2ND MULTIDISCIPLINARY NEURODEGENERATION CONGRESS

ABSTRACTS BOOK

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Abstracts Book

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Prof Dr. Nevzat TARHAN

Üsküdar University, Founder Rector

Nörodejenerasyon, dünyada en çok merak edilen tıbbi konulardan biri. Özellikle son yıllarda bilimin yeni uzay alanı, "beyin" olarak tespit edildi. Beyin alanında yapılacak çalışmalar, birçok hastalıkların tedavisinde bize ufuk açan, ilham verici çalışmalara gebe bir alandır. Bu özelliği nedeniyle, biz üniversite olarak bu alanı AR-GE olarak belirledik.

Bir prensip vardır, bir konuyu seçip derinleşirsin. Eğer bu olursa AR-GE olur. Biz de bu alanda derinleşmeye çalışıyoruz. Bununla ilgili çok güçlü bir veri tabanımız da var. Laboratuvar alt yapımızla Türkiye'de birçok ilki başlattık. Kusura bakmayın, bu konuda mütevazı olamayacağım. Üsküdar Üniversitesini kurarken bu konsepti tema olarak seçtik. NPİSTANBUL Beyin Hastanesi mesela bunun bir parçası. Uygulama konusunda bize destek verdi. Nörogenetik çalışmalarıyla ilgili, kök hücre ile ilgili çalışmalar başlattık. Tüm bunlarda şunu hedefliyoruz: Nörobilimler ile davranış, psikoloji bilimlerinin birlikte olduğu disiplin alanlarında çalışıyoruz. Üniversitemiz ilk kurulduğunda, özellikle bilgisayar ve yazılım mühendisliklerini, biyomühendislik bölümünü ilk sene açtık ve mezun verdik. Mezun olan biyomühendisler piyasada aranan eleman oldular ve işe girdiler. Geleceğin mesleği olarak ön gördüğümüz için öncelik verdik, gençler de faydasını gördüler.

Otizm, alzheimer hastalığı, nöro-gelişimsel rahatsızlıklar gibi hastalıkları AR-GE olarak seçtik. Şizofreni için 'nörodejeneratif hastalıklardan değildir' diyemiyoruz mesela. Özellikle beyindeki hastalıkla ilgili, konnektomlar anlaşılmaya başlandı. İleride belki de 'konuşamama bozukluğu beynin şu bölgesinde' diyeceğiz. Patolojiden hareketle tanı koyacağız. Mesela nörologlar şu an şizofreni ile daha çok ilgileniyor. Psikiyatristler oldukları yerde sayarlarsa şizofreniyi davranış nörologlarına, otizmi de çocuk nörologlarına emanet edecekler. Psikiyatristin elinde bir tek depresyon kalacak bu gidişle. Psikiyatri, nörobilimdeki yenilikleri kabul etmezse depresyon uzmanlığına yönelebilir. Depresyonun ön beynin hastalığı olduğuna dair kanıtlar o kadar çok ki…

Psikoloji profesörleri bugün kliniksel çalışıyorsa, hastaya dokunmak istiyorsa, beyni bilmek zorunda. Beyni bilmeyen insan, temel bilgilere sahip olmayan insana psikoloji diploması vermemiz de etik değil. Üsküdar Üniversitesinde Nöropazarlama Yüksek Lisans Programı açtık. 'Nöroloji ve pazarlama bir arada nasıl olur?' diye YÖK de kararsız kaldı. Ama o zamanki YÖK başkanı, bilim insanı olduğu için bizim teklifimizi araştırdı ve onayladı.

Nörobilimle ilgili strateji hedefimizin doğru olduğunu gördük. Bununla ilgili yayınlarımız çoğaldı. AR-GE ve yenilikçi politikalarımız ile ilgili bir yapı da oluştu. TÜBİTAK projelerinin alınması ve uluslararası çalışmalar alabilmek önemli.

Davranış nörolojisinde de dünyadaki öncülerden, İstanbul doğumlu Marek Marsel Mesulam Hoca da misafirimiz olacak, dinleyeceğiz. Oğuz Tanrıdağ Hoca da konuşacak. Bu bilimin öncülüğünü yapan bir kadro var ülkemizde. Biz de bu kadroyla birlikte, burada, genetik ayağının, beyin uyarım tedavilerinin, mikro uyarım tedavilerinin öncülüğünü yapıyoruz. Burada, beyin haritalama görüntülerinin dalgaların oranını onayladı. Bu tür hastalıklarda biyolojik kanıt üzerinden tedavi etmeye çalışıyoruz. Tedavilerde yeni bakış açısı getirmeye çalışıyoruz. Yaptıklarımızla katkı sağlıyor, tecrübe paylaşıyoruz. Literatüre katkı sağlıyoruz… Kongrelerin verimli geçmesi çok önemli. Bu kongrenin bildirilerinin toplanıp Üsküdar Üniversitesi Yayınları arasında basılması da bir o kadar önemli. Kendi kongrelerimizin yayınlarını yapmakla ilgili ilkesel kararımız var. Yayın Kurulumuz bunu onayladı. Bir de bu kongrelerin seneye de devam etmesinde fayda var. Bu bağlamda organizasyonda emeği geçenleri kutluyor, başarılı bir kongre olmasını diliyorum.

Prof. Dr. Oğuz TANRIDAĞ

Üsküdar University, Faculty of Medicine, Neurology

Prof. Marsel MESULAM, 1945 yılında İstanbul'da doğdu. Amerikalıların Florence Nightingale Hastanesi ile bilikte İstanbul'da kurduğu Robert Academy'de liseye gitti. Bosphorous Chronicle isimli okul gazetesinin baş editörü oldu ve gazetenin baskı biçimini değiştirerek modern hale getirdi. Okul yıllarında öğrenci konseyi başkanlığı yaptı ve birçok ödül kazandı. Liseyi bitirdiğinde Yale, Columbia, MIT ve Harvard'a başvurdu ve hepsinden kabul aldı. Harvard'a gitmeye karar verdi. Ona göre, bir öğrencinin hayatıyla ilgili hangi alanı tercih edecekse o konuda her türlü imkanı sağlayan Harvard'da önce edebiyat, fizik ve iktisada ilgi gösterdi. Daha sonra nedenini bilmediği bir biçimde Freud'la ilgilenmeye başladı ve bir dizi kurs alarak psikiyatrist özellikle de psikoanalist olmak istedi. Freud 1895 tarihli "Bilimsel Psikoloji İçin Proje" isimli denemesinde "Id, ego ve süper egoya sahip olmak harikülade bir şey ama biyoloji bunların beyinle ilişkisini söylemek için henüz hazır değil!" diyordu. Dikkati bu yöne çevrildi ve zihin-beden problemiyle ilgilenmeye başladı. Psikofizyoloji kursu almaya karar verdi. Tıp fakültesi yıllarında sayısız araştırma yaptı. Stajyerliğini Pennsylvania Üniversitesi Hastanesi'nde yaptıktan sonra nöroloji hocalarından modern davranış nörolojisinin kurucusu Norman Geschwind'in dikkatini çekti. Geschwind ona yanında nöroloji asistanlığı teklif etti. Bu eğitimi Boston Şehir Hastanesi ve Beth Israel Hastanesi'nde yaptı. Harvard Tıp Fakültesinde nöroloji profesörü oldu ve nöroloji bölümü başkanlığını yaptı. 1994'de Northwestern Üniversitesi'ne geçti. Kısa zaman sonra bu üniversiteyi çalıştığı alanda A.B.D.'de birinci sıraya yükseltti. Halen Mesulam Center for Cognitive Neurology and Alzheimer's Disease direktörüdür. Sayın Mesulam her zaman Türkiye'ye geri dönmeyi düşündü. Ancak Tıp fakültesi ve uzmanlık eğitimleri sebebiyle bu yıllar boyunca gerçekleşmedi. Daha sonraları vatandaşlık hakkını kaybetmemek için Türk ordusunda askerlik görevini yerine getirdi. Askerliğini tankçı olarak yaptı.

Marsel Mesulam bizim için her zaman yaptıklarını izlediğimiz ve izinden gitmeye çalıştığımız bir örnek olmuştur. Modern literatürde Mesulam Sendromu olarak geçen Primer Progresif Afazi, özellikle beyinde dil işlevleri yönünden baskın olan sol yarının nörodejenersayonuyla başlayan ve seyreden özel bir beyin hastalığıdır. Literatüründe Mesulam Sendromu'nu andıran en erken bildirim, 1893'de Serieux tarafından 47 yaşındaki kadın bir hasta nedeniyle bildirilen vaka raporudur. PPA sendromu ilk olarak 1982'de Mesulam tarafından beyin

biyopsisi bulgularıyla bildirilmiştir. Genellikle sonu demans ile biten hastalıklar gibi 65 yaş öncesinde başlar. İlk 1-2 yılda nörolojik ve demansiyel belirtiler ve dil bozukluğu belirtileriyle (tutuk konuşma, kelime bulma zorluğu) seyrettikten sonraki 2-10 yıılık süreler içinde yavaş bir seyirle daha genel bir demans sendromuna evrilir. Cinsiyet arasında benzer sıklıkla görülür Beyin incelemelerinde asimetrik soldaki etkilenme sağdaki etkilenmeden daha büyük olmak üzere kortikal atrofi, hipoperfüzyon ve hipometabolizm vardır. PPA, aralarında Alzheimer hastalığı ve frontotemporal lobar dejenerasyonun da bulunduğu bir hastalık grubunun genetik ve patolojik özelliklerini bazı bakımlardan paylaşabilir.

Dementia Heterogeneity and Language Neuroanatomy in Primary Progressive Aphasia.

Prof. Dr. M.-Marsel Mesulam - Northwestern University, Director, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Primary progressive aphasia (PPA) is a dementia syndrome associated with several neuropathologic entities, including Alzheimer's disease (AD) and all major forms of frontotemporal lobar degeneration (FTLD). It is classified into agrammatic (PPA-G), semantic (PPA-S) and logopenic (PPA-L) subtypes on the basis of the language domain that is most impaired. The asymmetric neurodegeneration of the hemisphere dominant for language (usually left) is the one consistent feature of all PPA variants.

Three features define PPA: 1) Adult-onset and progressive impairment of language (not just speech). 2) Absence of other consequential behavioral or cognitive deficits for approximately the first two years. 3) Neurodegenerative disease as the only cause of impairment (1). These criteria help to filter out patients where progressive aphasias arise in conjunction with equally prominent speech apraxia, behavioral disturbances, loss of memory for recent events, associative agnosias, or visuospatial deficits.

Research on PPA is offering new insights into the anatomy of language. For example work on PPA-S is showing that the left anterior temporal lobe (ATL) should be considered a core component of the language network, a relationship that was overlooked by classic aphasiology. In our cohort, all right-handed patients with severe word comprehension impairment have also had substantial left ATL atrophy extending all the way into the pole. However, some patients with such a location of atrophy may have severe anomia in the absence of word comprehension impairment. In these patients, the distinctive comprehension impairment of PPA-S emerges as the atrophy extends posteriorly from the anterior tip of the left temporal lobe into adjacent parts of the middle portion of the temporal lobe, especially the middle temporal gyrus (2). Damage to the left ATL may therefore be necessary but not always sufficient for word recognition impairment while posterior expansion of damage into the middle parts of the temporal lobe may also be required. The left ATL can be conceptualized as a transmodal region of cortex where sensory word form information is linked to the multimodal associations that collectively encode the meaning of the word (2-4).

Also in contrast to the expectations based on classic aphasiology, clinicoanatomical correlations in PPA-L have shown that severe degeneration of Wernicke's area does not impair single word comprehension. Furthermore, investigations on PPA-S have shown that an intact Wernicke's area is not sufficient to sustain word comprehension if the ATL is damaged. The body of work on PPA therefore leads to the conclusion that Wernicke's area is neither necessary nor sufficient for word comprehension. Evidence from other experiments, however, does show that Wernicke's area plays an ancillary role in word comprehension. Its impairment does not cause overt word comprehension impairments in daily life but it decreases the computational flexibility of the language network in handling difficult and rapid word recognition tasks. In contrast to its ancillary (or participatory) role in word comprehension, clinicoanatomical correlations in PPA show that Wernicke's area has a critical function in language repetition, a finding that is in keeping with observations in stroke aphasia (5). Wernicke's area is important for language repetition presumably because it links phonologic word-form codes to their articulatory sequences (6-8).

In our group of 97 consecutive autopsies, the primary neuropathology was FTLD with tauopathy (FTLD-tau) in 29%, FTLD with transactive response DNA binding protein 43 (FTLD-TDP) in 25%, and AD in 44%. All 3 major neuropathologic forms of FTLD-tau (Pick's disease, corticobasal degeneration (CBD), progressive supranuclear palsy (PSP)), and all 3 major forms of FTLD-TDP (types A, B and C) were represented. There were some disease-specific preferential patterns of atrophy. For example, AD almost always led to peak atrophy that included the temporoparietal junction; TDP-C almost always led to severe anterior temporal atrophy; Pick's disease routinely caused combined atrophy of anterior temporal and prefrontal cortex; PSP and CBD tended to be associated with surprisingly modest cortical atrophy, usually in dorsal premotor or inferior frontal cortex. The relationship of PPA variants to the underlying neuropathologic entity is probabilistic rather than absolute (9). Autopsy data show that the vast majority of PPA-S cases have had TDP-C pathology but approximately 20% have had Pick's disease; the majority of PPA-G cases have had FTLD-tau (all types) but approximately 30% have had FTLD-TDP or AD; the majority of PPA-L cases have had AD but 30% have shown FTLD-tau or FTLD-TDP. Through this clinicopathologic heterogeneity, the same neuropathologic entity can cause more than one aphasic variant and that the same PPA variant may be caused by more than one neuropathologic entity.

The one common denominator of nearly all cases is the leftward asymmetry of the atrophy. What is surprising is that the asymmetry is almost always maintained up to the time of death. The initial predilection of the language-dominant left hemisphere is therefore not a random

event at disease onset but a core biological feature of the syndrome. The mechanisms that underlie this selective vulnerability remain unknown. Patients with PPA and their first-degree relatives have a higher incidence of dyslexia than controls and patients with other dementias (10). This finding has led to the speculation that some cases of PPA arise on a developmentally or genetically based vulnerability of the left hemisphere language network. In some family members this vulnerability interferes with the acquisition of language and lead to dyslexia while in others it makes the language network a locus of least resistance for the effects of an independently arising neurodegenerative process, leading to PPA (11).

The heterogeneity of PPA highlights the need to individualize therapeutic approaches. Interventions should target the underlying disease as well as the symptom complex. An initial step is to use biomarkers to determine the nature of the underlying disease. The goal is to prescribe approved medications (e.g. cholinesterase inhibitors if AD) and to channel the patient to relevant disease-specific clinical trials. Non-pharmacologic interventions include speech therapy and brain stimulation modalities such as transcranial magnetic stimulation or transcranial direct current stimulation (12). Recent developments in telemedicine raise the possibility of delivering speech-language therapy in the home of the patient (13, 14). A future goal would be to combine speech and language therapy with transcranial stimulation modalities.

In summary, investigations on PPA have shown that there is more to dementia than memory loss, that the same clinical syndrome can be caused by multiple neuropathologies, that the same neuropathology can cause multiple syndromes, and that the relationship of syndrome to neuropathology is probabilistic rather than deterministic. Future work on this syndrome is likely to generate new insights related to the heterogeneity of dementias, the principles of selective brain vulnerability, and the neuroanatomy of the language network.

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Axonal Transport, Motor Neuron Disease and Neuronal Signaling

Prof. Dr. Scott T. Brady- University of Illinois at Chicago, College of Medicine, Anatomy and Cell Biology

Mutations in more than 40 different genes have been implicated in familial amyotrophic lateral sclerosis (ALS), but the clinical presentation is remarkably consistent in exhibiting the characteristics of a dying back axonopathy preferentially affecting upper and lower motor neurons, typically leading to death within five years after diagnosis. Further, sporadic cases of ALS with no family history or none mutations present with the same neuropathological features as familial forms of ALS. The consistent clinical and neuropathological features of ALS raise the possibility that a common pathogenic mechanism may be involved in most if not all cases of ALS. Initial studies on various pathological forms of Superoxide Dismutase type 1 (SOD1) focused attention on MAP kinase signaling pathways leading to P38 MAP kinases. Recent studies have indicated that multiple mutations associated with ALS involve convergent pathogenic mechanisms that may illuminate selective vulnerability of motor neurons in ALS and suggest novel therapeutic interventions for this devastating disease.

Neuroinflammation, Neurodegeneration and MicroRNAs

Assoc. Prof. Belkıs Atasever Arslan- Üsküdar University, Head of Molecular Biology and Genetics (Turkish)

Neuroinflammation is a phenomenon that occurs with systemic inflammation, and microglia cells play a major role in this process. Systemic inflammations such as obesity, metabolic syndrome, insulin resistance, trauma initiate the neuroinflammation process. Another type of cell involved in inflammatory processes are astrocytes.

When the pro-inflammation and anti-inflammation effects of microglia are compared, the transport of glial transmitters as well as cytokines in the environment can lead to simultaneous activity changes in different regions of the brain due to gap-juncitons in astrocytes. These morphological changes can also lead neurons to the neurodegeneration process. However, neuroinflammation accompanies neurodegenerative diseases in general, although not all of them, but it may be thought that neuroinflammation is a trigger in some cases only. "Is neuroinflammation the result of neurodegeneration or is it a process that triggers neurodegeneration?"

It is known that the cytokine explosion that occurs in lymphocytes also occurs in microglia cells if it is in the brain. In this case, excessive activation of T lymphocytes, especially in the adaptive immune system, and together with astrocytes, this can lead to synaptic losses and neurodegeneration.

Axonal transport is of great importance in the early stages of neurodegeneration. Because; Axonal transport is a conduction path in the communication of neurons and the onset of the first damage here can lead to rapid development of the loss of function of the neurons. There are two neuroprotective pathways, the AKT pathway and the CDC42 pathway, in the mechanism of axonal transport.

Determination of Memory Lateralization Using Functional MR

Assoc.Prof. Barış Metin- Üsküdar University, Üsküdar Faculty of Medicine, Neurology

Objective: Functional magnetic resonance imaging (fMRI) is being increasingly used to determine language and memory lateralization, and to predict the risk of amnesia risk. The literature includes studies that have used multiple paradigms and analysis methods, and the findings have been inconsistent due to differences in the paradigms and regions of interest used. We recently aimed to compare the accuracy of multiple paradigms and masks for predicting memory decline after temporal lobe surgery. To test the accuracy of fMRI in predicting postoperative decline in memory we recruited 37 patients scheduled to undergo anterior temporal resection (23 with left-side temporal lesion and 14 with right-side temporal lesion) that were tested preoperatively using a language and a memory paradigm, using both verbal and non-verbal items, while fMRI was performed. In addition, verbal and non-verbal memory were assessed pre-operatively and post-operatively using standardized measures. A series of masks was used to determine which was most strongly associated with postsurgical decline in neuropsychological function. In the patients that underwent left temporal lobectomy there was a correlation between the fMRI verbal memory laterality index, measured using whole-brain gray matter activation, and post-operative decline in verbal memory. In addition, language laterality index was related to decline in verbal memory. In contrast, in the patients that underwent right temporal lobectomy there was no significant correlation between the laterality indices and postoperative decline in verbal and non-verbal memory. The findings provide additional evidence of the efficacy of using fMRI for predicting memory decline, and indicate that use of whole-brain activation during memory paradigms and language-related activations can predict memory decline after anterior temporal lobectomy. In this talk, I will present our own results for determining language lateralization using fMRI and will provide a sumamry of the literature.

Using Eye Movement Tracking to Detect Comprehension Deficits in Neurodegenerative Aphasia.

Asst. Prof. Dr. Mustafa Seçkin- Acıbadem Mehmet Ali Aydınlar University Faculty of Medicine, Department of Neurology

Aphasia caused by neurodegenerative diseases progress slowly and early stages of comprehension impairment in neurodegenerative aphasia may be undetectable using traditional tests. A new and sensitive method known as eye movement tracking provides an excellent opportunity to examine comprehension deficits in patients even at the early stages of progressive aphasia. In the current clinical setting, failure in word-to-object matching tasks would be regarded as evidence indicating single word comprehension deficits. However, the majority of these tasks are designed as pencil and paper tests and patients with prominent impairment in these tasks already have significant atrophy in language areas. On the other hand, eye movements during a word-to-object matching task can be used as probes of lexico-semantic associations for an on-line assessment of the dynamic search of stored semantic representations. Therefore, impairment in lexico-semantic associations may be evident in effortful visual search characterized by back and forth fixations between the target and distractors even in trials where the target is eventually recognized. In other words, a correct response will not mask underlying impairment as eye movements reveal uncertainty that precedes more severe disruption of the linkage between words and their semantic representations. Eye tracking may also help understand the mechanisms of dissociation between single-word and sentence comprehension deficits which is critical for distinguishing semantic aphasia from agrammatic aphasia.

Modeling Neurological Diseases in *Drosophila melanogaster*

Prof. Dr. Arzu Çelik Fuss- Boğaziçi University, Department of Molecular Biology and Genetics

Aim:

Intellectual disability (ID); defined as significant deficit in intellectual functioning and adaptive behavior, is one of the largest unsolved problems of healthcare affecting approximately 1-3% of people worldwide, and genetic factors are considered as one of its main contributors. In recent years due to the advent of next generation sequencing, large scale systematic studies are being performed to identify genes involved in the pathology of ID and over 700 genes are identified for different types of this heterogeneous disorder. In order to confirm this growing number of candidate ID genes uncover their molecular function we aimed to generate a *Drosophila melanogaster* model for ZBTB11.

Methods:

We are using RNAi knock-down, CRISPR/Cas knock-out, generation of transgenic fly lines to undertake our research. We also use mammalian cell culture to assess changes in subcellular localization of the mutant protein of interest. Immunofluorescent staining and behavioral analyses are used to analyze the phenotypes.

Results:

Using RNAi knock-down we show that *CG6215/CkIIα-i1* affects the development of the learning center in the *Drosophila* brain and causes a drastic decrease in mushroom body neuron numbers. Cell culture experiments showed that mutant ZBTB11 is not correctly localized in its subcellular structure. We have generated *CG6215/CkIIα-i1* mutants and 'humanized' flies and are currently analyzing their function.

Discussion:

Our results suggest strong evidence that *CG6215/CkIIα-i1* is the fly homolog of ZBTB11 and that it severely affects brain morphology. Behavioral analyses will hopefully support our initial data. Our project is funded by TUBITAK project number 119Z309.

Functional Connectivity in Parkinson's Disease Patients with Parkin Gene Mutation

Asst.Prof.Dr. Merve Çebi - Uskudar University, Psychology Department

Aim:

Parkin gene mutation is the most common form of autosomal recessive type of genetically inherited Parkinson's Disease. The aim of this study was to explore the functional connectivity changes in Parkinson's Disease Patients with Parkin Gene Mutation.

Method:

In this study, resting state functional and structural magnetic resonance imaging was performed with 12 PD patients with Parkin mutation (PP-PD), 14 PD patients without Parkin mutation (PN-PD) and 16 healthy controls (HC).

Results:

The results of this study showed that PP-PD and PN-PD group showed decreased functional connectivity in sensorimotor network as compared to HC. In addition, PP-PD group displayed increased functional connectivity in precuneal network as compared to PN-PD.

Discussion:

Parkin gene mutation might be related to functional connectivity changes in the brain which are distinct from idiopathic Parkinson's disease.

Keywords: Parkinson's Disease, Parkin mutation, functional magnetic resonance imaging

The Effectiveness of Speech And Language Therapy in Management of Primary Progressive Aphasia

Dil. Kon. Ter. Uz. İbrahim Yaşa - Üsküdar University, Spreech and Language Therapy Department

The term neurodegenerative aphasia (primer progressive aphasia) describes a group of neurodegenerative disorders with predominant speech and language disabilities as their main characteristics. The semantic variant, the nonfluent or agrammatic variant and the logopenic variant are three main variants and each has specific speech and language based deficits and different neuroanatomical structure. There are currently no curative treatments or symptomatic pharmacological therapies for its treatment. However, speech and language therapists have developed several deficits-based interventions and compensatory strategies to treat them in the clinical context. This study highlights this inequity and the reasons why people with PPA should be guided to speech and language therapies and what kind of techniques and strategies can be used to treat them properly for gaining communicative abilities in their daily life. With this perspective, “primer progressive aphasia”, “speech and language therapies in primer progressive aphasia”, “speech therapy in neurodegenerative aphasia” key words were searched in PubMed, ScienceDirect and Google Scholar academic research websites. 34 research and review academic studies were found and their abstract were also analyzed. 7 studies were selected and their results discussed. The results show that speech and language therapy is a good option for people with PPA and has a critical role to gain communicative competence. It helps to slow down the neurodegenerative loss and also reinforce the speech and language abilities.

Neuropsychological Assessment and Neuropsychological Profiles in Neurodegenerative Diseases

Uz. Psk. İnci Birincioğlu - Üsküdar University, Psychology

Neurodegenerative diseases are a heterogeneous group of disorders that are characterized by the progressive degeneration of the structure and function of the central and peripheral nervous system. Common neurodegenerative diseases include Alzheimer's disease and Parkinson's disease. Degenerations in central nervous system can cause many cognitive disfunctions which show a serious decline over time paralell to the atrophy seen in patients brain tissue. By using techniques such as EEG, MRI and Neuropsychological Testing it is possible to determine patients diagnosis of neurodegeneration type, stage of the disease and patients current cognitive profile. The term ‘cognitive profile of neurodegenerative disorder’ refers to the result of the neuropsychological assessment of functional cognitive networks such as linguistic skills, complex visual-spatial perception, executive functions like abstact thinking, decision making, cognitive inhibition or verbal fluency. Each neurodegenerative disorder cause a unique cognitive decline of its progression at early and late phases so that several scientific predictions about next expected cognitive loss can be made. In this presentation we will discuss the types of cognitive profiles of neurodegenerative disorders and learn how to use this knowledge for patient’s and their caregiver’s advantage.

Molecular Mechanisms of Neurodegeneration: Vitamin D-VDR Pathways.

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It is becoming increasingly evident that the receptors in neurons do not exist as stand-alone units, but instead are part of large macromolecular complexes of interacting proteins. The protein components of these signal networks are very dynamic according to time and space. Clarifying the exact sequence of interacting proteins involved in regulation and signaling mediated by a known target protein has become the main goal of neurobiology. Dr Adolf Windousin, who received the Nobel Prize in 1928, achieved this honor due to his role in the discovery of the vitamin D hormone. This unique secosteroid hormone is of particular importance in many cellular mechanisms and diseases. Eyles et al detailed how vitamin D differentiates brain cells, how it controls axonal growth, calcium signaling, production of brain-derived reactive oxygen derivatives, and how it regulates neurotrophic factor synthesis. Our group's in vivo and in vitro studies and other articles in the field revealed the effect of vitamin D in neurodegeneration and Alzheimer's disease (AD), but the cellular mechanisms involved in this effect have not been fully clarified. In our studies, the surprisingly complex effects of vitamin D receptor (VDR) silencing or 1,25-Dihydroxyvitamin D3 applications at different doses and times, and the effect of amyloid beta on VDR suppression, which we detected in our previous studies, could not be explained only by transcriptional regulation. This proposition has led us to investigate the possibility of VDR being found on the neuron plasma membrane as a possible signal-emitting protein or secretase complex (amyloid precursor protein-APP-processing enzymes) regulator. A very limited number of studies have suggested that classical VDR, which plays a role in gene transcription, may also be associated with or located in the vicinity of the cavity in the plasma membrane of osteoblasts. Bartoccini et al showed that VDR is localized in lipid-rich microregions in nuclear membranes, which are equivalent to the microspecs found in the plasma membrane of structurally developing hippocampal neurons. Since one of the main roles of Vitamin D is the regulation of calcium

and phosphate metabolism, we created a hypothesis that VDR, its receptor, can also be found in the neuron plasma membrane and can act as part or a regulator of various protein complexes. As a result, we have shown that VDR is localized in the neuron plasma membrane. Also, for the first time, we detected the co-localization of VDR in the neuron plasma membrane with APP, ADAM10, Nicastrin and limited co-localization with presenilin 1. This presentation will summarize the role of vitamin D and related mechanisms in neurodegeneration and amyloid pathology.

Keywords: Neurodegeneration, vitamin D deficiency, VDR, amyloid beta

Multimodal Neuroimaging in Neurodegenerative Disorders

Prof. Dr. Hakan Gürvit- İstanbul University, İstanbul Faculty of Medicine, Neurology

During the second half of the twentieth century, neuroanatomic tracing methods enabled the illumination and mapping of anatomic connectivity patterns of the non-human primate brain. High genetic homology allowed drawing analogies between primate and human brains, and human cognition has become conceived as represented within large-scale neural networks (LSNNs) possessing similar connectivity patterns. However, since human cognition is a unique feature of our species, this analogy might be somewhat far-fetched. By the turn-of-the-century, the discovery of intrinsic connectivity networks (ICNs) by a new neuroimaging method that is resting-state MRI (rsMRI) enabled the imaging of functional neural networks or ICNs, both sensory-motor and cognitive. Although those ICNs have some overlaps with the previously suggested LSNNs, they are not entirely identical and named with a new nomenclature. In a short-while, evidence suggesting the vulnerability of discrete ICNs to different neurodegenerative disorders started to accumulate. In the present time, rather than one-to-one correspondence between the neural networks and the disease states, the relationship between the neuropsychiatric disorders, within a spectrum, ranging from the Alzheimer's disease (AD) to schizophrenia and neural networks, has been started to be conceived as an alteration among the dynamic interaction of ICNs. Recently, in Hulusi Behçet Cognitive Neuroimaging Lab, we have also started to use multimodal neuroimaging methods to contribute to this effort that is prevalent among the international cognitive neuroimaging teams. Our focus can be said to be on rsMRI. However, we also use classical task-based functional MRI (fMRI), diffusion tensor imaging (DTI) for structural connectivity, arterial spin labelling-MRI (ASL-MRI) for cerebral blood perfusion, and magnetic resonance spectroscopy (MRS) for the metabolic alterations accompanying neurodegenerative disorders. In this talk, the results from our research on the AD continuum, cognitive impairment in Parkinson's disease, and spinocerebellar ataxia will be presented.

Intrinsic Connectivity Networks in Neurodegenerative Diseases

Prof. Dr. Tamer Demiralp- İstanbul University, İstanbul Faculty of Medicine, Physiology

The functional neuroimaging with MRI (fMRI) is mostly based on the temporal dynamics of the blood oxygen level dependent (BOLD) signal that in addition to task-dependent changes in hemodynamic activity shows on-going fluctuations, also during the so-called "resting-state" of the brain. The presence of reproducible temporal dependencies among BOLD fluctuations of distributed and even anatomically distinct brain locations with functional closeness, the specific modulations of these dependencies with experimental conditions and their associations with inter-individual differences of brain function suggest a strong basis for fMRI-based functional connectivity studies. The overall resilience of the resting-state networks (RSNs) with certain modulations during task conditions gave rise to the more comprehensive term of intrinsic connectivity networks (ICN). The ICN changes observed in the early stages of neurodegeneration, suggest the usability of these signals for following the time course of the pathophysiological process. While there are various techniques to discover the ICNs in fMRI data, they can be divided into two main categories. The hypothesis-driven approach based on the selection of specific seed regions proposed as central cores of ICNs computes temporal BOLD correlations among the seeds and the rest of the brain, while data-driven approaches are based on the decomposition of the whole-brain BOLD signal into component maps according to certain theoretical constraints. Independent component analysis (ICA) based on the independence among the spatial network patterns is proven a reliable data-driven approach for estimating the ICNs. The estimation of the ICNs adapted to the specific group data and reconstruction of the individual ICNs based on these group patterns further provide the possibility of calculating a scalar expression score based on the similarity of individual ICNs to the group ICNs. At Hulusi Behçet Neuroimaging Lab, we performed such analyses on data from patients with Alzheimer's and Parkinson's diseases with different levels of cognitive impairment, which will be presented in the talk.

Brain Connectome Analysis via Machine Learning

Prof. Dr. Burak Acar- Boğaziçi University, Electrical & Electronics Engineering

The segregative view of the brain is a composition of distinct regions responsible for certain tasks. Since late 19th century, this view has gradually evolved to, first an associationist view that, in principal, considers the relations between the regions, and more recently to the connectionist view that primarily models the brain as a collection of overlapping networks responsible for tasks. The connectionist approach studies brain networks that are composed of (primarily) cortical regions and their structural and/or functional connectivities, which we term as structural (sNET) and functional (fNET) connectomes, respectively. A major approach to build sNETs and fNETs is via diffusion MRI and functional MRI data, respectively, where the 3D tractography results and correlations of BOLD (Blood Oxygen Level Dependent) signals are used to establish the connectivities between pairs of cortical regions. There are a multitude of algorithms proposed to this end, without a common agreement. Despite this variability, the reported results show a certain degree of agreement, indicating the potential merit of connectome analysis. With the recent advances in data analytics, especially in machine learning and *graph* analysis, new approaches to brain connectome analysis, that are mathematically *graph* structures, have been proposed. Among them, tensor factorizations and graph embeddings are two promising lines of research. The former offers a joint representation and analysis of multiple connectomes, while the latter exploits the power of deep learning. The VAVlab group at Bogazici University, Electrical & Electronics Engineering Department (Istanbul, Turkey) is one of the first groups that pursued these approaches for connectome analysis for neurodegenerative diseases, such as Alzheimer's Disease. Initial results of our joint work with Istanbul University, ITF, Neurology Department and Koc University, Department of Physics, show the potential of these approaches in deciphering the neurodegenerative diseases.

ORAL PRESENTATION

Clock Drawing Test Analysis in Patients with Primary Progressive Aphasia and Behavioral Frontotemporal Dementia

Celal Şalçini, Dr, Üsküdar University, NPiSTANBUL Brain Hospital, Department of Neurology

OBJECTIVE: Clock drawing test (CDT) is a commonly used cognitive screening test. The aim of this research is to investigate the support that CDT will give to differential diagnosis between Behavioral Frontotemporal Dementia (bFTD) and agrammatic/nonfluent Primary Progressive Aphasia (naPPA) patients by using four points scoring system of CDT.

METHOD: The clinical data of 12 bFTD and 16 naPPA patients followed in NPIstanbul Brain Hospital were evaluated retrospectively. CDTs were scored according to the Sunderland and Borson's four points scoring system that have Turkish validation (1-3). In addition, Mini Mental Test (MMT) and CDT were applied to 20 healthy individuals. All patients met the criteria for the diagnosis of bFTD as recommended by Gorno-Tempini and naPPA by Rascovsky (4-5).

RESULTS: The bFTD group was significantly older than the naPPA group, but no significant difference was found for education and MMT scores (Table 1).

Table 1. Demographic characteristics of the participants, Mini Mental Test and Clock Drawing Test results

	bFTD (*n* = 12) *M (SD)*	**naPPA** (*n* = 16) *M (SD)*	**Kontrol** (*n* = 20) *M (SD)*
Age (year)	68.38 (8.37)	61.83 (5.98)	61.44 (6.76)
Education (year)	11.55 (4.22)	12.43 (4.55)	12.74 (5.46)
MMT (max = 30)	25.83 (1.02)	25.78 (0.80)	28.72 (0.35)
	3.45 (0.78)	3.55 (0.56)	3.86 (0.35)
CDT (max = 30)			

Abbreviations: bFTD, Behavioral Frontotemporal Dementia; naPPA, agrammatic / nonfluent Primary Progressive Aphasia; MMT, Mini Mental Test; CDT, Clock Drawing Test; n, number; M, mean; SD, standard deviation.

There was no significant difference between the CDT scores of bFTD and naPPA patients, while the error named “frontal pull” was observed more frequently in bFTD patients. Frontal pull was observed as 7/12 in bFTD patients and 3/16 in naPPA patients ($p < 0.05$).

DISCUSSION: The purpose of this short research is quantitative and qualitative review of the support that CDT will give to differential diagnosis between bFTD and naPPA patients. In the differential diagnosis of these two diseases, neurocognitive test batteries are also widely used in addition to clinical evaluation, neuroimaging methods and functional imaging tools (4-5). Although we did not find a score difference in the two groups in our study, we detect a significant difference in the frequency of “frontal pull” error which is defined as stimulus-dependent behavior (stimulus-dependent behavior) in bFTD group. The fact that the CDT has a narrow score range (0 to 4) and the low number of patients suggest that it may affect possible significant results in the quantitative evaluation of the application if number of patients decrease. However, in the qualitative evaluation, it was thought that the frontal pull error between the two groups was due to the different anatomical and pathophysiological involvement of this two diseases. While naPPA is known to begin as left inferior frontal insula and anterior temporal dysfunction, bFTD starts from frontal lobes (6). The frontal pull phenomenon is linked with dysfunction of frontostriatal pathways, and the fact that the frontal regions are affected at early stages of bFTD support this hypothesis (7). This articles suggest that CDT can help in differential diagnosis between dementias.

Keywords: Clock Drawing Test, Primary Progressive Aphasia, Behavioral Frontotemporal Dementia

Tedaviye Dirençli Depresyonda Kronotipin rTMS Tedavisine Cevap ile İlişkisi

Gökben Hızlı Sayar, Hüseyin Ünübol, Nevzat Tarhan- Üsküdar University

Giriş: Sirkadyen ritim bozukluklarının majör depresif bozukluğun önemli bir bileşeni olduğu bilinmektedir. Yirmi dört saatlik sirkadyen ritimlere bağlı görülen fizyolojik ve psikolojik değişikliklere göre bireyler "sabahçıl" ve "akşamcıl" olarak sınıflanabilmektedir. Geçmiş çalışmalar akşamcıl tipin daha şiddetli depresif belirtiler ile ilişkili olduğunu düşündürmektedir. Bu çalışmanın amacı sabahçıl – akşamcıl tip sirkadyen ritmin tedaviye dirençli depresyonda transkranial manyetik uyarım tedavisine (rTMS) cevap ile ilişkisini incelemektir.

Yöntem: Çalışmada tedaviye dirençli depresyon tanısı ile standart protokol rTMS uygulanmış olan sağ elli, kadın hastaların verileri retrospektif olarak incelenmiştir. Majör depresif bozukluğu eşlik eden tıbbi tanısı olmayan, geçmişte iki ayrı antidepresanı yeterli doz ve süre kullanıma rağmen tedaviye cevap vermemiş olan 74 olgunun verileri kullanılmıştır. rTMS protokolü tüm olgularda sol DLPFC alandan %110 MT, 25 Hz, 1000 vuru, toplam 20 seans olarak uygulanmıştır. Bu olgular İnsan Sirkadiyen Ritminde Sabahçıl Akşamcıl Tipleri Belirlemede Kendi Kendini Değerlendirme Anket Formu ile değerlendirilmiştir. 74 olgunun 20'si akşamcıl, 28 i sabahçıl, 26 sı ara tip olarak gruplanmıştır.

Bulgular: Üç grup arasında tedaviye cevap oranları istatistiksel olarak anlamlı farklılık göstermemiştir. Geçmiş depresif nöbet sayısının azlığı, depresif nöbetin süresinin kısalığı ve genç yaş tedaviye cevabın yüksekliği ile ilişkili bulunmuştur.

Tartışma: Literatürde sabahçıl tip kronobiyolojinin depresyonda daha düşük belirti şiddeti ve daha iyi antidepresan tedavi cevabı ile ilişkili olduğu bildirilmiştir. Bu araştırmada ise literatürde ilk kez kronobiyolojik tip ile rTMS'e cevabın ilişkisine bakılmış ve ilişki bulunamamıştır. Bu konuda daha geniş örneklem ile yapılacak kontrollü çalışmalar, kişiye özel tedavi seçeneklerinin belirlenmesi noktasında kronobiyolojik tipin kullanımı için yol gösterici olabilecektir.

Anahtar sözcükler: kronotip, depresyon, rTMS, tedavi cevabı

Baseline Prepulse Inhibition Levels Determine the Response to Sleep Deprivation and Orexinergic System Activation

Pınar Öz- Üsküdar University, FENS, Molecular Biology and Genetics

Orexinergic system is a key element of wakefullness and sleep transition, therefore, how it is involved in the etiology of sleep disorders and how it is modulated by sleep deprivation demands detailed research of medical cases and animal models. Here, we aimed to study the interaction between orexinergic system, sleep deprivation and prepulse inhibition (PPI) in rats. The rat population displays a natural diversity in PPI responses, therefore, the rats were grouped as low-PPI and high-PPI animals depending on their basal PPI responses. Then, 72 hour REM sleep deprivation (REMSD) was applied. The impact of orexinergic system was also investigated via chronical i.p injection of orexin A (OXA) for 96 hours with and without REM-SD. Our result show that (1) there is a baseline PPI dependency on the impact of REMSD on PPI, where only high-PPI animals display the PPI response disruption. (2) The effect of OXA is also dependent on baseline PPI and similarly only the PPI response of high-PPI animals were attenuated by chronic OXA administration. (3) OXA does not have a significant disruptive or protective effect when administered during REMSD.

Safety Aspects of Transcranial Direct Current Stimulation Concerning Conduction Aphasia Patients

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Transcranial direct current stimulation (tDCS) is an increasingly used method in the clinical practice for treatment purposes and in scientific studies for research purposes due to the changes in the cortical excitability it creates. The aim of this study is to examine the tDCS sessions in the treatment of conduction aphasia, a neurodegenerative disease, in terms of side effects. In the study, twenty-one conduction aphasia patients aged between 27-79 years who received active (n=11) or sham (n=10) stimulation participated in 2 mA and 20-minute anodal stimulation sessions to the left inferior frontal gyrus for 5 consecutive days. The tDCS Side Effects Questionnaire was administered to the participants after each tDCS session. The questionnaire includes evaluations that measure the presence and severity of conditions such as headache, neck pain, pain in the scalp, burning of the scalp, tingling, redness of the skin, drowsiness, problems with attention and acute mood change. Accordingly, side effects were reported due to tDCS stimulation by 38% of all 105 stimulation sessions and a total of 64 side effects were reported, of which only 39% (n=25) were reported after active stimulations. The most common side effects reported during active stimulation were redness of the skin (n=5), pain in the scalp (n=4), and tingling (n=4). However, the severity of these effects was rated as mild by the participants. These results reveal that the side effects reported after tDCS sessions were quite low in both frequency and severity, and suggest that tDCS is a safe and tolerable method.

Keywords: side effects, transcranial direct current stimulation (tDCS), safety study, anodal stimulation, conduction aphasia

Primary Progressive Aphasia in Turkish: A Case Study

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Aim: Primary Progressive Aphasia (PPA) is a neurological syndrome in which language abilities are slowly and gradually impaired. This study aims to determine and describe the language abilities, neuropsychological profile and daily living activities performance of a Turkish speaking person with PPA.

Method: In order to assess language, 'Language Assessment Test for Aphasia' (ADD); to evaluate neuropsychological abilities Judgement of Line Orientation Test, Benton Face Recognition Test, Clock Drawing Test, Trail Making Test, Simultanagnosia Test, Password Test, 3 Words 3 Shapes Test, Copying item of the Standardized Mini Mental Test; to examine motor abilities Edinburgh Handedness Inventory, Constructional Apraxia Test, Oral Apraxia Test, Diadochokinesis Test, Luria's Three-step Motor Test; to assess daily living participation Daily Living Activities Scale, Neuropsychiatric Inventory, Frontal behavioral Inventory, Social Network Index Scale and Caregiver Burden Scale have been administered.

Results: Regarding Aphasia Language Assessment Test, patient's speech fluency, auditory comprehension, automatic speech, repetition, naming, reading and writing abilities are severely affected. In addition to decline in the patient's language disorders, memory, attention and reasoning abilities are also affected and he has coexisting speech apraxia and orobuccal apraxia. Daily living activities are also negatively affected and it was determined that there is a significant decline in self-dependence.

Conclusion: Language, cognition and daily activities are affected in primary progressive aphasia. Interventions should be established by considering these areas. Keywords: primary progressive aphasia, dementia, language, cognition, daily living activities.

Keywords: primary progressive aphasia, dementia, language, cognition, daily living activities

Investigation of the Early Stage of Alzheimer's Disease at Proteomic and Metabolomic Level in the 5XFAD Transgenic Mouse Model

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Aim: Transgenic 5XFAD mice exhibit severe AD pathology by recapitulating amyloid-B-plaques, neuronal and synaptic loss and show differences in behavioral tests at 12th month. This study aims to identify proteins and metabolites with altered level of expression in 5XFAD mice at 3rd month in order to investigate possible early pathologic alterations in Alzheimer's disease (AD).

Methods: Cortical dissections from 5XFAD transgenic and control mice were performed at 3rd month (n=6). For proteomic analyses, cortex samples were treated according to FASP (Filter Aided Sample Preparation) protocol. All samples were analyzed using M-Class UPLC coupled to Xevo G2-Xs system (Waters) using CSH C18 column. For metabolomic analysis, cortical tissues were homogenized (n=6) with steel beads by bead beater. A prechilled methanol/water solution (1:1) was used for metabolite extraction. UPLC BEH HILIC column was used for analysis. Data analysis were performed with Progenesis QIP and Progenesis QI for proteomic and metabolomic analyses respectively. ClustVis software was used for statistical analyses. STRING and IPA software analyses were used for bioinformatic analyses.

Results: LC-MS/MS analyses were resulted in 1720 protein identifications. Among those, 78 proteins were found statistically significant ($p<0.05$ and fold change>1.3). 2200 metabolites were identified by Progenesis QI software. Alterations in several biological pathways were determined.

Conclusions: Proteomic and metabolomic alterations could give in-depth understanding of pathological mechanisms occurs in the early stages of AD and further analysis should be pursued for the evaluation of potential biomarkers for the early diagnosis of AD.

Keywords: Alzheimer's disease, proteomics, metabolomics.

Optical Coherence Tomography Findings in Alcohol Use Disorder

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Objective: Alcohol and illicit drugs affect neurons through various mechanisms and are detected by neuroimaging techniques. The optical coherence tomography (OCT) device has just been used in research on substance use disorders. In this study, we compared the retinal nerve fiber layer (RNFL), the ganglion cell layer (GCL), the inner plexiform layer (IPL), and choroid layer of alcohol use disorder (AUD) and healthy subjects.

Material and Method: We included 38 male patients and 38 male healthy controls of similar age ($p=0.714$) in the study, prospectively.

Results: Monthly income ($p=0.001$) and stable employment ($p=0.001$) were lower in the patient group. There was a significant difference between patient and control groups in terms of RNFL sectors, choroid, GCL, IPL values of both eyes were significantly different ($p<0.05$). When the effect of age and liver damage was controlled in the patient group, a correlation was found between alcohol unit/year and nasal superior ($r=-0.474$, $p=0.004$), temporal ($r=-0.402$, $p=0.015$) sectors of the RNFL. The regression analysis indicated that the sensitivity and specificity of mean N ($p=0.060$), mean choroidal thickness ($p<0.001$), mean GCL ($p=0.013$), and mean IPL ($p=0.017$) related to the diagnosis of AUD were 78.9 percent and 81.6 percent (-2 Log likelihood=57.57, Nagelkerke $R^2=0.622$), respectively.

Conclusion: Alcohol has neurotoxic effects, either directly or indirectly, with withdrawal. Our study results suggest that RNFL, the non-myelinated white matter tissue, can be a follow-up marker of neuronal damage due to cumulative alcohol intake.

Keywords: Retinal Nerve Fiber Layer, Alcohol Use Disorder, Optical Coherence Tomography

Investigation of Neurodegenerative Mechanisms in Neonatal 5XFAD Transgenic Mouse Model with MALDI-IMS

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Aim: Alzheimer's Disease (AD) is one of the most common neurodegenerative diseases in which cognitive impairment occurs in memory with age. Although the studies that cover the late stage of the disease elucidated many unknown, the fact that at which point the AD pathology begins and how it starts has not been elucidated. In our previous proteomic studies, it was observed that the neonatal proteome was similar to the postmortem AD human proteomic studies in the literature and the transgenic mouse model studies with the symptomatic period proteomic studies. These results have led to the idea that AD may exist as early as birth, then enter a latent period silenced by some mechanisms, and reappear in old age when the brain is more vulnerable to damage. The aim of this study is to investigate the changes in the brain of the neonatal AD mouse model in detail and to reveal the early stage molecular traces of AD pathology using MALDI-IMS technique.

Method: In this study, the AD transgenic mouse model containing 5 mutations (5XFAD), one of the useful in-vivo mouse models in AD studies was used. Sections of brain tissues dissected from neonatal (24 hours) 5XFAD mice were taken on glass slides coated with Indium tin oxide (ITO) with the aid of a cryostat (Thermo). Following the application of trypsin, the slides were incubated for trypsinization and then the suitable matrix for peptide analysis was applied on the slides. All of the MALDI-IMS analyzes were performed using the Bruker RapiFlex Tissuetyper MALDI- TOF/TOF device. The data obtained by MALDI-IMS was analyzed using SCILS 2D (Bruker) software and then various statistical methods were applied.

Results & Discussion: No MALDI-IMS studies of neonatal mice were found in the literature. Therefore, sample preparation in MALDI-IMS analysis required optimizations due to the lack of a reference point for MALDI-IMS experiments and the nature of the brain tissues dissected

from neonatal mice. The optimized protocol was applied to MALDI-IMS analyses. Then, segmentation analysis was performed on the obtained images using SCILS 2D software and a distinct regional separation was observed in the tissues. When the differences between regions were examined, statistically significant m/z values were obtained. These results showed that the regions can have different proteomic profiles and can be separated from each other. MALDI-IMS analyzes will provide us with valuable regional information on how brain physiology changes in the neonatal 5XFAD mouse model that cannot be obtained with expression studies. It is thought that the data obtained as a result of this study will reveal the underlying mechanisms of the early stage AD pathology.

Keywords: Neonatal, 5XFAD, Alzheimer's Disease, MALDI-IMS, Proteomics

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Cannabis Sativa And Alzheimer's Disease

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Alzheimer's disease (AD) is an irreversible, progressive brain disease that occurs in the middle and late age population, slowly destroying memory and doing simple tasks such as thinking skills. before the age of 65 in Turkey affects 5% of young people over 65 years old was seen in AD 30-40000, while the population over age 85 is observed in 30-50%. The disease is characterized clinically by the formation of synapses and neurons, gliosis, amyloid plaque and neurofibrillary tangles, which affect multiple systems such as memory, speech, high cerebral functions and visual spatial skills, progressive loss of cognitive functions, and neurological terms. Genetic, biochemical and neuropathological data show that Aβ aggregation plays an important role in the pathogenesis of AD. As a result of cutting APP, a normal neuronal membrane protein, an extracellular fragment called A diye 40/42 is formed around them. These neurotoxic fragments are produced and pooled together; Oligomerization of Aβ 40/42 results in plaque formation [1]. Under normal physiological form, glutamate is the first excitatory neurotransmitter in cortical and hippocampal cells and it has been reported that glutamate is responsible for 75% of the transmission in the central nervous system. Here, NMDA (N-methyl D-aspartate) stimulates its receptors, causing calcium ions to flow through the postsynaptic cleft into the neuron. Calcium ions transmitted to the neuron achieve high-level functions such as learning and memory in the brain. Aβ 40/42 plaques accumulating in Alzheimer's disease trigger excessive Ca^{+2} production with glutamate NMDA receptors. Excessive content of Ca^{+2} nitrite increases oxide, causing mitachondrial barrier and depletion of intracellular ATP levels, leading to neuronal energy loss, neuronal dysfunction, and cell death [2,3].

The use of cannabis (Cannabis sativa) is used for many medical and non-medical purposes, including in Asia. Although about 200 flights before Christ are mentioned in the Therapeutic Chinese Pharmacopoeia, the ability of cannabis to help elucidate the working agent (cannabinoids) structures and pharmacological action mechanisms has shed light on intensive studies conducted in the last 100 years at the time of knowledge [4]. In the studies, 538 natural compounds of Cannabis have been identified. In the literature, different studies about important active ingredients such as Tetrahydracannabiol (THC), Cannabidiol (CBG) are included in tea. It has been reported that it creates beneficial effects in disease pathogenesis

by reducing neuronal loss. It has also been stated that CB_1 receptor signals support nerve progenitor cell growth and regulate nerve cell differentiation. However, studies have not found enlightening results in the treatment of Alzheimer's disease.

Keywords: Alzheimer's Disease, Cannabis, Cannabis sativa

Executive Functions And Prospective Memory Changing in Mild Cognitive Impairment And Early Stage Alzheimer Type Of Dementia

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AIM: The aim of the study was investigating executive functions (EFs) and prospective memory (PM) in mild cognitive impairment (MCI) and early stage of Alzheimer type of dementia (EATD).

METHOD: The study sample included 30 MCI, 28 EATD and 21 healthy controls who applied to Erzincan Mengücek Gazi Training and Research Hospital Neurology clinic with complaint of forgetfulness. Participants were required to be 50 years or older and to have at least primary school education. WCST, Trail Making Test (TMT) and Controlled Oral Word Association Test (COWAT-KAS) were used to measure EFs; event and time based memory tasks were used to measure PM.

RESULTS: Results showed that MCI and EATD groups were significantly different from healthy controls in terms of many EFs test scores. Also, there was a significant difference between three groups in the total word number of K, S and K,A,S letters in COWAT-KAS (K letter: χ^2= 41,50, p< ,001; S letter: χ^2= 26,29, p< ,001; K, A, S total: χ^2= 34,84, p< ,001). Likewise, the three groups differed significantly from each other in some sub-scores of the PM tasks (event-based: χ^2= 45,86, p< ,001; time-based: χ^2= 43,35, p< ,001).

CONCLUSION: In this study it was found that EFs and PM were most impaired in EATD, performances of MCI participants were higher than EATD but lower than the healthy controls. The EFs test scores that reflects especially attention and inhibition and also PM test scores were lower while the perseveration test scores were higher in MCI and EATD than the healthy controls. In this context, the findings which obtained from the current study supported the literature findings which suggest that the impairment in EFs and PM that started in the MCI gradually increases in the EATD as parallel to cognitive deterioration.

Keywords: Mild cognitive impairment, Alzheimer type of dementia, executive functions, prospective memory

Investigation of Proteomic Changes in the Brain Tissue of Huntington's Disease Transgenic Mouse Model by MALDI-MSI

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Introduction

Huntington's Disease is an autosomal dominant neurodegenerative disease that occurs with the increase of CAG repeats in the huntingtin gene. In various studies, the mechanism of the disease has been revealed by genetic research. Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry Imaging (MALDI-MSI) is a recent proteomics technique that works directly on tissue sections. The number of proteomics-based studies on the disease are small and the expressional differentiation of proteins has not yet been demonstrated with MALDI-MSI. MALDI-MSI analyzes of brain tissues belonging to the 12-months-old YAC128 transgenic mouse model has been carried out in order to explore various mechanisms of the disease and to contribute to the literature. In data processing, in addition to SCILS-Lab software, a new calculation method that is developed in our lab with literature review has been used. Proteins with expression differences between transgenic and control groups have determined by MALDI-MSI.

Material-Methods

Open field test has been applied to evaluate the locomotor activity and anxiety of transgenic and control mice at 12 months. Following the behavioral experiments, mice have been sacrificed and their brain tissues have been sectioned for MALDI-MSI. Various statistical tests (t test, Cohen's d test) have been applied after m/z values obtained from MALDI-MSI analysis of transgenic (n = 6) and control (n = 6) brains were grouped among each other.

Results

Transgenic and control mice have differentiated statistically according to the behavioral test results. With the identification of the proteins belonging to m/z values obtained from MALDI-MSI analysis, 22 proteins that differ in transgenic and control mice have been determined.

Conclusion

By combining the strong features of LC-MS/MS and MALDI-MSI proteomics techniques, regional proteome changes on the tissue have been detected.

Keywords: Neurodegeneration, Huntington's Disease, MALDI-Imaging, Proteomics, YAC128

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Molecular Effects of Natural Coumarin Compounds in the Treatment of Alzheimer's Disease

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Objective: Alzheimer's disease (AD), the most common form of dementia in the elderly, is a neurodegenerative disease characterized by cognitive impairment, advanced behavioral disorders, and death. The number of individuals diagnosed with AD and the social and economic burden on society is increasing rapidly with each passing day. However, there is still no treatment that halts or reverses the progression of the disease. In this project, we aim to identify potential drugs and reveal the molecular working mechanisms of coumarins, which are reported to be promising for AD treatment with in-vitro and in-silico.

Method: 2 natural coumarins with 2 different doses: Scopoletin (8mg/kg), Scopoletin (16mg/kg), Pteryxin 1 (P1), Pteryxin 2 (16mg/kg) were administered i.p for 7 days to 12 month-old (pathological stage) 5xFAD transgenic mice (n = 6-8). Possible effects of the coumarins on the learning and memory of the mice were detected by the Morris water maze (MWM) test. Action mechanism of the coumarins was investigated in 3 different regions of the brain, which are the cerebellum, cortex, and hippocampus via LC-MS/MS-based protein expression analysis. Differentially expressed proteins (DEPS) were analyzed with various bioinformatics methods. Finally, the amyloid-beta (Aß) load was evaluated by immunohistochemistry (IHC) and quantified by ImageJ.

Results: A statistical improvement was detected in P2-injected 5xFAD mice (P2) on the 6th day of the learning phase of the MWM. 1630, 2290, and 1233 proteins were identified in the cortex, hippocampus, and cerebellum, respectively. DEPs ($p \leq 0.05$, $q \leq 0.05$, fold change >

1.3) in the cortex were analyzed by various bioinformatics tools such as hierarchical clustering and principal component analysis indicated that P2 evidently stood out from the others. 47 DEPs were detected that altered only in P2 such as apolipoprotein E (APOE), amyloid precursor protein (APP), glial fibrillary acid protein (GFAP), and vimentin, which were approximately 2-fold decreased. However, no statistically significant change was detected in the Aß load in P2 mice cortices.

Discussion: Improving the learning in MWM and having DEPs closely related to AD point out that P2 has a promising effect on the AD mouse model. APP, APOE, GFAP, and vimentin proteins are generally related to aß plaque load. Even though there was no change detected by IHC, we speculate that these proteins might indicate that P2 prevents further increase of plaque load. Also, the longer duration of injections or higher doses of pteryxin would have been effective. These results showed that further studies should be carried for investigation of the pteryxin as a promising therapeutics to alleviate AD pathology.

Keywords: Alzheimer's Disease, 5xFAD, Scopoletine, Pteryxin, Label-free Proteomics
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The Importance of Event-Related Potentials in Neurodegenerative Diseases

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Neurodegenerative diseases including Parkinson's disease, Alzheimer's disease, Multiple Sclerosis, which are frequently seen today; Neurons in the central nervous system are formed as a result of structural or functional loss and permanent damage. Major mechanisms of neuronal loss include excitotoxicity, mitochondrial energy metabolism disorders, increased intracellular calcium levels and free radicals. Since the treatment of many neurodegenerative diseases, the inability to inoculate the blood-brain barrier, the limited neurogenesis, the presence of active inhibitory substances and the development of neuroglial scar tissue, a definitive treatment method has not been found yet. In addition to the difficulties in treatment, most neurodegenerative diseases are progressive and early diagnosis is very difficult. Event-related potentials (ERPs) are the activations applied to electrical signal or or the electrical signals that occur in the brain against stimulus the individual by electroencephalography (EEG) Time-dependent voltage changes close to the discharge rate of these neural signals obtained for sensory, motor or cognitive states are a reliable method for psychophysiological analysis of cognitive connections. The data obtained from ERP's can be examined experimentally by using visual, auditory or somato-sensory stimulants in order to prepare for cognitive processes. Event-related potentials studies help to obtain extensive knowledge not only about psychophysiological processes but also about neurodegenerative diseases with motor and nonmotor effects. Event-related potentials are thought to have a very important place in both the early diagnosis and treatment of many neurodegenerative diseases.

Keywords; Neurodegenerative diseases, Event related potentials, ERP, ERP, Electroencephalography. Electrophysiology.

Effect of Interactive Metornoma Therapy On Neurodegenerative Diseases

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Rhythm and timing training is a stimulation that replaces a damaged function that controls muscle movement or temporal element that has an impact on the neurological aspect and movement of the brain. Interactime Metronome Therapy is the only educational program that develops in a systematic, flexible and attractive format to organize time rotation in the brain. Individuals can now not only adapt to rehabilitative shortcomings, but also re-function the brain's temporal processing network. However, conversational training physiologically alters the brain by helping to teach teaching networks. These networks are likely to be able to handle this damage. This is because timing is a general mechanism. The general timing mechanism is a "all-work" mechanism that shows in the overall efficiency of walking, sleep cycles, speech patterns, ability to participate over time, and brain communication. The exercises of IM include using complex, precisely timed movements that are mixed in focus, using time in the brain and cognitive processing and decision making to synchronize. IM treatment can not only help prevent the progression of Alzheimer's, but also help restore functions before.

Keywords: Interactive metronome, nuerodegenerative diseases

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