAD65 or GABAAα1 Modifies Audiogenic Seizure Activity in Long-Evans Rat

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Abstract

Gene transfer technology is useful to study and modify neurological disorders including epilepsy and motor diseases. Audiogenic seizure (AGS) behaviors were used to examine effects of viral vector alterations of GABA neuron proteins in inferior colliculus (IC) which generates AGS--a developmentally primed disorder. Replication-defective lentivirus vectors that upregulate GAD65 or GABAAα1 subunit expression, or both combined, along with 10% lac-Z (for neuron identification) were bilaterally injected into IC central nucleus of Long-Evans rats made seizure-sensitive animals by intense postnatal sound exposure. GAD65 injection increased wild running (WR) and clonus (CL) latencies, and reduced incidence of both compared to lac-Z, unoperated and vehicle seizure groups. GABAAα1 injection marginally decreased CL incidence only and produced contrasting posttest WR latencies. Vector animals with modified seizure symptoms showed β-galactosidase staining of typical IC multipolar/stellate and fusiform neurons.

Risk Factors and Limb Exercise Tasks Mitigating the Progression of Mild Cognitive Impairment to Dementia: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Most fundamental and clinical studies on dementia risk reduction have shifted focus to mild cognitive impairment (MCI), which is the preclinical stage of dementia and is the transition phase between normal aging and dementia. MCI constitutes an early stage of various types of dementia and neurodegenerative disorders. MCI is a short, progressive, high-risk, and unstable stage, and therefore, it presents an ideal intervention time window for mitigating the risk of dementia. The purposes of this study were to conduct a systematic review and Meta-analysis to determine the risk factors for the progression of MCI to dementia in high-risk groups, as well as the influencing factors of interventions. The study also investigated the pathogenic mechanisms underlying the progression of MCI to dementia, and the effectiveness of limb movement tasks as interventions to provide guidance for delaying or reversing progressive cognition disorders.

Methods: A systematic review and Meta-analysis method was used to determine the risk factors for the progression of MCI to dementia in high-risk groups, as well as the influencing factors of interventions. The data collection was focused on the RCTs studies that related to limb movement tasks as interventions for patients with MCI, and retrieved from the following databases: PubMed, FMRS, Embase, the Cochrane Library, CNKI, WanFang, VIP, MEDLINE, PEDro, and OpenSIGLE. Data of trials published before September 2017 was retrieved. Two researchers independently sorted the collected literature, extracted primary data, and performed a risk of bias assessment on the selected RCTs. The RCTs studies were subsequently subjected to a meta-analysis using RevMan 5.3 and GRAEDprofiler 3.2.2.

Results: The results of the study showed: (a) the risk factors for progression of MCI to dementia were complicated and related to many variables, such as genetic factors, biomarkers, neuropsychiatric symptoms, chronic diseases, and changes in imageology. Moreover, facilities with adequate clinical teaching and effective limb movement interventions require further improvement. (b) The meta-analysis included seven RCTs studies (n = 256). The age of the participants ranged from 63 to 72, and the intervention duration ranged from 6 to 12 weeks. The meta-analysis results indicated that patients who had undergone constant training sessions involving aerobic, strength, balance, coordination, and sensitivity tasks for 6, 8, and 12 weeks had significantly different performance levels on various tests such as MoCA, mini mental state examination, compared with the control group. The FTT, PPT, HIS, EEG, magnetic resonance imaging, ADL, and GDS, with the weighted mean difference (95% confidence interval) values being 13.89 (4.53, 23.25), 9.45 (3.67, 15.23), and 7.81 (1.96, 13.65) at the three time points, respectively.

Conclusions: The risk factors for progression from MCI to dementia were determined to be complicated and related to many variables. Limb movement tasks as interventions effectively improve neuropsychiatric conditions, enhance cognitive function, and ameliorate chronic diseases in patients with MCI; such interventions have no side effects and are easy to execute. The interventions are more economical than other treatments and are essential to delaying or reversing cognitive function impairment. The findings of this study suggest that clinicians may adopt limb movement tasks as supplementary treatments.

Effectiveness and Safety of Rufinamide at Treatment of Different Complicated and Drug-Resistant Epilepsy Syndromes (Real-World Practice Simulating Meta-Analysis Model)

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Abstract

Resource environment of neurologic services in Russian Federation complicate correct diagnostic management of hard seizure disorders. Due to lack of budget support many epileptic cases get no adequate differential diagnose. So the impact of real-world practice conditions comprising full scale of prevalent rare and refractory epilepsy syndromes is actual for Russian health care services.

Objective: Expanded meta-analysis was done to evaluate rufinamide safety and effectiveness in numerous heterogeneous groups of patients with scope of severe and drug resistant epileptic disorders – Lennox-Gastaut syndrome (LGS), Dravet syndrome, hard partial epilepsy with and without secondary generalization, unclassified epilepsy.

Material and methods: Meta-analysis was configured in "pragmatic" paradigm to model real-world practice condition and overcome small-group barrier which is usual for rare epilepsy forms (LGS etc.) medication trials. There were 164 relevant articles available via medico-clinical periodic databases, but only 15 have been chosen suitable for meta-analysis. All together 1847 participants aged 4 month – 80 years old were included into common massive, with mentioned epileptic forms. 1169 were administered rufinamide additionally to typical anti-epileptic medications (experimental group, composed from rufinamide groups of selected studies). 686 received treatment with common practice drugs without rufinamide (compound control group).

Results: Patient with more than 50% seizures reduction were more numerous in rufinamide group ($\chi 2 = 89.7$ with $p = 0.000...$; OR = 2.9 with 95% CI 2.3—3.7). Number needed to treat was 5. The probability of successful treatment/ positive clinical effect in compound rufinamide group was 3 times higher than in compound control group. Most frequent and statistically reliable complications of rufinamide use were headache/dizziness and nausea/vomiting. Drowsiness and fatigue in compound rufinamide group was not statistically different from same parameters of compound control group ($\chi 2 = 1.242$ with $p = 0.265$ for drowsiness; $\chi 2 = 1.09$ with $p = 0.297$ for fatigue).

Conclusion: Rufinamide is safe and effective for treatment of different epilepsies including LGS and drug-resistant partial seizures. Rufinamide may be suitable as second-line adjuvant for routine medications of severe seizure disorders.

Pharmacoeconomic Evaluation of Adjuvant Rufinamide use for the Lennox-Gastaut Syndrome Treatment: Pragmatically-Integrated Independent Groups Meta-Analysis of Real World Practice

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Abstract

Lennox–Gastaut syndrome (LGS) is one of the most severe epileptic encephalopathies. There is approximately 1400 to 9240 children of 14 years or younger with LGS in the Russian Federation. It is problematic to develop new methods of LGS treatment in Russia because of difficulties in detection of rare scattered people who is ill and in concentration of LGS-patients to specialized medical centre. That is why comparative randomized studies of new LGS treatment strategies are hard to be organized and evidences are lacking. Somehow new drugs like Rufinamide encourage new hopes for LGS management. Rufinamide is one of the most powerful agents being used for the adjuvant therapy of LGS. Rufinamide has unique features to control generalized tonic-atonic seizures.

Objective: was to produce systematic review and meta-analysis of Rufinamide use according to global scientific data of

trials and independent/ retrospective researches, and to perform primary pharmaco-economic evaluation of adjuvant Rufinamide treatment in LGS-patients of 4 years and older relevantly for conditions of Russian Federation.

Materials and Methods: Systematic search of the respective clinical studies revealed 120 scientific articles about therapy of refractory LGS. 11 articles were selected for generation of pooled groups and meta-analysis. End-point was number of patients with 50% seizures reduction ("responders"). To match ITT and real-world-practice criteria and to increase statistical reliability meta-analysis was "pragmatically" upgraded: control and experimental groups were configured with summation of several independent trials and independent retrospective studies.

Results: Rufinamide used as an adjunctive therapy in joint experimental group (N = 250) against joint control group (N = 216) has been shown to substantially increase the chances of successful result (OR = 3.1 [2.0; 4.9], p = 0.000). Addition of Rufinamide to second-line medications is able to grow 3-times higher the seizure reduction and stable remission probability. Pharmacoeconomic modelling (a decision-tree type) showed that the use of rufinamide adjunctive therapy for the Lennox–Gastaut syndrome is able to reduce total treatment and nursing costs by 5-8% when dosages 200 – 400 mg/day are applied. Maximal dosage of 1000 mg/ day saves only 2% of treatment and care expenses.

Conclusion: Though Rufinamide is expensive imported drug in conditions of Russian health care system, this adjuvant to second-line LGS-therapy saves budget costs of medication illness control and increase social adaptation possibilities for LGS-patients.

Treatment of Refractery Partial-Oncet Epilepsy with Perampanel: Pharmaco-Economical Efficiency Analysis for Russian Federation Health Care System

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Abstract

There is 128669 patients with refractory partial-onset epilepsy in Russia (2016 data). Perampanel 8 mg daily adjunctive to basic treatment is one of optimal options for such patients.

Objective: To calculate in models the direct costs and national expenses for treatment of patients 14 years and older suffering of partial-onset epilepsy with and without secondary generalization with history of drug resistance in Russian Federation.

Materials and Methods: 3 pivotal randomized phase-III trials were selected to estimate outcome frequencies principal for direct costs calculations. Annual expenses of one patient adjunctive perampanel use were obtained with direct costs modeling. Assessment of total yearly expenses during all Russian patients' refractory partial-onset epilepsy treatment also took place.

Results: Perampanel use will lead to 42% respond rate and 5% complete seizures stop in model when administered 8 mg daily. Drug-refractory partial-onset epilepsy management costs 70394 rubles for one patient per year in 2017 (without perampanel). 100% seizure reduction costs 28774 rubles for one patient per year, 50% seizure reduction costs 40375 rubles for one patient per year in 2017 (including perampanel).

Conclusion: Adjunctive perampanel use for refractory partial-onset epilepsy may reduce 30% costs of treatment or more (up to 3 – 4 mlrd. rubles annually) until 2020.

Recount of Former Data of Brain Positron Emission Tomography with 2-18F-2 Deoxi-D-Glucose of Patients with Dystonia and Essential Tremor by Means of Z–Score Method has Detected Differences between these Disorders

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Abstract

We studied patients with dystonia (D) and essential tremor (ET) using positron emission tomography (PET) equipped with Cortex ID software. This allowed PET brain visualisation to be compared to scans of a control group by means of the z-score. The study revealed hypo-metabolism in both D and ET groups, and additionally revealed a difference between these two groups of patients in certain areas of the brain. These two nosological forms overlap in clinical features and are difficult to differentiate. The PET picture may help to provide a differential diagnosis in addition to the biochemical difference in dopamine

exchange previously revealed by us in this group of patients.

It Started with Shingles: Lumbar-Onset Amyotrophic Lateral Sclerosis with Frontotemporal Dementia

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Abstract

A 68-year-old male with a history of hypothyroidism and depression was seen by his physician for a shingles follow-up. The patient complained of postherpetic neuralgia and confusion. Two days later he checked into emergency with a similar complaint. Computed tomography (CT) of the head and laboratory work-up were negative. He was given lorazepam and discharged with instructions to return to his physician. A head magnetic resonance imaging (MRI) was scheduled and significant only for "chronic microvascular disease." Interestingly, the patient's family history was notable for dementia and neuropathy. Within six weeks, he developed increasing cognitive impairment. Repeat head CT and head/neck CT angiography were negative. However, brain positron emission tomography demonstrated a decrease in metabolic activity in the parietotemporal cortex, with "patchy areas of possible minimal decrease" in the frontal lobes. The report suggested early Alzheimer's. Three weeks later the patient presented with subtle difficulty in right lower extremity movements. MRI of the lumbar spine was inconclusive. Within two and a half months he developed visual hallucinations, facial asymmetry, and right foot drop. During this interim consults were obtained. Electromyography studies at the University of Michigan Neuromuscular Clinic pointed towards amyotrophic lateral sclerosis (ALS). At a multidisciplinary clinic the diagnosis was expanded to include frontotemporal dementia (FTD). The patient was referred to hospice in mid-2017 and succumbed less than one year from initial presentation.

This case illustrates the challenge in diagnosing a mixed ALS-FTD pathology; although rare, early recognition can be achieved by paying close attention to pertinent family history.

Agmatine as a Therapeutic Candidate for the Hyperexcitation Type of Brain Transmission in Autism Spectrum Disorders

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Abstract

The prevalence of autism spectrum disorders (ASD) continues to rise while researchers have gained little progress in treating this heterogeneous disability. The excitatory/inhibitory imbalance theory emerges as a unifying explanation to the purported mechanisms of ASD. In many animal models of ASD, hyperexcitability of glutamate receptors has been a major observation. Various researchers including us have established the valproic acid (VPA) exposed animal model as a clinically relevant environmental model of ASD, which exhibits social impairments and some forms of repetitive behaviors. Here, we tested a novel candidate treatment for ASD using an endogenous NMDA receptor antagonist called agmatine. We found that a single injection of agmatine can normalize the social deficits, repetitive behaviors and hyperactivity in the VPA exposed rats. In the same way, agmatine attenuated the overt activation of Erk1/2 signaling in the prefrontal cortex and hippocampus of those rats. Peripheral administration of agmatine increased its concentration in the brain up to 1 week of treatment without showing any sign of toxicity. These results present a proof-of-concept in the restoration of E/I imbalance as a therapeutic strategy for ASD.

Quantification of Seizurogenic Activity with Multiwell Microelectrode Array Technology for Proconvulsant Risk Assessment

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Abstract

The lack of advancement in anti-epileptic drugs (AEDs) over the last 30 years, along with the continued need for improved proconvulsant screening in drug safety, motivates the need for new assays of seizurogenic neural activity. Previous work has established an *in vitro* approach for detecting and quantifying seizurogenic activity using multiwell microelectrode array (MEA) technology, providing a predictive and high-throughput avenue for the evaluation of the efficacy of AEDs and the proconvulsant risk of other drug candidates. Here, we present an updated assay of seizurogenic activity based upon guidelines developed in the HESI NeuTox consortium, which is a collection of academic, commercial, and pharmaceutical representatives working towards the development of *in vitro* assessment of proconvulsant risk. We used previously published metrics for the detection of burst spiking events and the quantification of synchronization across a neural population, in spontaneous and evoked conditions. Data are included from cryopreserved rat cortical neurons evaluated with the 10 compounds selected by the NeuTox consortium, which include reference compounds with known proconvulsant risk via multiple mechanisms and negative control compounds. Our results support the combined use of evoked and spontaneous neural activity, collected using multi-well MEA technology, for the high-throughput evaluation of complex neuronal networks *in vitro* to quantify the proconvulsant risk of candidate pharmaceuticals in a pre-clinical setting.

Effect of Virtual Rehabilitation in Patients with Parkinson Disease and Its Correlation with *In-vivo* Cerebral Metabolism

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Abstract

Objective: To evaluate the effects of a Virtual Reality protocol applied to patients with Parkinson's disease in motor performance, quality of life and cerebral metabolism (18F-fluorodeoxyglucose Positron Emission Computed Tomography - PET-FDG).

Background: VR can be an alternative tool for the treatment of PD motor symptoms. A combined approach using PET-FDG to assess *in vivo* brain metabolism related to motor symptoms and quality of life changes in Virtual Reality may provide valuable information for understanding the effects and therapeutic planning.

Method: 20 volunteers with Parkinson´s disease performed a Virtual Reality protocol (Kinect® Adventures games) during 8 weeks of supervised training. Motor outcomes were assessed before and after the intervention using the following scales: Unified Parkinson's disease rating scale part III, Berg balance scale, Parkinson's disease questionnaire and PET-FDG brain images were acquired in a PET-MR system.

Results: VR protocol was associated with a reduction of 9 points on the UPDRS scale ($p < 0.001$), increase of 5.3 on the Berg balance scale ($p < 0.001$) and reduction of 14.4 points in PDQ-39 ($p < 0.001$). We observed a reduction in brain glucose metabolism in the following regions: right supplementary motor area ($p = 0.01$), frontal and medial right frontal gyri ($p = 0.07$), right and left frontal dorsolateral gyri ($p = 0.03$ and $p = 0.027$) and in the right frontal lobe ($p = 0.012$).

Conclusions: We observed improvement in motor symptoms, quality of life and an association of these improvements with brain glucose metabolism changes.

Stroke Survivors: Needs, Wellness and Warning Signs

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Abstract

Introduction: According to the Centers for Disease Control and Prevention (CDC) Almost 800,000 patients suffer a stroke each year, with 140,000 patients dying each year. Those who survive suffer long-term physical and mental damage, including speech impediments, cognitive deficiencies, and more. Each patient is distinct, thus requiring a distinct treatment option, as well as patients may desire rehabilitation and treatment options outside of those already utilized/suggested by their care provider.

Objective: An observational study to determine the needs of stroke survivors, their knowledge of warning signs and whether their care provider had been helpful in acquiring the treatment/rehabilitation services that the patients' needed and informed them of stroke warning signs.

Design: Online SurveyMonkey distributed through the Stroke Survivors Empowering Each Other (SSEEO) facebook page and website.

Participants: 52 anonymous participants; not limited to, but including stroke patients, caretakers, amongst others. All patients were members of the SSEEO support group.

Methods: One time administration of a five question quiz, of we focused on two questions related to their most pressing needs after a stroke with two more for stroke warning signs and such knowledge provided by care providers. Patients could also choose not to respond to questions. Each response was then categorized, and a percentage of certain responses against the 52 individuals was computed.

Results: 40 out of the 52 individuals stated that they had knowledge of the warning signs of a stroke, whilst 2 out of the 52 individuals did not, and 10 chose to skip the question. However, out of the 52 individuals, only 22 individuals had been talked to about the warning signs of a stroke from their primary care physician, whilst 19 had not been talked to and 11 individuals chose to skip the questions. Due to this skip, the induced non response bias leaves open the possibility that a majority of people did not actually know about the warning signs of a stroke. 14 out of 52 respondents desired physical therapy, which was followed by 9 respondents desiring support group, 7 respondents requiring financial aid, 6 respondents desiring speech therapy, 3 respondents each named education, and occupational therapy their primary priorities, 2 respondents each listed driving, transportation and employment, 1 respondent required medical equipment whilst no respondents desired support calls. In additional, we received three written responses, which selected multiple categories as their top priority. The first of these three respondents named all of the following as priorities, but could not respond due to technical errors: physical therapy, occupational therapy, speech therapy, support group, support calls, medical equipment the next respondent named physical and occupational therapy, speech therapy and a support group as their top priority. The third respondent illustrated a need for all of the categories. No respondents skipped this question. In addition, when asked about the aid their care providers provided after their stroke. 20 respondents said care providers were "very helpful", 15 respondents said "somewhat helpful", and 7 respondents said "Not at all helpful", whilst 10 respondents skipped out of the 52 total respondents.

Prevalence of Bruxism in Individuals with Cerebral Palsy

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Abstract

In individuals with cerebral palsy, where neurological maturation is retarded or inexistent, the presence of parafunctional habits exhibits a unique behaviour. Several studies described the high prevalence of bruxism among this population and multiple facts have been suggested to justify this high prevalence such as: myofunctional disorders, muscle hyperactivity within the stomatognatic system, inherent neurological alterations and disorders in dopaminergic function. The aim of this study was to determine the prevalence of bruxism in individuals with cerebral palsy, evaluating the various factors and associated comorbidities. The results showed a high prevalence of bruxism in this population with urgent need of treatment in a way for trying to prevent nefarious consequences in the stomatognatic system. Based on the conclusions of this work, more studies are needed with standardized diagnostic protocols and representative samples to evaluate the factors that influence the presence of bruxism in this population and to establish an appropriate treatment planning.

Prevalence of Malocclusion in Individuals with and without Intellectual Disability

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Abstract

Oral health is one of the health needs with greatest demand and urgency for treatment in special needs populations. In general, the prevalence and severity of the oral pathologies in special needs patients is higher when compared with the general population. Malocclusion is among the most prevalent oral problems in this population, and can be an obstacle to their acceptance and social integration. The aim of the study was to compare the prevalence of malocclusion between a population of individuals with intellectual disability and a control group without disability. The results showed that the prevalence of malocclusion was higher and more severe in participants with intellectual disability. The dental practitioner should understand the particular relevance of this problem especially in patients with intellectual disabilities where impaired oral functions and poor appearance may further complicate oral health and increase negative social responses.

The information of the distribution of malocclusion in the population with and without intellectual disability provides us the knowledge to be used in future comparisons, orienting decision making, treatment planning, and public health policies.

Polymorphisms in Inflammatory Pathway Related Genes and Susceptibility to Ischemic Stroke

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Abstract

Aim: To investigate whether common polymorphisms in the inflammatory pathway genes influence ischemic stroke (IS) risk among Chinese patients.

Methods: The distribution of SEPS1-rs34713741 and rs4965814, MIF-rs755622, FasL-rs763110 were analyzed in 479 subjects grouped in 239 IS and 240 healthy controls. Genotyping was performed with Taqman probe technology of RT-PCR.

Results: The allele and genotype frequencies of SEPS1-rs34713741, MIF-rs755622, FasL-rs763110 did not differ significantly between patients and controls. But analysis of SEPS1-rs4965814 markers evidenced differences between patients and healthy controls. SELS-rs4965814 T/C polymorphism (P = 0.03, OR = 1.54, 95% CI:1.04-2.28) was associated with ischemic stroke. SELS-rs34713741 C/T(P = 0.14, OR = 1.24, 95% CI:0.86-1.77) , MIF-rs755622G/C P = 0.12, OR = 1.35,95% CI:0.93-1.97), FasL-rs763110 C/T (P = 0.82, OR = 0.96,95% CI:0.67-1.37) were not associated with ischemic stroke. However its possible association with disease risk which need to be confirmed in a larger sample size.

Conclusion: Our results suggest that the SELS-rs4965814 T/C variation may influence IS susceptibility in the Chinese population.

Identification of Binding Affinities of Some Pyrethroid-Like Cyclopropane/Cyclobutane Ligands with VG SCN and NMDA Receptor

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Abstract

Functionally substituted cyclopropane and cyclobutane are known as potent neural drugs. It should be noted, that cyclopropane based pyrethroid insecticides primarily affect the Na^+ channels of excitable tissues, prolonging the Na^+ current and resulting

insect paralysis. We studied the interaction of newly synthesized pyrethroid - like Cyclopropane/Cyclobutane compounds: 1,3-dichloro-2,2-dimethyl-4-(trichloromethyl)cyclobutanecarboxylic acid [CB acid], 1-chloro-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid [Cl-permethric acid], their derivatives and known pyrethroids (Permethrin, Cypermethrin and Deltamethrin), in computer modeling and molecular docking experiments with the mammalian N-methyl-D-aspartate receptor [Rattus norvegicus NMDAR2A (pdb 2A5T)] and bacterial voltage-gated Na^+ channel [Arcobacter butzleri (pdb 3RW0)]. Docking analysis was done by Auto Dock Vina and the binding characteristics of the individual stereoisomeric compounds of synthesized racemic cyclobutane and cyclopropane derivatives were calculated. Was revealed that binding energy of cyclobutane and cyclopropane derivatives are more than two orders of magnitude higher as compared to the binding energies of the corresponding acids. These derivatives and known pyrethroids bind similarly to tested systems. The obtained data identified micro molar dissociation constants for studied ligand-macromolecule complexes regardless of the model used, with ΔG in the range of -5.0 up to -9.8 kcal/mol.

Based on docking analysis it was shown, that in all of the received strong interactions the ligand (of cyclobutane or cyclopropane nature) binds to the groove of the macromolecule regardless of its nature: NMDA or sodium channel. We think, that this grooves will compose the hole of hexamer channel.

ICF: Longitudinal Study in Severe Brain injury

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Abstract

Background: The ICF, based on the bio-psycho-social model, is a tool used to classify health and related states.

Aims: The following study has two objectives: 1. Identification of ICF codes (B and S domains) most used in the clinical practice of the Adelphi Center, as probable pathology identifiers (core -set). 2. Identification of ICF codes (domains E and D) as indicators of outcome and/or follow app.

Materials and Methods: Study conducted from April 2012 to September 2013 On a sample of 37 subjects, between men and women Data collection: Use of the ICF MANUAL with 2nd level classification. For each DOMAIN: identification of 6 codes more significant than the type of users examined. Attribution of the only generic qualifier in DOMAIN B. Attribution of only the first qualifier in DOMAIN S. Allocation of a single qualifier in DOMAIN D, which includes the average value of the two performance and capacity qualifiers to facilitate comparability of data. Attribution of the only qualifier with meaning or negative or positive in DOMAIN E. Extrapolation of data from the computerized medical record through the application of queries. Percentage analysis of the average values of the qualifiers at T0 and at T1.

Results:

• in DOMAIN B the most important chapters are:
1 mental functions
2 f. sensory and pain
3 f. of voice and speech
7 f. neuro-musculoskeletal and related to movement (100% sample number).
• in DOMAIN S the most important chapters are:
1 Structures of the nervous system (100% sample number)
2 Eye, ear and related structures
3 Structures involved in ... and speaking
4 Structures of the cardiovascular, immunological and respiratory system
7 Structures related to movement (100% sample number)
• in the DOMAIN D the chapters are almost all used in rather large percentages, excluding the main areas of life item.
• In DOMAIN E the chapters are almost all used in rather variable percentages.

Conclusions: The aforementioned study could be understood as an attempt aimed at the identification of a list of ICF categories, to be used for the development of specific "core sets" for GCA (from a traumatic or vascular outcome). the DOMAINS B and S are not subject to particular modifications, a phenomenon that, instead, has been found in DOMINI D and E. The observation of the modifications of the initial and final qualifiers in Domains D and E can give indications regarding the quality of the rehabilitative trend.

Family Medical Intervention Model of Senile Dementia with Behavioral and Psychological Symptoms

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Abstract

Objective: To explore family medical intervention model of senile dementia with behavioral and psychological symptoms.

Methods: Four streets of Changning District in Shanghai were randomly selected and subjects were enrolled according to the inclusion criteria, who were randomly divided into the intervention group (n = 71) and control group (n = 70). The intervention group received door-to-door service from psychiatric doctors, given drug treatment and psychological intervention. Subjects were evaluated by several scales, including Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), Mini-Mental State of Examination (MMSE), Activity of Daily Living Scale (ADL), Quality of Life-Alzheimer's Disease (QOL-AD), and Generic Quality of Life Inventory-74 (GQOLI-74), at baseline and by the end of 6 months and 12 months.

Results:

1- There was no significant difference in the total scores and all factor scores of BEHAVE-AD between the two groups before intervention ($P > 0.05$). Repeated measures analysis of variance revealed a significant main effect of time ($P < 0.001$). The between-group effect was significant in the total scores of BEHAVE-AD, and the factor scores of affective disorder, anxiety and terror ($P < 0.001$). The interactive effect of time×group was significant in the total scores of BEHAVE-AD, and the factor scores of delusion and affective disorder ($P < 0.05$).

2- Inter-group comparison of the BEHAVE-AD scores indicated that by the end of 6 months, factor scores of hallucination, circadian rhythm disorder, affective disorder, anxiety and terror of the intervention group were remarkably better than those of the control group and the differences were statistically significant ($P < 0.01$). By the end of 12 months, total scores of BEHAVE-AD, and factor scores of delusion, conduct disorder, affective disorder, anxiety and terror of the intervention group were remarkably better than those of the control group and the differences were statistically significant ($P < 0.01$).

3- There was no significant difference in the scores of MMSE, ADL, QOL-AD and GQOLI-74 between the two groups before intervention ($P > 0.05$). Repeated measures analysis of variance revealed a significant main effect of time ($P < 0.001$). The between-group effect was significant in the scores of MMSE and QOL-AD ($P < 0.001$). The interactive effect of time×group was significant in the scores of MMSE, ADL, QOL-AD, and GQOLI-74 ($P < 0.05$).

4- Inter-group comparison of MMSE, ADL, QOL-AD, and GQOLI-74 scores indicated that by the end of 6 months, scores of MMSE of the intervention group were remarkably better than those of the control group and the differences were statistically significant ($P < 0.05$). By the end of 12 months, scores of MMSE, ADL, QOL-AD, and GQOLI-74 of the intervention group were remarkably better than those of the control group and the differences were statistically significant ($P < 0.05$).

Conclusion: The family medical intervention model of door-to-door services from psychiatrists integrating multidisciplinary team is effective to attenuate the mental and behavioral symptoms of senile dementia patients, and can improve the quality of life of patients and caregivers. The effect of persistent implementation will be more remarkable.

Virtual Rehabilitation Effects in Parkinson's Disease Patients and Their Correlations with Striatal Dopamine Transporter Density

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Abstract

Objective: To evaluate the effects of a virtual rehabilitation (VR) protocol on motor signs and quality of life in Parkinson's disease (PD) patients and to verify if these effects are followed by changes in the *in vivo* density of dopamine transporters (DAT) in the striatum.

Background: PD is the second most common neurodegenerative disease with high cost of health care. VR offers a dynamic and interactive non-pharmacological treatment environment that can deliver an efficient platform to treat motor signs and improve these patient's quality of life.

Methods: We performed a VR protocol using Kinect® Adventure games in a group of 19 patients with PD, during 8 weeks of the supervised training. We used standard measurements to quantify motor signs (UPDRS part III), balance (Berg Balance Scale), quality of life (PDQ-39) and dopamine transporter density in the striatum before and after the intervention using Single Photon Emission Computed Tomography with [99mTc] -TRODAT-1.

Results: We did observe changes in the score of the three questionnaires used, suggesting motor and functional benefits (UPDRS reduction of 9 points, $p < 0.001$; Berg Balance Scale increase of 5.3 points, $p < 0.001$ and PDQ-39 reduction of 14.4 points, $p < 0.001$) and an increase in DAT in right caudate and putamen, although without statistical significance. On the other hand, we found statistically significant decrease in the same regions on the left.

Conclusions: The positive change in the scales used reinforces that VR aids in the motor and functional improvement of the patients and possibly DAT changes may follow these clinical benefits.

Designing an Expert System for Screening Children with Intellectual Disability (ID)

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Abstract

Intellectual disability (ID) is characterized by below-average intelligence and a lack of skills necessary for day-to-day living. Although people with ID can and do learn new skills, however they learn new skills more slowly than typically developed people. In this paper we propose a statistical expert system to distinguish between children with ID, and typically developed children. At the beginning, we used a researcher-made questionnaire, consisting of 158 questions related to the adaptive behaviors, as the features to determine ID. The questionnaire is supposed to be answered by children's parents. The questions can be answered online at anytime and anywhere in the world and data can be gathered and processed simultaneously. The questionnaire is tested on 375 children between 4 to 12 years of age. 189 children were ID and the rest, i.e. 186 children, were normal. Then machine learning methods are used to analyze the data and determine the most important features (questions) that can be used to distinguish between these two groups of children. The screening capability of this tool becomes important especially in the developing countries which have limited medical resources. The results show that, the expert system has the capabilities to be used as an assessment tool for diagnosing children with ID. We have observed that the questionnaire may/needs to be further improved to increase its sensitivity to be able to distinguish between multiple cognitive impairments such as ID, Autism, and ADHD.

Citation: Proceedings of the 4th Neurological Disorders Summit (NDS-2018). *J Neurol Exp Neurosci* 4(Suppl 1): S1-S50.

Received: August 07, 2018 **Accepted:** August 13, 2018 **Published:** August 15, 2018