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The Journal of Neurobehavioral Sciences (JNBS) is a peer-reviewed open-access neuroscience journal without any publication fees. All editorial costs are sponsored by the Üsküdar University Publications and the Foundation of Human Values and Mental Health. Each issue of the Journal of Neurobehavioral Sciences is specially commissioned, and provides an overview of important areas of neuroscience from the molecular to the behavioral levels, delivering original articles, editorials, reviews and communications from leading researchers in that field.

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Preclinical and clinical studies are equally considered for publication. We also invite manuscripts on the methods of computational modeling of psychiatric and neurological disorders, and treatment outcome.

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BU SAYI HAKKINDA
ABOUT THIS ISSUE

JNBS 2. sayısı ile ülkemizde ilkleri gerçekleştirmeye devam ediyor. Türkiye' nin tamamı ile tek nörobilim temalı dergisi olan "Nörodavranış Bilimleri Dergisi" bu sayısında dünyaca ünlü Davranışsal Nörobilim Profesörü Dr. Gyula Telegy'nin Nöromedin S molekülünün transmiter aracılı etkilerini araştırdığı makalesine yer vermektedir.. Bunun yanı sıra dünyada ve ülkemizde önemi git gide artan 'Spor Genetiği' konusunda ülkemizin tanınmış araştırmacılarından Korkut Ulucan'ın Türk Basketbol Oyuncuları üzerinde tamamladığı araştırması da göze çarpmaktadır. Bu sayının bir diğer araştırma makalesi ise alkol kullanımı olan bireylerde Brezilya örnekleminde psikiyatrik eş-tanıların gözlemlendiği Dr. Fortunata' nın yaptığı araştırmadır.

Bunların yanında 'Sistemler Sinirbilimi' konusunda önemli çalışmalara imza atmış olan Bilkent Üniversitesi'nden Dr. Hulusi Kafalıgönül, görme sistemi konusunda doyurucu ve en güncel bilgileri içeren gözden geçirilmiş makalesi ile bu sayımıza önemli katkı sağlamıştır. Bir başka gözden geçirilmiş makale ise günümüzün trend konularından olan Alzheimer Hastalığı'nda erken tanıya yönelik yeni bir olay ilişkili potansiyel yöntemi Fatma Keskin Krzan'a ait... Koku duyusu ile ilgili bozulmuş olay ilişkili potansiyellerin Alzheimer hastalığında henüz daha belirtiler başlamadan ortaya çıktığına ilişkin son dönemde çok önemli çalışmalar bulunmaktadır. Krzan, gözden geçirmesinde bu çalışmalara kognitif sinirbilim perspektifinden önemli bir bakış sunmaktadır.

Bütün bu çalışmalara ek olarak bu sayıda, şizofrenide nikotin ve alkol bağımlılığı ile ilgili mini-gözden geçirme, klinik likantrofi ile ilgili olgu sunumu ve son olarak psikiyatrinin yeni trendlerinden olan yapay zeka algoritmalarının kullanımı ile ilgili editöre mektup yer almaktadır.

Keyifli okumalar dileği ile,

Assist. Prof. Cumhur Taş

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REVIEW ARTICLE

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VISION: A SYSTEMS NEUROSCIENCE PERSPECTIVE

GÖRME: SİSTEMSEL SİNİRBİLİMİ BAKIŞ AÇISI

Hulusi Kafalıgönül[*1]

Abstract

The visual system is the most studied part of the cortex, providing a basis for understanding not only visual processing per se but also the fundamental operations of the brain in general. Significant progress has been made in understanding neural structures sensitive to different visual attributes such as form, surface brightness, color and motion. Here, the basic neural structures and processing pathways for these visual features are reviewed. Dysfunctions in these processing pathways lead to deficits in the perception of different aspects of a visual object. In recent years, there is a growing interest in applying accumulated knowledge in vision science to investigate altered neural structures and abnormal perceptual processing observed in neurological disorders. Key issues and clinical studies are also discussed within the context of visual feature processing.

Keywords: visual cortex, dorsal pathway, ventral pathway, form perception, surface brightness, color, visual motion, abnormal visual processing

Özet

Görsel sistem korteksin en çok incelenen parçasıdır.Bu durum görsel sistemin sadece görmenin temelindeki sinirsel işlemler hakkında değil beynin genel çalışma prensiblerini anlamaya dayalı bir temel teşkil etmesinden kaynaklanmaktadır. Şu ana kadar farklı görsel özelliklere (örneğin şekil, yüzey aydınlığı, renk, hareket) duyarlı sinirsel yapıları anlamaya yönelik çok önemli ilerleme kaydedilmiştir. Bu makalede, görsel özelliklere duyarlı temel sinirsel yapılar and işlevsel yollar gözden geçirilmiştir. Herhangi bir işlevsel yoldaki fonksiyonel bozukluk farklı görsel özelliklerin algısında eksikliklere yol açmaktadır. Son yıllarda, görsel bilimdeki bilgi birikimini nörolojik bozukluklarda rastlanan sinirsel yapı değişikliği ve buna dayalı anormal algısal işlemleri anlamada kullanmaya yönelik artan bir ilgi bulunmaktadır. Bu yönde gerçekleştirilmiş kilit konular ve klinik çalışmalar da görsel özellik işlemesi bağlamında tartışılmaktadır.

Anahtar Kelimeler: görsel korteks, dorsal işlevsel yolu, ventral işlevsel yolu, şekil algısı, yüzey aydınlığı, renk, görsel hareket, anormal görsel işleme

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1. Introduction

A central problem in systems neuroscience is to understand how neural activity gives rise to perception and behavior. Vision provides an excellent model system to study how this happens. One third of the human cerebral cortex is dedicated to analyzing visual information and the processing hierarchy for visual information is very similar to the general functional structure in the brain. Therefore, deep understanding of visual system provides substantial information in order to shed light on this central problem of systems neuroscience. As a consequence of its general importance, the visual system is the most thoroughly studied of all sensory systems. The general organization, key neural structures and processing pathways have been identified for different aspects of a visual object such as form, surface brightness, color and motion.

I begin this review article with the overall organization of the visual system and key neural structures for vision. Developments in systems neuroscience and computational modeling suggest the existence of separate pathways for processing different attributes of a visual object. These developments and the data that support the existence of distinct processing pathways is the primary focus of the review. Moreover, dysfunctions in these distinct visual pathways and their influences on perception are discussed within the context of recent studies on schizophrenia.

2. Organization of the visual cortex

The visual system consists of hierarchically organized distinct anatomical areas (Felleman & Van Essen, 1991). These visual areas are interconnected through ascending feedforward projections, descending feedback projections, and projections from areas at the same hierarchical level (Van Essen & Gallant, 1994). The visual areas and their connections with each other lead to distinct pathways functionally specialized for processing different aspects of a visual object (Figure 1a). In fact, this specialization starts from the retina. There are three types of retinal ganglion cells magnocellular, parvocellular and koniocellular (Merigan & Maunsell, 1993). Magnocellular and parvocellular cells constitute the major population of the ganglion cells (90%). Magnocellular cells have fast-phasic responses, larger receptive fields and a rapidly saturating contrast response, whereas parvocellular cells have slow-tonic responses, smaller receptive fields and a linear contrast response (Kaplan & Shapley, 1986;

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Purpura et al., 1988; Schmolesky et al., 1998). These two populations of cells project to distinct layers of the lateral geniculate nucleus (LGN) and form two afferent pathways, the magnocellular (M) and the parvocellular (P). In addition to these feedforward connections, the LGN gets most of its input from the higher visual areas by feedback connections and acts as a regulator or filter of information passing to the cortex (Lamme & Roelfsema, 2000; Merigan & Maunsell, 1993).

The parallel pathways (M and P) start intermixing in the cortex (Merigan & Maunsell, 1993; Van Essen et al., 1992). In the primary visual cortex (V1), located posteriorly in the brain, neurons code simple features of a visual stimulus, such as orientation and edges. Moreover, neighboring points in the retinal image are projected onto neighboring points in cortex. This type of mapping is referred to as retinotopy. Further functional subdivisions and arrangements of neurons in V1 (blob and interblob regions) and V2 (thick, thin, and interstripe regions) have been identified by using a technique called Cytochrome Oxidase (CO) staining (Horton, 1984; Horton & Hubel, 1981; Tootell et al., 1983). The blobs in V1 contain neurons that are selective for color and relatively unselective for orientation. However, the opposite is true for the interblob regions (Livingstone & Hubel, 1988). Corresponding properties are found in the thin stripes and interstripes in V2 and color-sensitive neurons are far less common in V1 layer 4B (Lamme & Roelfsema, 2000).

In higher visual areas, more anterior in the brain, increasingly more complex features are processed. Receptive fields become larger and retinotopy breaks down. According to their connections, two cortical pathways emerge: dorsal and ventral (Figure 1a). The dorsal, magno-dominated, pathway flows to MT(V5) and parietal cortex and is mostly involved in space, movement and action. The ventral, parvo- dominated, pathway flows into temporal areas and is mostly concerned with object and pattern recognition (Milner & Goodale, 1995; Mishkin et al., 1983). Furthermore, large differences exist between response latencies of dorsal and ventral stream areas partly because of the different temporal dynamics of the magno- and parvo- pathways feeding into these areas.[1]

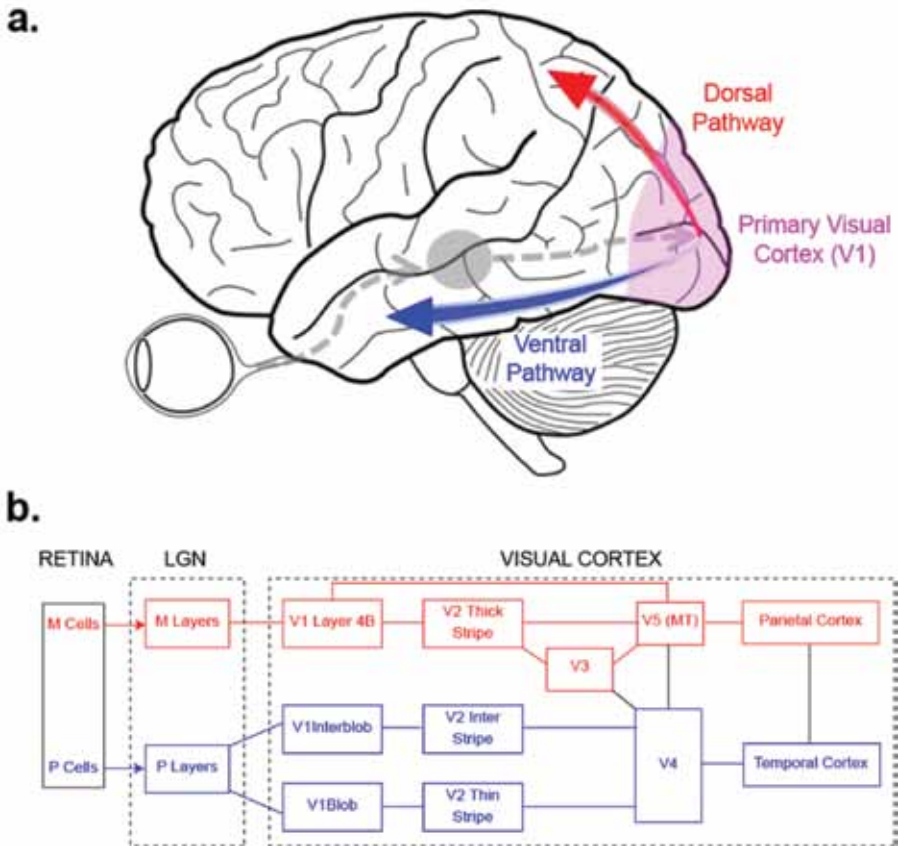

Figure 1. Hierarchical organization of the visual system. a) Schematic illustrating information flow from retina to primary visual cortex (V1) through lateral geniculate nucleus (LGN). The gray circle corresponds to LGN and the dashed gray arrows represent anatomical connections from retina to visual cortex. After primary visual cortex, visual processing continues in dorsal (red) and ventral (blue) pathways. b) The segregations and connections between early visual areas. Boxes correspond to visual areas or neural structures/ compartments within a visual area. The connections between different neural structures are represented by solid lines. To avoid clutter, only key neural structures and connections are shown.

3. Processing pathways for different attributes of a visual object

Form, Surface Brightness and Color

Perception of form (i.e., contour) and surface features (e.g., brightness and color) are essential for recognition of objects in the environment. It is widely believed that these features are processed by different sub-systems within the parvo-dominated ventral pathway. Neurons at early stages of the visual system (V1 interblob) have orientation selective receptive fields and these receptive field types are accepted to contribute to the functional basis of form perception (Hubel & Wiesel, 1962). The outputs of these oriented contrast detectors are grouped over spatially long distances to generate the outline of a visual shape at the later stages of the processing stream. Form processing continues mainly by neurons in V2 interstripe and neural compartments in V4 specialized for shape processing. On the other hand, brightness and color processing is mostly carried out by neurons in V1

[1]The interactions between two pathways at different hierarchical levels are essential. Early level interactions and their perceptual consequences are briefly mentioned within the context of backward masking in the following sections.

blob, V2 thin stripe and neural compartments specialized for surface features in V4 (Figure 1b). Accumulating evidence by experimental and modeling studies support the existence of two sub-systems and also report that their processing dynamics is different: a fast system concerned with extracting contours and a slower system with assigning surface brightness and color (Breitmeyer et al., 2006; Grossberg & Mingolla, 1985; Lamme et al., 1999; Rogers-Ramachandran & Ramachandran, 1998).

In order to have a coherent representation of a visual object, these two sub-systems processing complementary information must be able to communicate and interact with each other. Several perceptual completion phenomena suggest that the interaction is achieved by means of spreading mechanisms and filling-in. The filling-in hypothesis states that brightness is perceived via a filling-in process initiated by luminance contrast boundaries. In some way, a response initially biased toward the boundaries fills-in to represent the interiors of uniform surfaces (Neumann, 2003; Pessoa et al., 1998). The filling-in hypothesis is supported by many studies (Pessoa et al., 1998). An interesting behavioral demonstration is designed by Paradiso and Nakayama (1991). They used a visual masking paradigm to investigate the role of edge information in determining the perceived brightness and the temporal dynamics of proposed filling-in hypothesis. In their experiments, they used a disk as a target. The disk was briefly flashed and after a variable stimulus onset asynchrony (SOA), a mask was presented. In different stimulus configurations, the mask stimuli consisted of a bright line, a circle, or an incomplete rectangle. For SOA values between 50 and 100 ms, the brightness of the central area of the disk was greatly reduced. The brightness of the central region was largely unaffected for SOA values greater than 100 ms. The striking result is that the decrease in perceived depended on the distance between target and mask and maximal suppression occurred at later times for larger distances. Basically, the temporally following contour mask seems to suppress the active spreading of the surface information in this visual phenomenon. Paradiso and Nakayama (1991)'s results are consistent with the hypothesis that brightness signals are generated at the borders of their target stimuli and propagate inward at a rate 6.7-9.2 ms/deg.

Visual motion

The processing of visual motion is essential for survival in a dynamic world. Visual motion is a source of information that can serve many functions for a behaving animal. These functions include establishing the three dimensional environment, estimating other objects' trajectories and velocities (Nakayama, 1985). One of the earliest computational models of motion detection was developed by Hassenstein and Reichardt (1956). Their behavioral measurements from Cholorphanus beetle led to a correlation model which is known as the "Reichardt detector". In order to detect motion, a Reichardt detector requires three basic operations: sampling, asymmetry, and nonlinear interaction. The input should be sampled at more than one location since motion is a vector that needs at least two points for its detection. These sampled data have to be processed in a slightly different way from each other to discriminate the direction of motion. Otherwise, the inputs to the Reichardt detector could be interchanged without affecting the output. Thus, the detector would not be directionally selective if it were symmetric. Furthermore, the outcomes are combined and compared by using a nonlinear operation. A simple way to do this final step is by multiplying (correlating) the two processed inputs. A similar motion detection mechanism was identified by neurophysiological studies of rabbit retina (Barlow & Lewick, 1965). Later, motion energy models were proposed as an alternative to the correlation models. Motion energy models emphasize the processing of motion in the spatiotemporal frequency domain. Although the underlying computations of the two models are equivalent, their neural implementations are different and later neurophysiological experiments from visual cortex appear to support the motion energy model implementation (Albright & Stoner, 1995; Borst, 2000; Clifford & Ibbotson, 2003).

These early models of motion detection assume that our perception of motion is driven by first-order changes in the intensity of light on the retina. However, subsequent psychophysical experiments have shown that we can still perceive motion in the absence of first-order cues, when only second-order properties of the image such as contrast, chromatic content or spatial frequency change. Motion systems which are sensitive to the first and second order properties of a stimulus are called first and second order motion systems, respectively. These two motion systems are primarily monocular. Moreover, third order motion systems are identified by several studies of motion perception (Lu & Sperling, 2001). Third order motion systems are binocular and extract motion information from the spatiotemporal properties of salience (figure ground). Higher level visual areas and processes such as attention mechanisms are involved in the third order motion systems (Lu & Sperling, 2001). As mentioned below, the distinction between different motion systems have also been identified by recent functional imaging studies (Claeys et al., 2003; Ho & Giaschi, 2009).

Although some of the cells in the retina and thalamus respond to moving contours, it is generally agreed that explicit computation of motion starts at the primary visual cortex (V1) by directionally selective cells (Blake et al., 2003; Hubel & Wiesel, 1962). The neurons in V1 have small receptive fields and can only detect local motion signals inside their receptive fields. So, directionally selective neurons in V1 are considered as the low level motion detectors and called "local motion detectors". This situation shows a certain limitation of this first stage motion processing and leads to a well-known aperture problem (Adelson & Movshon, 1982; Hildreth, 1984; Wallach, 1935). When an observer views a long straight line through an aperture, the observer cannot discriminate different motion directions of the long straight line and can only detect motion orthogonal to the local contour. The aperture problem implies that directionally sensitive neurons in V1 always respond to a contour that crosses their receptive field (Hildreth, 1984; Nakayama & Silverman, 1988). In order to overcome the aperture problem and to obtain a coherent pattern motion, the local motion signals need to be integrated. It is widely believed that this second stage of motion processing starts at middle temporal gyrus (MT) and neurophysiological

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studies show that a substantial fraction of MT neurons have sensitivity to pattern motion (Rodman & Albright, 1989). Area MT gets most of its input from directionally selective cells in V1 and thick stripes of V2 (Movshon & Newsome, 1996; Zeki, 1974).[2] The integration of these local motion signals takes place in area MT and neurons in this area start responding to the true pattern motion with a 60 ms delay (Pack & Born, 2001).

Motion computation continues at the medial superior temporal area (MST). Neurons in MST have even larger receptive fields and show selectivity to binocular disparity and optic flow such as expansion and contraction. MST neurons are also sensitive to non-retinal information about eye movements (Blake et al., 2003; Duffy & Wurtz, 1991a, b). As one ascends the visual hierarchy in the magno-dominated dorsal pathway, cortical areas become sensitive to more complicated motion types. For instance, cortical area Inferior Parietal Sulcus (IPS: homologous to macaque area VIP and LIP) and lateral parietal cortex get input from visual and auditory areas and they can be selectively activated by both visual and auditory motion (Lewis et al., 2000). Inferior Parietal Lobe (IPL) gets activated by high-level attention based motion (i.e., third order motion) and it is considered a key neural structure for the bilateral higher-level saliency-based system (Claeys et al., 2003).

4. Dysfunctions in Visual Processing

Dysfunctions in early-stage visual processing impair our perceptual performance in a wide variety of visual tasks. These perceptual abnormalities have been documented even in neurological disorders (e.g., autism spectrum disorder, schizophrenia) and age related changes typically associated with higher-level cognitive processing (Butler & Javitt, 2005; Raudaia et al., 2010; Simmons et al., 2009). There has been an increasing interest to extend this line of research as an avenue to understand the altered neural circuitry and the resulting information processing for different aspects of a visual object in schizophrenia. Accordingly, several perceptual paradigms have recently been recommended for translational use in clinical trials by initiatives organized by National Institute of Mental Health (Gold et al., 2012; Green et al., 2009).

Several studies indicate that schizophrenic patients have abnormal form perception, contour integration as well as contextual influences on perceived brightness such as brightness induction and collinear facilitation (Green et al., 2009; Must et al., 2004; Yang et al., 2013). Even though these studies point out distinct early-stage dysfunctions in form and brightness processing, research using backward masking paradigm received the most attention. In backward masking, the visibility of a target stimulus is suppressed by a surrounding stimulus, called mask, following target. Typically, the reduction in target visibility is highest when the SOA between target and mask is around 30-80 ms. When the SOA becomes smaller or higher than this optimal value, the visibility of the target recovers. This U shaped nature of the target visibility has been used as a tool to gain insights into the temporal dynamics of brightness perception and relative timing of signals ascending through the visual system via different pathways (Breitmeyer & Ogmen, 2006). The dual-channel hypothesis has been influential and leading approach to account for the neural mechanisms underlying backward masking (Breitmeyer & Ogmen, 2006). According to the dual-channel approach, a visual stimulus generates a fast transient and a slow sustained activity in M and P pathways, respectively. These two pathways start interacting at early parts of the visual cortex. The slow sustained activity of the target is inhibited by the fast transient activity of the following mask through interaction between these two pathways. This inter-channel inhibition depends on the SOA between two visual stimuli and it accounts well for the U shaped visual backward masking function. Several research groups independently found that schizophrenic patients show a larger magnitude of masking and the masking effect is prolonged to higher SOA values relative to healthy participants. These results have been interpreted by changes in the interaction between two pathways due to M pathway dysfunction in schizophrenic patients (Butler & Javitt, 2005; Green et al., 2011).

Another well documented atypical perception in schizophrenia is visual motion perception. Schizophrenic patients have lower sensitivity to global motion and poorer speed discrimination relative to healthy controls (Chen et al., 1999). Moreover, center-surround interactions such as motion repulsion have been found to be abnormal in schizophrenic patients (Yang et al., 2013). These studies together with findings from backward masking and neuroimaging emphasize early-stage dysfunctions in the magnocellular pathway and deficits in key neural structures in the magno-dominated dorsal stream. The relationship between the early stage dysfunctions (and resulting abnormal perception) and social aspects of schizophrenia is still not clear. Future studies aimed at understanding this relationship will have significant contributions to the development of diagnostic tools and strategies for the treatment of this mental disorder.

5. Concluding Remarks

The visual system is the most thoroughly studied of all the sensory systems. This is due not only to the importance of the area covered in the brain by the visual system but also to its organization and pathways for different attributes of an object such as form, color and motion. Information processing is distributed in that neurons specialized in processing different stimulus attributes such as color and motion tend to cluster in distinct anatomical areas. Moreover, these distributed activities at distinct anatomical sites have different temporal dynamics. Significant progress has been made in understanding how the spatio-temporally distributed processing dynamics of the visual system is correlated with the basic features of a visual object. The accumulated knowledge and paradigms developed in vision research can be applied for understanding early-stage dysfunctions

[2] Besides these early neural structures, several studies (e.g., Tootell et al., 1997) found that neurons in area V3A are sensitive to visual motion and they have strong direction selectivity.

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in information processing and perceptual deficits in neurological disorders such as schizophrenia.

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IS DETECTING EARLY ONSET OF ALZHEIMER'S DISEASE IS GAINING A "NEW IDENTITY"? OLFACTORY DYSFUNCTION AS AN ERP BIOMARKER OF ALZHEIMER'S DISEASE.

ALZHEİMER HASTALIĞINDA ERKEN TANI YENİ BİR KİMLİK Mİ KAZANIYOR? ALZHEİMER HASTALIĞINDA BİR ERP BİYOMARKERİ OLARAK KOKU DİSFONKSİYONU

Fatma Keskin Krzan[1*]

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Abstract

The olfactory system is vital mechanism for our survival to interact with the environment, influencing not only on odor detection but also on nutrition, social behavior and well-being. Current findings suggest that before the onset of any cognitive decline reflecting early sign of dementia, dysfunction in the areas processing olfactory information is present at the early stages of Alzheimer's disease (AD). Behavioral test including thresholds, odor identification, recognition memory tasks are the most common types of odor measurement. However, recent neuroimaging techniques using measures of brain response, including Olfactory Event Related Potentials (OERPs) suggested the potential for detection of AD at the early preclinical stage. The importance of olfactory event related potentials and their relation with AD appear to be very promising.

Keywords: Olfactory Event Related Potentials (OERPs), Alzheimer's disease, Age, Olfaction, Apolipoprotein E

Özet

Koku alma sistemi bizim çevre ile etkileşimimizde hayatta kalmamız sağlayan, sadece koku algılamayı değil aynı zamanda beslenme, sosyal davranış ve iyi olma halini etkileyen hayati bir mekanizmadır. Güncel bulgular, koku bilgi işleme alanlarında fonksiyon bozukluğunun, Alzheimer hastalığının (AH) erken aşamalarında, erken bunamayı yansıtan herhangi bir bilişsel gerileme başlamadan da mevcut olduğunu göstermektedir. Koku eşikleri, koku tanımlama, tanıma bellek görevleri koku ölçümü için kullanılan en yaygın davranış testi türleridir. Ancak, beyin yanıt ölçülerini kullanan yeni nörogörüntüleme teknikleri Alzheimer hastalığının klinik öncesi aşamasında, Koku Olaya İlişkili Potansiyeller'in (KOİP), hastalığın tespitinde önemini vurgulamaktadır. Koku olaya ilişkin potansiyeller'in (KOİP) Alzheimer hastalığı ile ilişkisi ve önemi çok umut verici görünmektedir.

Anahtar Kelimeler: Koku Olaya İlişkili Potansiyeller (OERPs), Alzheimer Hastalığı, Yaş, Koku Alma, Apolipoprotein E

1. Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disease, related with early cognitive and behavioral dysfunctions, particularly in memory domain (Chapman et al., 2011). Although the disease mostly seen in the elderly, it can occur in middle to late adult life. This irreversible and progressive disorder insidiously destroys short – term memory, and finally goes further to destroy long term memory accompanied by cognition loss and functional decline; thinking, deterioration of language, perceptual and motor skills, mood instability (DSM-IV). AD worsens as it progresses, unresponsiveness occur in advanced stages followed by severe loss of mobility and control of bodily functions, and eventually leads to death (National Institute of Aging). According to NHS (National Health Service), the worldwide prevalence of Alzheimer's disease was 26.6 million in 2006. Current therapeutic advances and preventive approaches have small impact on the progression of the disease, yet can significantly contribute to delay in the global burden of AD (Brookmeyer et al., 2006). However, such contributions do not give significant outcomes, since the causes of AD are not yet known and postmortem autopsy and brain biopsy are the primary features for a definite diagnosis (Morgan and Murphy, 2012; Brookmeyer et al., 2006).

Genetic studies have confirmed that 10 percent of cases

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begin before the age of 60 are emerging as a result of a genetic mutation which is called the Apolipoprotein (ApoE) ε4 allele: a genetic risk factor for AD (Bertram and Tanzi, 2005; Teter et al., 2002; Farrer et al,. 1997; Blacker, 1997). Being carrier of even a single the Apolipoprotein (ApoE) ε4 increases the emergence of the disease by a factor of three in men and four in women (Morgan and Murphy, 2012; Blacker, 1997; Combarros et al,. 2002; Bertram, 2005; Farrer et al., 1997). Presence of the allele is associated with olfactory deficit accompanied by dysfunction in olfactory threshold sensitivity, odor identification, odor recognition memory, and odor fluency (Morgan and Murphy, 2012). Neuroimaging studies have found that degenerative changes in the olfactory system can be detected with using Olfactory Event Related Potentials (OERP) before the onset of any cognitive decline reflecting early sign of dementia, dysfunction in the areas processing olfactory information is present at the early stages of Alzheimer's disease (AD).

2. The Olfactory System

The olfactory system is vital mechanism for our survival to interact with the environment, influencing not only on odor detection but also on nutrition, social behavior and well-being (Huart et al., 2013; Ozdener and Rawson, 2004). These regions involved in olfactory system are located in medial temporal areas which are essential for conscious memory for facts (Squire et al., 2004). Odor identification is particularly sensitive to several cognitive changes with dementia (Morgan and Murphy, 2012). During the preclinical stage, although there is no any alarming cues about dementia, toxic changes, particularly in olfactory system, take place in the brain, and during this latent period, these areas undergo early neuropathological change in Alzheimer's disease (Squire et al., 2004; Murphy, 1999; National İnstitute of Aging). It was shown that abnormal accumulation of proteins that form amyloid plaques and tau tangles known as a primary marker of Alzheimer's disease throughout the brain (Huart et al., 2013; National İnstitute of Aging). This process causes neurons to work less efficiently, and eventually losing their ability to function, communicate with each other, and eventually ends in death (National Institute of Aging; Huart et al., 2013). Figure 1 shows Alzheimer type degenerative changes in the olfactory system, depicting the accumulation of neurofibrillary tangles (a protein as a primary marker of Alzheimer's disease).

Odor molecules reach the olfactory cleft, stimulating the olfactory receptor neurons that synapse with neurons at the olfactory bulb. The olfactory information is then carried to the primary olfactory cortex, including piriform cortex, located in the telencephalon and relates to the perception of smell (Piredda et al., 1985); entorhinal cortex which is located in the medial temporal lobe and functioning as center in a widespread network for memory and navigation (Hafting et al., 2005); periamygdaloid cortex located in the rhinencephalon; anterior olfactory nucleus, olfactory tubercle (Ozdener and Rawson, 2004). The information is then projected via primary olfactory cortex, among other areas, including the orbitofrontal cortex located in the frontal lobe, involved in the cognitive processing of decision-making (Kringelbach, 2005); the insular cortex located within the lateral sulcus, involved in consciousness

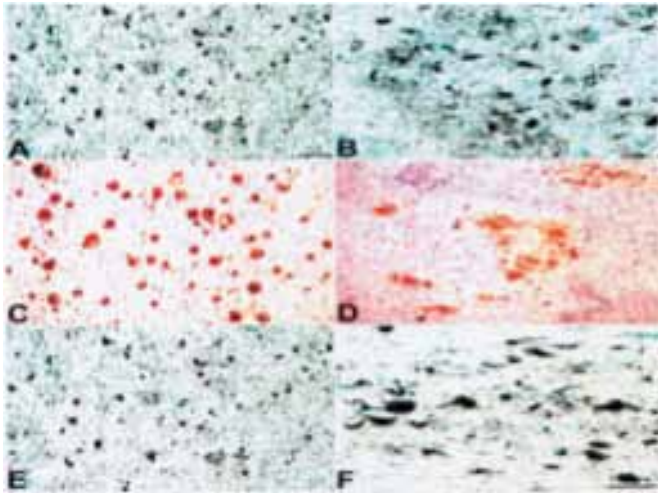

Figure 1. Photomicrographs illustrating the AD-type degenerative changes in the olfactory system in Alzheimer's disease (AD), depicting the accumulation of neurofibrillary tangles (a protein as a primary marker of Alzheimer's disease) in the frontal cortex (A) and in the olfactory bulb (B) (Gallyas silver technique). C and D also present amyloid ß deposition in senile plaques of the frontal associative cortex and olfactory bulb, respectively. E/ F depict an accumulation of neurofibrillary tangles in the frontal associative cortex (E) and anterior olfactory nucleus (F) showing degenerative changes of the olfactory system in the case of a young familial Alzheimer's disease. Adapted from Christen-Zaech and et al. 2003.

and related to emotion (Phan et al., 2002) or the regulation of the body's homeostasis (Oppenheimer et al., 1992); thalamus situated between the cerebral cortex and the midbrain, playing roles in the relaying of sensory and motor signals to the cerebral cortex (Sherman, 2006), and regulation of sleep and alertness; Hippocampus, a major component of the brain located in the medial temporal lobe and part of limbic system, having vital functions including the consolidation of information from short-term memory to long-term memory and spatial navigation (Kheirbeck and Hen, 2011). Additionally, it is the one of the first regions of the brain that shows a disruption as one of the earliest signs of Alzheimer's disease, leading a memory loss and disorientation (Hampel et al., 2008; Prull et al., 2000). Hypothalamus is the last destination where the information is processed for further analysis, and it is located below the thalamus. It has several major functions, including the regulation of hormone secretion, body temperature and some activities of the autonomic nervous system; hunger, thirst, fatigue, sleep, and circadian rhythms, as well it plays role on important aspects of parenting and attachment behaviors (Blair et al., 2006; Saper and German, 1987). Figure 2 shows a significant correlation between Alzheimer type cortical changes and the density of neuropil threads (loss of axon, dendrites and synapses), neurofibrillary tangles and senile plaques (extracellular deposits of beta amyloid in the gray matter of the brain) in the olfactory system.

Taking into consideration the fact that studies of the functional processes of the olfactory system will shed light on early diagnosis and prevention of Alzheimer's disease and may lead to new therapeutic approaches in the treatment of AD.

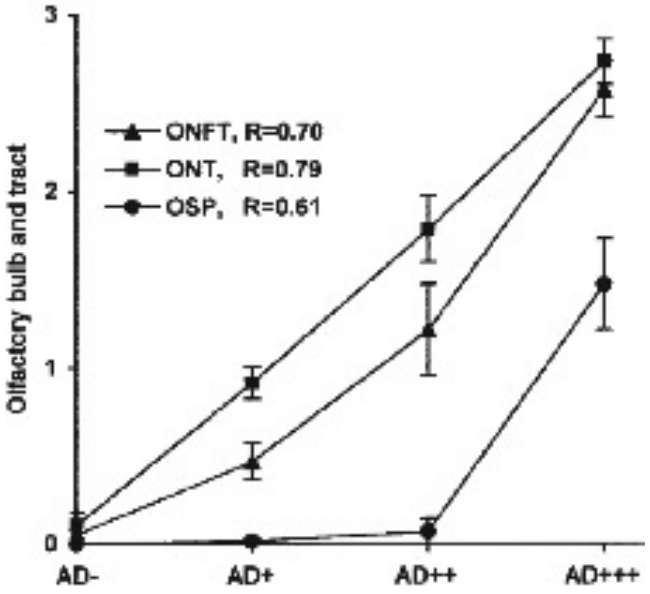

Figure 2. Early Olfactory Involvement in Alzheimer's disease. The severity of the changes in the olfactory system are significantly associated with the densities of neurofibrillary tangles (ONFT), neuropil threads (ONT) and senile plaques (OSP) in the olfactory system in the groups: without Alzheimer's disease (AD-), with discrete (AD+), moderate (AD++) and with severe (AD+++) cortical involvement, progressively increased with the severity of the cortical involvement. Adapted from Christen-Zaech et al., 2003.

3. The Olfactory event related potentials

There are many ways to measure olfaction. Behavioral test including thresholds, odor identification, recognition memory tasks are the most common types of odor measurement. However, recent neuroimaging techniques using measures of brain response, including fMRI and Event Related Potentials suggested the potential for detection of AD at the early preclinical stage (Bondi et al., 2005; Morgan and Murphy, 2012; Peters et al., 2003). Depending on ApoE status, recent OERP studies have found significant brain activity during odor identification, however fMRI studies revealed mixed results showing increased activation in ApoE+ individuals (Han et al., 2007; Bookheimer et al., 2000; Lind et al., 2006) or reduced activation in ApoE+ carriers (Lind et al., 2006) (Morgan and Murphy, 2012). Backman et al. demonstrated that individuals who were positive for the genetic risk factor the ApoE+ showed greater activation in the left and medial frontal gyrus, bilateral fusiform gyri, left pyramis and the parietal cortex (1999; Morgan and Murphy, 2012). Peters et al. also demonstrated electrophysiological findings of individuals with AD and with mild cognitive deficit, showing significantly lower olfactory functioning than healthy age-matched comparison group (Peters et al., 2003). More recently, Morgan and Murphy indicated that individuals with the ApoE+ showed different ERP latency with the onset of olfactory stimuli, however visual stimuli did not elicit any significant ERP component (2012). One of the robust findings from their study was to show significant different olfactory event related responses (OERP) based on ApoE+ condition and interactions with the age for each group. ApoE+ individuals produced significantly longer N1 and P2 latencies in comparison with ApoE- individuals.

A few previous studies using olfactory event-related potentials have demonstrated contradictory results. Despite the absence of psychophysical dysfunction of olfactory system, Sakuma et al. (1996) reported abnormal potentials, however, although the individuals odor identification scores were abnormal Hawkes and Shepard (1998) found normal event related potentials (Peters et al., 2003).

Despite few contradictory studies, a major effort is emerging to identify ERP biomarker of AD during odor identification. The most common peaks examined in OERP research are the N1, P2, and N2 are early exogenous components (stimulus driven activation) of the olfactory event related responses (OERP) that are associated with odor threshold and odor identification (See Figure 3) (Tonoike et al., 1990; Murphy, 1994, Morgan and Murphy, 2012; Krauel et al., 1998). These OERPs are more sensitive than classical behavioral methods measuring odor identification, and show higher specificity to ERPs obtained in other domains e.g. auditory or visual (Wetter and Murphy, 2001). A recent fMRI study revealed that behavioral tests showed no significant differences between male and female individuals, however increasing age correlated with a decline in odor identification performance (Evans et al., 1995). A significant correlation has been found between P2 latency and the generation of olfactory processing. Age related decline has been observed in N1-P2 inter-peak amplitude (Evans et al., 1995). It was also demonstrated that when the visual stimuli were demonstrated individuals with the ApoE+ showed different OERP latencies for identification of olfactory stimuli but not visual stimuli (Murphy and Morgan, 2012; Wetter & Murphy, 2001). ApoE+ individuals correctly identified and quickly responded to picture identification task, whereas the same ApoE+ individuals showed difficulties at odor identification.

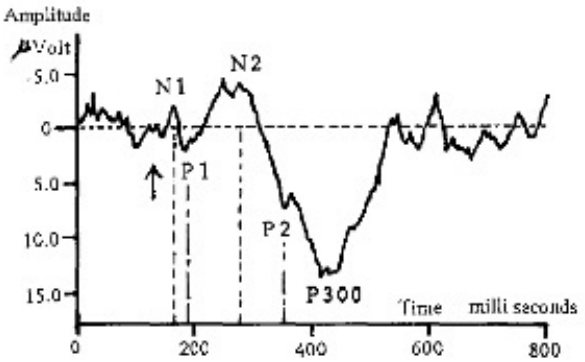

Figure 3. An illustration of the Olfactory Event Related Potentials (OERP) waveform with labeled peaks: The early major negative components N1 and N2 are followed by second late positive component P2 and P3 as endogenous potential with a latency of 250-600 msec reflecting processes involved in stimulus evaluation or categorization. Adapted from Tonoike et al., 1990.

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In another OERPs study, when the N1, P2, and N2 OERPs were compared to traditional olfactory psychophysical testing in an age related study, they found that when the odorant stimulus presented to the individuals the older participants showed smaller peak latencies and also longer ISIs (Inter-Stimulus-Intervals). Peak amplitudes also increased with longer ISIs for older males (Morgan et al., 1997; Morgan and Murphy, 2010, 2012). The P3 component reflecting cognitive processing; classification speed, evaluation of the stimuli is also used in OERP studies (Polich, 2007). The findings revealed that P3 peak latency correlates with neurophysiological test, measuring memory and classification speed (Covington et al., 1999; Murphy and Morgan, 2012).

Forecasting the early onset of AD, Chapman et al. used OERP to compare individuals with Mild Cognitive Impairment (MCI) (2007). Several different ERPs related memory storage and stimuli relevancy and P3 component obtained in a perceptual/cognitive paradigm. MCI individuals were separated into two groups: AD progress and stable groups, indicating the disease is progressing and there is no progress, respectively. They demonstrated that MIC progress individuals showed smaller P3 amplitude to relevant stimuli than MCI stable groups, implying that difficulty in evaluating and discriminating of relevant and irrelevant stimuli may predict AD-like cognitive decline (Chapman et al., 2011).

Current findings suggest that before the onset of any cognitive decline reflecting early sign of dementia, dysfunction in the areas processing olfactory information is present at the early stages of AD (Doty, 1994; Murphy, 1999). Furthermore, although the olfactory alterations related to AD may appear together with agedness, individuals at the early stage of AD with mild dementia show poor performance on olfactory identification task than age-matched control group (Peters et al., 2003; Geisler et al., 1999; Doty et al., 1987). Overall, the results suggest that compared with other methods, olfactory event related potentials (OERPs) reflecting online measures of olfactory processing with fine-grained temporal resolutions are more sensitive to changes in the olfactory system (Morgan and Murphy, 2012; Luck, 2005). The importance of olfactory event related potentials and their relation with AD appear to be very promising. Further researches on this topic are rewarding and may deepen our understanding of the nature of AD. Finally, this method may give opportunity to capture the early onset of dementia at the very earliest stages and yet enhance diagnosis of AD.

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RESEARCH ARTICLE

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OCCURRENCE AND PREDICTIVE FACTORS OF PSYCHIATRIC COMORBIDITY IN INDIVIDUALS WITH ALCOHOL USE DISORDERS.

ALKOL KULLANIM BOZUKLUĞU OLAN HASTALARDA PSİKİYATRİK KOMORBİDİTE OLUŞUMU VE YORDAYICI FAKTÖRLER

Mariana F. Donadon[1], Flávia L. Osório[1]*

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Summary

Alcoholism is a disorder caused by an excessive and maladaptive pattern of alcohol consumption. A series of impairments can arise from such consumption, including psychiatric comorbidities. The objective of this study was to evaluate the rate of occurrence of anxiety and depression comorbidities in alcoholics and to investigate the associations of such comorbidities with the dose of ingested alcohol, period of alcohol use, personality traits and the presence of early emotional trauma. The sample consisted of 110 alcoholics, evaluated by the Structured Clinical Interview for DSM-IV (SCID-IV – clinical version) and recruited at the Hepatopathy Outpatient Service of a University Hospital. Data collection was individual and took place through the application of self-evaluation instruments. Statistical analysis was performed using parametric statistics with a significance level of $p \leq 0.05$. The main results showed that 46.3% of alcoholics had psychiatric comorbidities with mood disorders and/or anxiety. In addition, according to the logistic regression model, the increase in the doses of alcohol ingested and the presence of early emotional traumas were risk factors for the development of such comorbidities in alcoholics: (ODDS=1.18; p=0.005) and (ODDS=1.17; p=0.001), respectively. These data indicate the need for early intervention with regard to the primary care of both alcoholics who suffered early trauma and alcoholics who ingest large amounts of alcohol daily to decrease the risk of psychiatric comorbidities in this high-risk group.

Keywords: Alcoholism; psychiatric comorbidity; early trauma; depression; anxiety.

Özet

Alkolizm, alkol tüketiminin aşırı ve uygunsuz şekilde kullanılmasının neden olduğu bir bozukluktur. Böyle bir tüketimden, komorbid psikiyatrik bozukluklar dahil, bir dizi bozukluk ortaya çıkabilir. Bu çalışmanın amacı, alkoliklerde anksiyete ve depresyon görülme oranını değerlendirmek ve bu tür komorbiditeler ile alınan alkolün dozu, alkol kullanım süreci, kişilik özellikleri ve önceden duygusal travmanın varlığı arasındaki bağlantının incelenmesidir. Çalışmanın örneklemi, DSM-IV için Yapılandırılmış Klinik Görüşme (SCID-IV- klinik versiyon) ile değerlendirilmiş, bir üniversite hastanesinin Hepatopati biriminde ayaktan tedavi servisinden alınmış 110 alkolikten oluşmaktadır. Veriler bireysel olarak ve öz-değerlendirme ölçeklerinin uygulanmasıyla elde edilmiştir. İstatistiksel analizler $p \leq 0.05$ anlamlılık düzeyinde parametrik istatistikler kullanılarak gerçekleştirilmiştir. Çalışmanın ana sonuçları, alkoliklerin %46.3'ünde duygudurum bozuklukları ve/veya anksiyete ile psikiyatrik komorbidite olduğunu göstermiştir. Buna ek olarak, lojistik regresyon modeline göre, alınan alkol dozundaki artış ve önceden duygusal travmanın varlığı alkoliklerde bu tür komorbiditenin gelişmesi için risk faktörleridir: sırası ile (ODDS=1.18; p=0.005) ve (ODDS=1.17; p=0.001). Bu veriler, hem önceden travmanın varlığından zarar görmüş alkoliklerden, hem de günlük olarak yüksek miktarda alkol tüketen alkoliklerden oluşan yüksek risk grubunda psikiyatrik komorbidite riskini azaltmak için birinci aşama tedavi ile ilgili olarak erken müdahaleye ihtiyaç olduğunu göstermektedir.

Anahtar Kelimeler: Alkolizm; psikiyatrik komorbidite; erken travma; depresyon; anksiyete.

1. Introduction

Alcoholism is a highly prevalent disorder caused by an excessive and maladaptive pattern of alcohol consumption (American Psychiatric Association, 2013). According to the World Health Organization (2004), two billion people in the world ingest alcohol, and 76.3 million of them have some type of disorder related to alcohol use, which is associated with social, financial and clinical losses.

Among the clinical aspects, comorbidity with other psychiatric disorders, such as mood disorders and anxiety, is prevalent. Clinical studies by Vicente et al.. (2001), Gratzer et al. (2004) and Ndetei et al. (2012) show comorbidity rates with mood disorders and anxiety ranging between 32% and 80%. These rates represent important clinical impacts and implications with regard to the treatment and prognosis of both disorders (Greenfield et al., 1998; Haver, 2003; Morley et al., 2013).

There are several different variables that may favor the

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associations between alcoholism and different psychiatric comorbidities, including the presence of genetic factors (Wang et al., 2004; Baigent, 2005), early emotional traumas (Fergusson et al, 2008), increased alcohol consumption (Logue, 1978; Morley et al., 2013), the influence of gender (Zilberman et al., 2002) and even the onset of alcohol withdrawal syndrome (Schuckit & Monteiro, 1988; Schuckit & Hesselbrock, 1994).

In this context, the objective of this study is to evaluate the rates of comorbidity with anxiety and depression in a sample of active alcoholics with clinical comorbidities at the liver level. Additionally, the associations of this condition with alcohol doses ingested, period of alcohol consumption, personality traits and the presence of early emotional traumas is analyzed.

2. Methods

2.1. Subjects

The sample consisted of 110 male patients over 18 years of age under treatment for alcoholic liver disease (hepatopathy and/or cirrhosis of the liver) in a University Hospital Center. All patients were diagnosed with alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), module E, applied via the Structured Clinical Interview (SCID-IV-clinical version).

2.2. Instruments

2.2.1. Structured and Clinical Interview for DSM-IV (SCID-IV - Clinical Version) – developed by First et al. (1996) and translated, adapted and validated for the Brazilian Population by Del-Ben et al. (2001).

2.2.2. Beck Anxiety Inventory (BAI) – developed by Beck and Steer (1993). Translated, adapted and validated for the Brazilian population by Cunha (2001). This self-administered instrument consists of 21 items that evaluate the severity of anxiety symptoms, which are scored on a Likert scale between zero and four. We considered a score above 20 as an indicator of pathological anxiety.

2.2.3. Patient Health Questionnaire (PHQ-9) – a self-rating instrument consisting of nine items based on the criteria of major depression proposed by the DSM-IV. The version translated and validated for Brazilian Portuguese was used in this study (De Lima Osório et al, 2009). We considered a score greater than or equal to 10 as an indicator of depressive symptoms.

2.2.4. Early Trauma Inventory Self Report – Short Form (ETISR-SF) – a self-rating instrument consisting of 27 items divided into four dimensions (general trauma, physical abuse, emotional abuse and sexual abuse) and scored on a dichotomous scale (yes/no). It was translated and adapted for the Brazilian population by Osório et al. (2013).

2.2.5. Revised NEO Five Factor Inventory – Short Form (NEO-FFI-R) – a self-rating instrument, proposed by Costa Júnior and McCrae (1985) and translated and validated for Brazilian sample by Costa Júnior and McCrae (2007), consisting of sixty items, scored on a Likert scale of zero to four points, which provide indicators of personality characteristics based on the Theory of the Five Factors (Conscientiousness, Neuroticism, Extraversion, Openness, Agreeableness).

2.3. Data Collection and Analysis

The data were collected individually and included in a database. The data were analyzed using parametric statistics, namely, a-) descriptive statistics to analyze the sociodemographic and clinical characteristics of the sample; b-) the Chi-square test and Student's t-test to compare groups; and c-) logistic regression to analyze predictive variables. The level of significance adopted was $p<0.05$.

The study was conducted in accordance with Declaration of Helsinki Research Ethic and was approved by the local ethics committee (Process HCRP no. 2316/2011).

3. Results

The sample consisted of 110 male subjects diagnosed with alcohol dependence. The average age was 53.78 years (SD=8.24), and 58.2% of subjects were married (N=64), 21.8% were widowers and/or divorced (N=24) and 20% were single (N=22). Education level varied, with a preponderance of subjects who completed elementary school (68.2%; N=62). With regard to employment, only 43.6% (N=48) of subjects were actively working. Clinically, 77.2% (N=85) of the sample had a diagnosis of cirrhosis of the liver due to alcohol, while the rest (27.8%; N=25) had other alcohol-related hepatopathies.

With regard to the presence of psychiatric indicators related to depression and anxiety, 46.3% (N=51) of subjects had signs and symptoms of depression and/or pathological anxiety, while 18.2% (N=20) had both conditions simultaneously. Separately, the rate of occurrence of depression indicators was 31.8% (N=35) and of pathological anxiety indicators was 33.7% (N=36).

Based on these rates, the subjects were separated into two different groups, one with psychiatric comorbidity (N=51; G1) and the other with no such condition, 64.9% (N=59; G2). The groups were compared with regard to certain sociodemographic indicators, and the results are displayed in Table 1.

According to Table 1, the groups differ in two variables: the presence of previous psychiatric treatment and employment status. With regard to the former, subjects in G1 underwent more psychiatric treatments than subjects in G2. Moreover, with regard to employment status, G1 had more inactive individuals than G2.

Table 2 compares the groups with regard to different clinical indicators. Accordingly with comorbidities have been alcoholics for a shorter period of time, ingested more doses of alcohol/day and experienced more emotional traumas in childhood than subjects with no comorbidities. Personality characteristics did not differ between groups.

When the regression model composed of the clinical indicators studied (listed on Table 2) was analyzed, a final model consisting of the variables alcohol doses/day (ODDS=1.18; p=0.005) and early emotional trauma (ODDS=1.17; p=0.001) was obtained. According to this model, the increase in doses ingested and the presence

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Table 1: Sociodemographic characteristics of the subjects according to the presence or absence of psychiatric comorbidity.

Variables		G1 (N=51) N	%	G2 (N=59) N	%	Statistics
Age/ Years	X (DP)	52.57	(7.30)	54.83	(8.89)	t=1.44; p=0.15
Level of education	ES	30	58.8	32	54.2	
	SE	18	35.2	18	30.5	x^2=2.49; p=0.28
	HE	3	5.8	9	15.2	
Professional Status	Active	17	33.3	31	52.5	
	Inactive	34	66.3	28	47.5	x^2=4.10; p=0.04*
Civil Status	Single	11	21.5	11	18.6	
	Marriage	29	56.8	35	59.3	x^2=0.14; p=0.92
	Widow/Divorced	11	21.5	13	22.0	
Psychiatric treatment	No	38	74.5	54	91.5	x^2=5.78; p=0.01*
	Yes	13	25.4	5	5.05	

Notes: N = frequency; (%) = percent; p = level of significance; X = average; SD = standard deviation; x^2= chi-Square test; ES = elementary school; SE = secondary education; HE = higher education/college; * = statistically significant; G1 = alcoholics' groups with psychiatric comorbidity; G2 = alcoholics' groups without psychiatric comorbidity.

Table 2: Clinical characterization of subjects according to the presence or absence of psychiatric comorbidity.

Variables		G1 (N=51) X (SD)	G2 (N=59) X (SD)	Statistics
	Time of alcoholism/Years	27.45 (10.5)	31.02 (11.7)	t=1.66; p=0.01*
	Doses of alcohol /day	9.04 (5.8)	6.42 (2.6)	t=-2.98; p<0.004*
	Early Emotional Trauma	10.47 (6.0)	6.59 (5.2)	t=-3.59; p<0.001*
	Openness (O)	13.04 (3.7)	14.12 (3.6)	t=1.54; p=0.13
Personality Factors	**Agreeableness (A)**	13.84 (4.0)	14.71 (5.7)	t=0.90; p=0.37
	Conscientiousness (C)	9.12 (4.6)	10.41 (7.1)	t=1.10; p=0.27
	Extraversion (E)	13.06 (3.3)	14.32 (5.0)	t=1.56; p=0.12
	Neuroticism (N)	13.31 (4.4)	13.22 (5.1)	t=-0.10; p=0.92

Notes: p = level of significance; X = average; SD = standard deviation; t = student's t-test; * = statistically significant; G1 = alcoholics' groups with psychiatric comorbidity; G2 = alcoholics' groups without psychiatric comorbidity.

of early emotional trauma are risk factors for the development of the psychiatric comorbidities studied in alcoholic patients.

4. Discussion

This study evaluated, among other aspects, the rate of occurrence of alcoholism comorbidities with indicators of mood disorders and/or anxiety.

In this context, the high rates of comorbidity occurrence found in this study, approximately 46.3%, are important. These rates are much higher than the ones found by Almeira-Filho et al. (2007), for example, who found anxiety rates of approximately 15.2% and depression rates of 13.4% in subjects who consumed alcohol daily. Additionally, with regard to impairment, the sample in the Almeira-Filho et al. (2007) study is believed to be better preserved, minimizing the impacts of other clinical conditions on physical condition, quality of life or even mood. Moreover, the sample consisted of individuals from the general population who did not necessarily fulfill the diagnostic criteria of alcohol dependence because such dependence was evaluated only by scales and questionnaires about alcohol consumption habits.

However, when the statistics from our study are compared to other clinical studies involving subjects diagnosed with alcohol dependence, differences in the opposite direction to the ones found in this study are observed. This difference is because in this study, rates substantially lower than the values in the study by Vicent et al. (2001) were found. Vicent et al. (2001) found occurrence rates of 78% moderate or severe depression among alcohol dependents, 20% moderate anxiety and 80% severe anxiety, evaluated by screening instruments different from the ones used in this study. In addition, in the study by Ndetei et al. (2012), the rate of alcohol dependence diagnosis associated with the presence of depression comorbidities reached approximately 63.8% of the sample. Such differences may be explained by the fact that the first study had a sample of alcoholic subjects hospitalized in gastroenterology and psychiatric wards, which had higher rates of impairment. Such impairments could be observed both at the time of data collection, considering the clinical need for a hospitalization treatment regimen and the experience of stress factors associated with alcoholism, and in the long term because the rate of suicide attempts in the sample was 30%.

In the second study, however, the difference may be explained by the fact that the sample was recruited in a rehabilitation center, where 22% of the sample made use of other psychotropic substances, which may contribute to a higher level of mood disorders.

With regard to the variables studied, both early emotional trauma and the number of alcohol doses ingested per day are important risk factors for the association between alcoholism and psychiatric comorbidities. These findings corroborate previous studies, which showed that individuals exposed to adverse experiences during childhood (Fergusson et al 1996; Anda et al., 2002; Fergusson et al., 2009) or who consumed a high number of alcohol doses (Logue, 1978; Boden & Fergusson, 2011; Morley et al., 2013) had an increased risk for the development of alcoholism conditions associated with psychiatric comorbidities in adult life.

In contrast to findings by Kotov et al. (2010), no association with personality traits was found. Kotov et al. (2010) observed that alcoholics with psychiatric comorbidities displayed greater neuroticism and less conscientiousness. A possible explanation for the absence of such evidence in this study may be the low score displayed by both groups for these two traits (approximately 20 points below the average score found in the normative study by Costa Júnior & McCrae, 2010), which may have prevented differences from being observed.

Ultimately, the results of this study have important clinical implications because of the high rates of co-occurrence of disorders with the observed risk variables. Thus, the need for early intervention in alcoholic subjects who suffered early traumas and/or who ingest large doses of alcohol is important and may contribute to a decrease in the presence of disorders and/or pathological symptoms of mood changes. Such a decrease is essential because the presence of psychiatric disorder indicators strengthens the existing barriers to the treatment of alcohol dependence and increases the clinical, social and economic losses experienced both at the individual and societal levels (Haver, 2003; Fergusson et al 2009; Morley et al., 2013). Therefore, integrated treatments that focus not only on the treatment of dependence but also on the reduction of further impairments are necessary. Moreover, the specific treatment of mood disorders and anxiety is also necessary, considering that in this study, only 25% of the subjects with comorbidities had received previous treatment for these conditions.

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ANALYSIS OF SOLUTE CARRIER FAMILY 6 MEMBER 4 GENE PROMOTER POLYMORPHISM IN YOUNG TURKISH BASKETBALL PLAYERS.

GENÇ TÜRK BASKETBOL OYUNCULARINDA SLC6A4 PROMOTOR POLİMORFİZMİNİN ANALİZİ

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Abstract

The serotonin transporter (5-hydroxytryptamine transporter, 5- HTT) gene (SLC6A4) is considered to be one of the most important candidate genes for genetic involvement in psychiatric conditions like anxiety, self- confidence and motivation. In the present study, we aimed to analyze the distribution of SLC6A4 promoter long and short (L and S, respectively) polymorphism in young Turkish basketball players. We enrolled 24 players in the study, 17 were females and 7 were males. 12%, 35% and 53% of the females had SS, LS and LL genotype, respectively; whereas 28,5% of the males had SS and the same percentage of them had LS, and 43% had LL genotype. When we examined the allelic counts, L allele was recorded as 71% in females and 57% in males; S allele was 29% in females and 43% in males. Our results were in agreement with the previous ones, indicating the presence of L allele in individuals dealing with sport. We suggest that SLC6A4 promoter analysis is important for genetic counseling for the individuals who are prone to be successful in sports.
Keywords: Serotonin transporter, sports, genetics, polymorphism

Özet

Serotonin taşıyıcı (5- hidroksitriptamin taşıyıcı, 5-HTT) geni (SLC6A4), anksiyete, kendinden eminlik ve motivasyon gibi psikolojik durumlara genetik yatkınlıklara neden olabilecek en önemli genlerden biri olarak nitelendirilmektedir. Bu çalışmada, genç Türk basketbol oyuncularında SLC6A4 geninin promotor bölgesi uzun ve kısa (sırasıyla L ve S) polimorfizminin dağılımını analiz etmeyi amaçladık. Çalışma da 17' si kız, 7' si erkek 24 kişi dahil olmuştur. 17 kız basketbolcunun sırasıyla %12, %35 ve %53' ü SS, LS ve LL genotipindedir, erkek basketbolcuların ise %28.5' inin genotipleri SS ve LS, %43' ünün de LL olarak bulunmuştur. Allel sayıları incelendiğinde L alleli kızlarda %71, erkeklerde %57; S alleli de kızlar da %29 ve erkeklerde %43 olarak bulunmuştur. Sonuçlarımız, sporla uğraşan bireylerde L allelinin bulunmasını destekleyen önceki çalışmaları desteklemektedir. Sonuçlarımıza dayanarak başarılı sporcu olma potansiyali olan bireylere genetik danışma verilmesinde SLC6A4 promotor bölgesinin genotiplenmesini önermekteyiz.
Anahtar Kelimeler: Serotonin taşıyıcı, spor, genetik, polimorfizm.

1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is a monoamine neurotransmitter synthesized from amino acid, tryptophan. Approximately, up to 90% of serotonin is located in enterochromaffin cells in the gut, regulating the intestinal movements; the rest is synthesized in serotonergic cells of central nervous system (CNS) (Berger et al., 2009). In CNS, 5-HT system, including serotonin, its receptors and downstream molecules, has various functions, like memory, learning, in cognitive and neuroendocrine functions and it is considered to be a contributor of the feelings happiness and self- confidence (Young, 2007). 5-HT system also involves in stress- related mood disorders in humans (Loughridge et al., 2013).

Serotonin is released to the synaptic cleft by serotonergic neurons, activates its receptors on the postsynaptic neurons, and the excess serotonin is taken back to the presynaptic neuron by carrier proteins and recycled in serotonin metabolism. This uptake process is maintained by serotonin transporters (5-HTT). The gene that encodes this carrier protein is solute carrier family 6 (neurotransmitter transporter), member 4 gene (SLC6A4) and is located at 17q11.1–q12 (Nakamura et al., 2000). Promoter region of SLC6A4 contains a functional

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polymorphism (5-HTTLPR), 14 or 16 repeats of a sequence leading to short (S) or long (L) alleles, respectively (Heils et al., 1996). Short allele and SS genotype is associated with decreased transcription of the gene, leading to the decreased number of carrier proteins, and increase in extracellular 5-HT. Decreased transcription rate and increased extracellular 5-HT may trigger the self-inhibition of 5-HT1A receptors. Therefore, S allele is considered to be responsible for some of the anxiety-related personality traits, hostility and depression (Lesch et al., 1996; Lesch and Merschdorf, 2000). On the other hand, L allele is the high- expression allele, and associated with resistance to stress and trauma (Caspi et al., 2003). Effect of this allele in psychological development of English national-level swimmers was reported before (Golby and Sheard, 2006).

Recent studies reported the association of 5-HT system and exercise. Rethorst et al. (2010) showed the antidepressant effects of exercise across 5-HTTLPR genotypes in 18–23 aged individuals and suggested the effect of this polymorphism in the treatment for depression. Prolonged exercises have influences in the development of fatigue due to the increase in extracellular serotonin concentrations (Meeusen et al., 2006). Works from the 1980s expressed the possible effects of exercise on serotonin metabolism in rats and the effect of exercise on positive mood psychology (Chaoulof, 1997). Animal models showed the increase of 5-HT after exercise (Jacobs, 1994). Chronic wheel running decreased 5-HTT mRNA levels in rat dorsal and medial raphe nuclei (Greenwood et al., 2005). Newsholme et al. (1987) were the first to relate 'central fatigue hypothesis' to the CNS 5-HT levels, other studies followed that to support the hypothesis (Trushkin et al, 2011). However, forced swimming, which is accepted as a model for depressive- like behavior in rodents, decreased the 5-HT concentrations in rats hypothalamus and amygdala (Shishkina et al., 2008). But the molecular studies including human subjects are not adequate to explain the exact mechanism in humans.

To date, reports trying to explain the effect of SLC6A4 5-HTTLPR polymorphism in sports are limited. The aim of the study is to examine the allelic distribution of SLC6A4 in young male and female basketball players and evaluate the possible effects of allelic differences on their sport motivation.

2.Methods

2.1. Subjects

A total of 24 basketball players, composed of 7 male and 17 females, aged between 15 and 18, were enrolled in the study. All the participants were the members of high school team and also playing for club teams, as well. They had at least 4 training sessions in different days of the week. All the players enrolled in the study showed their willingness to be a successful player, and doing their training for at least 3 years. The players who showed their unwillingness to be a basketball player and the one who had a decision to give up playing basketball were excluded from the study.

The study protocol was approved by the Üsküdar University Ethics Committee and the study procedure was in accordance with the principles of the Declaration of Helsinki II. Written informed consents were provided prior to enrollment from one of the parents who were in charge.

2.3. DNA sample collection: DNA was isolated from buccal cells by using Quick Extract DNA Extraction solution (Epicenter, Madison, WI, USA). The procedure for isolation was conducted according to the manufacturers' instructions.

2.4. SLC6A4 Genotyping

Functional polymorphism located in the promoter region of SLC6A4 is genotyped by using the primers 5'- GGCGTTGCCGCTCTGAATGC-3' and 5'-GAGGGACTGAGCTGGACAA CCAC-3'. PCR reactions were carried out in a 50 µl mixture containing 100ng genomic DNA, 5 µl 10X Taq buffer (1X final concentration), 1,5 mM MgCl2, 0,5 mM dNTP, 10 pmol of each primer and 2 U Taq DNA polymerase (Fermentas, Vilnius, Lithuania). The reaction was completed after 35 cycles and included pre-denaturation at 94°C for 7 min, denaturation at 94°C for 30 sec, annealing at 64°C for 30 sec, extension at 72°C for 30 sec and a final extension at 72°C for 10 min. 'L' allele gave rise to 528 bp after electrophoresis in 2,5% agarose gel visualized with ethidium bromide (0.2 g/mL) under ultraviolet light, whereas 'S' allele had 484 bp (Figure 1).

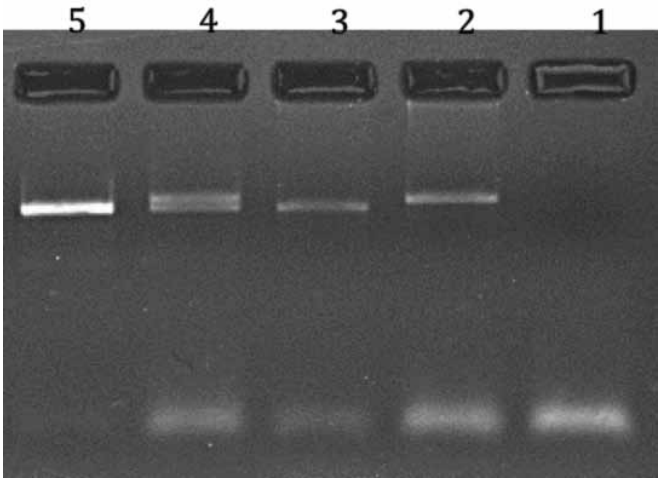

Figure 1. Agarose gel electrophoresis and the genotype results. Lanes; 1: SS genotype (484 bp); 2: LS genotype (484 and 528 bp); 3: SS genotype; 4: LL genotype (528 bp); 5: negative control.

3. Results

A total of 24 young basketball players were genotyped for the SLC6A4 promoter polymorphism in the present study (Table 1). Males constituted 29% of the study cohort and the females the rest. 2 of the males had SS genotype, again the same number of the males had LS, and 3 had LL genotype. In females 2, 6 and 9 had the genotypes SS, LL and LL, respectively (Table 1). Direct allelic count showed that 'L' allele dominated the 'S' allele in both genders (Table 1). 'L' allele direct count was found as 32 in the study cohort and lead to a 67% of the all genotyped individuals (data not shown in Table 1). Similarly, 'L' allele had a percentage of 71% in females, when compared to males, which was 57%.

Genders	Number (Percentage to the study cohort)	Genotype (Percentage in the same gender cohort)			Alleles (Percentage in the same gender cohort)	
		SS	LS	LL	S	L
Male	7 (29)	2 (28.5)	2 (28.5)	3 (43)	6 (43)	8 (57)
Female	17 (71)	2 (12)	6 (35)	9 (53)	10 (29)	24 (71)
Total	24 (100)	4	8	12	16	32

Table 1: Genders, genotype and allelic distribution of the study cohort. Percentage of the genotype and allelic counts were determined within the same gender groups, percentage of the genders were determined within the study cohort.

4. Discussion

Genetic and environmental factors such as nutrition play crucial roles on the development of individuals who have predisposition to sports. Hard-working, discipline, self and high motivation are some of the personal traits that are found in most successful players, or athletes, regardless to the nature of the sport they involve. Sport is associated with a high emotional and psychological pressure on players and endurance of stress has gaining great importance for sportive achievements. Therefore, not only training and nutritional stability, being in the best mood conditions, or staying away from depression and anxiety feelings is also important for the players or athletes during sports activity or in daily life.

Serotonin system is one of the key important systems regulating our mood condition, happiness or stress, and the role of serotonin in this system and motor control is complex (Takahashi et al., 2000). The biological metabolism underlying the process of serotonin and willingness to exercise is still not clear, but the possible role of serotonin in exercise was evaluated in some model organism. Meeusen et al. (1996) showed a rapid increase in the hippocampus 5-HT level at the onset of a moderate running in food-deprived rats. Gomez-Merino et al. (2001) reported a delayed increase in extracellular 5-HT in ventral hippocampus and the frontal cortex parts of rat brain after an acute intensive running. In addition to these findings, the increase in tissue 5-HT after prolonged or exhaustive exercise had been shown (Blomstrand et al., 1989). Another study showed the activation of serotonergic system in pedal exercise and reported that this exercise improved the negative emotion (Ohmatsu et al., 2014).

The studies including human subjects and 5-HTTLPR polymorphism in sport predisposition are very limited. In our study cohort, we analyzed the SLC6A4 promoter 5-HTTLPR polymorphism. We examined 24 young basketball players. Analysis revealed us that 12 of the players were LL, this genotype and L allele is regarded as active allele, and 4 of the players had SS genotype, this genotype and S allele refers the under- expression allele. 8 of the players were LS, which is regarded as intermediate genotype. 20 players had at least one L allele. We also expressed the gender differences; but this polymorphism and sport activities were not associated with gender differences before. Saunders et al. (2006) examined the related polymorphism in 428 Caucasian male triathletes, and showed that LL and LS genotypes, genotypes that are regarded as L allele, were much higher than the SS genotypes. Trushkin et al. (2011) evaluated the same polymorphism in 223 male endurance athletes and found that LL genotype was higher in athletes when compared to non- athletes. Our findings were similar with the findings of previous studies. In our cohort, L allele number (n=32) was twice as the S allele number (n=16). Sysoeva et al. (2009) examined 62 synchronized Caucasian female swimmers, and showed the higher percentage of LL genotypes when compared to control non- sport group.

It is very difficult to associate the 5-HTTLPR polymorphism with the sport metabolism. This gene was associated with neuroticism and anxiety before (Lesch and Merschdorf, 2000), but not in all studies (Willis-Owen et al., 2005). Also Sysoeva et al. (2009) showed the high aggressiveness and Novelty Seeking scores for the SS compared to LL carriers in synchronized swimmers. As the L allele was associated with resistance to stress and trauma, the possible explanation for this allele to dominate in our study cohort is that individuals are more prone to be successful in aggressive and stressful sports, like basketball. It is a known fact that genetic and environmental factors have roles on being an elite and successful player, or an athlete. But the exact biological system underlying this situation is hard to explain by only with the 5-HTTLPR polymorphism.

However our results evaluated the importance of L allele in basketball players, the number of the players enrolled in the analysis is the main limitation of the present study. Detection of the impact of the genetic influence to a certain phenotype requires large study cohorts. Our study group was consisted of 24 players, and this was the number of the individuals playing in that team. Despite the limitation, our results suggested the role of the 5-HTTLPR genotype in basketball activities. This was the first study carried out in Turkish young basketball players, according to best of our knowledge. Before, we reported ACTN3 analysis in young sprinters (Ulucan et al., 2014) and ACTN3 and ACE analysis in wind- surfers (Ulucan et al., 2013; Ulucan and Göle, 2014) but this study is the first trying to associate the serotonergic system and sport in young Turkish basketball players. Further studies with the high numbers of samples and including different sports types are needed to be carried out to fulfill the role of 5-HTTLPR genotype in sports.

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TRANSMITTER-MEDIATED ACTION OF NEUROMEDIN S ON PASSIVE AVOIDANCE LEARNING IN RATS

SIÇANLARDA TRANSMİTER ARACILI NÖROMEDİN S'İN PASİF KAÇINMA ÖĞRENME ETKİSİ

Gyula Telegdy[*1,2], Zsolt Bagosi[1] and Miklós Jászberényi[1]

Abstract

The possible involvement of different neurotransmitters in the action of neuromedin S (NMS) in the memory consolidation of passive avoidance behavior was studied by pretreating rats with different receptor blockers which alone did not change the test. The involvement of cholinergic, dopaminergic, adrenergic, serotonergic, opiate and GABA-ergic receptors and nitric oxide was tested. The animals were pretreated with the non selective muscarinic acetylcholine receptor antagonist, atropine, the non selective β-adrenergic receptor antagonist phenoxybenzamine, the β-adrenergic receptor antagonist propranolol, the D2, D3, D4 dopamine receptor antagonist haloperidol , the non selective 5-HT2 serotonergic receptor antagonist cyproheptadine, the nonselective opioid receptor antagonist naloxone,. the γ-aminobutyric acid subunit A (GABA-A) receptor antagonist bicuculline, or the nitric oxide synthase inhibitor nitro-L-arginine. Atropine, haloperidol, phenoxybenzamine, propranolol, cyproheptadine, naloxone and nitro-L-arginine prevented the effects of NMS on passive avoidance learning. Bicuculline did not change the effects of NMS.

The results demonstrate that muscarinic acetylcholine, α- and β- adrenergic, dopaminergic , 5-HT2 serotonergic and opioid receptors and nitric oxide are involved as mediators. In the action of NMS on the consolidation of passive avoidance learning.

Keywords: Neuromedin S passive avoidance learning, transmitters

Özet

Tek başına testi değiştirmeyen farklı reseptör blokerleri ile önceden muamele edilmiş sıçanlarla, pasif kaçınma davranışının bellek konsolidasyonunda yer alan nöromedin S (NMS) aksiyonuna farklı nörotransmiterlerin olası katılımları çalışılmıştır. Kolinerjik, Dopaminerjik, Adrenerjik, Serotonerjik, Opiat ve GABA-erjik reseptörlerin ve nitrik oksit katılımı test edilmiştir. Hayvanlara önceden non- selektif muskarinik asetilkolin reseptörü antagonisti atropin, non-selektif α-adrenerjic reseptör antagonisti fenoksibenzamin, β-adrenerjic reseptör antagonisti propranolol, D2, D3, D4 dopamin reseptör antagonisti haloperidol, non-selektif 5HT2 serotonerjik reseptör antagonisti siproheptadin, nonselektif opioid reseptör antagonisti nalokson, γ-aminobütirik asit altbirimi A (GABA-A) reseptör antagonisti bikukulin veya nitrik oksit sentez inhibitörü nitro-L-arjinin ile muamele edilmiştir. Atropin, haloperidol, fenoksibenzamin, propanolol, siproheptadin, nalokson ve nitro-L-arjinin, NMS'nin pasif kaçınmalı öğrenme üzerindeki etkilerini önlemiştir. Bikukulin NMS'nin etkilerini değiştirmemiştir. Sonuçlar muskarinik asetilkolinin, α- ve β- adrenerjik, dopaminerjik, 5-HT2 serotonerjik ve opioid reseptörlerin ve nitrik oksitin pasif kaçınmalı öğrenmenin konsolidasyonunda NMS aksiyonuna mediyatör olarak katıldığını göstermiştir.

Anahtar Kelimeler: Nöromedin S, pasif kaçınmalı öğrenme, transmiterler

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1. Introduction

Neuromedin S (NMS) is a new member of the neuromedin peptide family (Mori et al., 2005),. is highly expressed in the suprachiasmatic nucleus of the hypothalamus. Although NMS shares its C-terminal structure with neuromedin U (NMU), the N-terminal portion has no sequence homology to other known peptides, and these two neuromedins are coded by two different genes (Mori et al., 2005). NMU and NMS have been demonstrated to share their receptors, FM-3/GPR66 and FM-4/TGR-1. On the other hand, while they exhibit similar affinities for FM-3/GPR66, which may be responsible for the similarities in their effects, NMS binds with higher affinity to FM-4/TGR-1 (Mori et al., 2005), the receptor which may mediate the genuine physiological actions of this neuropeptide. The FM-4/TGR-1 receptor is confined almost exclusively to the CNS and its expression is highest in the hypothalamus, especially in the pararaventricular (Guan et al., 2001) and suprachiasmatic nuclei (Nakahara et al., 2004). The paraventricular expression argues for a putative role of the receptor in regulation of the pituitary-adrenal (HPA) axis and feeding, while the suprachiasmatic receptors may govern the sleep/wake cycle and the circadian rhythm of temperature, motor phenomena and hypothalamic hormone (e.g. gonadotropin hormone releasing hormone and corticotrophin releasing hormone CRH) secretion. Moreover, the distribution (abundant hypothalamic expression, mainly in the suprachiasmatic, paraventricular and arcuate nuclei) of NMS the expression itself raises the possibility that, similarly to other neuromedins (and

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especially NMU), it may play a role in the regulation of the above-mentioned hypothalamic functions (Mori et al., 2005, Murakami et al.2005). A recent publication has demonstrated that the expression of NMS is markedly higher than that of NMU in the hypothalamus (Rucinski et al. 2007), which suggests that NMS may predominate in central regulatory processes. Although few data are available as yet regarding its functions, they all reinforce this initial hypothesis. NMS has been demonstrated to influence the circadian rhythm (Mori et al., 2005), feeding (Ida et al., 2005; Shousha et al., 2006) and pituitary luteinizing hormone secretion (Vigo et al., 2006). In the background of these processes, the activation of paraventricular CRH secretion and pro-opiomelanocorotin release from the arcuate nucleus appear to play crucial roles (Ida et al., 2001). These data suggest that other CRH-related endocrine (HPA activation), autonomic (core temperature) and behavioral (anxiety-related motor phenomena) processes may also be influenced by NMS.

We earlier demonstrated that NMS exerted dose-dependent effects on the HPA system, which were inhibited by antalarmin, a CRHR1 receptor antagonist. It also activated grooming and decreased the entries to and time spent in the open arms during the elevated plus maze (EPM) test. The grooming response was abolished by haloperidol and antalarmin pretreatment, while diazepam and antalarmin displayed a tendency to attenuate the response evoked in the EPM test. In superfusion studies, NMS enhanced the release of dopamine from amygdala slices. These results demonstrate that NMS stimulates the HPA axis through the CRHR1 pathway, and evokes stereotyped behavior and anxiety through mesolimbic dopamine and CRH release. (Jászberényi et al.2007)

There have been no published data regarding the action of NMS on learning and memory processes and the possible involvement of certain neurotransmitters in these processes. It has been reported that, outside the hypothalamus, the NMS receptor is found in highest concentrance in the hippocampus, the amygdala, the thalamus and the cerebellum (Raddatz et al, 2000), which suggests its possible role in the regulation of cognitive, emotional and motor phenomena. The aim of the present study was to elucidate the role and action of NMS on fear- motivated learning and memory processes following i.c.v administration and the possible involvement of transmitters in these processes, by pretreatment of rats with receptor blockers.

2. Materials and Methods

2.1. Animals

Male Wistar rats weighing 150-250 g were used.. The animals were kept and handled during the experiments in accordance with the instructions of the University of Szeged Ethical Committee for the Protection of Animals in Research. The rats were kept in their home cages at a constant room temperature on a standard illumination schedule with 12-h light and 12-h dark periods (lights on from 6.00 a.m.). Commercial food and tap water were available ad libitum. The rats were allowed a minimum of 1 week to acclimatize before surgery. To minimize the effects of nonspecific stress, the rats were handled daily.

2.2. Surgery

For i.c.v. peptide, or nitro-L-arginine administration, the rats were implanted with a stainless steel Luer cannula (10 mm long) aimed at the right lateral cerebral ventricle under Nembutal (35 mg/kg, ip.) anaesthesia. The stereotaxic coordinates were 0.2 mm posterior, 1.7 mm lateral to the bregma, 3.7 mm deep from the dural surface, according to the atlas of Pellegrino et al. (1979). Cannulas were secured to the skull with dental cement and acrylate. The rats were used after a recovery period of 5 days. The correct location of the cannula was checked by dissecting the brain following completion of the experiments. Only animals with the correct location of the cannula were used in the evaluation of the experiments. All experiments were performed in the morning period.

2.3. Treatment

The peptide and nitro-L-arginine was given icv. The antagonists of neurotransmitters was given intraperitoneally. Following receptor blockers were used: Atropine sulphate from EGYS (Budapest, Hungary);); haloperidol from G. Richter (Budapest, Hungary); Phenoxybenzamine hydrochloride from Smith Kline & French (Herts, UK); propranolol hydrochloride from ICI Ltd. (Macclesfield, UK); cyproheptadine hydrochloride, from Tocris (Bristol, UK and); naloxone hydrochloride (Endo Labs, Wilmington USA). Nitro-L-Arginine methylester hydrochloride (Sigma St Louis USA). bicuculline methiodide from Sandoz (Basle, Switzerland were obtained. The receptor blockers doses were selected so that the blocker alone were ineffective but were able to block the action of a neuropeptide as described in previous studies (Telegdy et al. 2005 and 2013). Telegdy and Adamik 2013a,b, Tanaka and Telegdy 2014).

2.4.1. Passive avoidance test

One-trial learning, step-through passive avoidance behavior was measured according to Ader et al 1972. Briefly, mice were placed on an illuminated platform and allowed to enter a dark compartment. Since mice prefer dark to light, they normally entered within 5 s. Two additional trials were delivered on the following day. After the second trial, unavoidable mild electric footshocks (0.75 mA, 2 s) were delivered through the grid floor. Having entered the box, the animals could not escape the footshock. After this single trial, the mice were immediately removed from the apparatus and were treated. The consolidation of passive avoidance behavior was tested 24 h later. For consolidation, the animals were treated icv with neuromedin S, 0.5, 1.0 and 2.0 ug. in 2 ul volume. For further test the 2 µg was selected. The receptor blocker was given following the learning trial and 3o min later, the neuromedin S (2 µg). In the 24 h testing each animal was placed on the platform and the latency to enter the dark compartment was measured up to a maximum of 300 s. Each animal was used only once.

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2.5. Statistical analysis

Two way ANOVA test was followed by Tukey's test for multiple comparisons with unequal cell size. Probability values (P) of less than 0.05 are considered significant.

3. Results

The effects of NMS were tested on passive avoidance learning. in doses of 0.5, 1 and 2 µg i.c.v. 2 µg given i.c.v significantly facilitated the consolidation of passive avoidance learning ($F(3,22)= 9.21$; $p<0.05$) while 0.5 and 1.0 µg were ineffective (see figure 1). For combined treatment with each receptor blocker 2 µg i.c.v. was used.

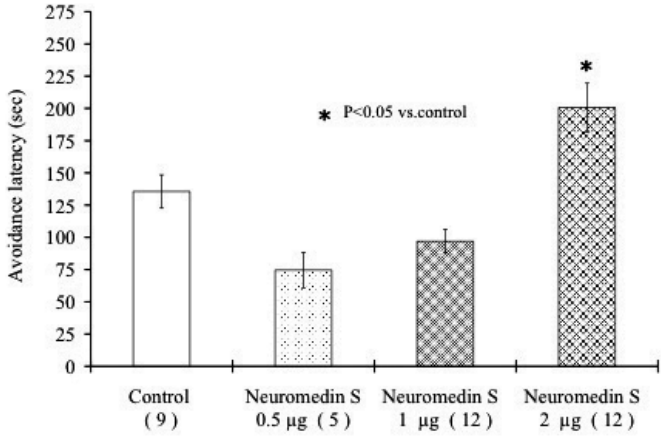

Fig. 1 The effect of different doses of neuromedin S on consolidation of passive avoidance learning. 0.5 and 1.0 μg were not significant in the passive avoidance response, while 2.0 μg i.c.v lenghtened the response. The mean ± S.E.M. are shown. Number in parentheses denote the number of animals used.

Atropine (a nonselective muscarinic acetylcholine receptor antagonist in a dose of 2 mg/kg b.w.,i.p. alone did not influence the test , however fully blocked the NMS (2 µg/ i.c.v.) facilitation of the passive avoidance learning. NMS alone significantly facilitated the passive avoidance learning ($F(3,22)= 10.63$; $p<0.05$; see figure 2)

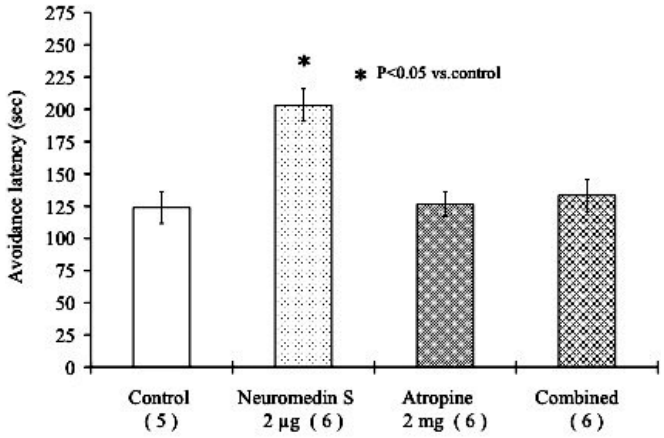

Fig. 2 The effect of nonselective muscarinic acethycholine receptor antagonist, atropine on the neuromedin S-induced (2 ug i.c.v) consolidation of passive avoidance learning (neuromedin S P<0.05 vs. control),combined (atropine 2 mg/kg i.p + neuromedin S 2.0 μg i.c.v). The mean ± S.E.M. are shown. Number in parentheses denote the number of animals used.

Haloperidol (10 µg/kg b.w. i.p.), (a D2 ,D3,D4 dopamine receptor antagonist) did not change the task, however fully blocked the NMS (2 µg/i.c.v) caused facilitation of passive avoidance learning. NMS alone facilitated the passive avoidance memory consolidation ($F(3,23) = 11.45$; $p<0.05$; see figure 3)

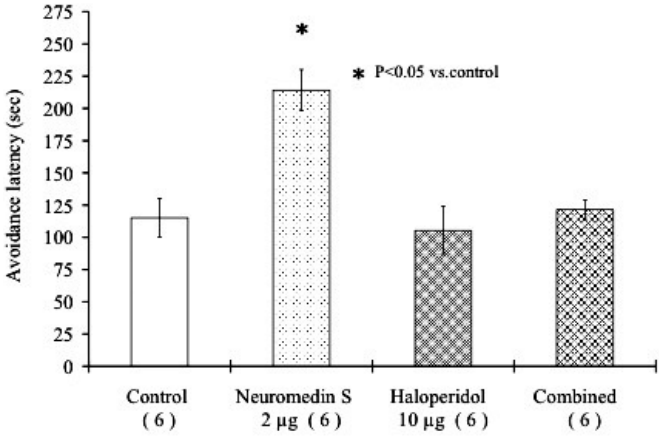

Fig. 3 The effect of a D2,D3,D4 dopamine receptor antagonist haloperidol on neuromedin S (2.0 μg i.c.v.)-induced consolidation of passive avoidance learning.(Neuromedin S *p<0.05 vs control) Combined (haloperidol 10 μg/kg i.p.+ neuromedin S 2.0 μg i.c.v). The mean ± S.E.M. are shown. Number in parentheses denote the number of animals used.

Phenoxybenzamine, (a nonselective α-adrenergic receptor antagonist) treatment (2 mg/kg b.w.,i.p.) alone did not change the task, however blocked the NMS (2 µg/ i.c.v) caused improvement of passive avoidance learning. NMS significantly facilitated the passive avoidance learning ($F(3,22) = 9.49$; $p<0.05$; see figure 4)

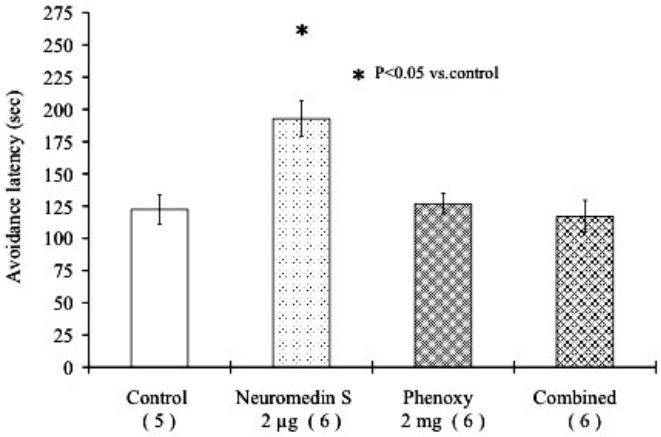

Fig. 4 The effect of a nonselective α-adrenegic receptor antagonist, phenoxybenzamine (Phenoxy) on neuromedin S-induced (2 μg i.c.v) consolidation of passive avoidance learning.(Neuromedin S *P<0.05 vs. control). Combined (phenoxybenzamine 2 mg/kg i.p.+ neuromedin S (2 μg i.c.v). The mean ± S.E.M. are shown. Number in parentheses denote the number of animals used.

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Propranolol (a β-adrenergic receptor antagonist, 5 mg / kg b.w.,i.p) alone had no action on the task, however partially blocked the NMS (2 µg/i.c.v) caused improvement of passive avoidance learning. NMS (2 µg/ i.c.v) alone significantly facilitated the passive avoidance learning ($F(3,21) = 6.40$; $p<0.05$; see figure 5)

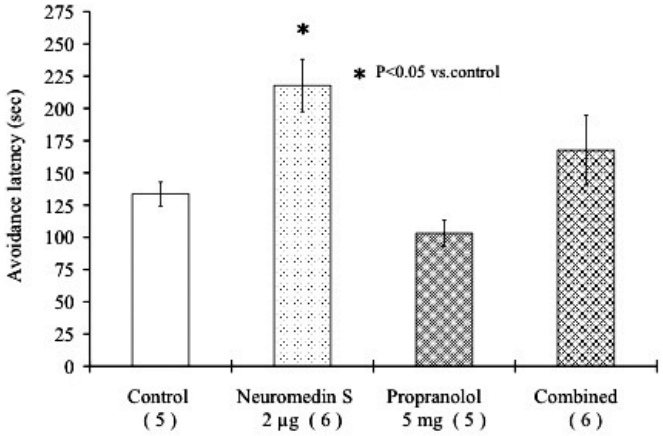

Fig. 5 The effect of β-adrenergic receptor antagonist propranolol on neuromedin S-induced (2 μg i.c.v) consolidation of passive avoidance learning.(Neuromedin S *P<0.05 vs. control). Combined (propranolol 10 mg/kg)i.p.+ neuromedin S-induced (2 μg i.c.v). The mean ± S.E.M. are shown. Number in parentheses denote the number of animals used.

NMS (2 µg/i.c.v) combined with cyproheptadine (a nonselective 5-HT2 serotonergic receptor antagonist, 5 mg/kg b.w.,i.p) pretreatment, cyproheptadine blocked NMS

(2 µg/i.c.v) facilitated the passive avoidance learning. Cyproheptadine had no action alone on the passive avoidance learning. NMS significantly facilitated the passive avoidance learning. ($F(3,22) = 7.88$;$p< 0.05$; see figure 6).

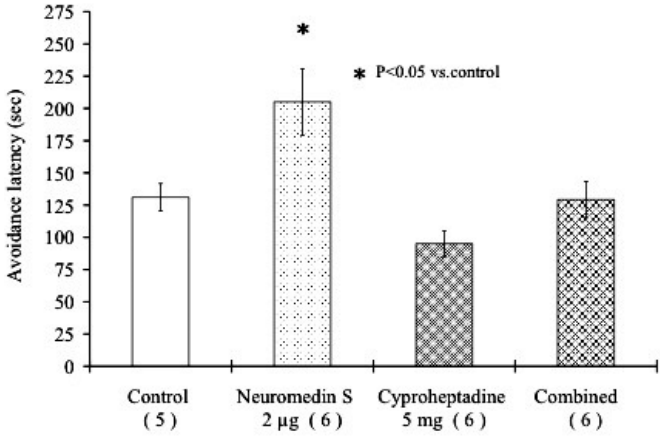

Fig. 6 The effect of cyproheptadine (5 mg/kg i.p.) a non-selective 5-HT2 serotonergic receptor antagonist on neuromedin S-induced (2 μgl i.c.v) consolidation of passive avoidance learning. (Neuromedin S *P<0.05 vs. control). Combined (cyproheptadine 5 mg/kg)i.p.+ neuromedin S (2 μg i.c.v). The mean ± S.E.M are shown. Number in parentheses denote the number of animals used.

Naloxone (0.3 mg/kg, b.w i.p.) a nonselective opioid receptor antagonist) alone had no action on the task, however blocked the NMS (2 ug/i.c.v) caused improvement of passive avoidance learning. NMS alone significantly facilitated the passive avoidance learning ($F(3,20) = 7.38$; $p<0,05$; see figure 7)

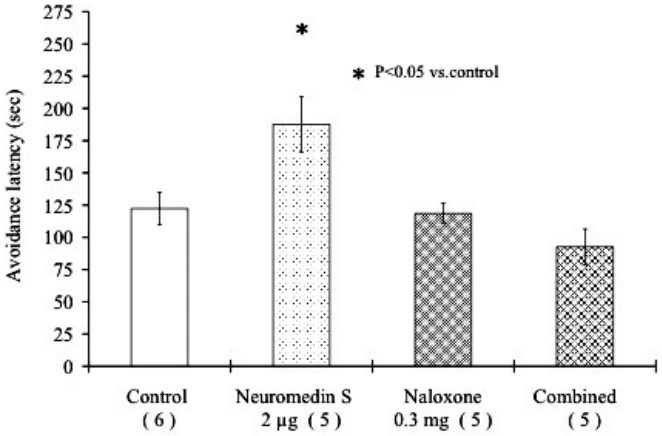

Fig. 7 The effect of a nonselective opioid receptor antagonist, naloxone (0.3 mg/kg i.p.) on neuromedin S-induced (2 μg i.c.v) consolidation of passive avoidance learning. (Neuromedin S *P<0.05 vs. control). Combined (naloxone 0.3 mg/kg i.p)+ neuromedin S (2 μg i.c.v). The mean ± S.E.M are shown. Number in parentheses denote the number of animals used.

Nitro-L-arginine (a nitric oxide synthase inhibitor), (10 µg/kg i.c.v) alone had no action on the task, however blocked the NMS (2 µg/i.c.v) caused improvement of passive avoidance learning. NMS alone significantly facilitated the passive avoidance learning ($F(3,20) = 9.44$; $p<0.05$; see figure 8).

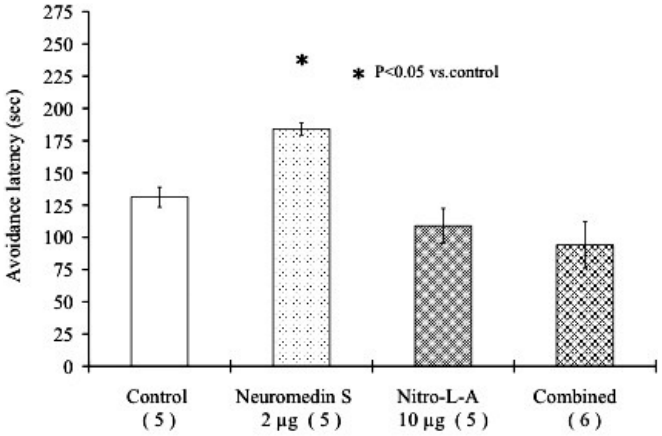

Fig. 8 The effect of a nitro-L-arginine (10 μg/kg i.c.v) (a nitric oxide synthase inhibitor) on neuromedin S-induced (2 μg i.c.v) consolidation of passive avoidance learning. Neuromedin S *P<0.05 vs. control. Combined (nitro-L-arginine 10 μg/kg i.c.v) + neuromedin S (2 μg i.c.v). The mean ± S.E.M are shown. Number in parentheses denote the number of animals used.

Bicuculline (1 mg/kg b.w. .i.p) (a γ-aminobutirc acid subunit (GABA-A) receptor antagonist) did not change the passive avoidance response significantly. Pretreatment with NMS (2 µg/i.c.v) bicuculline did not alter the NMS caused improvement of passive avoidance learning. NMS (2 µg/i.c.v) significantly facilitated the passive avoidance learning (F(3,23)= 3,79 P<0.05; see figure 9)

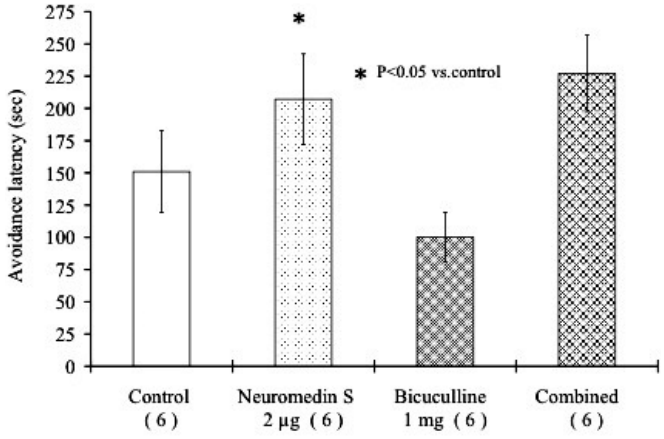

Fig. 9 The effect of a γ-aminobutyric acid subunit A (GABA-A) receptors antagonist bicuculline (1 mg/kg i.p.) on neuromedin S-induced (2 ug i.c.v) consolidation of passive avoidance learning. Neuromedin S *P<0.05 vs. control. Combined (bicuculline 1 mg/kg)i.p.+ neuromedin S (2 μg i.c.v). The mean ± S.E.M are shown. Number in parentheses denote the number of animals used.

4. Discussion

In this paper we demonstrate that NMS facilitate the passive avoidance learning and memory consolidation in rats. This action is mediated by number of neurotransmitters.

A fear-motivated learning, memory consolidation is a rather complex physiological process, which involves motivation, learning, memory consolidation, movement etc . It is generally accepted that neuropeptides are acting mainly as neuromodulators changing the activity of certain transmitters, however usually the transmitters involved in these processes are very seldom studied. In our previous study we proved that dopamine is important in the NMS action on HPA axis, grooming response, and anxiety. Furthermore in vitro superfusion study with NMS enhances dopamine release from the amygdale slices (Jászberényi et al 2007).

Comparing the transmitter mediation in passive avoidance response with other neuropeptides, although they are structurally different, the outcome of facilitating the passive avoidance response are the same, the transmitters are differ. Urocortin 1, apelin-13, kisspeptin-13 and NMS all are using cholinergic, α-adrenergic, serotonergic transmissions and the last 3 peptides, nitric oxide .The first 3 are using GABA-A receptors, however NMS is not. Nitric oxide has been used for apelin-13, kisspeptin-13 and NMS, however for urocortin1 is not. Dopaminergic receptor is used with the exception of kisspeptin-13 for all other three neuropeptides (Telegdy et al. 2005, 2013, Tanaka and Telegdy 2014, Telegdy and Adamik 2013ab) . These similarities and dissimilarities suggest that these peptides utilizing different neurotransmitters which finally will lead to a learning and memory processes. The exact nature of this details are at the present poorly understood. If we will know exactly all details (fear, motivation, movement, hormonal background etc) we could localize the side of action in term of transmitter interaction.

The close structural relation with neuromedin U (NMU) our previous work give a chance to compare the similarities and dissimilarities in action of the two neuropeptides Both peptides facilitate the activity of the pituitary-adrenal cortex (Jászberényi et al 2007, Ida et al.2005), however NMU is anxiolytic (Telegdy and Adamik 2013b) while NMS is anxiogenic (Jászberényi et al 2007). The transmitter mediation is not studied for NMS in depression and anxiety , while we have done it for NMU. (Telegdy and Adamik 2013b, Tanaka and Telegdy 2014). Further studies with NMS on anxiety and depression could explain the difference in receptor affinity which can be observed between NMS and NMU.

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NICOTINE AND ALCOHOL DEPENDENCE IN SCHIZOPHRENIA

ŞİZOFRENİDE NİKOTİN VE ALKOL BAĞIMLILIĞI

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Abstract

Schizophrenia is a neurodevelopmental brain disease and a severe psychiatric disorder which is seen approximately in 1% of the society. About the half of the individuals diagnosed with schizophrenia have substance abuse story, and this rate is higher than the general population. Alcohol dependence, smoking and substance abuse has been reported very often in schizophrenia. Especially smoking rate is very high in patients with schizophrenia. The aim of this paper is to briefly review the literature related to the relationship between schizophrenia and nicotine-alcohol dependency.

Keywords: schizophrenia, nicotine, alcohol, abuse, addiction

Özet

Şizofreni toplumun yaklaşık %1'inde görülen ağır bir psikiyatrik bozukluk ve nörogelişimsel beyin hastalığıdır. Şizofreni tanısı alan bireylerin neredeyse yarısı madde kötüye kullanım bozukluğu öyküsüne sahiptir ve bu oran genel popülasyondan çok yüksektir. Alkol bağımlılığı, sigara içme ve madde kötüye kullanımının şizofreniye eşlik ettiği çok sık bildirilmiştir. Özellikle sigara içiminin şizofreni tanısı almış hastalarda çok yüksek oranda olduğu dikkati çekmektedir. Bu yazının amacı, şizofreni ile nikotin ve alkol bağımlılığı arasındaki ilişki ile ilgili literatürün kısaca gözden geçirilmesidir

Anahtar Kelimeler: şizofreni, nikotin, alkol, kötüye kullanım, bağımlılık

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1. Introduction

Schizophrenia is a neurodevelopmental brain disease and a severe psychiatric disorder which is seen approximately in 1% of the society. This neurodevelopmental disorder's onset is at young ages with a peak of early 20's. The disease affects individual's thoughts, perception, mood and behaviors; it causes devastating psychopathological impacts in occupational, social and private life (Arslan et al., 2011).

Before 1960s, schizophrenia and substance abuse comorbidity has not been defined as a serious problem. Clinical interest in comorbidity of schizophrenia and substance abuse disorders has increased in the last two decades (Westermeyer, 1992; Mueser et al., 1998). Many studies suggest that the most common comorbidities in schizophrenia are substance abuse disorders (Ziedonis et al., 1994; Jimenez-Castro et al., 2010), and it is known that comorbidity worsens the prognosis and leads to negative symptomatic and functional consequences (Karakuş et al., 2012).

2. Epidemiology

In Epidemiologic Catchment Area Study (ECA) of American National Institute of Mental Health, it has been demonstrated that 47% of patients with schizophrenia spectrum disorders has been diagnosed with substance abuse disorder (Verma et al., 2002). In this study, it has been found that the prevalence of substance abuse disorders in patients with schizophrenia is 4.6 times more than the substance abuse disorders in the general population. Alcohol is the mostly abused substance in both general population and patients with schizophrenia, and the second one is cannabis (Aras, 2013). Alcohol and cannabis were followed by benzodiazepines and cocaine (Mueser KT et al., 2000) and amphetamines (Cantor-Graae et al., 2001) in the list of abused substances. Additionally, in another study 58-90% of the patients with schizophrenia were reported to be nicotine addicts (Dalack GW et al., 1998).

A study in Canada revealed that 37% of patients with schizophrenia met the criteria of substance abuse or dependence, in 14% of the patients cannabis abuse was diagnosed (Addington J et al., 2001). In a study conducted in Germany with 232 patients with a diagnosis of schizophrenia, it was found that 13% of the patients had cannabis abuse (Hambrecht et al., 2000). In Sweden, 50.6% nicotine abuse, 47.1% alcohol abuse and 48.3% substance abuse was found in patients with schizophrenia (Cantor-Grae et al., 2001)

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Although the number of studies with Turkish population is limited, the research performed about comorbidity of schizophrenia and substance abuse has revealed that, comorbidity is not that much as mentioned in the literature. A study has reported that 50 of 100 patients with schizophrenia were neither drinking alcohol nor using any substance, 22 were reported to abuse only alcohol, 17 were alcohol and substance, and 11 were only substance abusers (Aras, 2013). The prevalence of smoking in schizophrenic population is 30-60% higher than the general population's prevalence (Akvardar et al., 2003). In Turkey, substance abuse both in the general population and patients with schizophrenia is lower than western countries. It may be due to religion, traditions or not reporting during surveys. Additionally in patients with schizophrenia, high rates of smoking and alcohol abuse, and low rates of other substances' abuse may be associated with accessibility of the substance.

According to the research on patients with schizophrenia, young male patients had higher comorbidity of substance abuse than elders and female patients (Jimanez-Castro et al., 2010; Dervaux et al., 2003). Male patients have two times more substance abuse disorder and four times more alcohol abuse disorder than women (Myers JK et al., 1984).

3. Etiology

The relationship between schizophrenia and substance use disorders is not clear yet. However, there are some assumptions in this regard. Patients with schizophrenia use substances that reduce symptoms of psychotic disorder, or that reduce the side effects of the medication used for treatment. This is called "self-medication" (Khantzian, 1990). Some patients were reporting that alcohol and other substances relieve symptoms such as social problems, insomnia, and depression (Brunette et al., 1997). Researchers suggest that patients with schizophrenia use substances to regulate negative emotions (Dilbaz et al., 2011). Another theory suggests that patients with schizophrenia develop addiction to certain substances in accordance with their neurobiological susceptibility. Dysfunction of mesocorticolimbic dopamine pathways underlying schizophrenia symptoms is also responsible for the dysfunction of brain's reward system in patients with substance abuse disorder. It is well known that abuse of the substances such as stimulants, hallucinogens and cannabis trigger psychotic disorders, suggesting a common neurobiological pathway (Krystal et al., 1999).

4. Schizophrenia and Smoking

Tobacco use has been only started to be seen as substance abuse in recent years because it does not affect productivity and does not arise any socially undesirable condition. As a result of research in 1988, it has been reported that nicotine is the substance in cigarettes that cause addiction, and has behavioral and pharmacological effects like in addiction of heroin or cocaine. In 1994, in the U.S. Congress, it has been declared as an addictive substance by the FDA.

As smoking in patients with schizophrenia was seen as part of the illness, it was overlooked by the clinicians (Schneier et al., 1987). Research in the U.S.A. has revealed that, in patients with schizophrenia, smoking rate is 58-90% which is 2.5-4.5 times higher than the general population (DeLeon J et al., 2005). In a study in Turkey, it was found that smoking prevalence in patients with schizophrenia was 57.5% while it was 47.3% in the healthy population (Üçok et al., 2001). In a study on patients with schizophrenia in 1994, it was found that smoking patients' negative symptoms were decreased, and positive symptoms were increased (Ziedonis et al., 1994).

Cigarette together with the various ingredients used in it and drugs interact pharmacokinetically and pharmacodynamically. Pharmacokinetic factors may be responsible for the patient's unresponsiveness or variable response to treatment (Preskorn, 2004). Polycyclic aromatic hydrocarbons in cigarette induce cytochrome P450 CYP1A1, CYP1A2, and most probably CYP2E1, CYP1A1 enzymes (Zevin et al., 1999) Polycyclic aromatic hydrocarbons in tobacco that induce CYP1A2 enzyme cause significant changes in the clozapine level (De Leon et al., 2003). The studies show that non-smoker patients' plasma clozapine levels were 3.2 times higher than the levels of smokers (Ozdemir et al., 2001).

5. Schizophrenia and Alcohol

The availability and legality of alcohol leads to widespread abuse among people with schizophrenia as well as in the general population. Alcohol is the most common substance of abuse, other than nicotine (Cuffel 1996). Alcohol abuse in patients with schizophrenia has been identified as 25-45% (Schneier et al., 1987). A study in Turkey revealed that the frequency of lifetime alcohol use in patients with schizophrenia is 63.3%, alcohol abuse and addiction rates are 8.1% (Dilbaz et al., 2011).

People with schizophrenia presumably use alcohol and other drugs for several similar reasons as others in community, but various factors have been hypothesized to contribute to this group's high percentages of substance use disorders (Drake et al 2000). Alcohol and other drugs might be used by the patients with schizophrenia to alleviate the symptoms of schizophrenia or the side effects of the antipsychotic medications prescribed for schizophrenia (Chambers et al. 2001). Research evidence does not fully confirm this opinion, however. For example, alcohol abuse often precedes schizophrenia and numerous substances of abuse exhibit a spectrum of different effects but generally exacerbates rather than reduce symptoms of schizophrenia (Chambers et al. 2001).

The underlying neuropathological abnormalities of schizophrenia may promote the positive reinforcing effects of substance use. A common neurological evidence for schizophrenia and the reinforcing impacts of substance use may predispose people to both conditions. This common basis involves the dysregulation of the dopamine (Koob and Roberts 1999). Another possible mechanism of the alcohol abuse in schizophrenia may be related to the weakened thinking, disturbed judgment and reduced impulse control which are common in schizophrenia.

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Due to the trouble to balance benefit/ratio or difficulty of anticipating the risk, people with schizophrenia are especially vulnerable to the substance use. Thus, even when using relatively small amounts of psychoactive substances, these people are prone to exhibit notable substance-related behavioral problems that lead to a a diagnosis of substance use disorder (Mueser et al. 1998).

A psychosocial mechanism that may drive to alcohol abuse in schizophrenia is the fact that many people with schizophrenia report that they use alcohol and other drugs to relieve the dysphoria of mental illness, poverty, limited opportunities, and boredom. Alcohol use reported to facilitate the development of a social network (Dixon et al. 1990).

Cross-sectional research point out that alcohol using disorders among people with schizophrenia is linked with various manifestations of adverse outcomes and poor quality of life such as relationship difficulties, increased risk of recurrence of psychiatric symptoms, psychosocial disturbance, cross-dependence of other substances, increased risk of legal and financial problems, medical problems such as HIV infection and hepatitis. (Drake and Brunette, 1998). One of the major reasons for the increased social problems in alcohol dependency in schizophrenia is the fact that alcohol use causes or exacerbates poor adjustment. A study of the outpatients with schizophrenia ascertained that those with co-occurring alcohol dependency had greater incidences of hospitalization and depression compared to those with schizophrenia only.

Conclusion

High rates of comorbid nicotine and alcohol abuse or dependency are observed in patients with schizophrenia. However, causes of substance abuse in patients with schizophrenia are not fully elucidated yet. This comorbidity is believed to affect the treatment process adversely, and the patients shall be in terms of substance abuse disorders in the treatment of schizophrenia.

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CASE REPORT

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MAN TRANSFORMING INTO WOLF: A RARE CASE OF CLINICAL LYCANTHROPY

KURDA DÖNÜŞEN ADAM: NADIR GÖRÜLEN BIR KLINIK LIKANTROFI OLGUSU

Gökben Hızlı Sayar* [1] , Eylem Özten[1], Gaye Kağan[2],

Abstract

Clinical lycanthropy is defined as a rare psychiatric syndrome that involves a delusion that the affected person can transform into, has transformed into, or is a non-human animal. Its name is connected to the mythical supranatural stories of lycanthropy, in which humans are said to physically shape shift into wolves. According to suggested diagnostic criteria for lycanthropy, either a delusional belief in current or past transformation or behavior that suggests a person thinks of himself as transformed is considered evidence of clinical lycanthropy. Hereby we present a case of clinical lycanthropy in a male patient reporting moments of feeling himself as a wolf and behaving in a manner that resembles wolf behavior, for example howling and growling.

Keywords: lycanthropy, delusion

Özet

Klinik likantofi, etkilenen kişinin bir hayvana dönüştüğü ya da bir hayvan olduğu sanrısının var olduğu nadir bir psikiyatrik sendromdur. Likantrofi, adını efsanevi doğaüstü kurtadam hikayelerinden alır. Klinik likantrofi için önerilen tanı kriterleri kişinin halen ya da geçmişte bir hayvana dönüşüm yaşadığına olan inancı, ya da kişinin bir hayvana dönüştüğüne inandığını gösterir biçimde davranmasıdır. Bu olgu sunumunda zaman zaman bir kurda dönüştüğüne inanan ve kurda benzer uluma ve hırlama davranışları gösteren bir erkek hasta sunulacaktır.

Anahtar Kelimeler: likantrofi, sanrı

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1. Introduction

Clinical lycanthropy is described as a rare psychiatric syndrome that involves a delusion that the affected person can transform into, has transformed into, or is a non-human animal (Surawicz et al., 1975) Its name is related to the mythological supranatural narratives of lycanthropy, in which humans are supposed to shape shift physically into wolves. According to proposed diagnostic criteria for lycanthropy, "either a delusional belief in current or past transformation" or "action that implies a person believe of himself as transformed" is considered evidence of clinical lycanthropy. Despite it has been classically described as a fear of being transformed into a wolf, the animal species being attributed to by the patient is extensively determined by his/her socio-cultural background along with factors such as abundance and fear of that animal (Kulhara et al., 2001).

Hereby we present a case of clinical lycanthropy in a male patient describing times of feeling himself as a wolf and behaving in a way that resembles wolf behavior, for instance howling and growling.

2. Case:

A 21-year-old male who experienced delusions that lasted up to several hours admitted to the psychiatric examination. He had presented to the psychiatric emergency service with his parents, complaining of anxiety, restlessness and episodes of howling since two months, with a recurrence of once in a week. He did not have any psychiatric or physical complaint before. He had not any history of alcohol or substance abuse. Blood biochemistry, brain imaging and urine toxicology results did not show any abnormality. He was claimed to have been in a street fight at the same day morning and soon after he developed intense fear and severe anxiety. After succeeding 2 hours, patient began making intermittent bouts of growling sounds that were not under his control and insisted that he was transforming to a wolf. On attempting to question the belief, patient was not appeared agreeable for discussion. He was designating visual perceptions of hair extension or other bodily differences such as sharpening of teeth and lengthening of nails, expanding and growing of the chest, increased hair growth on arms and 'hardening' of the jaw and facial muscles. Patient was given 15 mg/day of aripiprazole and 1 mg/day lorazepam with a diagnosis of psychotic disorder not otherwise specified or reactive psychosis. After four weeks, he admitted as an outpatient and he was considered to be euthymic and free of any delusions.

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3. Discussion:

Lycanthropy can be clinically characterized with the presence of a delusion of human-to-wolf transformation. Perceptual abnormalities may accompany the delusion and may involve perceptions of hair growth or other physical switches. The term partial lycanthropy is used when delusional ideas about excessive hair growth are attended by a wolf-like appearance, but not by delusional beliefs about wolf or werewolf transformations (Silva et al., 2000).

Animals introduced in the literature by the lycanthropy case descriptions were bee, bird, frog, gerbil, goose, horse, rhinoceros, snake, wild boar, and six unspecified animals. There were two cases of multiple clinical zoanthropy (i.e. one involving dog as well as bull, and one involving wolf, dog, cat and horse). As transcribed in previous reviews by Moselhy (1999) and Verdoux et al. (1989), the continuance of the symptoms varied from only a hour to decades. The clinical diagnoses were fairly variable in the literature, although there was a marked overrepresentation of schizophrenia spectrum disorders, psychotic depression and bipolar disorder. The treatment, reported in 58.9% of the cases, often comprised pharmacological intervention in accordance with the set clinical diagnoses and treatment guidelines. In five cases, pharmacotherapy was augmented with electroconvulsive treatment. The outcome reported for the cases were complete remission (35.9%), incomplete remission (46.2%), no remission (5.1%), and mortality (12.8%).

Several etiologic assumptions have been introduced to account for this phenomenon. Illis recommended that the phenomena is related to primitive, fear-ridden communities as some form of bestial transformation (Illis, 1964). Porphyria is decribed by photosensitivity, discoloration of the urine by porphyrins, ulcerating skin lesions with progressive mutilation of fingers, eyelids, ears, and nose, hyperpigmentation of photosensitive areas, red teeth due to deposition of porphyrin, and chronic hemolytic anemia with splenomegaly. These manifestations could explain the "lycanthropic" symptomatology, especially when associated with delirium, psychosis, and seizures as is frequently the case in this disorder.

This case was considered as a reactive psychosis or psychotic disorder NOS due to loss of insight and presence of delusion about metamorphosing into a wolf. This case could also be an atypical presentation of dissociative motor disorder involving vocal cords, but the associated belief makes it less likely.

4. Conclusion:

This rare condition tends to occur in the context of major psychiatric disorders such as schizophrenia, psychotic depression, bipolar disorder or psychotic disorder NOS. However, cases of secondary clinical lycanthropy in particular warrant proper investigations to rule out any underlying organic pathology, notably in cerebral somatosensory areas and those representing the body scheme and sense of self.

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LETTER TO EDITOR

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ARTIFICIAL INTELLIGENCE APPROACHES IN PSYCHIATRIC DISORDERS

PSİKİYATRİK BOZUKLUKLARDA YAPAY ZEKA YAKLAŞIMLARI

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To editor;

The contribution of artificial intelligence (AI) methods to various fields of study such as medicine, manufacturing, finance engineering, art and social sciences has broadened the scope of AI. Nowadays, classification of psychiatric disorders by combining neuroimaging methods and artificial intelligence approaches is becoming one of major focus of research. The combination of feature selection (FS) and classification methods appreciate the value of biological biomarkers and contribute to the treatment process of psychiatric and neurological diseases.

The value of clinical factors in various psychiatric diseases is extremely limited and a shift towards biomarkers is evident. With the Personalized Medicine approach to psychiatric diseases, genetic and neuroimaging biomarkers have been explored and generated promising outcomes in aiding treatment process using pre-treatment and post-treatment measures. The methods used to classify diseases, to predict treatment outcomes of diseases and FS techniques to underline informative features are valuable approaches in medicine contributing to early diagnosis, treatment planning and monitoring of disease progression processes. This has revealed structural and functional alterations in several disorders including, amongst others, mild cognitive impairment, probable dementia of Alzheimer type, major depression, bipolar disorder, schizophrenia and generalized anxiety disorder (Arnone et al., 2011; Davatzikos & Resnick, 2002; Ellison-Wright & Bullmore, 2010; Etkin & Wager, 2007; Smieskova et al., 2010; Zakzanis et al., 2003).

Despite much interest in the use of neuroimaging studies for diagnostic and prognostic purposes, neurologists and psychiatrists are still forced to rely on traditional and often ineffective diagnostic and prognostic tools. One of the reasons for the limited impact of the findings on clinical practice is that neuroimaging studies have typically reported differences between patients and controls at group level. Thus over the past few years, there has been growing interest to machine learning (ML) techniques in order to address the considerations of neuroimaging community (Hastie et al., 2001).

ML algorithms include two main phases; in the first phase they try to find a model for the class attribute as a function of other variables of the datasets, and in the second phase, they apply previously designed model on the new and unseen datasets for determining the related class of each record. There are different methods for data classification such as Decision Trees (DT), Rule Based Methods, Logistic Regression (LogR), Linear Regression (LR), Naïve Bayes (NB), Support Vector Machine (SVM), k-Nearest Neighbor (k-NN), Artificial Neural Networks (ANN), Linear Classifier (LC) and so forth (Tan et al., 2006; Kantardzic, 2003; Witten & Frank, 2005). Compared to traditional methods of analysis based on the general linear model, the advantages of applying ML methods to neuroimaging data could be expressed with two steps. Firstly, ML methods allow characterization at the level of the individual therefore yielding results with a potentially high level of clinical translation. Secondly, as inherently multivariate approaches, ML methods are sensitive to spatially distributed and subtle effects in the brain that would be otherwise undetectable using traditional univariate methods which focus on gross differences at group level.

Besides classification accuracy of proposed ML approaches, FS process is a sustaining step improving classification accuracy eliminating less informative features. Several techniques are developed to address the problem of reducing irrelevant and redundant variables which are a burden on challenging tasks. Those algorithms that differ in their optimality and computational cost have been developed to search the solution space which are namely, Tabu Search (TS), Simulated Annealing (SA) and Genetic Algorithm (GA). Another trend of search procedures is based on swarm intelligence, which adopts the social insect metaphor that emphasizes distributedness and direct or indirect interactions among relatively simple agents. Swarm intelligence methods, particularly the Ant Colony Optimization (ACO) and Particle Swarm Optimization (PSO) were also utilized as search procedures in FS problems. Nature inspired algorithms such as Artificial Bee Colony, Firefly Algorithm and Bee Colony Optimization are being used to appreciate the value of FS process as well.

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For future perspective, prevailing application of AI methods in the diagnosis and treatment process of psychiatric disease will be valuable and highly applicable to clinical studies requiring diagnostic results.

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