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Meeting Abstracts

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Structure and Functional Models of Amyloid β42 (Aβ42) and A-synuclein Assemblies Containing GM1 Gangliosides

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Abstract

Amyloids are associated with three major diseases: Aβ with Alzheimer's disease, α-synucleins with Parkinson's disease, and amylin (aka IAPP) with type 2 diabetes. These amyloids all form soluble oligomers, fibrils, and transmembrane ion channels. Although some fibril structures have been determined, much less is known about structures of more toxic soluble oligomers and transmembrane assemblies. Polymorphism is a major impediment. Amyloid assemblies are dynamic. Sometimes they are disordered, the number of peptides forming assemblies usually vary, even their secondary structures change with time and environment, and multiple forms are usually present simultaneously. We do not know which assemblies are vital and which are pathogenic. Our team is attempting to fill this void by developing atomic-scale models of both synucleins and Aβ. Only the Aβ42 isoform forms discrete channels in neurons. Its toxicity is enhanced by GM1 gangliosides, which are included in our latest generation of β-barrel models. Our models have both radial and usually P2 symmetries and have only one or two peptide conformations; constraints that limit the number of possible structures enormously. They are consistent with well-established β-barrel structure theory, numerous NMR, microscopy, biophysical, and biochemical studies, and with established molecular modeling principles and techniques. The number of feasible models is large because numerous different assemblies exist. Also, we are modeling how Aβ42 and α-synuclein may participate in the formation of fusion pores during synaptic transmission by surrounding synaptophysin and expanding enormously when membrane tension is applied by the surrounding SNARE synaptotagmins and complex in complex.

Targeting Early Genetic Risk Factor during Aging to Improve Brain Metabolism

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Abstract

It is projecteddementia2050, 106.23 million adults will be living with Alzheimer's disease (AD) and AD-related dementias (ADRD) worldwide. In this project, we sought to identify the genetic pathways that induce neurodegeneration during aging. Long noncoding RNAs (lncRNAs) have a central role as regulators of gene expression and cellular function. Prior research established that lncRNA GAS5 regulates insulin signaling and inflammatory pathways. Here we evaluated the expression of GAS5 in the aging brain. An unbiased, transcriptomics screen followed by validation using qPCR was performed to determine the levels of the lncRNA GAS5 in human brain samples obtained from individuals over the age of 75 with AD (Male and female samples, de-identified). The results demonstrate that GAS5 is decreased in human AD brain, and in aged or T2D mouse models. We developed a GAS5-targeting small molecule NPC86 and its derivative NPC67 and *in vitro* functional assays demonstrated that GAS5 regulates neuronal insulin signaling, neuronal survival, tau metabolism, and neuroinflammation. Next, the safety and efficacy of NPC86 was established *in vivo* in a mouse model. Results demonstrated efficient uptake and biodistribution of NPC86 using an intranasal delivery route. Further, biochemical, and histological analysis demonstrate improved

neuronal signaling and decreased neuroinflammation in aged mice treated with the drugs. The study demonstrates that GAS5 contributes to pathways associated with neurodegeneration and the GAS5-targeting small molecule has tremendous therapeutic potential to prevent the advent of neurodegenerative diseases and dementia.

Identifying Hidden GEMs in Neurological Diseases

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Abstract

GEMIN5 is essential for core assembly of small nuclear ribonucleoproteins (snRNPs), the building blocks of spliceosome formation. We identified biallelic mutations in GEMIN5 among patients presenting with developmental delay, motor dysfunction and cerebellar atrophy. We found that these GEMIN5 variants perturb snRNP complex protein expression and assembly. While doing a genetic screen, we identified SMN as a genetic suppressor of GEMIN5-mediated neurotoxicity in drosophila. We discovered that an increase in SMN expression by either genetically or the antisense oligonucleotide (ASO) nusinersen, significantly upregulated the expression of GEMIN5 in mammalian cells and mutant GEMIN5 derived iPSC neurons. Furthermore, we identified a strong functional association between the expression patterns of SMN and GEMIN5 in patient spinal muscular atrophy (SMA) derived motor neurons harboring loss of function mutations in the SMN gene. Interestingly, SMN binds to the C-terminus of GEMIN5 and regulates GEMIN5 expression through the tudor domain. Lastly, we observed that SMN upregulation ameliorates defective snRNP biogenesis and alternative splicing defects caused by loss of GEMIN5 in iPSC neurons and *in vivo*. Collectively, these studies indicate that SMN is a potent regulator of GEMIN5 expression and neuropathologist.

TAR DNA Binding Protein-43 (TDP-43) Pathology Causes Differential Expression of Retrotransposons in a TDP-43-Q331K Mouse Model

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Abstract

TDP43 is a nucleic acid binding protein with important functions such as translational regulation, stress granule formation and, most recently, retrotransposon repression. Pathological aggregates of TDP43 are seen in patients with ALS, FTD and AD. Retrotransposable elements (RTE) are mobile elements capable of inserting copies into different genomic locations. Studies in flies have established the causal role of RTEs in mediating both the intracellular toxic effects of TDP43, and the intercellular spread of that toxicity from glia to neurons. The role of TDP43 in RTE regulation has also been replicated in postmortem human tissue. Here, we establish the first rodent model to examine the effects of TDP43 pathology on RTEs. We look at TDP43 proteinopathy in a mouse model where the human TDP43 transgene, with or without the Q331K familial ALS mutation, is overexpressed 1.5 times. We see a significant upregulation of RTE at 3 months in TDP43 - Q331K animals and at 15 months in TDP43 - WT animals. We crossed these mice to the L1-EGFP reporter mouse that expresses EGFP after a retrotransposition event occurs. TDP43 - Q331K animals show significantly higher GFP positive glia and neurons, which occur in large clusters in the striatum (Str) and nucleus accumbens (NA) at 3 months and in the MC at 6 months. TDP43-WT animals show similar clusters in the NA and Str at 10 months. In conclusion, we show evidence of RTE expression and retrotransposition events in a cell type, brain region specific, and age-dependent manner in TDP43 pathology mice.

Clinical Measures of Disease Progression in Amyotrophic Lateral Sclerosis Type 4

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Abstract

ALS4 is a slowly progressive degenerative disease of the nervous system caused by mutation in the senataxin gene (SETX). This autosomal-dominant form of ALS is characterized by early-onset, muscle atrophy, weakness, and hyperreflexia. 15 patients with a 1166 T > C (p.Leu389Ser) mutation in SETX were evaluated at the National Institutes of Health Clinical Center (Bethesda) at baseline. Neurological examination was done on all subjects, with follow-up examinations in 14 subjects at 1 year and 7 subjects evaluated at 2 years of follow-up. Dual-energy X-ray absorptiometry (DXA) and thigh muscle MRI were performed during the follow-up period. Clinical measurements of quantitative muscle testing (QMT) of the upper and lower extremities, 6-minute timed walk test (6MTWT), timed up and go (TUG), 30 second chair stand test, pinch strength, SF-36 quality of life questionnaire, and grooved pegboard test were performed. We designed a series of siRNAs to target the RNA transcript from the ALS4 allele with the c.1166T > C mutation. In ALS4 primary fibroblasts transfected with candidate siRNAs, there was a dose-dependent decrease in the amount of mutant SETX mRNA. Further, RT-PCR of cDNA demonstrated a decreased amount of endogenous mutant SETX mRNA relative to the wildtype SETX mRNA. This study has established the framework for measuring changes in clinical and imaging measurements in patients with ALS4. Development of an allele specific therapy may provide potential benefit in familial ALS and the measurements established here could help to assess therapeutic efficacy in future clinical studies.

Mechanism of R-loop-mediated Neurodegeneration in ALS4

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Abstract

Mutation in the senataxin (SETX) gene causes amyotrophic lateral sclerosis 4 (ALS4), which is an autosomal dominant neuromuscular disorder characterized by degeneration of spinal cord motor neurons. R-loops are formed during the transcription and consist of three nucleic acid strands, nascent RNA hybridized to transcribing DNA strand (RNA:DNA hybrid) and a complementary DNA strand. Alteration in R-loop levels is associated with many neurological disorders, including spinal muscular atrophy (SMA) and ALS. SMA is an autosomal recessive disease caused by mutation in the survival motor neuron 1 (SMN1) and characterized by motor neuron degeneration. In this study, we examined disease models: ALS4, characterized by low levels of R-loops, and SMA, characterized by high levels of R-loops. The molecular mechanism of R-loop-mediated neurodegeneration is unclear. We show that the zinc finger protein 1 (ZPR1) recruit SETX onto R-loops and is critical for the assembly of functional R-loop resolution complexes (RLRC) and resolution of R-loop. In SMA, the low levels of SETX and ZPR1 onto R-loops result in reduced efficiency of R-loop resolution causing accumulation of R-loop levels in SMA. ZPR1 overexpression increases SETX levels resulting in increased SETX recruitments onto R-loops, which increases R-loop resolution and rescues pathogenic phenotype in SMA neurons and patient cells. We found that the interaction of SETX with ZPR1 is disrupted in cells derived from ALS4 patients that have heterozygous SETX (L389S) mutation. ZPR1 fails to recruit mutant SETX homodimer but recruit's heterodimer with partially disrupted SETX and ZPR1 interaction. Notably, disruption of SETX-ZPR1 complexes causes an increase in R-loop resolution activity leading to fewer R-loops in ALS4. Modulation of ZPR1 levels regulates R-loop accumulation and rescues the pathogenic R-loop phenotype in ALS4 patient cells. These findings provide insight into the mechanism of R-loop resolution under the normal and ALS4 disease conditions.

Peripheral Organs Defects in Spinal Muscular Atrophy: Actin Dysregulation

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Abstract

Spinal Muscular Atrophy (SMA) is a devastating neurodegenerative disease characterized by the loss of alpha motoneurons, primarily investigated in the context of central nervous system pathology. However, emerging evidence suggests that SMA pathology extends beyond the nervous system, implicating peripheral organs. Initial investigations have unveiled a crucial role

for actin cytoskeleton dysregulation in the pathogenesis of SMA in neuronal tissues. Two major action associated proteins, profilin and cofilin have previously been linked with this dysregulation. However, given the ubiquitous expression of SMN, it is paramount to identify abnormalities in peripheral organs. Here, we employed a comprehensive approach to investigate actin dysregulation as a key patho mechanism in peripheral organs of SMA. We analyzed peripheral organs from different post-natal timepoints using the Taiwanese and 2B-mouse models representing severe and less severe SMA phenotype. We aimed to elucidate the expression and phosphorylation levels of the two critical proteins, profilin and cofilin. We also preformed long-read RNA sequencing to produce a detailed analysis of gene expression profiles in heart, kidney, and lung tissues. These studies highlight a highly dynamic and organ-specific dysregulation of actin dynamics in SMA. Our study expands understanding of SMA and #39;s molecular intricacies, offering insights into potential treatment targets outside the central nervous system, ultimately improving SMA patients and #39;s well-being.

Dysregulated S-glutathionylation and Redox Enzymes in Multiple Murine Organs of Spinal Muscular Atrophy

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Abstract

Spinal muscular atrophy (SMA), once solely regarded as a neurodegenerative disorder, is now recognized as a multi-systemic condition. The survival motor neuron protein (SMN) is a crucial protein, and mutations or biallelic deletions of its SMN1 gene underlie the disorder. This has led to the development of three FDA and EMA approved SMN replacement therapies. However, the complexity of SMA's disease manifestations across various types have prompted a shift investigating SMN-independent pathways in a multi- systemic context. In our laboratory, we have initiated a multi-organ investigation into the redox post- translational modification of thiol proteome, specifically S-glutathionylation (S-Glu), utilizing a Taiwanese mouse model of SMA. S-Glu is a reversible oxidative modification that protects proteins from irreversible oxidation or acting as a regulatory modification triggering signaling cascades. Our findings reveal a multi-organ dysregulation of the S-Glu mechanism in SMA mice compared to control littermates. This dysregulation is accompanied by the decreased expression of redox enzymes particularly at the symptomatic stage. To comprehensively analyze the proteome of neuronal and peripheral organs in SMA mice in an unbiased manner, we conducted multi-organ global protein quantification. This involved SMA mice and control littermates, either injected with low amounts of SMN antisense oligonucleotides to slightly increase SMN levels or left untreated. This approach confirmed that cysteine metabolism and glutathione homeostasis are downregulated in SMA and differentially affected by SMN replenishment. Our objective is to determine the extent to which SMN replacement positively modulates redox pathways and whether upstream redox-related transcription factors represent key targets for combinatorial therapy.

Screening for Early Biofluid Markers of Alzheimer's Disease in an At-risk Population: Design of the Predictom Study

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Abstract

The introduction of the first disease-modifying therapy has underscored the necessity of readily available biomarkers to enable early diagnosis of Alzheimer's disease (AD) and other dementias. Biofluids such as blood, saliva and stool show great promise due to their accessibility and recent intensive research focus. The aim of predictom is to leverage biofluid biomarkers alongside magnetic resonance imaging (MRI), electrophysiological and digital biomarkers to develop an artificial intelligence (AI)-driven screening platform for early AD detection. Predictom is a Europe-wide, multicenter cohort study that seeks to recruit individuals at risk of developing dementia. In the first phase, finger-prick blood, saliva, and stool samples from 4000 participants will be assessed, focusing on existing protein and genomic AD markers. Together with digital and physiological biomarkers as well as data from existing databases, these biofluid-derived markers will guide the selection of a sub cohort of 615 individuals categorized as high or low risk for AD development. In the second phase, a comprehensive analysis of biofluid makers will be conducted, paired with MRI and physiological data. Venous blood will be analyzed for protein AD markers, glycan structures as well as exosomal protein and RNA profiles. Finally, diagnostic evaluation based on the clinical gold standard will confirm or rule out an AD diagnosis. Predictom aims to contribute to the transition to an early AD diagnosis through both established and novel biomarkers supported by AI technology.

Development of Rapid Large-area Sensing Technology for Early Detection of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a degenerative neurological disease caused by excessive accumulation of insoluble protein plaques in the brain. Cerebrospinal fluid (CSF) biomarkers for detection of amyloid-beta, tau protein, and beta-amyloid precursor protein are known to have high accuracy for early diagnosis of AD. In this study, we introduced a large-area fluorescent biosensing technology using a rough nanofilm upheaved by carbon nanotube (CNT) growth and verified its performance in detecting AD biomarkers in both artificial CSF and monkey CSF. The fabrication process enabled optimization of the nanofilm surface roughness in a 2.5 mm × 2.5 mm large sensing area for better identification of biomarkers. CNTs grown for 10 min produced the best surface area, hardness, and roughness of the upheaved nanofilm. The nanofilm treated by plasma was found to maximize the adsorption of AD biomarkers. In addition, fluorescence detection over a large area was possible with high sensitivity (up to 0.1 fM) for the detection of AD biomarkers in two CSF solutions. The CNT growth-upheaved nanofilm has great potential for use in rapid large-area sensing platforms for clinical applications.

Plasma Astrocytic Biomarker in Patients with Alzheimer's Disease

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Abstract

Background: Alzheimer's disease (AD) is an unquestionably global disorder, due to its high prevalence worldwide. Mounting evidence indicates that levels of glial fibrillary acidic protein (GFAP), which is primarily located in the astrocytes, may be related to amyloid burden, neurodegeneration, and stroke but its clinical utility in neurodegenerative diseases, including AD is still under investigation. Thus, the purpose of the present study was the assessment of GFAP potential diagnostic usefulness in AD by measurement of plasma concentrations of this protein and compare the results with the classical CSF biomarkers of AD.

Methods: Plasma concentration of GFAP was measured by using a single molecule array (Simoa). The quantitative assessment of classical biomarkers (Aβ-42, Aβ-42/Aβ-40, tau, and pTau181) in the cerebrospinal fluid (CSF) of patients with AD and elderly subjects without cognitive deficits were performed by ELISA technique.

Results: Significantly higher plasma concentrations of GFAP were noticed in AD patients as compared to non-demented controls. The levels of plasma GFAP correlated negatively with mini-mental state examination (MMSE) score and CSF Aβ-42 concentration as well as positively with CSF tau proteins levels in the study group.

Conclusions: The results of the present study indicate that plasma GFAP could be potentially a valuable biomarker for detecting and tracking Aβ pathology as well as might be useful in therapeutic strategy of AD.

Mediating and Moderating Effects of Plasma Proteomic Biomarkers on the Association Between Poor Oral Health Problems and Incident Dementia: The UK Biobank Study

Hind A. Beydoun[1*], May A. Beydoun[1], Nicole Noren Hooten[1], Jordan Weiss[2], Zhiguang Li[1], Michael F. Georgescu[1], Christian A. Maino Vieytes[1], Osorio Meirelles[1], Lenore J. Launer[1], Michele K. Evans[1] and Alan B. Zonderman[1]

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Abstract

Plasma proteome can mediate poor oral health problems (POHP)'s link to incident dementia. We screened 37,269 UK biobank participants 50 - 74 years for prevalent POHP, further tested against 1,463 plasma proteins and incident dementia. Total effect of POHP-dementia through plasma proteomic markers was decomposed into pure indirect effect (PIE), interaction referent (INTREF), controlled direct effect (CDE) or mediated interaction (INTMED). POHP increased the risk of all-cause dementia by 17% ($p < 0.05$), with GDF15 exhibiting strongest mediating effects (PIE > 0, $p < 0.001$). A first principal component encompassing top mediators explained 11% of the POHP-dementia effect. Pathway analysis including all mediators ($k = 175$ plasma proteins) revealed the involvement of the immune system, signal transduction, metabolism, disease, and gene expression, while string analysis indicated that top mediators within the first principal component were also represented in the two largest proteomic clusters. In summary, dementia is linked to POHP mediated by GDF15 among several proteomic markers.

Caregiver Strain and Quality of Life: Assessing the Moderating Role of Age among Caregivers of Offspring with Intellectual and Developmental Disabilities

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Abstract

The number of diagnosed cases of people with intellectual or developmental disabilities (I/DD) has exploded in recent years, and members of this population have witnessed a substantial extension of their lifespan. These increases, along with policy changes and residential preferences, have led to an unprecedented number of aging offspring with I/DD living at home with their families. Caring for people with I/DD is considerably stressful, and many caregivers report high levels of caregiver strain. Researchers have reported that older caregivers are especially susceptible to caregiver strain, as these caregivers are confronted with challenges not typically experienced by younger caregivers. Caregiver strain impacts the quality of life of not only the caregiver, but the entire family unit, given the reciprocity inherent in family subsystem relationships. Since research in the area

is limited, the purpose of this study is to explore caregiver age as a moderator in the association between caregiver strain and caregiver quality of life. A moderation analysis will be used to assess the main effect of caregiver strain, the main effect of caregiver age, and the interactions between caregiver strain and age on caregiver quality of life. Understanding factors which may moderate the relationship between caregiver strain and caregiver quality of life can inform strategies to improve service delivery models to support more targeted, age-related interventions.

Neurobiological Basis of Bioelectronic Medicine in Treating Pediatric ADHD and Autism

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Abstract

Attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) have been extensively studied, with researchers determining the correlation between these two necrologies, how they affect adults, and how they can affect work and family life. Despite this, a gap exists in research exploring how these mental disorders affect children's development. Thus, this paper bridges the gap with an in-depth review of existing scientific literature on ADHD and ASD and their social and academic impact. This was narrowed to findings from scientific articles on children diagnosed with ADHD and ASD aged approximately 5 - 21 years old. Moreover, this paper introduces the untapped potential of bioelectronic medicine as a novel approach to improving these disorders. This paper seeks to raise awareness about the impact of mental disabilities, the crucial role of navigating their challenges, as well as potential future medical advances that can help with these neurological disorders.

Mediating and Moderating Effects of Plasma Proteomic Biomarkers on the Association between Poor Oral Health Problems and Brain White Matter Microstructural Integrity: The UK Biobank Study

May A. Beydoun[1*], Hind A. Beydoun[1], Yi-Han Hu[1], Zhiguang Li[1], Michael F. Georgescu[1], Nicole Noren Hooten[1], Mustapha Bouhrara[1], Jordan Weiss[2], Lenore J. Launer[1], Michele K. Evans[1] and Alan B. Zonderman[1]

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Abstract

Plasma proteome mediates associations between periodontal disease (Pd) and brain white matter integrity (WMI). We screened 5,089 UK biobank participants aged 40 - 70 years for poor oral health problems (POHP). We examined the association between POHP and plasma proteome of 1,463 proteins in four-way decompositions into pure mediation, pure interaction, neither, or both through proteomic biomarkers for POHP related to WMI (fractional anisotropy (FA), mean diffusivity (MD), intracellular volume fraction (ICVF), isotropic volume fraction (ISOVF) and orientation diffusion (OD)). Total effect was decomposed into controlled direct effect, interaction referent, mediated interaction, and pure indirect effect. Structural equations modeling (SEM) was conducted adjusting for socio-demographic and cardiovascular health factors. POHP was more prevalent among men (12.3% vs 9.6%), and was associated with lower WMI on most metrics, in a sex- specific manner. Of 15 proteins strongly associated with POHP, growth differentiation factor 15 (GDF15) and WAP four-disulfide core domain 2 (WFDC2; also known as human epididymis protein 4; HE4) were consistent mediators. Both proteins mediated 7 - 8% of total POHP effect on FA mean with GDF15 exhibiting an additional 10% mediated interaction. SEM yielded significant total effects for FA mean, MD mean and ISOVF mean in full models, with % mediated by common latent factor (GDF15 and WFDC2) ranging between 13% F (FA mean) and 19% (ISOVF mean). For FA, mediation by this common factor was found for 16 of 49 tract-specific and global mean metrics. Protein metabolism, immune system, and signal transduction were the most common pathways for mediational effects. POHP was associated with poorer WMI, which was partially mediated by GDF15 and WFDC2.

Feasibility and Utility of Introducing Handgrip Strength Measurement (For Sarcopenia Assessment) for Outpatients Living with Parkinson's Disease

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Abstract

Patients living with Parkinson's Disease (PwP) who are sarcopenic are at significantly higher risk of falling. Handgrip strength is a useful tool to assess for sarcopenia but is not commonly measured in clinical practice, despite the consequences that sarcopenia poses for health.

Aim: This study aims to incorporate handgrip strength into the assessment of PwP. Secondary objectives are to explore whether exercise is associated with increased handgrip strength and to implement interventions for patients who have sarcopenia.

Methods: Questionnaires were designed to gather quantitative data about patients' demographics, how frequently they fall, disease severity2 and their weekly exercise. PwP attending the movement disorders clinic at Crawley hospital between February and October 2023 were targeted. Grip strength was measured using a standardized technique with a calibrated manometer.

Results: Handgrip strength was obtained for 125 of 271 patients (46%) attending clinic over this period. Initially healthcare workers took 9.2 min to complete the questionnaire and measurements, but this improved to 4.3 min in PDSA 2. Sixteen patients were excluded, leaving 51 females and 58 males: both with a mean age of 80. Grip strength reduced with PD severity when adjusted for gender; this was significant in males ($H = 51.9$, $p = 0.00$) but not females ($H = 4.8$, $p = 0.31$). Grip strength weakly correlated with exercise, although not significant ($r2 = 0.15$, $p = 0.15$) but did not appear to be related to frequency of falls ($r2 = 0.01$, $p = 0.92$).

Conclusion: Handgrip measurement can be successfully implemented into outpatient assessment. Handgrip strength could be used to monitor the effect of lifestyle change in individuals. Limitations include self-reporting bias about which activities classifies as exercise.

Dysregulated S-glutathionylation and Redox Enzymes in Multiple Murine Organs of Spinal Muscular Atrophy

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[3]Center for Rare Diseases, University Hospital of Cologne, Germany

Abstract

Spinal muscular atrophy (SMA), once solely regarded as a neurodegenerative disorder, is now recognized as a multi-systemic condition. The survival motor neuron protein (SMN) is a crucial protein, and mutations or biallelic deletions of its SMN1 gene underlie the disorder. This has led to the development of three FDA and EMA approved SMN replacement therapies. However, the complexity of SMA's disease manifestations across various types have prompted a shift investigating SMN-independent pathways in a multi- systemic context. In our laboratory, we have initiated a multi-organ investigation into the redox post- translational modification of thiol proteome, specifically S-glutathionylation (S-Glu), utilizing a Taiwanese mouse model of SMA. S-Glu is a reversible oxidative modification that protects proteins from irreversible oxidation or acting as a regulatory modification triggering signaling cascades. Our findings reveal a multi-organ dysregulation of the S-Glu mechanism in SMA mice compared to control littermates. This dysregulation is accompanied by the decreased expression of redox enzymes particularly at the symptomatic stage. To comprehensively analyze the proteome of neuronal and peripheral organs in SMA mice in an unbiased manner, we conducted multi-organ global protein quantification. This involved SMA mice and control littermates, either injected with low amounts of SMN antisense oligonucleotides to slightly increase SMN levels or left untreated. This approach confirmed that cysteine metabolism and glutathione homeostasis are downregulated in SMA and differentially affected by SMN replenishment. Our objective is to determine the extent to which SMN replacement positively modulates redox pathways and whether upstream redox-related transcription factors represent key targets for combinatorial therapy.

Ectoine Treatment Stimulates Protein Markers of Autophagy Efficiency in the Duchenne Muscular Dystrophy Mouse Model mdx

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Abstract

Duchenne muscular dystrophy (DMD) is a severe X-linked neuromuscular disorder caused by DMD gene defects and absence of dystrophin protein from muscle cell membranes, leading to progressive contraction-induced muscle damage. Despite advances in molecular therapies, a cure is lacking, making it worthwhile to continue investigations into supportive therapies. We were the first to test the Osmo protectant ectoine in the standard DMD disease model, the mdx mouse, and reported improved skeletal muscle histopathology and anti-inflammatory effects. In the current study, we focused on the autophagic proteome, as compromised autophagy is a pathogenic mechanism known to aggravate DMD muscle damage. Mice received 150 mg/kg ectoine in drinking water until postnatal day 21, at which point they were subjected to 20 daily intraperitoneal injections of 177 mg/kg ectoine, or saline in controls. Limb muscles were dissected, and western blotting was performed quantifying autophagy-related protein levels, normalized to content of the housekeeping protein glyceraldehyde 3-phosphate dehydrogenase (GAPDH). We observed that the ratio of activated microtubule-associated protein 1A/1B-light chain 3 (LC3 II) over sequestosome 1 (SQSTM1), a marker for autophagic degradation activity, was reduced 0.65 - fold in extensor digitorum longus and 0.82 - fold in gastrocnemius muscle of control mdx compared to healthy mice. Treatment with intraperitoneal ectoine on the contrary, led to LC3 II over SQSTM1 ratios increasing 1.75 and 1.41 - fold respectively. We propose ectoine supplementation could alleviate progressive muscle damage in the mdx via a compensation of the autophagic deficit, potentially improving clearance of defective cellular components, which warrants its further exploration as a therapeutic supplement for DMD.

Surgical Treatment of Parkinson's Disease after Medication Failure at the Central Military Hospital

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Abstract

Objectives: The forms refractory to medical treatment of our patients suffering from Parkinson's disease (PD), in which the side effects of therapy had become incompatible with decent self-sufficiency, benefited from a deep brain stimulation (DBS).

Methods: Since 2011, we have surgically treated eight patients amongst which 7 males and 1 female. Our choice focused on the idiopathic origin with a significant handicap, in spite of an optimized treatment and the preservation of sensitivity to L-dopa. The adhesion and motivation as well as PD progression of more than 5 years and over 6 months of therapeutic efforts are crucial conditions. Patients aged over 70, presenting a cerebral lesion or severe atrophy are all excluded from surgical treatment. The same applies to resistance to L-dopa or other counter-indications to any surgery (coagulopathy).

Results: The postoperative complications observed are: pneumocephalus, headaches and depression in one case each, hypersexuality and aggressivity in one case as well. Therefore, our results can be superimposed on all the major series, as clinical improvement and socio-professional reintegration were obtained in all cases.

Conclusions: It is strongly recommended to surgically manage PD following medication failure closely monitored by the neurologist. Reckoning that the patient selection suggested a multidisciplinary approach: neurology, neurosurgery, psychiatry, neuropsychology, and the final decision is made based on evaluations by each discipline.

Interrogation of the Chlorine Atom in the Atypical Antipsychotic Clozapine and *in-silico* Investigation of Other Potential Pharmacophores in this Context

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Abstract

This study examines the therapeutic role and importance of the chlorine atom in the clozapine structure. Many FDA-approved atypical antipsychotics, including clozapine, risperidone, olanzapine, and fluphenazine, have different atomic and structural combinations but are commonly prescribed for the treatment of schizophrenia. We know that benzodiazepines are an important component for bioactivity, but why is the chlorine atom in the structure of clozapine necessary? With this in mind, we

focused on the chlorine atom and the derivatization studies of clozapine with the various pharmacophores. These studies were performed using in silico medicinal methods (ADME, toxicity, docking studies, etc.). The results show that the newly designed clozapine derivatives are superior to clozapine. The designed molecular structures will also be tested by further experimental studies to verify the obtained results.

Rate and Predictors of Neurosurgical 30 - Day Readmission: A Single-center Experience

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Abstract

Readmissions of neurosurgical patients are major events in patient care. They significantly affect the well-being of the patients, and the overall care for these patients. This is a single-center retrospective study of patients treated for various neurosurgical diseases under the primary care of neurosurgical hospitalist team between 2020 and 2022. The rate of 30 - day readmission was 5.9% with infection being the most common cause. Asian race, disposition to rehabilitation facilities, and tumor-related admissions were significantly associated with high rates of readmission. Surprisingly, smoking was significantly associated with lower rates of readmission. We discuss the causes for readmissions, and we propose a course of action in each case.

Which Frequency Comes First in Intracranial EEG Ictal Onset: High or Low?

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Abstract

High frequency oscillations (HFO) 100 - 150 Hz are thought to be the earliest ictal onset frequencies which may be used to identify the epileptogenic zone for surgical resection. We analyzed EEG data sampled at 2 kHz from 10 patients with medically refractory partial epilepsy undergoing intracranial macroelectrode monitoring (5 depth electrodes, 5 subdural grids). Multiband frequency and power analysis were performed to characterize the predominating frequency during the interictal, pre-ictal, ictal, and postictal periods. Thirty-seven seizures 17 from subdural grid and 20 from depth electrodes were analyzed. In eight patients, power spectrogram between 0 - 100 Hz demonstrated the ictal onset was localized to one contact and was characterized by a significant increase of 10 - 30 Hz frequencies preceding the increase of 30 - 100 Hz frequencies by 3 seconds before propagation. Focal surgical resections were performed in the areas correlated to the synchronization of these alpha-beta frequencies and HFO prior to and during the patients' clinical seizures. These eight patients have seizure-free outcomes confirming the localization. In contrast, the alpha-beta frequencies synchronization was not seen in two patients (13 seizures) who did not become seizure-free. Previous studies of HFO from intracranial EEG recordings consistently show the frequencies at ictal onset above gamma range. In contrast, we found that HFO were preceded by lower frequencies, and the presence of the lower frequency synchronization correlated with post-operative seizure freedom. HFO may not be the first ictal manifestation in some cases and lower frequency ictal frequencies should not be overlooked. Larger studies are underway.

Neuromodulation by Upconversion Nanoparticles

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Abstract

We aim to develop a minimally invasive method to stimulate selective neuropathways located within the deeper structures of the nervous system. We intend to use a non- electromagnetic and non-electrode-based implantation approach to depolarize targeted neurons. Our objective is to replace a conventional method to emit visible light by stimulating dye-sensitized upconversion nanoparticles (UCNPs) using a near infrared-light emitting diodes (NIR-LED) illumination system with a broadband

excitation wavelength range of 800 nm. This enables us to activate light-sensitive ion channels in transfected neuropathways. To obtain visible (blue) light-emitting UCNPs, the NaYF4: NdYbTm@NaYF4: Nd are synthesized with the core-shell containing high upconversion efficiency and strong emission at 450 - 475 nm. Since cyanine derivatives have strong absorption properties at ~800nm, they are combined with UCNP, which significantly enhances the absorption ability of UCNP, thereby improving the upconversion emission effect. The proper ion doping concentration of UCNP and the dye/UCNP ratio ensure the maximum energy transfer efficiency. Thus, such dye-sensitized UCNP is expected to be excited by the NIR-LED illumination and effectively depolarize selective neurons. In addition, UCNPs are taken up by transfected neurons through endocytosis, allowing a much closer proximity to the ion channels of the targeted neuronal, further enhancing energy transfer efficiency. This neuromodulation approach is a powerful tool for targeting deeper neural pathways in the central, peripheral, and visceral nervous systems. Indeed, the UCNPs–NIR-LED system also enables safer access to regions beyond conventional intervention, such as invasive electrode implantation.

Differentiation between Alzheimer's Disease and Dementia with Lewy Bodies using Infrared Microscopy of White Blood Cells and Machine Learning Methods

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Abstract

Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) are the two most well- known types of dementia. These types share similar symptoms and traits, particularly in the early stages, which might cause DLB to be mistaken for AD and vice versa. Although neither of these neurological disorders can be specifically treated with medicine, accurate and objective diagnosis of DLB and AD is of great clinical importance since it gives the doctors a routine, objective test to back up their diagnoses and enable them to target therapy that can delay the onset of these dementias' symptoms over time, thereby enhancing patients' quality of life. The objective is to assess the potential of mid-infrared (IR) spectroscopy-based machine learning algorithms as a sensitive method to detect small changes in the biochemical structures that accompany the onset of AD and DLB using a straightforward peripheral blood test. White blood cells and plasma from 56 individuals - 26 controls, 20 AD patients, and 10 DLB patients - were measured using IR microscopy, and the measured spectra were analyzed using a support vector machine. Our encouraging results show that it can distinguish between dementia (AD and DLB) and controls with a success rate of 86%, and yields a success rate higher than 93%, to discriminate between DLB and AD patients. The encouraging success of this method enables us to suggest a novel, simple, and useful tool for mental health practitioners that can improve the precision and objectivity of diagnoses of AD and DLB.

Impact of Patient Demographics and Insurance Status on Recommendation for Surgery in Glioblastoma: A Retrospective Cohort Study

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Abstract

Background: Glioblastoma multiforme (GBM) is the most aggressive type of primary central nervous system cancer. The decision to recommend surgery for GBM depends on multiple patient- specific factors. This study examined whether demographic factors and health insurance status had an impact on recommendation for surgery in adults with GBM in the United States.

Methods: Patients with GBM were identified from the surveillance, epidemiology, and end results (SEER) database, a large US population-based cancer registry. Adult patients ≥ 18 years of age with GBM diagnosed between 2011 to 2015 were included in this study. Pearson's chi-square test and two-sample t test were used to analyze data. Statistical analyses were performed on SAS Studio software package.

Results: A total of 14,039 patients met eligibility for analysis, a majority of whom were male (N = 8,160; 58.12%) and White (N = 12,493; 88.99%). The mean age of diagnosis was 64.05 (SD ± 13.17) years. Most patients (N = 11,077; 78.9%) were offered surgery for their cancer. Older patients were less likely to be offered surgery (69.8 vs 62.5 years, $p < 0.001$). Patient sex ($X2 = 0.822, 1, p = 0.365$) and health insurance status ($X2 = 2.250, 1, p = 0.134$) had no impact on recommendation for surgery. Most patients died from GBM or its neurologic complications (N = 8,992; 64.05%).

Conclusion: Patient age was associated with recommendation for surgery in patients with GBM. Despite the healthcare access disparities encountered by uninsured patients, they were just as likely to be offered surgery as patients who were insured.

Heritable Effects of Moderate Traumatic Brain Injury in Rats

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Abstract

Introduction: Epidemiological studies find that children of parents with Traumatic Brain Injury (TBI) are more likely to develop psychiatric disorders. Such transmission is often assumed to result from TBI induced changes in parental personality or family dynamics - i.e., "social transmission" of the effects of TBI; however, observations that abnormalities are not only more profound in male offspring but also depend on whether the father or mother was affected by TBI1 indirectly support the possibility of a biological mode of intergenerational transmission of parental TBI effects. Depending on whether an individual or both modes of transmission are involved, different preventive strategies may be needed to alleviate adverse neurocognitive outcomes in offspring. The respective roles of biological vs. social factors in inherited effects of parental conditions can be challenging to disentangle in humans but can be readily assessed in male rats, as the sires' contribution is limited to conception. Therefore, we used young adult male rats to test the hypothesis that biological transmission is involved in mediation of intergenerational neurobehavioral effects of a moderate TBI.

Methods: Postnatal day 60 (P60) male Sprague-Dawley rats (F0 generation) in the TBI group underwent moderate TBI via a midline fluid percussion injury that involved craniectomy (surgery) and exposure to 3% sevoflurane (SEVO) for 40 min (the TBI group). F0 rats in the control group were placed in a new cage, one per cage, for the equivalent time duration. A subset of F0 rats was sacrificed on P66 to assess acute changes in hypothalamic pituitary adrenal (HPA) axis and inflammatory markers. The remaining F0 males were mated with naive females on P90 to generate offspring (F1 generation). The F0 males and F1 males and females were subsequently evaluated in the elevated plus maze, for prepulse inhibition of acoustic startle, in the Morris water maze, and for resting and stress levels of serum corticosterone starting on ~P105 (F0) and ~P60 (F1), followed by tissue collection for further analyses.

Results: Six days after TBI induction, the F0 TBI males had alterations in mRNA transcripts consistent with an increased hypothalamic and hippocampal Na^+ - K^+ - Cl^- (Nkcc1) Cl^- importer/K^+ ± $2Cl^-$ (Kcc2) Cl^- exporter ratio and decreased hippocampal glucocorticoid receptors (Gr), as well as increased serum levels of corticosterone, interleukin-1β (IL-1β), and biomarkers of activated hippocampal microglia and astrocytes. The F0 TBI males also exhibited persistent increases in corticosterone concentrations at rest and under stress, anxiety-like behavior, impaired sensory-motor gating, and impaired spatial memory. These abnormalities were underpinned by elevated serum levels of IL-1β, reduced mRNA levels of hypothalamic and hippocampal mineralocorticoid receptors (Mr), hippocampal Gr, and hypothalamic brain-derived neurotrophic factor (Bdnf). F1 male offspring of TBI sires exhibited similar behavioral abnormalities, whereas F1 females appeared less affected. F1 male, but not female, offspring also had reduced mRNA levels of hippocampal Mr, and Gr, as well as hypothalamic and hippocampal Bdnf.

Conclusions: These findings in rats suggest that offspring of sires with a history of moderate TBI are vulnerable to neurobehavioral deficiencies, independent of social interaction with the TBI-affected sires. Because our TBI model involved surgery under sevoflurane anesthesia, our findings in rats suggest that young adults with moderate TBI are vulnerable to accelerated neurocognitive decline after surgery/general anesthesia (i.e., perioperative neurocognitive disorder), as are their future offspring.

Identifying Delay in Glymphatic Clearance of Labeled Protons Post-acute Head Trauma Utilizing 3D ASL MRI (Arterial Spin Labeling): A Pilot Study

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Rich, Connor James Arrasmith, Ian Shepherd Dorman, Bradley Waman Clark, Kim Love, Ben Ferry and Mark E. Rolfs

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Abstract

Background: Concussive brain injury (CBI) disrupts the blood brain barrier (BBB), reducing capillary mean transit time (CMTT) and glymphatic clearance rates (GCR). Mild CBI, however, is currently diagnosed clinically using subjective questionnaires and exam findings. This case-controlled study aims to correlate ASL-MRI GCR with cognitive changes post-acute CBI and determine if GCR improves with clinical recovery.

Methods: 3D TGSE (turbo-gradient and spin echo), pulsed arterial spin labeling (PASL) 3T MRI with 7 long TI's (time to inversion) assessed GCR of labeled protons and the subsequent post-labeled protons at 2800 - 4000 MS in bifrontal, bitemporal, and biparietal regions, within 1 week of CBI and a second study when declared clinically recovered. Sport concussion assessment tool version 5 (SCAT 5) and brief oculomotor/vestibular assessment (VOMS), administered by sports physicians, evaluated injured student athletes' cognitive function prior to ASL MRIs.

Results: Pilot study demonstrated GCR improvement in frontal lobes (95% [CI] -0.06 to -0.03 acute; [CI] - 0.0772 to -0.0497 recovery; p and lt; 0.001) and in parietal regions (95% [CI] -0.0584 to -0.0251 acute; [CI] - 0.0727 to -0.0392 recovery; p = 0.024) at clinical recovery compared to acute injury in 9 subjects (8 female, 1 male, mean age 20). Six age/ activity matched normal controls (4 female, 2 male mean age 22) were also compared.

Conclusion: Acute head trauma disrupts the BBB reducing GCR measured using this 3D ASL MRI technique. ASL MRI is a potentially noninvasive biomarker of acute brain injury and subsequent recovery.

Action of Inflammation and Oxidative Stress in Neural Cells in Primary Culture, APP/PS1 Mice and in aMCI Patients: Treatments in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative illness with prevalence. The presence of amyloid plates, hyperphosphorylation of TAU and inflammation are characteristic. Using neural cells in primary culture (induced by Aβ), APP/PS1 mice (animal model of AD) and patients with amnesic mild cognition impairment (aMCI), we determined the changes in inflammation, cell death and signalization. The expression of chemokines, chemokines receptors, PPAR-γ, COX-2, iNOS, ERK, p-ERK, and other MAPK, cell death (apoptosis and necrosis) compared with control samples where higher compared with control cells. Furthermore, using different drugs to revert the changes occurred in the cells treated, we demonstrated a decrease in inflammation and cell death compared with control neural cells. Using the transgenic mice, APP/PS1 we showed a decrease or increase depending on the proteins analyses, compared with control mice. MCI patients present an alteration of cognitive function, and the illness is considered a precursor to AD. Vascular dysfunction is present in AD with affectation in mitochondria functionality. Despite the existing therapeutic alternatives, none of them have shown benefits, which is why new treatments are needed. Transcranial laser stimulation (TLS) activates cellular processes that improve vascular irrigation. Randomized, controlled, single-blind clinical trial for one week, carried out in the neurology service in Valencia (30 patients with aMCI), showed that 15th TLS group and 15th control group, presented differences after neuropsychologic test. Patients suffered no harm in health after using ETL and less development of the illness compared with aMCI control. Future studies will be needed to treat these patients.

Inflammation, Oxidative Stress and Cancer Protein Expressions in a Model of Alzheimer's Disease

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Abstract

A model of Alzheimer's disease (AD), APP/PS1transgenic mice, is used to demonstrate changes in the amyloid deposition studies in AD. Using Western-blot, and microarray techniques from 7 month cortex mice, we assay inflammation and oxidative stress mechanisms. Expression of 98 genes was analyzed demonstrating an increase of inflammation proteins in APP/PS1 compared to wild type mice. Our results demonstrated that the expression of inflammation proteins was higher in APP/PS1 compared to Wild type mice. At two old age transgenic mice, they developed cognitive dysfunction and reduced mRNA expression of several genes essential for long-term potentiation and memory formation. NMDA receptor, Sir-2, Mn-SOD, Cu/Zn-SOD, ERK1/2, NF-kB and PPAR-γ. Furthermore, we noted normal expression of genes related to cancer disease in transgenic mice compared to wild type mice with 7 month old age. In conclusion, APP/PS1 mice has an increase in chemokines and cytokines mediators' protein expressions related to inflammation state. Moreover, these mice present a diminished protein expression of cancer related genes demonstrating the imbalance between Alzheimer and cancer diseases.

Inflammation and Oxidative Stress after Aβ1-42 Addition and Effects of Ranolazine and/or Insulin in Astrocytes in Primary Culture

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Abstract

Ranolazine (Rn) is a compound derived from piperazine and with an innovative mechanism of action. It is used in the treatment of chronic coronary ischemia and has been shown to have beneficial effects on the central nervous system. The addition of the toxic peptide Aβ1-42 produced a decrease in astrocytes viability and proliferation. The purpose of this study was to investigate whether Rn could enhance the effects of insulin (Ins) in astrocytes in primary culture, after the addition of AB1-42 (10 μM) and Rn y/o Ins. Rn (10^{-6} μM, 10^{-5} μM, 10^{-4} μM, 10^{-3} μM) and/or Ins (10^{-8} μM, 10^{-7} μM, 10^{-6} μM, 10^{-5} μM, 10^{-4} μM, 10^{-3} μM) were added to cell cultures. The results showed that the concentration of 10^{-6} of Rn and 10^{-8} of Ins were the most appropriate concentration to detect changes with respect to control cells. Subsequently, using these concentrations, inflammatory and oxidative stress proteins were measured. Our results demonstrate that Aβ1-42 (24 h) decreased cell viability and proliferation. Addition of Rn and/or Ins during 24 h after addition of toxic peptide, increase in viability and proliferation were detected. Rn causes an increase in the expression of p-AKT, PI3K, NF-KB, PPAR-γ, p-ERK and p-JNK proteins, demonstrating an induction of the signaling pathway protection and short time increase in inflammation. Looking for changes in oxidative stress, we determined iNOS, COX^{-2}, Mn-SOD and Cu/Zn-SOD and detected increase of oxidative stress after toxic peptide addition. Ins +Rn decreases significantly oxidative stress proteins in astrocytes in primary culture.

Health Qigong Exercise on Inhibitory Function in Parkinson's Patients

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Abstract

Background and Purpose: Parkinson's patients often experience abnormal decline in executive function under the influence of the disease, primarily manifested as inhibitory function deterioration, leading to difficulties in controlling emotions and maintaining attention in daily life. Therefore, this study explores the impact of health qigong exercise as an intervention on inhibitory function in Parkinson's patients, aiming to mitigate the rate of inhibitory function decline.

Methods: Using experimental methods, a total of 28 participants who met the inclusion criteria were recruited, with 14 assigned to the experimental group (n = 14) and 14 to the control group (n = 14). Both groups received standard pharmacological treatment, with the experimental group additionally undergoing a 12 week health qigong exercise program consisting of three

sessions per week, each lasting 60 min, while the control group maintained their usual lifestyle and medication routines without intervention. Before and after the experiment, both groups of participants underwent the odder shifting test.

Results and Discussion: Highly significant difference indicator ($p < 0.01$): The accuracy rate in the test for the experimental group. Significant difference indicator ($p < 0.05$): The reaction time in the test for the experimental group. No statistically significant difference indicator ($p > 0.05$): Both the accuracy rate and reaction time in the test for the control group.

Conclusions: Health qigong exercise can enhance inhibitory function in Parkinson's patients, resulting in improved emotional stability and higher levels of focus to complete tasks, thereby improving their quality of life.

Insulin and Ranolazine Protective Action after Rotenone Addition on Nsc34 Motor Neuron Cells (Model of Parkinson's Disease)

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Abstract

Rotenone is a natural flavonoid from tropical legumes used as a pesticide since its discovery in the 19th century. The prevalence of Parkinson disease has been demonstrated increased in the farmers population after their crop's treatment with Rotenone. The isoflavone produced a mitochondria inhibition, α-synuclein accumulation or alteration, dopaminergic neurons destruction and decrease in dopamine neurotransmitter, damaging the brain neurons associated with movement. Furthermore, there is a clear link between the pathogenesis of Parkinson's disease and the mechanisms underlying the development of insulin resistance. Studies have found that these patients are prone to insulin resistance, even without being affected by diabetes mellitus. Preclinical studies and animal studies showed good neuroprotective effects when applying insulin or analogues, preventing neurodegenerative processes, and improving neuronal and synaptic functionality. On the other hand, different studies indicate that ranolazine behaves as an adrenergic antagonist, which could explain its anti-inflammatory, antioxidant, and metabolic effects, especially its antidiabetic effects as we demonstrated before. Due to the high prevalence of Parkinson's disease and its relationship with insulin resistance, this project aims to study the Ranolazine and/or insulin effects on NSC34 motor neuron cells after rotenone addition. Our results demonstrate that incubation with rotenone decreases cell viability, mitochondria, and lysosome number. Ranolazine and/or insulin increase cell viability (MTT assay), mitochondria-genesis and lysosome-genesis (detected by confocal microscopy), p-AKT/AKT and p-I3K/tubulin (Western-blot) protecting neuron cells from rotenone toxic action.

Delving into Oxidative Signaling in Parkinson's Disease, Unveiling Intricate Pathways and Novel Pleiotropic Therapeutic Avenues

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Abstract

To date there are no therapeutic strategies that limit the progression of Parkinson's disease (PD). The intricate mechanisms underlying PD-related neurodegeneration, particularly in the nigrostriatal pathway, are not fully elucidated, involving various modulating factors. Our prior investigations highlighted oxidative stress as a pivotal factor exacerbating multiple pathogenic responses in PD. In light of this, we explored a promising therapeutic avenue employing a clinically safe, multi- target agent, 10-nitro-oleic acid (10-NO_2-OA), known for its metabolic and inflammatory modulation properties, in a rat model of PD. 10-NO_2-OA demonstrated activation of Nrf2 regulated gene expression while concurrently inhibiting hyperactivation of NOX2 and LRRK2, oxidative stress, microglial activation, α-synuclein modification, and subsequent mitochondrial import impairment, with a resultant prevention of motor impairment and nigrostriatal protection. These findings delineate the broad neuroprotective effects of 10-NO_2-OA in PD models, suggesting its potential as a therapeutic candidate warranting further investigation. The pleiotropic action of 10-NO_2-OA, targeting multiple pathological events, signifies a promising approach for

attenuating or halting PD progression. Further research into the efficacy and safety of 10-NO_2-OA could pave the way for novel therapeutic interventions in PD.

Effect of Health Qigong Exercises on Cardiovascular Symptoms in Patients with Parkison's Disease

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Abstract

Background and Purpose: Cardiovascular autonomic dysfunction is a common symptom in PD, leading to cardiovascular manifestations such as abnormal heart rate, which can result in a decline in overall symptoms and deterioration in quality of life. Therefore, this study intervened with health qigong in patients with mild to moderate cardiovascular autonomic dysfunction to validate the intervention effect of health qigong on cardiovascular symptoms in PD patients.

Methods: A total of 34 subjects meeting the criteria were recruited, divided into a Parkinson's cardiovascular exercise program group (n = 18) and a Parkinson's blank control group (n = 16). Both groups received routine drug treatment without additional medication. The cardiovascular exercise program group underwent a 12 week program, exercising five times a week, each session lasting for 60 min. The blank control group did not engage in exercise. Data were collected before and after the experiment, followed by data sorting and analysis after the experiment.

Results and Discussion: Before and after the experiment intervention, the two groups were compared, showing significant differences at weeks 6 - 7 and after week 12 ($p < 0.01$); indicating improvement in cardiovascular symptoms of PD patients after 12 weeks of exercise, with a significant effect of the cardiovascular intervention program.

Conclusions: Abnormal heart rate is a common phenomenon in PD and is an important predictor of cardiovascular morbidity and mortality. Through Health qigong cardiovascular exercise programs can effectively intervene in the occurrence of this factor. It reduces the risk caused by cardiovascular autonomic dysfunction and improves the quality of life of Parkinson's patients.

Effect of Health Qigong Exercises on Range of Motion in Patients with Parkison's Disease

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Abstract

Background and Purpose: Parkinson's disease is a psych systemic disorder that causes symptoms such as muscle stiffness and slowed movement, which often limit range of motion in patients. Joints are the main joints that affect the body's mobility. Therefore, this study explores the effect of health qigong exercise as an intervention on range of motion in Parkinson's patients.

Methods: A total of 23 participants who met the inclusion criteria were recruited, were randomly divided into the experimental group (n = 12) and the control group (n = 11). Both groups received standard pharmacological treatment, the experimental group additionally received 12 weeks of health qigong exercise, three times a week, lasting 60 min each time; the control group maintained a normal lifestyle with no exercise intervention. Before and after the experiment, all people in both groups underwent a range of motion tests. At the end of the experiment, the data were collated and analyzed.

Results and Discussion: Before and after the experimental intervention, there were significant difference in both shoulder and right hip flexion in the experimental group ($p < 0.05$); there were no statistically significant difference in the control group, but the range of motion showed a decreasing trend. At the end of the intervention, the experimental group and the control group had highly significant differences in right hip flexion ($p < 0.01$).

Conclusions: Health qigong can improve the shoulder, hip, and knee range of motion of Parkinson's patients, thus improving the range of motion of Parkinson's patients and improving their quality of life.

Switching of the Default Mode Network is Different in Episodic and Chronic Migraine: Implications for Chronification

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Abstract

Background: Switching from eyes closed (EC) to eyes open (EO) during the resting state induces a change in the patterns of functional connectivity (FC) in healthy subjects. The switch results in reduced integration and greater modularity or specialization within neural networks.

Objective: Our aim was to investigate whether EC and EO brain network dynamics differ in patients with episodic migraine (EM) and chronic migraine (CM).

Methods: 51 women with EM (mean age ± SD 46.2 ± 7.8), 51 women with CM (mean age ± SD 45.9 ± 8.4) and 33 healthy matched women (mean age ± SD 43.7 ± 9.8) underwent resting- state functional magnetic resonance imaging (fMRI) scans on a GE 3.0T MRI system. Brain wise FC of the main hubs of the visual network (VN, primary, ventral, right-dorsal, and left-dorsal visual cortices) was investigated through a seed-based fMRI analysis.

Results: When switching from EC to EO, patients with CM showed a more pronounced fall in FC between the medial VS and the following three DMN hubs: frontal poles and paracingulate gyri (XYZ MNI coordinates -06 + 58 +14 mm; size 2.34 ml; peak T 5.36), left lateral occipital cortex and angular gyrus (XYZ MNI coordinates -40 + -62 + 16 mm; size 1.80 ml; peak T 5.11) and cingulate gyrus, posterior division, and precuneous (XYZ MNI coordinates -06 + -44 + 34 mm; size 1.42 ml; peak T 4.11).

Discussion: CM patients might tend to allocate their attention in a bottom-up or stimulus- driven manner. This would chronically lead to an increased distraction by task-irrelevant information and a more pronounced brain functional segregation, even during rest.

Iron-free Transferrin Improves Sensory Function in an Experimental Model of Intracerebral Hemorrhage

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Abstract

We have previously demonstrated that the post-stroke administration of iron-free transferrin (apo transferrin, ATf) is beneficial in different models of ischemic stroke (IS) through the inhibition of neuronal uptake of pro-oxidant iron. In this study, we investigated whether ATf is safe and beneficial given after the induction of intracerebral hemorrhage (ICH) in mice, and the underlying mechanisms. ICH was induced by striatal collagenase injection, and vehicle or human ATf was administered intravenously 40 min later. Body weight and neurological status were assessed 24, 48 and 72 h post-ICH induction. Hemorrhage volume, brain levels of active caspase-2, and iron-related mRNAs/proteins were measured 72 h after the treatment. Human ATf (hATf) treatment progressively improved the neurological impairment caused by ICH and attenuated the ICH-induced increase in mouse transferrin mRNA levels and active caspase-2, whereas it decreased levels of ferroptosis markers transferrin receptor (TfR) and 4-hydroxynonenal, and restored mRNA levels of the recently recognized cytosolic iron chaperone poly (RC) binding protein 2. Treatment with a single hATf dose reduced blood transferrin saturation in blood for at least 24 h; the hATf was still present in the brain 72 hours later. All that despite hATf did not alter hemorrhage volume or levels of classical ferroptosis GPX4/system xc- pathways. In conclusion, hATf treatment provides neurobehavioral benefits post-ICH associated to modulation of ferroptosis players. The beneficial effect of a single hATf dose shortly after the onset of ICH suggests that ATf might be a pre-hospital frontline safe treatment for IS and ICH before an accurate in-hospital differential diagnostic.

CT Perfusion in Acute Ischemic Stroke and its Overestimation and Underestimation of the Penumbra

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Abstract

Background and Aims: CT perfusion used in acute ischemic stroke to differentiate between ischemic core and ischemic penumbra. Our aim is to review cases of acute ischemic stroke when CTP showed over and underestimation of the penumbra or the infarct core and try to explain its likely causes.

Methods: We review June 2023, who were presented with acute ischemic stroke-like symptoms between April and June 2023 the imaging was reviewed by a stroke physician and confirmed by a neuroradiologist.

Results: We reviewed 51 patients between April, May and June 2023, there were 13 cases with overestimation of the penumbra and 2 cases with under estimation of penumbra. CTP was not completed in 4 patients, there were no mismatch in CTP in 20 patients, 12 CTP showed no mismatch and the following imaging including MRI brain showed no evidence of stroke, they were treated as mimics with seizure, functional neurological disorder and migraine being the common causes. 8 CTP showed no mismatch and the following imaging showed evidence of stroke.

Conclusions: Penumbra overestimation may occur in early and fast reperfusion; it can also happen in hemodynamic fluctuation at the time of imaging acquisition. There are various causes for CTP penumbra underestimation including partial reperfusion/clot migration, collateral improvement despite persistent occlusion, severe hypodensity marked as CSF space, poor contrast to noise ratio, and incomplete brain coverage of CTP slabs.

Factors Influencing Communication and Language Skills in Multiple Sclerosis

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Abstract

A clinical study aiming to identify which factors could potentially influence communication and language skills in individuals with multiple sclerosis (MS). For this study, 100 individuals with MS were recruited (43 males, 57 females), 73 individuals with relapsing-remitting MS (RRMS), 18 individuals with primary progressive MS (PPMS), and 9 individuals with secondary progressive MS (SPMS). Both demographic (age, sex) and clinical characteristics (MS subtype, EDSS score, disease duration) were collected. For the assessment of communication and language skills, communication, and language assessment in MS (CLAMS) was used. Cognitive function and depression were examined as potential factors. For the assessment of cognitive function, the brief international cognitive assessment for MS (BICAMS) was administered, including the symbol digit modalities test (SDMT), the Greek verbal learning test (GVLT), and the brief visuospatial memory test-revised (BVMT-R). For the assessment of depression, the Beck depression inventory fast screen (BDI-FS) was used. According to the statistical analysis, there was no significant difference identified between CLAMS scores in the different MS subtypes, and there was no correlation found between CLAMS and EDSS scores. However, negative correlations between CLAMS scores and BICAMS subtests were identified: SDMT (r: -0.2582; p: 0.0095), GVLT (r: -0.3582; p: 0.0003) and BVMT-R (r: -0.4607; p: < 0.0001). On the other hand, a positive correlation between CLAMS scores and depression was revealed (r: 0.6615; p: < 0. 0001). These results highlight the effect of cognitive and psychological factors on communication and language skills in individuals with MS. Limitations include small PPMS and SPMS subgroups.

Insecticide and Herbicide Urinary Metabolites in Relation to Neurobehavioral Performance in Ecuadorian Adolescents

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Abstract

Background: Insecticides, such as organophosphates and pyrethroids, impact children's neurobehavioral development, with limited evidence among adolescents. Herbicides, such as glyphosate and 2,4-D are widely used in agriculture but there is little epidemiological data on their neurobehavioral effects. Our study explores the links between urinary pesticide concentrations and neurobehavioral performance in adolescents from agricultural communities in Ecuador.

Methods: The study involved 522 participants aged 11 - 17 years in 2016. Mass-spectrometry measured urinary insecticide and herbicide metabolites, and neurobehavior was assessed through NEPSY-II (domains: attention/inhibitory control, language, memory/learning, visuospatial processing, social perception). Associations were examined using generalized estimating equations. Models adjusted for creatinine, demographic, anthropometric, and socioeconomic factors.

Results: The mean of each neurobehavioral domain score was between 7.0 and 8.7 (standard deviation range: 2.0 - 2.3). Herbicides: 2,4-D was negatively associated with all neurobehavioral domains, but especially with attention/inhibition (score difference per 50% higher metabolite concentration [β] = -0.19 (95% CI: -0.31, -0.07), language (β = -0.12 (-0.23, -0.01)) and memory/learning (β = -0.11 (-0.22, 0.01)). Organophosphates: 3,5,6-Trichloro-2-pyridinol (TCPy) was inversely associated with language (p = -0.11 (95% CI: -0.50, -0.02)) and para-nitrophenol (PNP) was inversely associated with social perception (p = -0.26 (95% CI: -1.07, -0.20)). Pyrethroids: 3-phenoxybenzoic acid (3-PBA), was inversely associated with language (p = -0.11 (95% CI: -0.48, -0.05)) and had a negative curvilinear association with attention/inhibitory control (p < 0.01). These associations did not differ by gender.

Conclusions: This study describes worse neurobehavioral performance associated with herbicide and insecticide exposures in adolescents; particularly with 2,4-D, and to some extent with organophosphate and pyrethroid metabolites. Replication studies among other pediatric and adult populations are needed.

Necessity of Multisensory Therapy in Children with Autism Spectrum Disorders

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Abstract

The aim of the current study was to improve the role of multisensory therapy in autism spectrum disorder (ASD) correction. Results help making recommendations about development efficiency. Retrospective quantitative research. Analyzed patient's parent's questionnaires and conclusions from psychiatrists. 2 - 5 years old children 72 with ASD, 28 healthy. After different types of therapy development has improved. Patient's abilities increased by 17 - 65%, depending on therapy type. Some children without therapy showed degradation. Starting study 16% of healthy children had developmental problems and only 9% showed results better than age norms. 3% of ASD patients showed results near age norms. In 6 months, development was improved only in 40% of study participants. There is no conflict of interest. Results are part of another study: "Development measurement for children with speech disorders."

The Effects of Postnatal Erythropoietin and Nano-erythropoietin on Behavioral Alterations by Mediating K-Cl co-transporter 2 in the Valproic Acid-induced Rat Model of Autism

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Abstract

Introduction: In this study, based on the excitatory/inhibitory imbalance theory of autism, the time window of GABA switch, the role of K-Cl co-transporter 2 (KCC2) in adjustment GABA switch, and brain permeability to erythropoietin (EPO), the effects of postnatal-EPO and-nano-erythropoietin (NEPO) have been evaluated in the valproic acid (VPA) rat model of autism.

Materials and Methods: VPA were administered for animal modeling of autism at gestational day (GD) 12.5 (600 mg/kg). Male offsprings were injected with EPO and NEPO in a clinically proper postnatal dosing regimen on postnatal days (PND) 1-5, and autistic-like behaviors were tested at the end of the first month. Then animals were sacrificed, and neuron morphology and KCC2 expression were examined by Nissl staining and Western blot.

Results: According to our findings, high-dose NEPO improved autism-associated phenotypes. Neuroprotective effects of EPO and NEPO have been shown in the hippocampus. Postnatal NEPO treatment reversed KCC2 expression abnormalities induced by prenatal VPA.

Conclusion: Our results might support the role of KCC2 in ASD and the excitatory/inhibitory imbalance hypothesis. We suggested nano-erythropoietin and other KCC2 interventions as a new approach to the early treatment and prevention of autism.

Training Attention and Cognitive Control Among Individuals with ADHD

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Abstract

Attention and executive control play a significant role in different types of learning, school readiness and academic achievements. Studies have shown that attention is greatly malleable and can be improved by training. Several studies have evaluated the benefit of cognitive treatments aimed at improving attention and cognitive control in children with attention deficit/hyperactivity disorder (ADHD), as well as in children on the autism spectrum. Although several studies did not find generalization effects, more recent studies, which targeted simple attention and/or cognitive control functions (such as, sustaining attention over a long period of time, maintaining information in working memory) showed encouraging effects. In my talk I will present data from several studies that have used the computerized progressive attention training program (CPAT) developed in my lab, in various populations, all of which characterized with attention difficulties. In summary, attention/cognitive training as induced in different programs targeting specific neural systems mediating attention, for children with developmental disorders, has a promising potential to improve a variety of cognitive mechanisms and to boost academic outcomes which in turn, may contribute to better self-efficacy and self-fulfillment. However, to achieve this imperative challenge it is essential to implement theory driven and evidence-based interventions, to consolidate the link between the targeted cognitive mechanisms and the everyday functions we would like to enhance, which is crucial to maximize near and far transfer effects.

Astrocyte Responses to Postnatal Erythropoietin and Nano-erythropoietin Treatments in a Valproic Acid-induced Animal Model of Autism

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Abstract

Background: Despite ample evidence of the potential protective effects of erythropoietin (EPO) on the developing brain, no study has addressed the effects of postnatal EPO on behaviors and brain tissue of animal models of autism. In the present study, we examined the therapeutic effects of postnatal EPO on stereotypic behaviors and astrocyte responses via glial fibrillary acidic protein (GFAP) and S100 calcium-binding protein B (S100B) immunohistochemistry in a valproic acid (VPA) animal model

of autism. Also, we compared the effects of EPO with EPO-loaded solid lipid nanoparticles (NEPO) because the blood-brain barrier has limited permeability to EPO.

Methods: Pregnant rats received a single dose of VPA (600 mg/kg) at gestational day 12.5. EPO (2000 U/kg) and EPO-loaded solid lipid nanoparticles (NEPO1000 and 2000 U/kg) were injected intraperitoneally from postnatal days 1 - 5. Repetitive behaviors in male offspring were assessed by a marble burying test. The immune-staining method was performed to evaluate S100B and GFAP-positive cells in the prefrontal cortex and hippocampal CA1 region.

Results: VPA animal models revealed more repetitive behavior and displayed higher astrogliosis in the prefrontal cortex (PFC) and hippocampus (CA1) regions. The repetitive behaviors were ameliorated relatively in VPA groups with NEPO2000 treatment, and astrogliosis was reduced even when VPA rats were treated with a lower dosage of NEPO.

Conclusion: Our results indicate beneficial effects of postnatal NEPO exposure in the VPA animal model of autism, which proposes it as an early treatment in infants with, or at risk of, autism.

Prevention of Cognitive Decline in Alzheimer's Disease by Novel Antioxidative Supplements

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Abstract

Alzheimer's disease (AD) involves multiple pathological factors such as amyloid plaque formation, mitochondrial dysfunction, and telomere shortening; however, oxidative stress and diabetes mellitus are significant risk factors. Preventing AD or using an effective treatment at an early stage is important. Twendee X® (TwX) is an antioxidant formulation consisting of eight ingredients. TwX has been proven to prevent the progression of dementia in patients with mild cognitive impairment (MCI) in a multicenter, randomized, double- blind, placebo controlled, prospective intervention trial. As well, positive data has already been obtained in several studies using AD model mice. Since both diabetes and aging are risk factors for AD, we examined the mechanisms behind the effects of TwX on AD using the spontaneous hyperglycemia model and the senescence model of aged C57BL/6 mice in this study. TwX was administered daily, and its effects on diabetes, autophagy in the brain, neurogenesis, and telomere length were examined. We observed that TwX protected the mitochondria from oxidative stress better than a single antioxidant. TwX not only lowered blood glucose levels but also suppressed brain neurogenesis and autophagy. Telomeres in TWX-treated mice were significantly longer than those in non-treated mice. There are many factors that can be implicated in the development and progression of dementia; however, multiple studies on TwX suggest that it may offer protection against dementia, not only through the effects of its antioxidants but also by targeting multiple mechanisms involved in its development and progression, such as diabetes, brain neurogenesis, telomere deficiency, and energy production.

Physical Frailty Trajectories in Older Stroke Survivors: Findings from a National Cohort Study

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Abstract

Background: To identify the different clusters of trajectories of physical frailty and its determinants in older stroke survivors.

Methods: Data were derived from the National Health and Aging Trends Study from 2015 to 2021. Physical frailty is operationally assessed by the physical frailty phenotype. Trajectories were identified by group-based trajectory modeling.

Results: A total of 663 were finally included in the trajectory modeling in the current study accounting for the full sample design. Most of the included old stroke survivors were middle-old/oldest-old (63.32%), female (53.99%), and White (80.54%). More than 30% of older stroke survivors reported breath problems. Two trajectory groups were identified (Group1: Low risk, robust; 49.47%; Group2: High risk, deteriorating; 50.53%). Individuals were more likely to be assigned to the high-risk and deteriorating group if they were middle-old (adjusted odds ratio (aOR: 2.16, 95% CI: 1.23 - 3.80) or oldest-old (aOR: 2.77, 95%

CI: 1.52 - 5.04), with fair self-reported health (aOR: 2.78, 95% CI: 1.53 - 5.07) or poor self-reported health (aOR: 3.37, 95% CI: 1.51 - 7.52); with comorbidities (aOR: 8.44, 95% CI:1.31 - 54.42), with breath problems (aOR: 2.18, 95% CI: 1.18 - 4.02) and balance problems (aOR: 1.70, 95% CI: 1.06 - 2.73).

Conclusions: The trajectories of physical frailty in older stroke survivors were different and affected by age, self-rated health status, comorbidities, breath problems, and balance problems. Early routine dynamic screening on stroke-related physical frailty and its risk factors might be beneficial for identifying the most vulnerable individuals. Both health professionals and older stroke survivors should engage in strategies to manage the progression of physical frailty.

Research on the Effect of Heart-lung Benefiting Tai Chi on Negative Emotions in College Students

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Abstract

With the development of the times, the issue of college students' mental health has been highly valued by the state. College students with healthy mental health can develop themselves better and improve their quality for individuals; for the society, they can inject fresh blood and reserve excellent talents, which can promote the development of the society and the prosperity of the country. College students are in the stage from late adolescence to early adulthood, and they begin to deal with things independently, but their mental state is in the semi-mature stage, so their emotional state fluctuates a lot, therefore, exploring the factors influencing the negative emotions of college students by heart-lung benefiting Tai Chi has an important reference value for them to have a healthy mental state. The purpose of this study is to investigate the effects of heart-lung benefiting Tai Chi on college students' negative emotions. College students with a total score of more than 20 on the negative emotions scale (PANAS) were selected as the target group, and heart- lung benefiting Tai Chi was performed three times a week for 90 min for 12 weeks, and PANAS and HRV were also tested. The results showed that tai chi for strengthening the heart and lungs had a favorable effect on negative emotions.

Marula Oil Nanoemulsion Improves Motor Function in Experimental Parkinsonism via Mitigation of Inflammation and Oxidative Stress

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Abstract

Introduction: Parkinson's disease (PD) is a neurologic condition exhibiting motor dysfunction that affects old people. Marula oil (M-Oil) has been used longley in cosmetics and curing skin disorders. M-Oil is particularly stable due to its high concentration of monounsaturated fatty acids and natural antioxidants. The current study formulated M-Oil in an o/w nanoemulsion (M-NE) preparations and tested its anti-inflammatory and antioxidant actions against experimental parkinsonism.

Methods: Four experimental groups of male albino mice were used and assigned as vehicle, PD, PD + M-Oil and PD + M-NE. Locomotor function was evaluated using the open field test and the cylinder test. Striatal samples were used to measure inflammatory and oxidative stress markers.

Results: The results indicated poor motor performance of the mice in PD control group then, improvements were recorded after treatment with crude M-Oil or M-NE. In addition, we found high expression and protein of inflammatory markers and malondialdehyde levels in PD group which were downregulated by using doses of crude M-Oil or M-NE. Hence, formulating M-Oil in form of M-NE enhanced its physical characters.

Discussion: This finding was supported by enhanced biological activity of M-NE as anti-inflammatory and antioxidant agent that resulted in downregulation of the inflammatory burden and alleviation of locomotor dysfunction in experimental PD in mice.

What is the Foix-Alajouanine Syndrome?

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Abstract

The Foix-Alajouanine syndrome is the subacute spinal vasculitis of viral origin described in 1926 by Foix and Alajonanine. In this connection non-specific body response to viral infection affects spinal arteries, leading to rapidly progressive myelopathy. There is a huge misunderstanding of Foix-Alajouanine syndrome. Numerous authors describe myelitis under this name caused either by arteriovenous malformation or thrombosis. However, both lesions were excluded by Foix and Alajouanine. The aim of our study is to elucidate the real etiology of the sporadic subacute disease of motor neuron in the 41 year old male patient. His clinical examination has revealed flaccid tetra paresis. Diaphragm strength is sharply reduced, breathing with the help of the ventilator. EMG has detected the signs of motor neuronal damage at the bulbar, cervical, and lumbar levels, more pronounced at the lumbar level. To study spinal MR angiography and spinal MR tractography were used. Spinal MR tractography has revealed lateral columns to be intact, which excluded amyotrophic lateral sclerosis. Spinal MR angiography has detected narrowing and tortuosity of spinal arteries, as well as the occlusion of the right twelfth intercostal artery. Meanwhile a generalized skin eruption in the form of erythematous rings testified the presence of coronavirus-19 infection. Thus, we presume that subacute myelopathy in our patient refers to Foix-Alajouanine syndrome. Our presumption is supported by the patient's immunogram, which revealed reduced antiviral immunity in the form of an imbalance of T and B lymphocytes with natural killers' deficiency and B lymphocytes (CD3 + CD19 + CD45) redundancy.

Illness Perceptions and Outcome in Multiple Sclerosis: Dissemination of the Findings from a Published Systematic Review

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Abstract

This talk will disseminate the findings of my published work titled "Illness perceptions and outcome in multiple sclerosis (MS): A systematic review of the literature". The cognitive appraisals regarding a disease, namely illness perceptions, may impact the outcome of chronic illnesses, such as MS. My systematic review aimed at synthesizing and critically appraising literature pertaining to the relationship between illness perceptions and outcome in persons with MS and their caregivers. A literature search was conducted in MEDLINE, PsycINFO, and CINAHL. Twenty papers were included and critically appraised. The findings of the review support the assumption that "positive" illness perceptions relate to better outcomes, while "negative" ones relate to worse outcomes.

Cognition and Gait in Normal Aging and Neurological Disorders

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Abstract

Several studies have reported that gait difficulties and cognitive impairment progressively increase with aging and represent a risk factor for falls. Indeed, more than 30% of older individuals have gait abnormality ranging from cautious gait to shorter

step and stride length. Notably, it has been reported that cognitive impairment is associated with physical inactivity, muscle weakness, pain, and falls. In this talk I will discuss the relationship between gait and cognition both in normal aging and in neurological disorders (i.e., Alzheimer's disease, Parkinson's disease, Idiopathic normal pressure hydrocephalus).

New Development of Antipsychotic Drugs in Schizophrenia

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Abstract

Schizophrenia and schizoaffective disorder are treated in most cases with antipsychotic drugs of the second generation. These drugs block dopaminergic and serotonergic receptors, i.e., D2 and 5-HT2A receptors, and cause different adverse effects, for example movement disturbances of the extrapyramidal system and adverse effects of vital parameters and of the heart. Among these newer antipsychotic drugs are cariprazine, brexpiprazole and lumateperone, which exert a partial agonistic effect at D2 and 5-HT2A receptors, pimavanserin a 5-HT2A receptor antagonist which treats negative schizophrenic symptoms as an add-on therapy, olanzapine combined with samidorphan, which reduces weight gain, and M4 or M1 receptor agonists, for example xanomeline with an antipsychotic effect combined with trospium, an anticholinergic drug. Neural networks were updated to deduce the antipsychotic mechanism of action of newer antipsychotic drugs, especially of xanomeline. The newer antipsychotic drugs cariprazine, brexpiprazole and lumateperone show antipsychotic, antimanic and antidepressive effects, however the efficacy on psychotic symptoms in a long-term treatment has not yet been examined. Pimavanserin reduces negative schizophrenic symptoms as an additional pharmacotherapy in schizophrenia. Olanzapine combined with samidorphan exerts good antipsychotic effects and reduces weight gain. The new antipsychotic drug xanomeline, the antipsychotic effect of which is quite different from the antidopaminergic effect, treats positive and negative schizophrenic symptoms well. The long-term efficacy should still be examined. Newer antipsychotic drugs are for example xanomeline, a M4 or M1 receptor agonist, which has been combined with trospium, an anticholinergic drug, the mechanism of action of which can be derived from the neural network suggested in this review.

Time Varying Analysis of Dynamic Resting-state Functional Brain Network to Unfold Memory Function

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Abstract

Recent advances in brain network analysis are largely based on graph theory methods to assess brain network organization, function, and malfunction. Although functional magnetic resonance imaging (fMRI) has been frequently used to study brain activity, the nonlinear dynamics in resting-state (fMRI) data have not been extensively characterized. In this work, we aim to model the dynamics of resting-state (fMRI) and characterize the dynamical patterns in resting-state (fMRI) time series data in left and right hippocampus and inferior frontal gyrus. We use sliding window embedding (SWE) method to reconstruct the phase space of resting-state (fMRI) data from left and right hippocampus and orbital part of inferior frontal gyrus. The complexity of resting-state MRI data is examined using fractal analysis. The main purpose of the current study is to explore the topological organization of hippocampus and frontal gyrus and consequently, memory. By constructing resting-state functional network from resting-state (fMRI) time series data, we can draw a big picture of how brain functions and step forward to classify brain activity between normal control people and patients with different brain disorders.

Language Deficits through Development Predicted from rs-fMRI Neural Network Connectivity in Utero

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Abstract

Introduction: Evidence about how the human language network develops in utero may allow us to formulate relations between objective metrics of neural connectivity, and the development of language capacity. We propose using resting-state functional magnetic resonance imaging (rs-fMRI) data, to examine the functional connectivity (FC) of the language network with cognition-related brain regions in utero and suggest how it relates to developmental outcomes.

Objectives: The goals of this study were to: 1) use rs-fMRI data to evaluate FC patterns between the primary auditory cortex and the frontal and temporal lobes of the brain and 2) assess interhemispheric connectivity between these regions.

Methodology: 25 mothers were scanned using MRI during the third trimester and completed the ASQ, a validated screening tool for identifying developmental delays in infants and young children when their infant was 3 months. Infants were divided into high and low communication groups based on the communication subscale of the ASQ using a median split.

Results: Left Heschl's gyrus showed enhanced connectivity with the precentral, superior frontal, and middle frontal gyrus in the high communication group. Furthermore, in infants with strong communication skills, critical language-processing areas such as the pars triangularis and pars opercular exhibit robust connectivity not only within the same hemisphere but also across hemispheres.

Conclusions: The enhanced connectivity observed in high-communication infants suggests a more efficient and widespread neural network supporting language skills, emphasizing the importance of early childhood development in shaping subsequent communication abilities. Identifying specific FC patterns associated with communication skills may inform targeted interventions for infants at risk of language delays.

Safety of Antidepressant Types Following Traumatic Brain Injury in Elderly Patients: A Retrospective Database Analysis

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Abstract

Introduction: Neuropsychiatric disorders such as depression are frequently observed after traumatic brain injury leading to treatment with antidepressants. The most used antidepressant types are selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). These medications do not come without risk and there is limited evidence to favor the use of one antidepressant type over the other. Here, we aim to investigate the safety of these medication types in elderly patients.

Methods: We used the online health record database, TriNetX, to compare adverse outcomes between elderly (≥ 65 years) patients taking SSRIs or TCAs within one year following a traumatic brain injury, via retrospective, propensity score-matched analyses. The adverse outcomes explored were ischemic stroke, hemorrhagic stroke, seizures, hypo-osmolality and hyponatremia, and gastrointestinal hemorrhage.

Results: Patients taking SSRIs had a significantly higher rate of hemorrhagic stroke ($p < 0.0001$) and seizures ($p < 0.0001$), while patients taking TCAs had a higher rate of hypo-osmolality and hyponatremia ($p = 0.0151$). There was no significant difference in the rate of ischemic stroke ($p = 0.2190$) or gastrointestinal hemorrhage ($p = 0.2758$).

Conclusions: The results of our analyses suggest that SSRIs may increase the likelihood of hemorrhagic stroke and seizures in older adults whereas TCAs may increase the risk of hypo-osmolality and hyponatremia. These findings should be taken into consideration when treating post-traumatic neuropsychiatric disorders in elderly patients. Furthermore, our results emphasize the need for future research to investigate the mechanisms responsible for these observed differences.

A 42 Year Old Male with Progressive Muscle Weakness and Joint Contractures

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Abstract

A 42 year old male with a history of hypertension and asthma presented with progressive muscular weakness involving both his upper and lower extremities. In childhood, no delay in reaching motor milestones was noted, however he was thought to be slower than his peers when performing specific tasks, such as pushing himself out of a swimming pool. Then, two years prior to presentation, he noticed the insidious onset of muscle weakness in his four limbs, left greater than right, especially the upper extremities. He had difficulties performing tasks such as getting up from a chair or running and started dropping objects from his hands. There was no dysphagia, dyspnea, vision abnormalities or facial weakness. His sister suffered from progressive muscular weakness since childhood. His examination was notable for prominent humeral and finger extensor weakness in the arms and hip girdle weakness in the legs, atrophy of the humeral and distal quadriceps muscle but hypertrophy of the calves. Notably he had hyperextensible thumbs yet multiple joint contractures, and a positive Bethlem sign (he was unable to extend his fingers when asked to put palms and fingers together as if praying). The sensation was intact. He had prominent calcanei. Workup included a skeletal muscle MRI that demonstrated a specific "outside-in" pattern of fibrofatty replacement as seen in congenital muscular dystrophies such as Bethlem myopathy. Genetic testing demonstrated a mutation in collagen type 6 (COL6A3 c.5524G > A heterozygous), confirming the clinical impression of Bethlem myopathy (collagen type 6 disorder).

Blocking an Epitope of Misfolded SOD1 Ameliorates Disease Phenotype in a Model of Amyotrophic Lateral Sclerosis

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Abstract

The current strategies to mitigate the toxicity of misfolded SOD1 in familial ALS via blocking SOD1 expression in the CNS are indiscriminative for misfolded and intact proteins, and as such, entail a risk of depriving CNS cells of their essential antioxidant potential. As an alternative approach to neutralize misfolded and spare unaffected SOD1 species, we developed scFv-SE21 antibody that blocks the β6/β7 loop epitope exposed exclusively in misfolded SOD1. The β6/β7 loop epitope has previously been proposed to initiate amyloid- like aggregation of misfolded SOD1 and mediate its prion-like activity. The AAV-mediated expression of scFv-SE21 in the CNS of hSOD1G37R mice rescued spinal motoneurons, reduced the accumulation of misfolded SOD1, decreased gliosis, and thus delayed disease onset and extended survival by 90 days. The results provide evidence for the role of the exposed β6/β7 loop epitope in the mechanism of neurotoxic gain-of-function of misfolded SOD1 and open avenues for the development of mechanism-based anti-SOD1 therapeutics, whose selective targeting of misfolded SOD1 species may entail a reduced risk of collateral oxidative damage to the CNS.

Prevention of Strokes by Inventions in Quantum Chinese Medicine

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Abstract

The theory of stroke prevention in Quantum Chinese medicine can be explained as follows:

It is hypothesized that solid water particles (SWP) make up the constituents of the meridian network. The meridian network plays a crucial role in carrying Qi and facilitating the flow of blood and nutrients to cells through capillaries. When the meridians become blocked, there is a reduced flow of blood and nutrients to cells. Consequently, cells and organs, which are composed of cells, can become unhealthy. Inflammation can occur when arteries or capillaries become obstructed. The temperature at the acupoint quze, located on the pericardial meridian, reflects the temperature of the capillaries flowing from the heart to the cerebral arteries. Meridians function as conduits for transmitting infrared radiation from areas of obstruction to the quze point, like optical fibers. When the temperature at the quze point is significantly elevated and appears white, it suggests that there is partial blockage in the arteries and capillaries, increasing the risk of a stroke. Therefore, consuming xenwater, which contains SWP, can deliver SWP to partially blocked arteries and capillaries, subsequently repairing these obstructions. As the blockage diminishes, the temperature at the quze point also decreases. Monitoring this temperature decrease through infrared imaging can serve as an indicator that a stroke is less likely to occur. To illustrate this concept, we present cases where individuals experienced a decrease in temperature at the acupoint quze after consuming xenwater, demonstrating its effectiveness in preventing strokes.

Membrane Insertion of Tyrosine-10 Determines Membrane Channel Formation by Unmodified and Pyro glutamylated Amyloid b Peptides

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Abstract

The amyloid b (Ab) peptide plays a major role in neurotoxicity during Alzheimer's disease. Ab is produced by proteolysis of the amyloid precursor protein and aggregates into fibrillar structures that form the characteristic extracellular plaques. However, the main neurotoxic species are the prefibrillar oligomers, which exert the toxic effect through multiple mechanisms, including dysregulation of the cellular ionic homeostasis by permeabilization of the plasma and intracellular membranes. Ab occurs in various forms; while the most abundant forms are the 42 and 40 amino acid peptides (Ab1-42, Ab1-40), N-terminally truncated and pyro glutamylated peptides (AbpE3-42, AbpE3-40) are present in significant quantities and are hypertoxic. In this work, ion-conducting channel formation activities of these four peptides in lipid membranes have been analyzed and correlated with their structural and morphological features. Solvent-induced splitting of the fluorescence of tyrosine-10 has been uncovered and used to assess the degree of membrane insertion of the peptides. Ab1-42 adopts a b-barrel-like structure, effectively embeds in lipid membranes including the N-terminal part harboring tyrosine-10 and induces well-resolved step- like single channels. AFM imaging identified annular, channel-like morphology for Ab1-42 in lipid membranes. Ab1-40 is mostly unordered with minimal amount b-sheet structure, is membrane-adsorbed rather than inserted, forms irregular assemblies, and produces bursts of current. The pyro glutamylated peptides are partially membrane-embedded with intermediate fractions of b-sheet structure, form channel like morphology, and produce both step-like and burst-like ionic currents of large conductance. This data provides clues to the structural basis of Ab cytotoxicity and underscores the importance of membrane insertion of tyrosine-10.

How Does Air Pollution Impact Alzheimer's Disease Development? Lessons Learned from Mouse Study

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Abstract

Background: Alzheimer's disease (AD) is a devastating neurodegenerative disorder that affects millions of lives worldwide. Despite great efforts in research, AD etiology and disease mechanisms remain multifactorial and elusive. It has been well documented that long term exposure to air pollution is associated with enhanced AD risk. However, the underlying mechanisms are poorly understood. In the current study, we sought to gain a better understanding of how polluted air may affect AD development.

Methods: We systemically evaluated the impact of airborne particulate matter (PM) on AD development by exposing transgenic AD mice to various sized PM, termed as ultrafine (< 2.5 um), fine (PM2.5) and coarse (PM2.5 - 10) particles. AD mice

were exposed to the PM for 6 h a day and 4 days a week. After 3, 6 and 12 months of PM exposure, mice were sacrificed for RNAseq and histology analyses.

Main findings: (1) PM exposure enhanced the expression of AD pathology markers Aβ42 and p-Tau; (2) PM exposure increased neuroinflammation in AD mice; (3) PM exposure widely altered the transcriptome of AD mouse brain; (4) PM exposure had a huge impact on the extracellular matrix regulation in AD mouse brain, resulting in downregulation of > 20 collagen genes and other ECM remodeling enzymes, such as ADAMTS (a) Disintegrin and metalloproteinase with thrombospondin motif) and ADAM family members; and (5) We also found a strong activation in mRNA Nonsense Mediated Decay pathway.

Conclusion: Our data demonstrated that exposure to airborne PM caused profound transcriptional dysregulation and accelerated Alzheimer's-related pathology.

Associations between Insulin-like Growth Factor-1 and Resting-state Functional Connectivity in Cognitively Unimpaired Midlife Adults

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Abstract

Insulin-like growth factor (IGF)-1 plays an important role in Alzheimer's disease (AD) pathogenesis and increases disease risk. However, prior research examining IGF-1 levels and brain neural network activity is mixed. The present study investigated the relationship between IGF-1 levels and 21 neural networks, as measured by functional magnetic resonance imaging (fMRI) in 13,235 UK Biobank participants. Linear mixed models were used to regress IGF-1 against the intrinsic functional connectivity (i.e., degree of network activity) for each neural network. Interactions between IGF-1 and AD risk factors such as apolipoprotein E4 (APOE4) genotype, sex, AD family history, and age were also tested. Higher IGF-1 was associated with more network activity in the right executive function neural network. IGF-1 interactions with APOE4 or sex implicated motor, primary/extrastriata visual, and executive function related neural networks. Neural network activity trends with increasing IGF-1 were different in different age groups. Higher IGF-1 levels relate to much more network activity in the sensorimotor network and cerebellum network in early-life participants (40 - 52 years old), compared with mid-life (52 - 59 years old) and late-life (59 - 70 years old) participants. These findings suggest that sex and APOE4 genotype may modify the relationship between IGF-1 and brain network activities related to visual, motor, and cognitive processing. Additionally, IGF-1 may have an age-dependent effect on neural network connectivity.

Protective Action after Use of TLS Technique in aMCI Patients

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Abstract

Mild cognitive impairment (MCI) is an alteration of cognitive function, considered a precursor to Alzheimer and #39;s disease and related to vascular dysfunction. Despite the existing therapeutic alternatives to delay the development of cognitive deterioration, none of them have shown benefit in the patient, which is why new treatments are needed to meet the needs of this population. Previous studies point out the possible benefits of using transcranial laser stimulation (TLS) in patients with MCI, since it stimulates cellular processes at the brain level that improve vascular irrigation. This effect could favor the delay of deterioration. It is estimated that the prevalence of MCI in the world is around 15% in people over 65 years of age, increasing

with age, and can reach 23% in the population over 85 years of age. Randomized, controlled, single-blind clinical trial measured for one week, was carried out in the neurology service of the University Hospital in Valencia with the participation of 30 adult patients with aMCI (amnesic MCI). 15th of them randomized to the intervention group (TLS) and 15th to the control group. Neuropsychologic tests were determined in these patients. Patients suffered no harm or significant changes in health after using ETL. We demonstrate a development deletion of the illness in these patients. The use of transcranial laser to prevent the development of Alzheimer and #39;s disease should be a future priority in clinical research. The enhancement of mitochondrial activity in brain cells may serve to prevent the neural death detected in the disease. In addition, daily use at home may help prevent the disease from further progressing.

Perceived Social Support, Normalization, and Subjective Well-Being among Family Members of a Child with Autism Spectrum Disorder

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Abstract

The experience of family members of children with autism spectrum disorder (ASD) is not uniform. This study focused on mothers of a child with ASD (Study 1) and typically developing siblings (TDSs) during their emerging adulthood (Study 2). Similarities and differences were explored regarding a proposed model examining the paths of perceived social support (PSS) and normalization (a coping strategy) with subjective well-being: satisfaction with life (SWL) and positive affect (PA). Similarities were found in the paths between PSS, normalization, and SWL, in mothers and TDSs, but differences emerged regarding PA. These findings highlight the importance of PSS as a resource that contributes to normalization and SWL. Professional awareness of family members; PSS and their engagement in normalization is needed.

Investigating the Effects of Long-term Leucine and Isoleucine Treatment on Cognition and Behaviour in Male BALB/c Mice

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Abstract

Metabolic disorders, such as insulin resistance, obesity, and type 2 diabetes (T2D), are significant risk factors for Alzheimer's disease (AD). This study aimed to assess the pathophysiological link between T2D and AD by focusing on the likely role of the branched-chain amino acids (BCAAs) leucine and isoleucine. Such metabolic disorders are characterized by raised levels of plasma BCAAs, and increased circulatory isoleucine has been linked to an increased risk of developing AD. We thus tested whether long-term leucine or isoleucine dietary supplementation in mice would cause alterations in cognitive function. Male BALB/c mice were treated with 1.5% w/v leucine or isoleucine in their drinking water for 9.5 weeks before being subjected to various behavioral tests - the rotarod, open field, elevated zero maze, novel object recognition, and nesting tests. The treated mice displayed intact locomotor function and nesting abilities (a murine equivalent of activities of daily living in humans) but increased anxiety was seen in leucine-treated mice compared to untreated control mice. This study is also the first to identify likely attentional deficits in BCAA-treated mice by implementing two novel cued versions of rotarod designed to increase distractibility during walking. Notably, these behavioral changes are reminiscent of the early cognitive symptoms seen in patients with preclinical AD and mild cognitive impairment, and further investigation is warranted to decipher the underlying mechanisms of potential leucine- and isoleucine-induced alterations in attention. Because vascular damage is a key pathological feature of T2D, and blood-brain barrier (BBB) disruption one of the earliest hallmarks of AD, which manifests long before the classical signs of amyloid and tau accumulation, the brains of these mice are currently assessed for likely BBB dysfunction, which may constitute a potential link between T2D and AD.

Assessing Environments for People Living with Dementia: A Review of Tools

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Abstract

Between 2020 and 2050, the number of older adults living with dementia is expected to nearly double from 75 to 132 million. While the majority will live at home, a significant number will relocate to shared residential long-term care settings. Since the work of Powell Lawton in the 1970's there has been a consensus that the designed environment of long-term care settings has an impact on older adults in general, and people living with dementia in particular. Increasingly care communities are responding to a changing set of care industry values that prioritize a holistic, quality-of-life-driven person-centered care model over a biomedical approach to long-term care provision. This shift is increasingly accompanied by dramatic changes in the designed environment. Starting in the 1980's numerous environmental evaluation tools have been developed in multiple countries, some of which barely address the values inherent in person-centered care, and some of which are deeply embedded in these values. A systematic literature review identified 13 different environmental assessment tools that address settings for individuals living with dementia. Presenters will review the tools, share insights, and offer cautionary advice that may be used for architectural planning and design, post-occupancy evaluations, and research initiatives that are both anticipatory and responsive to the needs of older adults living with cognitive and physical impairments, their companions, and personnel.

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