ISSN:2149-1909

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES

Volume-Cilt: 5
Issue Number-Sayı: 3 (Winter-Kış)
Year-Yıl: 2018

NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

JNBS Published by Üsküdar University

JNBS

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

Volume-Cilt: 5
Issue Number-Sayı: 3 (Winter-Kış)
Year-Yıl: 2018

IT/Teknik Servis
Hakan Özdemir

Period/Periyot
Published every 4 months (in Autumn, Winter, Spring), distributed free of charge.
4 ayda 1 (Bahar-Güz-Kış) yayınlanır, ücretsiz dağıtılır.

Yönetim Yeri/Administrative Adress
Altunizade Mah. Haluk Türksoy Sokak No: 14, 34662 Üsküdar/İstanbul
Bilgi Hattı/Contact: +90 216 400 22 22
Web: www.jnbs.org www.uskudar.edu.tr
e-mail: jnbs@uskudar.edu.tr

Graphic Design/Grafik Tasarım
MADWORKS
Esentepe Mah. Kore Şehitleri Cad. No:45 Daire:9
Şişli / İstanbul
Phone: +90 543 623 96 75 info@madworksistanbul.com
www.madworksistanbul.com

Printing office/Matbaa
G.M. Matbaacılık ve Tic. A.Ş.
100 Yıl Mah. MASSİT 1. Cad. No:88 Bağcılar / İstanbul
Phone: +90 212 629 00 24
Print Date/Baskı Tarihi: April-Nisan 2018

**The Journal of Neurobehavioral Sciences (JNBS) is a peer-reviewed open-access neuroscience journal without any publication fees.
Nörodavranış bilimleri dergisi hakemli, açık erişime sahip basım ücreti talep etmeksizin yayınlanan akademik bir nörobilim dergisidir.

**JNBS published both electronically and hard copy printed forms 3 times a year by Uskudar University.
JNBS hem elektronik hem de ciltli baskı olarak yılda 3 kez Üsküdar Üniversitesi tarafından yayınlanır.

**JNBS accepts articles written both in English and Turkish languages.
JNBS hem Türkçe hem de İngilizce dilinde makale kabul etmektedir.

ISSN:2149-1909

JNBS

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

JNBS 2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org

Volume-Cilt: 5
Issue Number-Sayı: 3 (Winter-Kış)
Year-Yıl: 2018

JOURNAL OF NEUROBEHAVIORAL SCIENCES ADVISORY COMMITTEE

NÖRODAVRANIŞ BİLİMLERİ DERGİSİ DANIŞMA KURULU ÜYELERİ

ABOUT THIS JOURNAL

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.

JNBS is published electronically and in the printed form 3 times a year by Uskudar University.

The official language of JNBS is English. However, starting from 2017, our board agreed upon accepting selective turkish articles that make significant impact to the neuroscience literature. Therefore, we encourage researchers to also submit their articles written also in Turkish language. Our editorial office provide Turkish abstracts in addition to English for each article. Please visit our university webpage for instructions written in turkish language (http://uskudar.edu.tr/tr/dergi/4/jnbs-dergileri).

Aims & Scope

The scope of the journal is broad. It covers many disciplines and spans molecules (e.g., molecular neuroscience, biochemistry) through systems (e.g., neurophysiology, systems neuroscience) to behavior (e.g. cognitive neuroscience) and clinical aspects (e.g. psychopharmacology). The journal covers all aspects of neuroscience with an emphasis on translational psychiatry and psychology, as long as the goal is to delineate the neural mechanisms underlying normal or pathological behavior.

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.

The journal has a special emphasis on psychiatric and neurological disorders.

However studies on normal human behavior are also considered. Studies on animals and technical notes must have clear relevance and applicability to human disease.

Case Reports that includes recent neuroscientific treatment or diagnosis methods are generally within the scope of JNBS.

Please see our editorial board section for information on specific sections.

In addition, the following two categories are further featured in JNBS:

- Mini-reviews that succinctly survey appropriate areas of current research or theory

- Commentaries that serve as vehicles for brief presentations of new theories, hypotheses, points of view, or critiques of current research

Papers will be selected on the basis of their methodology and negative results are strongly considered for publication.

The average time from submission to first decision is less than 30 days. Accepted articles are published online ahead of print in an average of 40 workdays, and articles are published in print 3-6 months after acceptance.

Please see our Guide for Authors for information on article submission. If you require any further information or help, please email us (jnbs@uskudar.edu.tr)

JNBS 2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org

JNBS

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

INTRUCTIONS FOR AUTHORS

Instructions for Authors

Prior to submission, please carefully read and follow the submission guidelines entailed below. Manuscripts that do not conform to the submission guidelines may be returned without review.

Submission

Submit manuscripts electronically (.doc format with including all figures inside) via the online submission system of our website (www.jnbs.org or www.scopemed.org/?sec=gfa&jid=34).

Cumhur Taş, MD PhD
Co-Editor, Journal of Neurobehavioral Sciences
Department of Psychology

Üsküdar University
Altunizade Mh., Haluk Türksoy Sk No: 14,
İstanbul-Turkey

General correspondence may be directed to the Editor's Office.

In addition to postal addresses and telephone numbers, please supply electronic mail addresses and fax numbers, if available, for potential use by the editorial and production offices.

Masked Reviews

Masked reviews are optional and must be specifically requested in the cover letter accompanying the submission. For masked reviews, the manuscript must include a separate title page with the authors' names and affiliations, and these ought not to appear anywhere else in the manuscript.

Footnotes that identify the authors must be typed on a separate page.

Make every effort to see that the manuscript itself contains no clues to authors' identities. If your manuscript was mask reviewed, please ensure that the final version for production includes a byline and full author note for typesetting.

Types of Articles

Brief Reports, commentaries, case reports and mini-reviews must not exceed 4000 words in overall length. This limit includes all aspects of the manuscript (title page, abstract, text, references, tables, author notes and footnotes, appendices, figure captions) except figures. Brief Reports also may include a maximum of two figures.

For Brief Reports, the length limits are exact and must be strictly followed.

Regular Articles typically should not exceed 6000 words in overall length (excluding figures).

Reviews are published within regular issues of the JNBS and typically should not exceed.

10000 words (excluding figures)

Cover Letters

All cover letters must contain the following:

A statement that the material is original —if findings from the dataset have been previously published or are in other submitted articles, please include the following information:

*Is the present study a new analysis of previously analyzed data? If yes, please describe differences in analytic approach.

*Are some of the data used in the present study being analyzed for the first time? If yes, please identify data (constructs) that were not included in previously published or submitted manuscripts.

*Are there published or submitted papers from this data set that address related questions? If yes, please provide the citations, and describe the degree of overlap and the unique contributions of your submitted manuscript.

*The full postal and email address of the corresponding author;

*The complete telephone and fax numbers of the same;

*The proposed category under which the manuscript was submitted;

*A statement that the authors complied with APA ethical standards in the treatment of their participants and that the work was approved by the relevant Institutional

Review Board(s).
*Whether or not the manuscript has been or is posted on a web site;

*That APA style (Publication Manual, 6th edition) has been followed;

*The disclosure of any conflicts of interest with regard to the submitted work;

*A request for masked review, if desired, along with a statement ensuring that the manuscript was prepared in accordance with the guidelines above.

*Authors should also specify the overall word length of the manuscript (including all aspects of the manuscript, except figures) and indicate the number of tables, figures, and supplemental materials that are included.

INTRUCTIONS FOR AUTHORS

Manuscript Preparation

Prepare manuscripts according to the Publication Manual of the American Psychological Association (6th edition).

Review APA's Checklist for Manuscript Submission before submitting your article. Double-space all copy. Other formatting instructions, as well as instructions on preparing tables, figures, references, metrics, and abstracts, appear in the Manual.

Below are additional instructions regarding the preparation of display equations and tables.

Display Equations

We strongly encourage you to use MathType (third-party software) or Equation

Editor 3.0 (built into pre-2007 versions of word) to construct your equations, rather than the equation support that is built into Word 2007 and Word 2010. Equations composed with the built-in Word 2007/Word 2010 equation support are converted to low-resolution graphics when they enter the production process and must be rekeyed by the typesetter, which may introduce errors.

To construct your equations with MathType or Equation Editor 3.0:

Go to the Text section of the Insert tab and select Object.

Select MathType or Equation Editor 3.0 in the drop-down menu.

If you have an equation that has already been produced using Microsoft Word 2007 or 2010 and you have access to the full version of MathType 6.5 or later, you can convert this equation to MathType by clicking on MathType Insert Equation. Copy the equation from Microsoft Word and paste it into the MathType box. Verify that your equation is correct, click File, and then click Update. Your equation has now been inserted into your Word file as a MathType Equation.

Use Equation Editor 3.0 or MathType only for equations or for formulas that cannot be produced as word text using the Times or Symbol font.

Tables

Use Word's Insert Table function when you create tables. Using spaces or tabs in your table will create problems when the table is typeset and may result in errors.

Abstract and Keywords

All manuscripts must include an English abstract containing a maximum of 250 words typed on a separate page. After the abstract, please supply up to five keywords or brief phrases. For the Turkish native speakers JNBS also requires a Turkish version of the abstract and keywords. However this rule does not apply to non-native speakers and our translation office will include the Turkish abstract free of charge.

References

List references in alphabetical order. Each listed reference should be cited in text (Name, year style), and each text citation should be listed in the References section.

In-text Citations

• For two or fewer authors, list all author names (e.g. Brown & Taş, 2013). For three or more authors, abbreviate with 'first author' et al. (e.g. Uzbay et al., 2005).

• Multiple references to the same item should be separated with a semicolon (;) and ordered chronologically. References by the same author in the same year should be differentiated by letters (Smith, 2001a; Smith, 2001b).

• Cite articles that have been accepted for publication as 'in press', include in the reference list.

• Cite unpublished work, work in preparation, or work under review as 'unpublished data' using the author's initials and surname in the text only; do not include in the reference section

The Reference Section:

• Journal Article:

Hughes, G., Desantis, A., & Waszak, F. (2013). Mechanisms of intentional binding and sensory attenuation: The role of temporal prediction, temporal control, identity prediction, and motor prediction. Psychological Bulletin, 139, 133–151. http://dx.doi.org/10.1037/a0028566

• Authored Book:

Rogers, T. T., & McClelland, J. L. (2004). Semantic cognition: A parallel distributed processing approach. Cambridge, MA: MIT Press.

• Chapter in an Edited Book:

Gill, M. J. & Sypher, B. D. (2009). Workplace incivility and organizational trust.

In P. Lutgen-Sandvik & B. D. Sypher (Eds.), Destructive organizational communication: Processes, consequences, and constructive ways of organizing (pp. 53–73). New York, NY: Taylor & Francis.

Figures

Graphics files are welcome if supplied as Tiff, EPS, or PowerPoint files. Multipanel figures (i.e., figures with parts labeled a, b, c, d, etc.) should be assembled into one file.

The minimum line weight for line art is 0.5 point for optimal printing.

JNBS 2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org

JNBS

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

PUBLICATION ETHICS AND PUBLICATION MALPRACTICE STATEMENT (ETHICAL GUIDELINES FOR PUBLICATION)

The publication of an article in the peer-reviewed journal JNBS is an essential building block in the development of a coherent and respected network of knowledge. It is a direct reflection of the quality of the work of the authors and the institutions that support them. Peer-reviewed articles support and embody the scientific method. It is therefore important to agree upon standards of expected ethical behaviour for all parties involved in the act of publishing: the author, the journal editor, the peer reviewer, the publisher and the society of society-owned or sponsored journals.

Uskudar University, as publisher of the journal, takes its duties of guardianship over all stages of publishing extremely seriously and we recognise our ethical and other responsibilities.

We are committed to ensuring that advertising, reprint or other commercial revenue has no impact or influence on editorial decisions. In addition, Editorial Board will assist in communications with other journals and/or publishers where this is useful to editors. Finally, we are working closely with other publishers and industry associations to set standards for best practices on ethical matters, errors and retractions - and are prepared to provide specialized legal review and counsel if necessary.

Duties of authors

(These guidelines are based on existing COPE's Best Practice Guidelines for Journal Editors.)

Reporting standards

Authors of reports of original research should present an accurate account of the work performed as well as an objective discussion of its significance. Underlying data should be represented accurately in the paper. A paper should contain sufficient detail and references to permit others to replicate the work. Fraudulent or knowingly inaccurate statements constitute unethical behavior and are unacceptable. Review and professional publication articles should also be accurate and objective, and editorial 'opinion' works should be clearly identified as such.

Authors are required to state in writing that they have complied with the Declaration of Helsinki Research Ethics in the treatment of their sample, human or animal, or to describe the details of treatment.

Data access and retention

Authors may be asked to provide the raw data in connection with a paper for editorial review, and should be prepared to provide public access to such data (consistent with the ALPSP-STM Statement on Data and Databases), if practicable, and should in any event be prepared to retain such data for a reasonable time after publication.

Originality and plagiarism

The authors should ensure that they have written entirely original works, and if the authors have used the work and/or words of others, that this has been appropriately cited or quoted.

Plagiarism takes many forms, from 'passing off' another's paper as the author's own paper, to copying or paraphrasing substantial parts of another's paper (without attribution), to claiming results from research conducted by others. Plagiarism in all its forms constitutes unethical publishing behavior and is unacceptable.

Multiple, redundant or concurrent publication

An author should not in general publish manuscripts describing essentially the same research in more than one journal or primary publication. Submitting the same manuscript to more than one journal concurrently constitutes unethical publishing behavior and is unacceptable.

In general, an author should not submit for consideration in another journal a previously published paper. Publication of some kinds of articles (e.g. clinical guidelines, translations) in more than one journal is sometimes justifiable, provided certain conditions are met. The authors and editors of the journals concerned must agree to the secondary publication, which must reflect the same data and interpretation of the primary document. The primary reference must be cited in the secondary publication. Further detail on acceptable forms of secondary publication can be found at www.icmje.org.

Acknowledgement of sources

Proper acknowledgment of the work of others must always be given. Authors should cite publications that have been influential in determining the nature of the reported work. Information obtained privately, as in conversation, correspondence, or discussion with third parties, must not be used or reported without explicit, written permission from the source. Information obtained in the course of confidential services, such as refereeing manuscripts or grant applications, must not be used without the explicit written permission of the author of the work involved in these services.

Authorship of the paper

Authorship should be limited to those who have made a significant contribution to the conception, design, execution, or interpretation of the reported study. All those who have made significant contributions should be listed as co-authors. Where there are others who have participated in certain substantive aspects of the research project, they should be acknowledged or listed as contributors.

The corresponding author should ensure that all appropriate co-authors and no inappropriate co-authors are included on the paper, and that all co-authors have seen and approved the final version of the paper and have agreed to its submission for publication.

Hazards and human or animal subjects

If the work involves chemicals, procedures or equipment that have any unusual hazards inherent in their use, the author must clearly identify these in the manuscript. If the work involves the use of animal or human subjects, the author should ensure that the manuscript contains a statement that all procedures were performed in compliance with relevant laws and institutional guidelines and that the appropriate institutional committee(s) has approved them. Authors should include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed.

Disclosure and conflicts of interest

All authors should disclose in their manuscript any financial or other substantive conflict of interest that might be construed to influence the results or interpretation of their manuscript. All sources of financial support for the project should be disclosed.

Examples of potential conflicts of interest which should be disclosed include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other

funding. Potential conflicts of interest should be disclosed at the earliest stage possible.

Fundamental errors in published works

When an author discovers a significant error or inaccuracy in his/her own published work, it is the author's obligation to promptly notify the journal editor or publisher and cooperate with the editor to retract or correct the paper. If the editor or the publisher learns from a third party that a published work contains a significant error, it is the obligation of the author to promptly retract or correct the paper or provide evidence to the editor of the correctness of the original paper.

Duties of editors

(These guidelines are based on existing COPE's Best Practice Guidelines for Journal Editors.)

Publication decisions

The editor of a peer-reviewed journal is responsible for deciding which of the articles submitted to the journal should be published, often working in conjunction with the relevant society (for society-owned or sponsored journals). The validation of the work in question and its importance to researchers and readers must always drive such decisions. The editor may be guided by the policies of the journal's editorial board and constrained by such legal requirements as shall then be in force regarding libel, copyright infringement and plagiarism. The editor may confer with other editors or reviewers (or society officers) in making this decision.

Fair play

An editor should evaluate manuscripts for their intellectual content without regard to race, gender, sexual orientation, religious belief, ethnic origin, citizenship, or political philosophy of the authors.

Confidentiality

The editor and any editorial staff must not disclose any information about a submitted manuscript to anyone other than the corresponding author, reviewers, potential reviewers, other editorial advisers, and the publisher, as appropriate.

Disclosure and conflicts of interest

Unpublished materials disclosed in a submitted manuscript must not be used in an editor's own research without the express written consent of the author.

Privileged information or ideas obtained through peer review must be kept confidential and not used for personal advantage.

Editors should recuse themselves (i.e. should ask a co-editor, associate editor or other member of the editorial board instead to review and consider) from considering manuscripts in which they have conflicts of interest resulting from competitive, collaborative, or other relationships or connections with any of the authors, companies, or (possibly) institutions connected to the papers.

Editors should require all contributors to disclose relevant competing interests and publish corrections if competing interests are revealed after publication. If needed, other appropriate action should be taken, such as the publication of a retraction or expression of concern.

It should be ensured that the peer-review process for sponsored supplements is the same as that used for the main journal. Items in sponsored supplements should be accepted solely on the basis of academic merit and interest to readers and not be influenced by commercial considerations.

Non-peer reviewed sections of their journal should be clearly identified.

Involvement and cooperation in investigations

An editor should take reasonably responsive measures when ethical complaints have been presented concerning a submitted manuscript or published paper, in conjunction with the publisher (or society). Such measures will generally include contacting the author of the manuscript or paper and giving due consideration of the respective complaint or claims made, but may also include further communications to the relevant institutions and research bodies, and if the complaint is upheld, the publication of a correction, retraction, expression of concern, or other note, as may be relevant. Every reported act of unethical publishing behavior must be looked into, even if it is discovered years after publication.

Duties of reviewers

(These guidelines are based on existing COPE's Best Practice Guidelines for Journal Editors.)

Contribution to editorial decisions

Peer review assists the editor in making editorial decisions and through the editorial communications with the author may also assist the author in improving the paper. Peer review is an essential component of formal scholarly communication, and lies at the heart of the scientific method. JNBS shares the view of many that all scholars who wish to contribute to publications have an obligation to do a fair share of reviewing.

Promptness

Any selected referee who feels unqualified to review the research reported in a manuscript or knows that its prompt review will be impossible should notify the editor and excuse himself from the review process.

Confidentiality

Any manuscripts received for review must be treated as confidential documents. They must not be shown to or discussed with others except as authorized by the editor.

Standards of objectivity

Reviews should be conducted objectively. Personal criticism of the author is inappropriate. Referees should express their views clearly with supporting arguments.

Acknowledgement of sources

Reviewers should identify relevant published work that has not been cited by the authors. Any statement that an observation, derivation, or argument had been previously reported should be accompanied by the relevant citation. A reviewer should also call to the editor's attention any substantial similarity or overlap between the manuscript under consideration and any other published paper of which they have personal knowledge.

Disclosure and conflict of interest

Unpublished materials disclosed in a submitted manuscript must not be used in a reviewer's own research without the express written consent of the author. Privileged information or ideas obtained through peer review must be kept confidential and not used for personal advantage. Reviewers should not consider manuscripts in which they have conflicts of interest resulting from competitive, collaborative, or other relationships or connections with any of the authors, companies, or institutions connected to the papers.

JNBS

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

JNBS 2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org

CONTENTS
İÇİNDEKİLER

JNBS 2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org

Year (Yıl) : 2018
Volume (Cilt) : 5
Issue Number (Sayı) : 3
Doi : 10.5455/JNBS.1525619232

Received/Geliş 29.05.2018
Accepted/Kabul 05.11.2018
JNBS, 2018, 5(3):131-136

NEUROPROTECTIVE EFFECT OF CITICOLINE AND GLUCOCORTICOSTEROID COMBINATION UNDER CONDITIONS OF EXPERIMENTAL DEMYELINATING MODEL OF CENTRAL NERVOUS SYSTEM

SİTİKOLİN VE GLUKOKORTİKOSTEROİD KOMBİNASYONUNUN MERKEZİ SİNİR SİSTEMİNİN DENEYSEL DEMİYELİNİZAN MODELİ KOŞULLARINDAKİ SİNİR KORUYUCU ETKİSİ

Alexander A. Nefodov[1], Igor F.Belenichev[2], Elena A. Nefodova[1], Nina V. Bukhtiyarova[2], Sergii V. Levich[2*], Sergii N. Dronov[2]

Abstract

Multiple sclerosis is a multifactorial, autoimmune, chronic inflammatory demyelinating disease of the central nervous system. Recent studies do not give possibility to estimate the contribution of neurodegenerative changes in neurological deficit of individual patient, to predict the disease development and the effectiveness of therapy. The goal of our research was to investigate methylprednisolone and citicoline co-administration effect to the processes of energy providing of the mitochondria of the cerebral cortex neurons in experimental allergic encephalomyelitis. Experiments were carried out on rats of both sexes weighing 150-180 g. Experimental allergic encephalomyelitis was induced by a single subcutaneous inoculation of encephalitogenic mixture in complete Freund's adjuvant. As material, we used brains. We studied markers of mitochondrial dysfunction and content of adenine nucleotides, lactate, malate, isocitrate, aspartate, pyruvate. We also studied the state of neurons, their area, RNA-content and proportion of apoptotic cells. Formation of experimental allergic encephalomyelitis (EAE) led to permanent disturbance of energy metabolism of brain. The administrations of methylprednisolone did not have a significant effect. Co-administration of methylprednisolone and citicoline exerted significant influence on some parameters of mitochondrial dysfunction and brain energy metabolism. We also found neuronal damage of sensorimotor cortex of experimental animals and to the neuroapoptosis activation. Administration of methylprednisolone resulted in direct neuroprotective effect. Combination of citicoline and methylprednisolone limit activity of unproductive anaerobic glycolysis and increases aerobic ATP synthesis reaction. Thus, the combination of citicoline and methylprednisolone does not affect the activity of malate aspartatic shunt in EAE conditions.

Keywords: experimental allergic encephalomyelitis; citicoline; methylprednisolone; mitochondria; neurons

[1]SE, Dnipropetrovsk Medical Academy of Ministry of Health of Ukraine, Dnipro, Ukraine
[2]Zaporizhzhya State Medical University, Zaporizhia, Ukraine
[*]Corresponding Author: Department of Biochemistry and Laboratory Diagnostic, Zaporizhzhya State Medical University, Mayakovskiy avenue, 26, 69035, Zaporizhzhya, Ukraine. E-mail: ifb1914@mail.ru

Özet

Multipl skeleroz çok bileşenli, otoimmün ve kronik inflamatuvar demiyelizan bir merkezi sinir sistemi hastalığıdır. Yakın zamanda yapılan çalışmalar hasta bireylerdeki nörodejeneratif değişiklerin nörolojik bozukluklara katkısını, hastalığın gelişimi ve terapinin etkisinin nasıl olacağını tahmin etme olanağı vermiyor. Araştırmamızın amacı, deneysel alerjik ensafalomiyelitdeki metilprednizolon ve sitikolinin birlikte kullanılmasıyla oluşacak etkinin serebral korteks nöronlarının mitokondrilerine enerji sağlamasını incelemektir. Deneyler her iki cinsiyetteki 150-180 gram ağırlığındaki farelerle gerçekleştirilmiştir. Deneysel alerjik ensefalomiyelit, tam Freund adjuvanı içindeki ensefallojenik karışımının tek bir deri altından aşılaması ile indüklenmiştir. Materyal olarak beyni kullandık ve adenin nükleotidleri, laktat, malat, isositrat, aspartat, piruvat içerikleri ile mitokondriyel bozukluk belirteçleri üzerine çalıştık. Aynı zamanda nöronların durumunu, alanlarını, RNA içeriğini ve apoptotik hücrelerin oranını da inceledik. Deneysel alerjik ensefalomiyelit (DAE) oluşumu, beynin enerji metabolizmasının kalıcı olarak bozulmasına yol açmaktadır. Metilprednizolon uygulamalarının anlamlı bir etkisi bulunamamıştır. Metilprednizolon ve sitikolinin birlikte uygulanması, mitokondriyal bozukluk ve beyin enerjisi metabolizmasının bazı parametreleri üzerinde anlamlı bir etki göstermiştir. Ayrıca deney hayvanlarının sensorimotor korteksinde nöronal hasar ve nöroapoptoz aktivasyonu da bulunmuştur. Metilprednizolon uygulaması doğrudan sinir koruyucu etki ile sonuçlanmıştır. Sitikolin ve metilprednizolon kombinasyonu, işlevi olmayan anaerobik glikoz parçalanmasını sınırlamakta ve aerobik ATP sentez reaksiyonunu arttırmaktadır. Bu nedenle, sitikolin ve metilprednizolon kombinasyonu, DAE koşullarındaki malat aspartatik devrenin aktivitesini etkilememektedir.

Anahtar Kelimeler: *deneysel alerjik ensafalomiyelit; sitikolin; metilprednizolon; mitokondri; nöronlar*

1. Introduction

Multiple sclerosis (MS) is a multifactorial, autoimmune, chronic inflammatory demyelinating disease of the central nervous system (CNS). It is generally accepted to have a diffuse defeat of white and gray matter of the CNS in MS patients, leading to the development of the brain and spinal cord atrophy. Severity of neurological symptoms in MS is largely related to the overall brain atrophy, manifesting by a decrease in volume of brain parenchyma, increased ventricular and subarachnoid spaces. The average age of debut of the disease is 29 years; the ratio of female and male cases is usually close to 3:1 (Gusev et al., 2011). Disability in MS is primarily associated with impaired motor function, visual impairment, coordination of pelvic functions. MS - the second most common cause of disability among young people is not only socially but also economically significant disease (Boiko et al., 2013; Orton et al., 2006). Until not long ago, it was believed that violation of the conducting function of axons in MS occurs only as a result of multifocal lesions of the myelin sheath (Popescu & Lucchinetti, 2012). However, more recent studies have shown that neurodegeneration (inflammatory damage to gray and white matter of the brain) occurs in the early stages of MS, and plays a large role in the formation of irreversible neurological deficit (Bjartmar et al., 2001; Geurts & Barkhof, 2008; Lucchinetti et al., 2011). Moreover, a clear correlation detected degree of disability in MS data with degenerative brain changes, while the magnetic resonance imaging pattern inflammatory changes can significantly dissociate with the clinical picture (DeStefano et al., 2001). Data on the primary pathogenesis of neurodegeneration in MS are very few, remain unclear underlying causes and mechanisms of development. These studies, available in clinical practice, do not give possibility to estimate the contribution of neurodegenerative changes in neurological deficit of individual patient, to predict the disease development and the effectiveness of therapy.

The goal of our research was to investigate the effect of methylprednisolone and citicoline co-administration to the processes of energy providing of the mitochondria of the cerebral cortex neurons and histomorphometric parameters of its formation in experimental allergic encephalomyelitis.

2. Materials and Methods

2.1. Animals

Experiments were carried out on 40 rats of both sexes weighing 150-180 g. Prior to the implementation of upcoming research protocol of the work was approved by the bioethics Commission of Zaporizhzhya State Medical University. According to the requirements of GLP and the European Convention for the Protection of Vertebrate Animals used for experimental and other purposes agreed by all the procedures related to the maintenance of the animals, the humane treatment of them and their use in experiments.

2.2. Experimental procedure

The experimental animals were kept in standard conditions with a light regime of day - night 12 hour / 12 hours at an air temperature of 20 - 22°C with free access to food and water. Experimental allergic encephalomyelitis (EAE) was induced by a single subcutaneous inoculation of encephalitogenic mixture (EGM) in complete Freund's adjuvant (CFA) at the rate of 100 mg of spinal cord homogenate homologous; 0.2 ml CFA (Mycobacterium killed content of 5 mg / ml) and 0.2 ml saline per animal. EGM was injected into the base of the tail under light ether anesthesia in a volume of 0.4 ml (Degano & Roth, 2000).

2.3. Biochemical analysis

Biochemical studies carried out on brain, for this purpose the animals were decapitated under anesthesia using Thiopental (30 mg/kg, intraperitoneally).

2.3.1. Material

Blood was rapidly removed from the brain; investigated pieces were separated from the meninges and placed

in liquid nitrogen. Then grounded in liquid nitrogen to a powder and homogenized in 10 times volume of the medium at (2 °C) containing (in mmol): sucrose - 250-HCl-Tris buffer - 20-1 EDTA (pH 7.4). Mitochondrial fraction was isolated by differential centrifugation in refrigerated centrifuge at the temperature of + 4 °C. To clean the mitochondrial fraction from large cell fragments it was previously centrifuged for 7 minutes at 1000 g. The supernatant was then re-centrifuged for 20 minutes at 17000 g. The supernatant was decanted and stored at -800 S. Mitochondrial pellet was resuspended in isolation medium containing bovine serum albumin (0.5 mg / ml) and again precipitated for 10 minutes at 17,000 g. The mitochondria were suspended in isolation medium suspension contained 40-60 mg protein / ml. For long-term storage mitochondria is frozen at -80 °C. To determine the speed potential of the inner mitochondrial membrane and opening of mitochondrial pores used suspension 0.5-1.0 mg protein / ml.

2.3.2. Enzymatic activity

Total activity of creatine phosphokinase (CK) and the cerebral fraction of the cytocholic isoenzyme of creatine phosphokinase (BB-CK) was determined in serum with Cormay Prestige 24i chemistry analyzer.

2.3.3. Energy metabolism

The state of energy metabolism was determined by the level of the most important intermediates – ATP, ADP, AMP, lactate, pyruvate and malate. The quantity of malate was detected according to method of Hohorst (Hohorst, 1970). The creation of renovated form of NAD+ is equal to the quantity of oxidized malate, the growth of which is indicated at 340 nm. Adenylate nucleotides were determined by thin layer chromatography (Prohorova, 1982). The content of pyruvate was determined by method of Zoh-Lompreht (Prohorova, 1982). The content of lactate was determined by the method of Hohorst (Hohorst, 1970). The creation of new form of NAD+ is equal to the quantity of oxidized lactate, the quantity growth of which is indicated at 340 nm.

2.3.4. Mitochondrial fraction

The development of experimental allergic encephalomyelitis was characterized by the magnitude of the mitochondrial inner membrane potential of mitochondria and the degree of mitochondria swelling.

For this purpose, brain of animals were washed with chilled 0.15 M KCl solution at 4°C. Then neuronal tissue was thoroughly comminuted and homogenized in 1000 % w/vol of the medium consisting of: sucrose – 250 mM, Tris-HCl-buffer – 20mM (pH 7.4) and EDTA – 1 mM. Mitochondria were isolated at 4°C by differential centrifugation in the refrigerated centrifuge Sigma 3-30k (Germany). For cleaning the mitochondrial fraction from large cell fragments primary centrifugation was conducted for 7 minutes at 1000 g, and then supernatant was centrifuged for 20 minutes at 17000g. The supernatant was decanted and stored at -80°C. The pellet of mitochondria was resuspended in the medium, containing bovine serum albumin (0.5 mg/ml) and then precipitated by centrifugation for 10 minutes at 17,000 g. The mitochondria were suspended in the isolation medium, suspension contained 40-60 mg protein/ml. To record the opening of MO, to incubation mixture, which consisted of 120 μM of KCl, 0.5 mM of KH2PO4, 2 mM of glutamate, 1 mM of malate and 20 mM of Tris-HCl-Molecular and biochemical mechanisms buffer (pH 7.4) was added 1 mg of mitochondria suspension.

Mitochondrial membranes barrier function changes were determined spectrophotometrically as a decrease in absorbance at 540 nm caused by mitochondria swelling. The process was induced by introduction of 50 μM of Ca2+ into non-mitochondrial medium after Ca2+ - recharge (ΔE) in the study samples, which characterized the intensity of the process.

The potential generated at the inner mitochondrial membrane, was recorded on a spectrophotometer, a two-wave mode (511 - 533 nm) with Safranin O. as a voltage-dependent probe (18 uM). Measurements were performed in 10x10 mm glass cell with a working volume of 2 ml. Measurement was carried out in 0.62 mM KCl; 40 mM Caps (3- [cyclohexylamino] -1-propanesulfonic acid) -KOH (pH = 10); protonophore-uncoupler FCCP and monensin antiporter were used to dissipate potential.

2.3.5. Morphometric analysis

Brain was fixed in 10% Bouin's fluid (24 hours) and was embedded in paraffin blocks. These blocks we used for preparation of 5-micron frontal histological sections of the postcentral gyrus (somatosensory bark). To study the morphological and functional state of neurons of IV-V cortical layers and for specific detection of RNA, histological sections were deparaffinized and then were stained by gallocyanin - chrome alum (Einarson method). Images of the cerebral cortex were obtained by microscope Axioskop (Zeiss, Germany), using an 8-bit CCD-camera COHU-4922 (COHU Inc., USA) and then were processed by computer image analysis system VIDAS-386 (Kontron Elektronik, Germany). Morphometric analysis of brain cells was performed in automatic mode using the VIDAS-2.5 software (Kontron Elektronik, Germany).

The following parameters were defined:

- density of neurons, glial cells, apoptotic and destructed neurons (number of cells per 1 mm2 of area of cerebral cortex section);

- area of bodies of normal, apoptotic and destructed neurons (μm2);

- RNA concentration in normal, apoptotic and destructed neurons (absorbance units, EOD), which was calculated as the logarithm of the ratio of the optical density of the cell body to the optical density of the intercellular substance.

Degenerating neurons were considered those showing signs of disease or cytolysis. Density of degenerating and surviving neurons, the ratio of intact neurons to perishing (neurodegeneration index) and ratio of the surviving neurons in the use of medication to intact neuronal density in control group (survival index improvement) were measured by software. The rate of the neurodegeneration index less than one unit testified the predominance of

the dying neurons number to surviving. The index of the survival improvement and activity of microglia more than one unit showed a positive pharmacological effect of the drug, less than one - negative. The functional state of the surviving neurons was evaluated on the basis of changes in the area of nuclei and nucleoli of nucleic acids neuronal content, nuclear-cytoplasmic ratio and the number of multinuclear cells (Chekman et al., 2016).

2.3.6. Statistical analysis

The results of the investigation were calculated using the standard analysis package of computer program «STATISTICA® for Windows 6.0» (StatSoftInc., №AXXR712D833214FAN5), as well as «SPSS 16.0», «Microsoft Office Excell 2003».Verification of normality was performed using the Shapiro-Wilk test. Data are presented as the sample mean. Accuracy of differences between sample means was assessed using Student t-test under normal distribution. The Mann-Whitney U test was used in the case of nonnormal distribution or analysis of ordinal variables. The analyses of variance (ANOVA) under normal distribution or Kruskal-Wallis test for nonnormal distribution were used for comparison of the independent variables in more than two samples. The difference p <0.05 (95%)

was considered statistical significant for all analyses (Zaycev et al., 2006).

3. Results

Formation of experimental allergic encephalomyelitis led to activating anaerobic glycolysis (increased lactate / pyruvate ratio), inhibition of oxidation in the Krebs cycle (reduction of malate by 51% and isocitrate 45 %) and power shortage (a decrease of 42% of ATP, ADP, 43% AMP against increase of 82%), malate-aspartate shunt inhibition (lowering of malate level by 51%, and aspartate by 40% in comparison with the intact group) (Table 1, 2).

Formation of EAE also led to the increasing of mitochondrial pore opening rate at 9.1 times and fall of the inner mitochondrial membrane potential by 78% (Table 3).

Co-administration of methylprednisolone and citicoline exerted significant influence on some parameters of mitochondrial dysfunction and brain energy metabolism. Thus, the introduction of this combination resulted in a significant reduction of mitochondrial pore opening speed by 66% and increase of the mitochondria inner membrane charge by 69%.

Multiple sclerosis experimental equivalent leads to neuronal damage of sensorimotor cortex of experimental animals. Thus, in a group of untreated animals with EAE neurons density decrease was observed in 19%, indicating the cell death, increasing their surface by 10%, indicating edema. It has also been found to decrease transcriptional processes in neurons of the sensorimotor cortex in the simulation of EAE, as evidenced by RNA decline by 21%. It was also observed neuroapoptosis activation. So, in animals with EAE increase in the density of apoptotic and destructive cells of the sensorimotor area of the cortex by 150% was observed (Tables 4-5). Percentage of apoptotic cells in the brain structure in animals with EAE increased from 3.4 to 15%, 7%, i.e. nearly 5 times. Administration of methylprednisolone to animals with EAE resulted in a significant increase in the cortical sensoromotor neurons density by 3% and reducing their size by 8%.

Tablo 1. Adenile nucleotides in the brain of animals with experimental allergic encephalomyelitis

Group of animals	ATP, umol/g of tissue	ADP, umol/g of tissue	AMP, umol/g of tissue
Intact	2,80 ± 0,15	0,27 ± 0,013	0,114 ± 0,008
Experimental allergic encephalomyelitis	1,60 ± 0,08 (-42%)	0,153 ± 0,010 (-43%)	0,208 ± 0,021 (+82%)
Experimental allergic encephalomyelitis + methylprednisolone	1,67 ± 0,13	0,148 ± 0,025	0,202 ± 0,016
Experimental allergic encephalomyelitis + methylprednisolone + citicoline	1,81 ± 0,11* (+13%)	0,178 ± 0,011* (+16%)	0,166 ± 0,011 (-20%)

Tablo 2. Markers of energetic metabolism in the brain of animals with experimental allergic encephalomyelitis

Group of animals	Lactate	Malate	Pyruvate	Isocitrate	Aspartate
	mcmol/ g of tissue				
Intact	2,41 ± 0,09 4,86	0,45 ± 0,02 0,22	0,498 ± 0,026 0,25	0,288 ± 0,018 0,158	11,7 ± 0,80 6,95
Experimental allergic encephalomyelitis (EAE)	± 0,20 (+101%)	± 0,03 (-51%)	± 0,026 (-49%)	± 0,010 (-45%)	± 0,64 (-40%)
Experimental allergic encephalomyelitis + methylprednisolone	4,87 ± 0,21 (+0,2%)	0,24 ± 0,04 (+9%)	0,246 ± 0,050 (-1,6%)	0,164 ± 0,030 (+4%)	7,60 ± 0,50 (+9%)
Experimental allergic encephalomyelitis + methylprednisolone + citicoline	3,52 ± 0,31 (-27%)	0,34 ± 0,05 (+54%)	0,338 ± 0,030 (+35%)	0,286 ± 0,018 (+81%)	8,00 ± 0,66 (+15%)

Tablo 3. Dysfunction indicators of brain mitochondria in experimental allergic encephalomyelitis

Group of animals	Opened mitochondrial pores, Δ E (540nM)	Mitochondrial membrane potential (Safranin-O)
Intact	0,019 ± 0,001	50,9 ± 2,05
Experimental allergic encephalomyelitis (EAE)	0,193 ± 0,013 (+915%)	10,9 ± 1,21 (-78%)
Experimental allergic encephalomyelitis + methylprednisolone	0,186 ± 0,015	13,0 ± 1,21
Experimental allergic encephalomyelitis + methylprednisolone + citicoline	0,065 ± 0,005* (-66%)	18,5 ± 1,8* (+69%)

Tablo 4. Morphological and functional indicators of neurons of the sensorimotor cortex brain of animals with experimental allergic encephalomyelitis

Group of animals	The density of neurons (neuron /mm^2)	Area neurons (um^2)	RNA content (Eon)
Intact	1250,2 ± 25,5	83,0± 3,86	9,52± 0,33
Experimental allergic encephalomyelitis	1006,7 ± 10,7 (-19%)	91,5± 3,93 (+10%)	7,45± 0,62 (-21%)
Experimental allergic encephalomyelitis + methylprednisolone	1037,4 ± 6,8* (+3%)	84,2± 2,73* (-8%)	7,33± 0,44 (-2%)
Experimental allergic encephalomyelitis + methylprednisolone + citicoline	1101,4 ± 7,4* (+9,4%)	84,2± 2,11* (-8%)	8,10± 0,42 +8,7%

In animals with EAE treated with a combination of methylprednisolone and citicoline neuronal density increased by 9.4%, their area has reached values of intact animals, RNA analysis of increased by 8.7%. The combination of methylprednisolone and citicoline slowed the sensoromotor cortex neurons neuroapoptosis in conditions of EAE. Thus, the density of apoptotic cells and destructive decreased by 19.5%, while the proportion of apoptotic cells decreased from 15.7% in the control of up to 9% in the group receiving methylprednisolone with citicoline (Table 5).

Tablo 5. Dysfunction indicators of brain mitochondria in experimental allergic encephalomyelitis

Group of animals	The density of optical and destructive cells for 1 mm^2	The proportion of apoptotic cells, %
Intact	59,4±6,89	3,4±0,96
Experimental allergic encephalomyelitis	148,0±16,4 (+149%)	15,7±1,7 (+361%)
Experimental allergic encephalomyelitis + methylprednisolone	141,6±11,0 (-4%)	15,0±1,0 (-4%)
Experimental allergic encephalomyelitis + methylprednisolone + citicoline	119,2±9,68* (-19,5%)	9,0±1,0* (-42%)

4. Discussion

Formation of experimental equivalent of multiple sclerosis - experimental allergic encephalomyelitis (Nefedov et al., 2014) led to permanent disturbance of energy metabolism of brain tissue (Table 1, 2). It led to inhibition of mitochondria-cytosolic compensatory shunts energy production, in particular malate aspartate shunt. Malate-aspartate shuttle transports the recovered equivalents generated in the cytoplasm during glycolysis in mitochondria in ischemia. Formed in the cytoplasm under conditions of low oxygen, NADH+ is used to convert oxaloacetic acid to malate, which penetrates into the mitochondria and takes part in the export of α-ketoglutarate. This mitochondrial malate is converted to oxaloacetic acid to form the NADH available for electronic transport chain (3 molecules of ATP are formed from 2 protons). Oxaloacetic acid formed from malate is converted to α-ketoglutarate and aspartate. α-ketoglutarate comes from mitochondria in exchange for malate, and aspartate is exchanged to glutamate. The transfer is due to the gradient of glutamate and high intramitochondrial relationship of glutamate / aspartate. The ratio of NADH / NAD + and malate / acetic acid are regulated by malate-dehydrogenase (MDH). In modeling the EAE malate-aspartate shunt inhibition was observed. These changes appear to be consequences of a secondary mitochondrial dysfunction. Studies of an isolated from the brain neurons mitochondria functional activity confirmed of this hypothesis.

The administrations of methylprednisolone to the experimental rats with EAE did not have a significant effect on the studied parameters of energy metabolism and mitochondrial dysfunction (Tables 1-3). In the same time methylprednisolone and citicoline co-administration exerted significant influence.

Multiple sclerosis experimental equivalent leads to neuronal damage of sensorimotor cortex caused by neuroapoptosis activation. Administration of methylprednisolone to animals with resulted in a significant increase in the cortical sensoromotor neurons density, indicating a direct neuroprotective effect of hormone therapy. However, the administration of methylprednisolone alone had no effect on the functional characteristics of neurons (RNA levels did not change) and had no effect on neuroapoptosis indicators. Administration to animals with EAE combination therapy of methylprednisolone and citicoline neuroprotection increased efficiency (Nefedov, 2015; Nefedov & Mamchur, 2015a; Nefedov & Mamchur, 2015b).

Neuroprotective agent Citicoline (Ceraxon) does not show a direct energy tropic action. The drug has a strong mitoprotective effect. Citicoline can maintain the integrity of the inner membrane of the mitochondria, as evidenced by the recovery of its capacity (Belenichev et al., 2015). This mechanism is associated with reduction of cardiolipin level in the inner mitochondrial membrane. It is also found that citicoline, indirectly, through increasing the activity of glutathione-related enzymes (glutathione-reductase and glutathione-transferase) regulates the level of reduced glutathione. Reduced glutathione, especially mitochondrial, inhibits oxidative degradation Red-Oxi - sensitive areas of the mitochondrial membrane and the formation of persistent mitochondrial dysfunction (Belenichev et al., 2014). Iincreasing of the reduced glutathione level can reduce Ceraxon nitrosating stress reaction and inhibit NO-dependent mechanisms of neuroapoptosis. Safety of recovered glutathione equivalents helps to limit the cytotoxic effects of NO and prevent nitrotyrosine accumulation. Balance of pro- and anti-apoptotic mechanisms in nitrosating stress is associated with the level of NO. In conditions of excessive active forms of oxygen level (primarily peroxynitrite and a hydroxyl radical) anti-apoptotic proteins are gone under the oxidative modification (bcl-2 and others), and the excess of NO-radical amid increased activity iNOS enhances the synthesis of pro-apoptotic proteins (FAS and APO-1) in neurodegenerative pathologies. When neurodegeneration, including EAE, proinflammatory cytokines expression is enhanced (IL-1, TNF-α, HIF-1) and the factors responsible for the transcription of NF-κB, AP-1, JNK as well, which indirectly enhance further formation of NO cytotoxic derivatives, leading to increased molecular reactions of mitochondrial dysfunction and neuroapoptosis. Strengthening of the methylprednisolone with Ceraxon (co-administration) neuroprotective effect can be explained by the prism of NO-dependent mechanisms of neuroapoptosis and mitochondrial dysfunction (Belenichev & Bukhtiyarova, 2014; Sukumaran et al., 2012).

Thus, on the basis of the foregoing, it can be concluded that the combination of citicoline and methylprednisolone limit activity of unproductive anaerobic glycolysis and increases aerobic ATP synthesis reaction by activation of oxidation in the Krebs cycle at tricarboxylic portion (isocitrate increase). Thus, the combination of citicoline and methylprednisolone does not affect the activity of malate aspartatic shunt in EAE conditions. Apparently, the effects of citicoline and methylprednisolone in EAE focus

JNBS 2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org

on mutual suppression of iNOS expression and activity.

References

Belenichev, I. F., Bukhtiyarova, N. V. (2014). The Thiol–Disulfide Balance and the Nitric Oxide System in the Brain Tissue of Rats Subjected to Experimental Acute Impairment of Cerebral Blood Flow: The Therapeutic Effects of Nootropic Drugs, Neurochemical Journal, 8(1), 24-27.

Belenichev, I. F., Chernij, V. I., Nagorna, E.A., Pavlov, S.V., Buhtiyarova N.V. (2015). Neuroprotection and neuroplasticity, Kiyv, Logos.

Belenichev, I. F., Suprun, E.V., Gromov, L.A. (2014). IL-1Ra stabilises the thiol–disulfide system in the brain tissues of rats with experimental diabetes and cerebral ischemia, European Neuropsychopharmacology, 24, 2, 236-239.

Bjartmar, C., Kinkel, R.P., Kidd, G., Rudick, R.A., Trapp, B.D. (2001). Axonal loss in normal-appearing white matter in a patient with acute MS, Neurology, 57(7), 1248-1252.

Boiko, A. N., Kukel, T. M., Lysenko, M. A., Vdovichenko, T. V., Gusev E. I. (2013). Clinical epidemiology of multiple sclerosis in Moscow. Descriptive epidemiology of the example of the population of one of the city's districts, Journal of Neurology and Psychiatry S.S. Korsakov, 10, 8-14.

Chekman, I. S., Belenichev, I. F., Bukhtiyarova, N. V., Nagornaya, E. A., Gorchakova, N. A., Gorbacheva, S. V. (2016). Preclinical study of the specific activity of potential drugs of primary and secondary neuroprotection, Teaching recommendations of the State Enterprise "Health Ministry of Ukraine State expert center.

Degano, A. L., Roth, G. A. (2000). Passive transfer of experimental autoimmune encephalomyelitis in Wistar rats: dissociation of clinical symptoms and biochemical alterations, J Neurosci Res, 59 (2), 283-290.

DeStefano, N., Narayanan, S., Francis, G. S. (2001). Evidence of axonal damage in the early stages of multiple sclerosis and its relevance to disability, Arch Neurol, 58(1), 65-70.

Geurts, J. J. G., Barkhof, F. (2008). Grey matter pathology in multiple sclerosis, Lancet Neurol, 7(9), 841-851.

Gusev, E. I., Zavalishin, I. A., Boiko, A. N. (2011). Multiple sclerosis, Clinical guidelines, Moscow, Real Time.

Hohorst H. J. (1970). Enzymatic method of the lactate concentration in blood. In: Bergmeyer HU, ed. Methods of Enzymatic Analysis. 1st ed. Weinheim, Bazel, B: Verl Chemie.

Lucchinetti, C. F., Popescu, B. F. G., Bunyan, R. F. (2011). Inflammatory cortical demyelination in early multiple sclerosis, N Engl J Med., 365(23), 2188-2197.

Nefedov, A. A. (2015). Evaluating the effectiveness of neuroprotective therapy of experimental allergic encephalomyelitis in a basic therapy Solu-Medrol, Biomedical and Biosocial Antropology, 24, 65-70.

Nefedov, A. A., Mamchur, V. I. (2015a). Experience in the use of citicoline in the experimental allergic encephalomyelitis simulated therapy, Bulletin problems of biology and medicine, 2, 4(121), 165-170.

Nefedov, A. A., Mamchur, V. I. (2015b). The possibilities of pharmacological correction of cognitive disorders in experimental equivalent of MS, Medical prospects, 20, 2, 4-11.

Nefedov, A. A., Mamchur, V. I., Kharchenko, Y. V. (2014). Modeling and assessment course of experimental allergic encephalomyelitis, Bulletin problems of biology and medicine, 4, 2(114), 205-208.

Orton, S-M., Herrera, B. M., Yee, I. M. (2006). Sex ratio of multiple sclerosis in Canada: a longitudinal study, Lancet Neurol., 5(11), 932- 936.

Popescu, B. F. G., Lucchinetti, C. F. (2012). Pathology of demyelinating diseases, Annu Rev Pathol, 7, 185-217.

Prohorova M. I. (1982). Modern methods of biochemical investigations (lipid and energy metabolism). 1st ed. Leningrad, L: Leningradskiy University Publishers.

Sukumaran, S., Lepist, E. I., DuBois, D. C. (2012). Pharmacokinetic/pharmacodynamic modeling of methylprednisolone effects on iNOS mRNA expression and nitric oxide during LPS-induced inflammation in rats, Pharm. Res., 29, 8, 2060-2209.

Zaycev, V. M., Liflyandskiy, V. G., Marinkin, V. I. (2006). Applied Medical Statistics: Textbook. 1st ed. Saint Petersburg: Foliant Publishers.

Year (Yıl) : 2018
Volume (Cilt) : 5
Issue Number (Sayı) : 3
Doi : 10.5455/JNBS.1530277827

Received/Geliş 29.06.2018
Accepted/Kabul 28.08.2018
JNBS, 2018, 5(3):137-139

EFFECTS OF ESTROGEN ON KYNURENINE PATHWAY AND NF-kB IN TNF-α INDUCED NEUROINFLAMMATION

TNF-α ARACILI NÖROİNFLAMASYONDA ÖSTROJENİN KİNÜRENİN YOLU VE NF-kB ÜZERİNE ETKİLERİ

Halime Eda Yalçın[1], Batu Kaan Aksulu[2], Fatih Ozen[1], Belkis Atasever Arslan[2*]

Abstract

Neuroinflammation involves glia activation, releasing of inflammatory mediators such as cytokines and chemokines, and formation of reactive oxygen and nitrogen species. It plays a central role in many neurodegenerative diases processes such as Alzheimer's disease, Parkinson's disease, dementia. Estrogen deprivation, commonly associated with aging, loss of learning and memory skills in postmenopausal women and Alzheimer's disease. In this study, we studied effects of 17-ßestradiol on kynunerine pathway and NK-kB gene expression in neuroinflammation. According to our results, estrogen increased expression of kynunerinase gene and decreased IDO-1 gene expression after TNF-alpha incubation in differentiated SH-SY5Y cells. However, it did not change NF-kB gene expression.

Keywords: estrogen; neuroinflammation; TNF-α; Alzheimer's disease; kynureninase; NF-kB; IDO-1

Özet

Nöroinflamasyon, glia aktivasyonunu, sitokinler ve kemokinler gibi inflamatuar mediatörlerin salınmasını ve reaktif oksijen ve nitrojen türlerinin oluşumunu içerir. Alzheimer hastalığı, Parkinson hastalığı, demans gibi birçok nörodejeneratif hastalık sürecinde merkezi bir rol oynar. Genellikle yaşlanmayla ilişkili olan östrojen yoksunluğu, özellikle menopoz sonrası kadınlarda öğrenme kaybı ve hafıza becerileriyle ilişkilidir ve Alzheimer hastalıgı ile ilişkilidir. Bu çalışmada, 17-b östradiolun, kynunerine yolağı ve NF-kB gen ifadesi uzerine etkisini arastirdik. Elde ettiğimiz sonuçlara göre östrojen, farklılaşmış SH-SY5Y hücrelerinde TNF-alfainkübasyonu sonrası kinüreninaz geninin ekspresyon düzeyini arttırırken, IDO-1 gen ekspresyon düzeyini azalttı. Bununla birlikte, NF- kB gen ekspresyon seviyesini değiştirmedi.

Anahtar Kelimeler: *östrojen; nöroinflamasyon; TNF-α; alzheimer hastalığı; kinüreninaz; NF-kB; IDO-1*

[1]Department of Bioengineering, Faculty of Engineering and Natural Sciences, Üsküdar University, Istanbul, Turkey
[2]Department of Molecular Biology and Genetics, Faculty of Engineering and Natural Sciences, Üsküdar University, Istanbul, Turkey
[*]Corresponding Author: Department of Molecular Biology and Genetics, Faculty of Engineering and Natural Sciences, Üsküdar University, Istanbul, Turkey
E- mail: belkisatasever.arslan@uskudar.edu.tr Phone: 90.216 400 22 22, Fax: 90 216 474 12 56

JNBS 2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org

1. Introduction

The neuroinflammation; is a response that includes all the cells, including the central nervous system, neurons, macroglia and microglia, and can be a negative factor in acute and chronic brain disorders in connection with the brain. Cellular and molecular immunological components such as cytokines, reactive oxygen and nitrogen species and glial cells; Activation of microglia and astrocytes causes neuroinflammation. Neuroinflammation plays an important role in many neurodegenerative diseases such as multiple sclerosis (MS), Alzheimer's disease (AD), ALS, Parkinson's disease and autism (Carson, Doose, Melchior, Schmid, & Ploix, 2006). In order to activate complex neuroinflammatory pathways and microglia; factors such as genetic, environmental, age and past experiences have significant effects(Hof & Mobbs, 2009).

There are many potential mechanisms that estrogen can influence the symptoms of Alzheimer's risk and phenotype (Rosini, Simoni, Caporaso, & Minarini, 2016). The degeneration of cholinergic neurons and accumulation of amyloid β plaques cause the disease to progress gradually (Chen et al., 2016) (Shamim & Laskowski, 2017).

Oxidative stress is thought to be one of the main causes of Alzheimer's disease. ROS induces neuroinflammation by stimulating gene transcription by the release of cytokines such as pro-inflammatory TNF-α (Akbar et al., 2016)(Morales et al., 2014). The levels of TNF-α in healthy people's brain are low and their physiological role is uncertain. An increase in TNF-α levels is observed in chronic inflammation and inflammation plays a leading role, especially in the early stages of the disease. Pro-inflammatory mediators and nuclear transcription factor (NF-B) are directly or indirectly involved in the production of a large number of pro-inflammatory cytokines such as TNF-α. NF-κB is a key control role in inflammation and is an important target for anti-inflammatory therapeutic interventions (Ivanenkov, Balakin, & Lavrovsky, 2011). In the TNF-α mediated inflammation model, it was observed that ER activation and 17-β estradiol inhibited nuclear translocation of NF-kB, (Ghisletti, Meda, Maggi, & Vegeto, 2005).

In addition to this, pro-inflammatory cytokines can directly induce the production of oxidative species by affecting neuronal functions (Yamada, Akimoto, Kagawa, Guillemin, & Takikawa, 2009). It has been shown that estrogen inhibits the inflammatory response in the brain, and therefore estrogen depletion leads to an inflammatory state and causes IDO-1 activation (Jayawickrama, Nematollahi, Sun, Gorrell, & Church, 2017).

2. Materials and Methods

2.1. Cell Culture

The SH-SY5Y (ATCC) neuroblastoma cells were grown on a complete medium of Dulbecco's Modified Eagled Medium (DMEM) medium supplemented with 10% fetal bovine serum, 100 U / ml Penicillin / Streptomycin and L-Glutamine on a recommended 37°C medium containing 5% .

2.2. Differentiation of SH-SY5Y Cells

SH-SY5Y was cultured in an incubator containing 37 ° C 5% CO2 in DMEM medium containing human neuroblastoma cell line, 10% FBS, 2mM glutamine, 100U / ml 100U / ml Penicillin / Streptomycin and L-Glutamine, 0.1% non essential amino acid. The cell medium was changed every 3 days to pass 90% density. All applications were glued when the cells reached a density of 75%. 24 hours after the cells were seeded, differentiation was initiated by reducing the FBS ratio in the culture medium to 1% and by adding 10 [mu] M retinoic acid on the 4th and 7th days. To evaluate the morphological differentiation in the cells, they were analyzed under inverted microscope at days 4 and 7 (Kalkan, Durasi, Sezerman & Atasever-Arslan, 2016).

2.3. TNF-α Implementation to SH-SY5Y Cell Line

Cells treated with SH-SY5Y RA were supplemented with 10 μM TNF-α in cell media on day 8 of RA-treated cells and incubated for 24 hours. The estrogen was dissolved in ethanol to prepare a 10 -7 M solution. The solution was added to the cells incubated with TNF-α for 24 hours and incubated with TNF-α for another 6 hours.

It was studied in 3 groups:

1.Differentiated-RA (SH-SY5Y TNF (-))

2.Differentiated-RA (SH-SY5Y TNF (+))

3.Differentiated-RA (SH-SY5Y TNF (+), estrogen (+))

2.4. RNA Isolation

After pipetting 1 ml of tri-reagent was added for 10 million cells, it was then allowed to stand at room temperature for 5 minutes, then 200 μl of chloroform was added. After 15 sec vortexing, it was left in the room for 2-3 minutes. Subsequently, centrifugation was carried out for 15 min at +4 ° C. and the upper phase was placed in a new tube and 500 μl of isopropanol was added. Vortexed and allowed to stand in the room for 5-10 minutes. Supernatant was centrifuged for 10 minutes at +4 degrees. 750 μl 75% EtOH was added. Supernatant was centrifuged for 5 min at +4 degrees. The alcohol was evaporated by standing on ice for 10 minutes. 50 μl RNAase free water was added to dissolve the RNA pellet. 5 ependorhea divided to -80 degrees. Each tube was prepared to be disposable and thus the degradation of the RNA was prevented.

2.5. cDNA preparation from RNA

The SensiFAST cDNA Synthesis Kit will be used to synthesize cDNA (complementer Deoxyribose Nucleic Acid). According to the kit protocol; To prepare the master mix, add 1 μg RNA, 4 μl 5x TransAmp buffer, 1 μl Reverse transcriptase enzyme and DNase / RNase free water to complete 20 μl. The program was programmed to heat 25 ° C for 10 minutes, 42 ° C for 15 minutes, 48 ° C for 15 minutes, 85 ° C for 5 minutes and finally 4 ° C incubation.

2.6. Real Time PCR

qPCR method was used to investigate changes in the expressions of NF-Kb, IDO-1, and kynureninase genes in the neuroinflammation models. RT-PCR The Roche LightCycler® FastStart DNA Master was performed with SYBR Green I.

3. Results and Discussion

The estrogen is required for the synthesis of the acetyl transferase enzyme and has been studied in postmenopausal women by elevating the acetyltransferase acetyl activity on the 17β-estradiol cognitive processes to reduce the likelihood of Alzheimer's disease progression and improve cognitive performance by estrogen replacement therapy. (Janicki and Schupf, 2010).

In this study, we established the cellular model of neuroinflammation induced with TNF-α pro-inflammatory cytokine, which triggers neuroinflammation and mediates the mechanism of action of 17-β estradiol in inflammatory response. Understanding the mechanism of action of 17-β estradiol is very important because of the limited study of how the molecular mechanism of action is affected in neuroinflammation models of 17-β estradiol.

First, we induced neuroinflammation in SH-SY5Y neuroblastoma cells differentiated with RA and incubated with TNF-α for 24 hours, and then we incubated a group of cells that were incubated with TNF-α for another 6 hours with 17-β estradiol. According to our results, estrogen increased expression level of kynureninase genes and decreased IDO-1 gene expression levels after TNF-α. incubation in differentiated SH-SY5Y cells. However, it did not change NF-kB gene expression level (Figure 1).

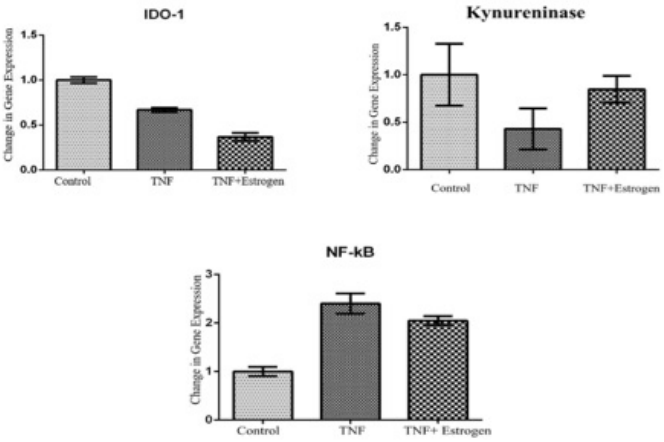


Figure 1. Expression levels of IDO-1, kynunerinase and NF-kB genes in SH-SY5Y cells differentiated-RA (SH-SY5Y TNF (+), estrogen (+)).

NF-kB is an important target for anti-inflammatory therapeutic interventions. In the inflammatory studies performed in recent years; 17-β estradiol is involved in the results obtained by inhibiting intracellular transport of NF-kB in inflammatory signal transduction pathways and inhibiting gene transcription induced by inflammatory agents (Tam, Mercado, Hoffmann, & Niwa, 2012) In our study, it was found that estrogen did not change NF-kB gene expression level in TNF-α induced neuroinflammation.

The expression of IDO-1, which is involved in the kynurenine pathway, is regulated by inflammatory cytokines, interferons, and TNF-α (Kincses, Toldi, & Vécsei, 2010). Also kynureninase is very important for kynurenine metabolism. Our results showed that estrogen has different effects on IDO-1 and kynureninase. While it increases kynureninase gene expression level, also it induces a decrease in IDO-1 gene expression. But its these effects do not change much against effects of TNF-α on the cells.

According to our results, 17-β estrodiol can have a protective effect on neuroinflammation. However, further investigations of estrogenic effects on neuroinflammation studies may improve therapeutic approaches to estrogen.

Acknowledgements

This study was supported by the Scientific and Technological Research Council of Turkey (TUBITAK) 2209-A (Project No: 1919B011702534). The authors have no conflict of interest

References

Akbar, M., Essa, M. M., Daradkeh, G., Abdelmegeed, M. A., Choi, Y., Mahmood, L., & Song, B. J. (2016). Mitochondrial dysfunction and cell death in neurodegenerative diseases through nitroxidative stress. Brain research, 1637, 34-55.

Carson, M. J., Doose, J. M., Melchior, B., Schmid, C. D., & Ploix, C. C. (2006). CNS immune privilege: hiding in plain sight. Immunological reviews, 213(1), 48-65.

Chen, W. W., Zhang, X. I. A., & Huang, W. J. (2016). Role of neuroinflammation in neurodegenerative diseases. Molecular medicine reports, 13(4), 3391-3396..

Ghisletti, S., Meda, C., Maggi, A., & Vegeto, E. (2005). 17β-estradiol inhibits inflammatory gene expression by controlling NF-κB intracellular localization. Molecular and cellular biology, 25(8), 2957

Hof, P. R. [Ed], & Mobbs, C. V. [Ed]. (2009). Handbook of the neuroscience of aging. Academic Press.

Ivanenkov, Y.A., V Balakin, K., & Lavrovsky, Y. (2011). Small Molecule Inhibitors of NF-□ B and JAK/STAT Signal Transduction Pathways as Promising Anti-Inflammatory Therapeutics. Mini reviews in medicinal chemistry, 11(1), 55-78.

Janicki, S. C., Schupf, N. (2010). Hormonal influences on cognition and risk for Alzheimer's disease. Current Neurology and Neuroscience Reports. 10(5),359-66.

Jayawickrama, G. S., Nematollahi, A., Sun, G., Gorrell, M. D., & Church, W. B. (2017). Inhibition of human kynurenine aminotransferase isozymes by estrogen and its derivatives. Scientific reports, 7(1), 17559.

Kalkan, Z., Durasi, İ. M., Sezerman, U., & Atasever-Arslan, B. (2016). Potential of GRID2 receptor gene for preventing TNF-induced neurodegeneration in autism. Neuroscience letters, 620, 62-69.

Morales, I., Guzmán-Martínez, L., Cerda-Troncoso, C., Farías, G. A., & Maccioni, R. B. (2014). Neuroinflammation in the pathogenesis of Alzheimer's disease. A rational framework for the search of novel therapeutic approaches. Frontiers in cellular neuroscience, 8, 112.

Rosini, M., Simoni, E., Caporaso, R., & Minarini, A. (2016). Multitarget strategies in Alzheimer's disease: benefits and challenges on the road to therapeutics. Future medicinal chemistry, 8(6), 697-711.

Shamim, D., & Laskowski, M. (2017). Inhibition of inflammation mediated through the tumor necrosis factor α biochemical pathway can lead to favorable outcomes in Alzheimer disease. Journal of central nervous system disease, 9(0).

Tam, A. B., Mercado, E. L., Hoffmann, A., & Niwa, M. (2012). ER stress activates NF-κB by integrating functions of basal IKK activity, IRE1 and PERK. PloS one, 7(10), e45078.

Yamada, A., Akimoto, H., Kagawa, S., Guillemin, G. J., & Takikawa, O. (2009). Proinflammatory cytokine interferon-γ increases induction of indoleamine 2, 3-dioxygenase in monocytic cells primed with amyloid β peptide 1–42: implications for the pathogenesis of Alzheimer's disease. Journal of neurochemistry, 110(3), 791-800.

JNBS 2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org

ORIGINAL ARTICLE-ARAŞTIRMA

Year (Yıl) : 2018
Volume (Cilt) : 5
Issue Number (Sayı) : 3
Doi : 10.5455/JNBS.1533938757

Received/Geliş 11.08.2018
Accepted/Kabul 12.08.2018
JNBS, 2018, 5(3):140-149

SOCIAL REWARD IN ACTION: REWARD MAGNITUDE AND VALENCE EFFECTS ON THE EEG MU RHYTHM

EYLEM İÇERİSİNDE SOSYAL ÖDÜLLER: ÖDÜL BÜYÜKLÜĞÜ VE DEĞER ETKİSİNİN MÜ AKTİVİTESİ ÜZERİNE ETKİSİ

Elliot C. Brown[1,2*], Fatma Keskin Krzan[3], Gokcer Eskikurt[4], Cumhur Tas[3]

Abstract

In social interactions, the values we associate with observed actions can influence how we process others' behaviors and the decisions we make. Some studies have suggested that different social contexts, and particularly the reward value of perceived actions can modulate motor system activity when observing others' actions. However, sensitivity to reward magnitude has never been tested in the action observation system. Here we used electroencephalography (EEG) to investigate the independent effects of reward valence and magnitude on the mu rhythm, an index of the motor mirror system, while participants (N=23) passively observed actions that led to high or low rewards or losses. Behavioral measures of social approach/avoidance, theory of mind and empathy were also taken. Results showed that reward valence significantly modulated mu rhythm, where losses led to greater mu suppression, but reward magnitude had no effect. The findings also demonstrated a novel association between the specific reward-related modulation of the mu rhythm and social cognitive skills, particularly cognitive empathy and emotional reactivity. This study provides further evidence for the role of reward processing in the mirror motor system, and highlights the relationship between value-based action perception and social cognitive traits, implicating a role for the mirror system in social decision-making.

Keywords: mu rhythm; action observation; EEG; mirror neurons; reward; social context

Özet

Sosyal etkileşimlerde, gözlemlenen eylemlerle ilişkilendirdiğimiz değerler, başkalarının davranışlarını ve aldığımız kararları nasıl yorumladığımızı etkileyebilir. Bazı araştırmalar, farklı sosyal bağlamların ve özellikle de algılanan eylemlerin ödül değerinin, başkalarının eylemlerini gözlemlerken motor sistem aktivitesini düzenleyebileceğini öne sürmektedir. Bununla birlikte, ödül büyüklüğüne olan duyarlılık, eylem gözlem sistemi boyutunda hiçbir zaman test edilmemiştir. Burada, katılımcıların (N = 23) pasif olarak yüksek veya düşük ödüllere veya kayıplara yol açan eylemleri gözlemlerken, ödül ritim değerinin ve büyüklüğünün mu ritm üzerindeki bağımsız etkilerini ve motor ayna sisteminin bir endeksini araştırmak adına elektroensefalografi (EEG) kullandık. Sosyal yaklaşım / kaçınma, zihin teorisi ve empatinin davranışsal ölçümlemeleri de alınmıştır. Sonuçlar, ödül değerliliğinin, kayıpların daha büyük mu süpresyona yol açtığını, ancak ritmin büyüklüğünün etkili olmadığını ve mu ritmde önemli ölçüde modüle olduğunu gösterdi. Elde edilen bulgular, mu ritim ve sosyal bilişsel beceriler arasında, özellikle bilişsel empati ve duygusal reaktivite ile ilgili ödül ile ilgili modülasyon arasında yeni bir ilişki olduğunu göstermiştir. Bu çalışma, ayna motor sistemindeki ödül işleme rolüne ilişkin daha fazla kanıt sunmakta ve değer bazlı eylem algısı ile sosyal bilişsel özellikler arasındaki ilişkiyi vurgulamakla birlikte toplumsal karar almada ayna sisteminin rolünü vurgulamaktadır.

Anahtar Kelimeler: *mu ritmi; aksiyon gözlemi; EEG, ayna nöronlar; ödül; sosyal içerik*

[1] Mathison Centre for Mental Health Research & Education, University of Calgary, Alberta, Canada
[2] Hotchkiss Brain Institute, University of Calgary, Alberta, Canada
[3] Department of Psychology, Uskudar University, 34662 Istanbul, Turkey
[4] Department of Physiology, Faculty of Medicine, Istinye University, Istanbul, Turkey
[*]Corresponding author: Mathison Centre for Mental Health Research and Education, 4th Floor TRW Building, Foothills Medical Campus, 3280 Hospital Drive NW. Calgary T2N 4Z6, Alberta, Canada Email: elliot.c.brown@gmail.com

1. Introduction

A crucial component required for successful social interaction involves the encoding of others' actions and intentions. The ability to learn from others' actions is critical for the development of social cognitive skills through interactive experiences early in life (Cook, Bird, Catmur, Press, & Heyes, 2014). The discovery of the mirror neuron system in primates, in which specific neurons fire during both the execution and observation of an action (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996), led to suggestions that others' actions are mapped onto one's own sensorimotor cortices (Keysers & Gazzola, 2006). There is much evidence to suggest that a comparable neural system exists in humans, which has common functional characteristics as the monkey mirror system (Bimbi et al., 2018; Chong, Cunnington, Williams, Kanwisher, & Mattingley, 2008; Kilner, Neal, Weiskopf, Friston, & Frith, 2009; Molenberghs, Cunnington, & Mattingley, 2012; Mukamel, Ekstrom, Kaplan, Iacoboni, & Fried, 2010; Press, Weiskopf, & Kilner, 2012). Subsequent studies have identified modulations of the mu-rhythm to be a possible electrophysiological marker of the putative human mirror system (hMS), which could provide insight into the underlying neural mechanisms behind social interaction (Oberman, Pineda, & Ramachandran, 2007).

Suppression of the rolandic mu rhythm represents an event-related desynchronization indicated by a reduction in power in the alpha (8-13Hz) frequency band resulting from excitation of the sensorimotor cortex associated with an action (Babiloni et al., 2002; Hari, 2006; Pfurtscheller & Neuper, 1994; Salmelin & Hari, 1994). The mu rhythm suppression is considered to be an index of the hMS because both show similar functional properties, primarily that they both respond not only to the execution of actions but also the observation of an action, and both respond only to goal-directed actions (Le Bel, Pineda, & Sharma, 2009; Oberman et al., 2007; Pineda, 2005). Furthermore, studies measuring functional magnetic resonance imaging (fMRI) and EEG concurrently during action execution and observation tasks demonstrated a close relationship between activity in the hMS and suppression of the mu rhythm (Arnstein, Cui, Keysers, Maurits, & Gazzola, 2011; Braadbaart, Williams, & Waiter, 2013). More specifically, a negative correlation was found between mu power and the BOLD response in putative mirror neuron areas, as a reduction, or suppression in mu power, thus reflecting greater sensorimotor cortical activity. Several studies have shown that the degree of mu rhythm suppression is modulated by the context of the perceived action, not only in terms of visual and spatial properties but also the social context. For example, differences in the orientation of spatial and temporal attention of the observer can modulate the mu suppression, whereby the direction of the spatial attention can have a somatotopic effect (Anderson & Ding, 2011; Ede, Köster, & Maris, 2012; Jones et al., 2010). Some studies have demonstrated that observed actions within a social interactive setting, or even when facial stimuli are directed towards participants, greater mu suppression can be induced, as compared to non-interactive contexts (Ensenberg, Perry, & Aviezer, 2017; Oberman et al., 2007; Perry, Stein, & Bentin, 2011). There is also evidence to show that the intention and social relevance of actions can influence the degree of mu suppression (Kilner, Marchant, & Frith, 2006; Perry, Troje, & Bentin, 2010). The social relationship between observer and performer can also affect activity in this system. One study demonstrated that an action perceived from an interactive partner induced greater mu suppression than actions seen performed by a non-interactive partner (Kourtis, Sebanz, & Knoblich, 2010). Another study found ethnic ingroup / outgroup biases in the mu rhythm, with stronger suppression when observing painful actions from an ingroup member (Riečanský, Paul, Kölble, Stieger, & Lamm, 2015). Furthermore, there is the hypothesis that populations with impairments in social functioning, such as autism spectrum disorders, may also show abnormalities in mu rhythm suppression (Oberman, Ramachandran, & Pineda, 2008). Therefore, it is evident that the mu rhythm likely has some special relevance for social context and social information.

In most social situations in our everyday lives we perform numerous value computations, which in turn, influence our subsequent behavior. Recently, there has been an increasing interest in the interplay between social cognition and decision-making (Frith & Singer, 2008) and particularly, the role of value computations and reward processing in social decision-making (Ruff & Fehr, 2014), which ultimately drive motivated social behaviors and social learning (Heyes, 2012). FMRI studies have found activation in common brain regions during the evaluation of both monetary and social rewards (Izuma, Saito, & Sadato, 2008; Lin, Adolphs, & Rangel, 2012). The striatum, an area central to reward processing and value computation, has consistently been shown to be activated when processing others' rewards and in linking one's own rewards to others' actions (Báez-Mendoza, Harris, & Schultz, 2013). There has been substantial work in patients with Parkinson's disease, a population known to have impairments in theory of mind, suggesting that that the basal ganglia may be involved in social cognition and mirror system activity (Alegre et al., 2010; Alegre, Guridi, & Artieda, 2011; Bodden et al., 2013). Taken together, these studies suggest that some regions central to reward processing are also involved in the integration of social actions and rewards. Further evidence comes from single neuron recordings in area F5 of primate premotor cortex, showing that mirror neurons are sensitive to the value associated with an observed grasping action (Caggiano et al., 2012). Rewards associated with an observed action have also previously been shown to modulate the mu rhythm in humans, whereby actions leading to monetary gains and losses showed greater mu suppression than actions that led to a neutral outcome (Brown, Wiersema, Pourtois, & Brüne, 2013) . Recently, a study confirmed these findings, demonstrating greater mu suppression for face stimuli associated with rewards (Trilla Gros, Panasiti, & Chakrabarti, 2015), further highlighting the influence of rewards on the mu rhythm. In addition to reward valence, affective valence has been shown to affect putative mirror system function in humans, as observed by corticospinal excitability during action observation (Enticott et al., 2012; Hill et al., 2013), as well as more directly in the degree of EEG mu suppression (Moore, Gorodnitsky, &

Pineda, 2012).

In summary, it is clear that the degree of mu rhythm suppression during the observation of others' actions can be modulated by the rewards associated with the seen actions, which has particularly been demonstrated in terms of the valence of rewards and losses. However, the relationship between reward processing and the hMS is still unclear. In addition, it is not clear as to how reward-related modulations in the motor system are specific to rewarding nature of stimuli. More specifically, it is not clear whether the reward-related modulations of the mu rhythm previously seen are driven primarily by reward per se, or by another process associated with rewards. To investigate this further, we developed an action observation paradigm to measure the EEG mu rhythm while participants observed actions that differed in reward valence and magnitude, independently. Our primary aim was to test whether the mu rhythm was affected by both valence and magnitude of rewards associated with the observed actions. As a secondary aim, we wanted to see if this modulation was related to the capacity of relevant social cognitive skills, particularly the ability to understand others' minds (i.e. theory of mind and empathy) and motivated social approach/avoidance behavior. We predicted that both reward valence and magnitude would modulate the degree of mu rhythm suppression during observed actions. More specifically, we hypothesized that we would see a graded effect of reward magnitude and valence, in which the greatest degree of mu suppression would be seen for large rewards, and the least for small losses. We also hypothesized that the degree of overall mu rhythm suppression would be related to theory of mind and empathy, and reward-related modulation of mu suppression would be related more specifically to motivated social approach/avoidance behavior.

2. Methods

2.1. Participants

Twenty-three healthy right-handed students (13 female) were recruited from Uskudar University with a mean age of 22.13 (±2.80; range 20-30), and mean years of education of 14.95 (±0.78). Participants with any history of psychiatric diagnosis or physical health problems that could potentially impair performance on the task were excluded. Everyone had normal or corrected-to-normal vision. All participants also gave written consent to participate, and the study was approved by the local ethics committee.

2.2. Behavioral measures

2.2.1. The Behavioral Inhibition and Activation System Scale (BIS/BAS):

The BIS/BAS self-report questionnaire measures individual differences in two motivational systems that drive behaviors: one being the behavioral approach / activation system (BAS) that regulates appetitive motives to move towards a desired goal, and the other being the behavioral avoidance / inhibition system (BIS), which regulates aversive motives to move away from undesired goals or unpleasant stimuli (Carver & White, 1994). The BIS/BAS consists of 24 items that are answered with a 4-point Likert scale, with answers ranging from '1=very true for me' to '4=very false for me'. Four factor scores are derived from the BIS/BAS scale, including one BIS and three BAS scales: BAS Drive, BAS Fun Seeking, and BAS Reward Responsiveness. It is not recommended to combine the three BAS factors to give one total BAS score.

2.2.2. Reading the Mind in the Eyes Test (RMET):

The RMET is a measure of theory of mind, emotion recognition and the ability to infer others' mental states (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). In the test, there are 36 items in which participants are presented with photographs of the eye-regions of individuals along with 4 possible adjectives describing emotional states. Participants are required to choose which emotional adjective corresponds best to the emotion that the person in the photograph is experiencing. Correct responses are summed to give the final score.

2.2.3. The Empathy Quotient (EQ)

The EQ is a self-report measure originally designed to measure multi-dimensional empathy in populations with impairments in social functioning, but is also a suitable measure of temperamental empathy in adults in the general population (Baron-Cohen & Wheelwright, 2004). The test consists of 60 items in which answers range from '1=strongly agree' to '4=strongly disagree'. 40 of these items are summed to give a total EQ score, with the other 20 being filler items. Three factors of the EQ have also been shown to tap into more specific components of empathy, namely cognitive empathy, emotional reactivity and social skills, in which the sums of different groups of questions reveal emotional capacity along these factors (Lawrence, Shaw, Baker, Baron-Cohen, & David, 2004).

2.3. Procedure, task design and stimuli

The action observation EEG task consisted of videos comprising a series of photographs presented sequentially in short succession (~12 frames per second). Each video showed a person (the performer) sitting at a table facing the camera, initially with their hands resting flat on a table. The table had three bowls on it: one in the center closer to the performer, and two others further from the performer, one black and the other white. As the video sequence began, the performer reached into the bowl closest to them, took out a colored coin that was either red or green, and placed it into one of the two other bowls. The performer then returned their hands back to the original resting position. Each trial consisted of one video in which either a red or green coin was taken from the center bowl and placed into one of the other two bowls. A red coin always represented a loss and a green coin always represented a win. Performers' faces were not included in the stimuli in order to try to control for possible confounding effects, such as ingroup and outgroup preferences. One trial lasted for a total of 4500ms, with the observed action lasting 2000ms,

followed by a 2500ms inter-stimulus interval in which the performer was seen sitting still in the resting position. One short practice block consisting of 8 trials was completed before the main experimental blocks. Two sets of three blocks of 50 trials each made up the experiment, which comprised a total of 300 trials. In one version of the experiment, for the first three blocks of trials coins only went into the white bowl, whereby red coins represented a small (-10 cents) loss and green coins representing a small win (+10 cents). In this version, for the second set of three blocks of trials, each coin represented big losses (-100 cents) and wins (+100 cents). Another version of the experiment presented the converse, i.e. big wins and losses in the first three blocks of trials, and small wins and losses in the second set of three blocks of trials. These two versions of the experiment were counterbalanced across participants.

Throughout the EEG experiment, participants were seated in front of the computer screen that was presenting stimuli, with their hands resting flat on the table. All participants were clearly instructed to stay as still as possible and to only keep in mind the cumulative amount they won in each block. At the start of each block, participants were told that they would start with 100 cents (for all blocks and conditions) and that the money will be added up at the end of the experiment. The experimenter recorded the amount participants had counted at the end of each block. This was done to ensure that participants were paying attention to wins and losses during each trial. Figure 1 illustrates the experimental task design, with example screenshots of stimuli.

2.4. EEG data acquisition and analysis

EEG activity was recorded at a sampling rate of 1000 Hz (Pycorder 1.9) using a Brain Products actiCHamp 32 channel system with active electrodes (Brain Products, Munich, Germany). Electrodes were positioned on the participant's heads according to the international 10-20 system, held in place by an elasticated electrode cap, with the reference and ground electrodes between Fz and Cz, and between FC1 and FC2, respectively. Horizontal eye movements were recorded by bilaterally electro-oculogram (EOG) electrodes placed at the outer canthi of both eyes. All electrode impedances were kept below 10 kΩ.

Preprocessing of EEG data was done offline using the BrainVision Analyzer software package (Brain Products, Munich, Germany). All data was first down-sampled from 1000Hz to 500Hz, and then re-referenced to the linked mastoids, and a high-pass filter of 0.1Hz, with a 50Hz notch filter applied. Ocular correction was done using an independent component analysis method (Jung et al., 2000). The 2000ms action epoch was segmented into 1000ms epochs and averaged for each condition (small win, small loss, big win, big loss), and these 1000ms epochs were then used as the main action epochs for further analysis. Movement artifacts were identified with criteria that rejected signal gradients greater than 50μV, or epochs where signal exceeded -300μV or 300μV, which resulted in ~5% of the data being removed. For the baseline epoch, the 1000ms preceding the onset of the action was taken and averaged across conditions. Baseline epochs were submitted to the same artifact

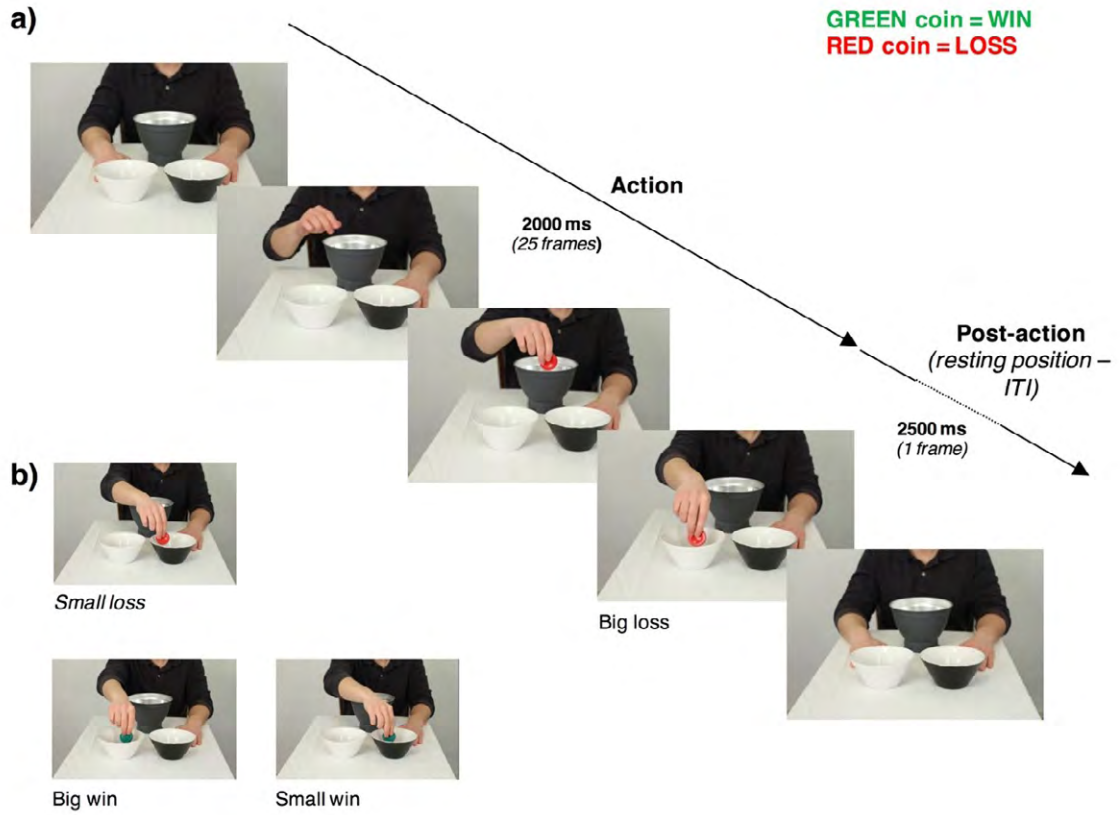


Figure 1. EEG experimental task design

rejection procedure. A Fast Fourier Transform (FFT) was performed on each of the 1000ms epochs and an average was then taken for each condition, and power values in the alpha frequency band (8-13Hz) were extracted.

Following previous studies, we determined mu suppression by calculating event-related desynchronization / synchronization (ERD/ERS) for central electrodes overlaying sensorimotor cortex (C3, Cz and C4) using the standard formula: [(alpha power during action epoch – alpha power during baseline) / alpha power during baseline) x 100] (Pfurtscheller & Neuper, 1994).

2.5. Statistical analysis

To investigate relationships between the behavioral measures, we performed a Pearson's correlation analysis with all scales and subscales of behavioral data collected.

For the EEG data, to test for effects of reward magnitude and valence on the mu rhythm, a repeated-measures ANOVA was performed using the mu rhythm suppression values for reward magnitude conditions (large, small), reward valence conditions (win, loss) and electrode positions (C3, Cz and C4) as within-subject factors. Post-hoc comparisons were conducted for significant main effects. In order to check for the regional specificity of significant effects, relevant post-hoc statistical tests were also performed on the frontal, parietal, and occipital electrodes that spanned the midline (F3, Fz, F4; P3, Pz, P4; O1, Oz, O2). Several studies have shown that age and sex are related to the degree of mu rhythm suppression (Cheng et al., 2008; Marshall, Bar-Haim, & Fox, 2002), therefore a further ANCOVA was performed to verify reward-related effects after covarying out the influence of age and sex.

In order to investigate relationships between the mu rhythm differences in response to reward valence / magnitude and behavioral measures, we calculated mu reward valence and reward magnitude effect scores. This was done by subtracting the mu rhythm for large wins / losses from small wins / losses (reward magnitude mu effect), and all wins subtracted from all losses (reward valence mu effect). Reward valence and reward magnitude mu effects were calculated for each individual to reflect the relative differences and individual variability in mu power between reward valence and magnitude conditions. Pearson correlation analyses were performed with behavioral scores and reward magnitude and valence mu effect scores. Furthermore, to control for the potential influence of age and sex, a partial correlation analysis was also done with significant correlations to further confirm significant relationships.

3. Results

Table 1 shows means and standard deviations for demographic data and scores on measures of social cognition.

3.1. EEG mu rhythm suppression

The results of the repeated-measures ANOVA revealed a main effect of reward valence (i.e. wins and losses), ($F(1, 22)=7.260$, $p=0.013$, $\eta p2=0.248$). However, no other main effects or interactions were found in any other factors (all $p>0.05$). Post-hoc comparisons showed significantly greater mu rhythm suppression for losses, compared to wins when pooling mu suppression values over central electrodes and reward magnitude conditions ($t=2.694$, $p=0.013$). Importantly, post-hoc comparisons for wins and losses over other regions showed that there were no significant differences over frontal, parietal or occipital areas (all $p>0.05$). Figure 2 shows mu rhythm suppression for wins and losses pooled over central electrodes.

Tablo 1. Demographics showing means and standard deviations (SD) for participants.

	Mean	SD
Age	22.13	2.80
Sex	10M / 13F	-
Education (yrs)	14.95	0.78
BIS	20.13	4.34
BAS reward	17.83	2.76
BAS fun	13.30	2.51
BAS drive	11.70	3.23
RMET	23.22	3.33
EQ total	25.78	13.04
EQ cog empathy	12.65	7.20
EQ emotional react	12.83	4.51
EQ social skills	6.30	2.88

Notes: M = male, F = female; BIS = Behavioral Inhibition System scale; BAS = Behavioral Activation System scale; RMET = Reading The Mind in the Eyes Test; EQ = Empathy quotient (3 factors; cognitive empathy, emotional reactivity, social skills).

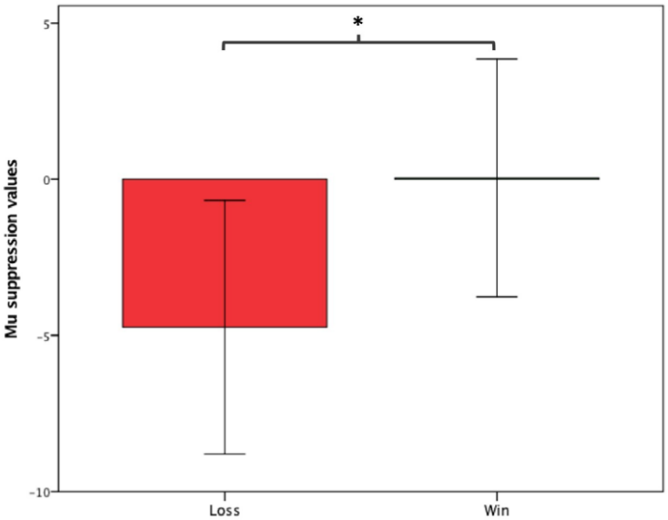


Figure 2. Bar chart showing percentage change in mu rhythm power for wins and losses during the action observation task, relative to baseline. Error bars represent one standard error of the mean (*$p<0.05$)

After controlling for age and sex as covariates with an ANCOVA with mu suppression values, the main effect of reward valence remained ($F(1, 20)=7.425$, $p=0.013$, $\eta p2=0.271$). As expected, we additionally saw a

significant interaction between reward valence and age ($F(1, 20)=6.285$, $p=0.021$, $p=$, $\eta p2=0.239$). No other main effects or interactions were significant (all $p>0.05$).

3.2. Relationship between mu suppression and behavioral data

Due to the significant main effect of reward valence, but a lack of effects for other conditions, mu rhythm values were pooled across reward magnitude conditions and electrodes, and only the reward valence mu effect was used for the correlation analysis with demographic variables and social cognition measures.

In line with the results from our ANCOVA analysis, we see a significant negative correlation between age and the reward valence mu effect ($r=-0.443$, $p=0.034$) whereby the effect of reward valence on the mu rhythm was less for older participants.

Most interestingly, we see a strong positive correlation between the reward valence mu effect and empathy as measured by the total EQ score ($r=0.731$, $p<0.001$). A scatterplot for this relationship is shown in figure 3. After controlling for age, the correlations between the reward valence mu effect and EQ scores remained significant, and even became stronger ($r=0.806$, $p<0.001$). In addition, significant correlations were found between the mu reward valance effect and the cognitive empathy ($r=0.433$, $p=0.039$) and emotional reactivity ($r=0.693$, $p<0.001$) factors of the EQ, but not with the social skills factor of the EQ ($r=0.164$, $p=0.454$). The correlations with cognitive empathy ($r=0.641$, $p=0.001$) and emotional reactivity ($r=0.712$, $p<0.001$) also remained significant after controlling for age. There were no other significant correlations between the reward valence mu effect and other behavioral measures. Importantly, there were also no other significant correlations between the mean mu rhythm values (pooled over all electrodes, reward magnitude and reward valence conditions) and any behavioral measures (all $p>0.05$).

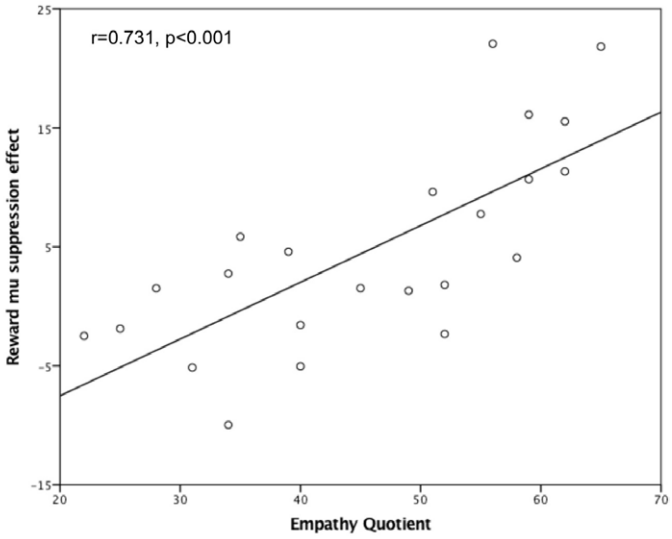


Figure 3. Scatterplot showing the relationship between the reward-valence mu rhythm effect (i.e. difference between wins and losses) and total scores on the Empathy Quotient.

4. Discussion

In this study, we sought to investigate the effects of reward valence and magnitude on the degree of EEG mu rhythm suppression during an action observation task in which the observed actions led to rewarding or loss outcomes of different financial values. As a secondary aim, we asked the question of whether the effect of rewards on the mu rhythm were related to demographic and social cognition variables, including age, motivated social approach/avoidance behavior, theory of mind and empathy. We showed that the mu rhythm was modulated by reward valence, but in the opposite direction to which we hypothesized, whereby greater mu rhythm suppression was evoked by action outcomes associated with losses, when compared to action outcomes associated with rewards. We demonstrated that this effect could not be accounted for by differences in age or sex. However, contrary to our hypothesis, we did not see any effect of reward magnitude on the degree of mu suppression. Interestingly, the effect of reward valence on the mu suppression correlated with levels of empathy, in which people with more empathy exhibited a greater reward valence mu suppression effect. Furthermore, the relationship between the effect of reward valence on the mu suppression and empathy was specific to cognitive empathy and emotional reactivity, but not social skills nor affective theory of mind. To our knowledge, this is the first study demonstrating a specific effect of reward valence on the mu rhythm, and not magnitude, and the first to show that this reward-related modulation was associated with levels of cognitive empathy and emotional reactivity.

Our main findings provide further evidence to support the role of reward processing in the mirror motor system, particularly during the observation of others' actions, which has previously been suggested by other mu rhythm studies (Brown et al., 2013; Brown, Gonzalez-Liencres, Tas, & Brüne, 2016) . The greater mu rhythm suppression in response to losses was in contrast to what we had hypothesized, as we had predicted that greater suppression would be seen for wins overall. Other studies from our group have shown some divergence in the direction of the mu rhythm change in response to monetary wins and losses using a similar paradigm (Brown et al., 2016), where we have found greater mu suppression for relative losses, compared to winning and neutral actions. This suggests that the link between rewards and the mirror system may not be as straightforward as we had expected. There has been some work investigating the influence of affective valence on motor cortex excitability, though it did not directly address reward processing. One such study by Hajcak et al. (Hajcak et al., 2007) used transcranial magnetic stimulation (TMS) to demonstrate that the magnitude of motor evoked potentials (MEPs) were greater when presenting participants with pleasant or unpleasant images, when compared to neutral images. Other more recent studies have also shown this bidirectional relationship with both positive and negative emotions increasing activity in the motor system (Hill et al., 2013). In contrast, there is also evidence showing that negatively valenced stimuli evoked greater motor-related corticospinal excitability when compared to positively valenced stimuli (Enticott et al., 2012; Anaelli

JNBS 2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org

A. Nogueira-Campos et al., 2016; Anaelli Aparecida Nogueira-Campos et al., 2014). The mixed results from these previous findings, and the possible bidirectional relationship between positive and negative emotions and possible modulations on the mu rhythm may depend upon individual differences in emotional processing and empathetic responses, especially as our findings show a relationship between empathetic capacity and the degree of reward-related mu suppression. Taken together, it is evident that both reward valence and affective valence have a role in the processing of one's own and of others' actions, which could shape motivational drives and thus influence our behaviors in social contexts.

One interpretation of our results is that the reward valence modulation of the mu suppression may be driven by salience, which could be a product of the subjective experiences of monetary losses or gains. The suggestion that salience drives our main findings may be supported by the correlation we see between emotional reactivity and the reward valence mu effect. In the reward processing literature, it is currently accepted that there are two motivational systems that drive reinforcement-learning processes, namely 'liking' and 'wanting' (Berridge, 2007). As no learning was involved in our paradigm, our results may speak more to the 'liking' dimension of reward processing, which represents the hedonic impact of the receipt of rewards, whereas the dopamine-mediated 'wanting' dimension induces incentive salience, which drives goal-directed behaviors to seek rewards. However, one very elegant study using a Pavlovian-to-Instrumental paradigm with real-time fMRI found enhanced responses in motivational areas including ventral striatum and amygdala upon presentation of reward-related cues during motor imagery (Mendelsohn, Pine, & Schiller, 2014). The authors highlight work showing the importance of ventral striatum and amygdala in signaling the incentive value of stimuli (Berridge, Robinson, & Aldridge, 2009; Everitt, Cardinal, Parkinson, & Robbins, 2003), and thus conclude that their results demonstrate a concurrent activation of the 'value' and 'action' networks. Additionally, Klein-Flugge et al. (Klein-Flügge, Kennerley, Friston, & Bestmann, 2016) demonstrated activation in a network that encompassed the dorsal anterior cingulate cortex (dACC) and supplementary motor area during both a reward value comparison task and an effort-discounting task. As we know that mu suppression is evoked by motor imagery (Pfurtscheller, Brunner, Schlögl, & Lopes da Silva, 2006), taking these findings into consideration, it would be reasonable to suggest that the reward-related mu rhythm effects we see in our study may also be representative not only of the experience of reward receipt, but also of the differences in reward valuation, especially as high and low rewards are presented relative to each other. There is also other evidence from patients with Parkinson's disease where authors have suggested a link between the reward circuit of the basal ganglia and the human mirror system (Alegre et al., 2010; Alegre et al., 2011). It is difficult to disentangle salience from the hedonic experience of rewards, although future studies could seek to integrate conditions of positively and negatively valenced salience and gains and losses of rewards in combination to compare the magnitude of these effects on mu suppression. Measuring emotional reactivity in future studies could also provide more insight into the possibility that salience could be contributing to the reward-related modulation of the mu rhythm. Future studies using combined EEG and fMRI with reinforcement-learning paradigms could also help to determine whether the reward-related modulation we see in the mu suppression also extends to the learning and 'wanting' aspects of reward processing.

The relationship we see between empathy and the mu suppression effect is supported by other studies, which have consistently demonstrated a generalized relationship between activity in the mirror system and trait levels of empathy (Cheng et al., 2008; Pfeifer, Iacoboni, Mazziotta, & Dapretto, 2008; Schulte-Rüther, Markowitsch, Fink, & Piefke, 2007; Yang, Decety, Lee, Chen, & Cheng, 2009). However, none of those studies have characterized this relationship specifically in terms of reward-related mu rhythm modulation. There is some evidence to suggest a relationship between empathetic capacity and a vicarious reward prediction error signal in the ACC when observing others' receiving a reward (Lockwood, Apps, Roiser, & Viding, 2015). The fMRI study from Lockwood et al. (2015) found that activation in the anterior cingulate cortex (ACC) in participants with less empathy corresponded to receipt of rewards for the self and others, whereas ACC activation in those with high trait empathy was related only to others' rewards. Interestingly, one study investigating the kinematic response during the simulation of feeding others in various emotional contexts found different kinematic profiles depending on the emotions expressed by the actors being fed (Ferri et al., 2010). These salience-driven effects on the motor system were modulated by the participants' empathetic attitudes, supporting our findings with regards to the relationship between individual differences in empathy and action processing in a social setting. It is important to note here, that one possible reason for not seeing a correlation with the other behavioral measures was because of their low variance. It seems that the empathy score was the only measure in which there was substantial variance between participants. Our results add to the literature by suggesting that the influence of trait empathy on social action processing also extends to reward valuation in the mirror system.

There were some unexpected findings in our study, some of which have already been discussed. A main finding that was contrary to our hypothesis was the lack of reward magnitude effects on the degree of mu suppression. One explanation for this may be due to our design and the distribution of our experimental conditions in trials and blocks. The conditions of reward magnitude were presented across different blocks of trials, whereas different reward valences were presented within each block. In other words, the relative comparisons of reward magnitude were more separated in time than comparisons of reward valence. Therefore, the relative difference between high and low reward magnitudes may have been less salient than the relative difference between wins and losses, resulting in the effect of reward valence overshadowing the relative response to differences in

magnitude. This issue of the relativity between conditions may have also accounted for the unexpected finding of a small mu suppression for wins, relative to losses. Due to the fact that we did not have a neutral condition, the trials that led to a win may have evoked a mu rhythm response that was relatively neutral when compared to a loss, which appeared to be more salient. Having a mixed design rather than the block design used here, may have made the relative effects of the reward conditions more balanced.

There were a number of limitations to our study, one of which was our lack of a neutral condition in which participants experienced neither reward nor loss. As already mentioned, this makes it hard for us to draw strong conclusions about the relative effects of high and low rewards and losses on mu suppression. Furthermore, there was no visual difference between small and large wins and losses, which may have dampened potential reward magnitude effects. Future studies may wish to make more distinct visual differences across conditions, and may also consider using a mixed block design to enhance possible reward magnitude effects. Another limitation of this study was due to the inherent lack of spatial resolution in EEG, which makes it difficult to make inferences about the source of the reward-related modulation of the mu suppression. Using a combination of fMRI and EEG to utilize both high spatial and temporal resolution in future studies would provide further insight into the source of this effect, alternatively, independent component analysis and dipole fitting could be used with EEG alone to localize the source of the signal. As already mentioned, the reward-related modulation may have been driven by salience, and so a final limitation of the study was that no behavioral measures related to individual differences in trait salience processing were collected.

This study is the first to demonstrate that the reward-related modulation of the human mirror system, as indexed by the mu rhythm suppression, is specific to reward valence but not reward magnitude. Furthermore, we reveal a novel relationship between the effect of reward on the human mirror system and trait empathy. We conclude that the mirror system may be sensitive to reward value encoding, which could be related to salience processing. In the larger context of social decision-making, the subjective value and salience we associate with social stimuli is likely to play a central role in what we attend to, and are drawn towards. Thus, value may shape the degree to which we engage in social interactions, as well as influencing from who, what and where we learn our social skills, and could guide the choices we make in our social lives.

Funding details

The author ECB was currently supported by a fellowship from Alberta Innovates Health Solutions (AIHS), and previously supported by a fellowship from the Mathison Centre for Mental Health Research & Education for a part of the duration of data analysis and manuscript preparation.

Disclosures

The authors report no conflicts of interest.

References

Alegre, M., Rodríguez-Oroz, M. C., Valencia, M., Pérez-Alcázar, M., Guridi, J., Iriarte, J., … Artieda, J. (2010). Changes in subthalamic activity during movement observation in Parkinson's disease: is the mirror system mirrored in the basal ganglia? Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 121(3), 414–425. https://doi.org/10.1016/j.clinph.2009.11.013

Alegre, M., Guridi, J., & Artieda, J. (2011). The mirror system, theory of mind and Parkinson's disease. Journal of the Neurological Sciences, 310(1–2), 194–196. https://doi.org/10.1016/j.jns.2011.07.030

Anderson, K. L., & Ding, M. (2011). Attentional modulation of the somatosensory mu rhythm. Neuroscience, 180, 165–180. https://doi.org/10.1016/j.neuroscience.2011.02.004

Arnstein, D., Cui, F., Keysers, C., Maurits, N. M., & Gazzola, V. (2011). μ-Suppression during Action Observation and Execution Correlates with BOLD in Dorsal Premotor, Inferior Parietal, and SI Cortices. Journal of Neuroscience, 31(40), 14243–14249. https://doi.org/10.1523/JNEUROSCI.0963-11.2011

Babiloni, C., Babiloni, F., Carducci, F., Cincotti, F., Cocozza, G., Del Percio, C., … Rossini, P. M. (2002). Human cortical electroencephalography (EEG) rhythms during the observation of simple aimless movements: a high-resolution EEG study. NeuroImage, 17(2), 559–572.

Báez-Mendoza, R., Harris, C. J., & Schultz, W. (2013). Activity of striatal neurons reflects social action and own reward. Proceedings of the National Academy of Sciences of the United States of America, 110(41), 16634–16639. https://doi.org/10.1073/pnas.1211342110

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. Journal of Child Psychology and Psychiatry, and Allied Disciplines, 42(2), 241–251.

Baron-Cohen, S., & Wheelwright, S. (2004). The empathy quotient: an investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. Journal of Autism and Developmental Disorders, 34(2), 163–175.

Berridge, K. C. (2007). The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology, 191(3), 391–431. https://doi.org/10.1007/s00213-006-0578-x

Berridge, K. C., Robinson, T. E., & Aldridge, J. W. (2009). Dissecting components of reward: "liking", "wanting", and learning. Current Opinion in Pharmacology, 9(1), 65–73. https://doi.org/10.1016/j.coph.2008.12.014

Bimbi, M., Festante, F., Coudé, G., Vanderwert, R. E., Fox, N. A., & Ferrari, P. F. (2018). Simultaneous scalp recorded EEG and local field potentials from monkey ventral premotor cortex during action observation and execution reveals the contribution of mirror and motor neurons to the mu-rhythm. NeuroImage, 175, 22–31. https://doi.org/10.1016/j.neuroimage.2018.03.037

Bodden, M. E., Kübler, D., Knake, S., Menzler, K., Heverhagen, J. T., Sommer, J., … Dodel, R. (2013). Comparing the neural correlates of affective and cognitive theory of mind using fMRI: Involvement of the basal ganglia in affective theory of mind. Advances in Cognitive Psychology, 9(1), 32–43. https://doi.org/10.2478/v10053-008-0129-6

Braadbaart, L., Williams, J. H. G., & Waiter, G. D. (2013). Do mirror neuron areas mediate mu rhythm suppression during imitation and action observation? International Journal of Psychophysiology, 89(1), 99–105. https://doi.org/10.1016/j.ijpsycho.2013.05.019

Brown, E. C., Wiersema, J. R., Pourtois, G., & Brüne, M. (2013). Modulation of motor cortex activity when observing rewarding and punishing actions. Neuropsychologia, 51(1), 52–58. https://doi.org/10.1016/j.neuropsychologia.2012.11.005

Brown, E. C., Gonzalez-Liencres, C., Tas, C., & Brüne, M. (2016). Reward modulates the mirror neuron system in schizophrenia: A study into the mu rhythm suppression, empathy, and mental state attribution. Social Neuroscience, 11(2), 175–186. https://doi.org/10.1080/17470919.2015.1053982

Caggiano, V., Fogassi, L., Rizzolatti, G., Casile, A., Giese, M. A., & Thier, P. (2012). Mirror neurons encode the subjective value of an observed action. Proceedings of the National Academy of Sciences of the United States of America, 109(29), 11848–11853. https://doi.org/10.1073/pnas.1205553109

Carver, C. S., & White, T. L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment:

The BIS/BAS Scales. Journal of Personality and Social Psychology, 67(2), 319–333. https://doi.org/10.1037/0022-3514.67.2.319

Cheng, Y., Lee, P.-L., Yang, C.-Y., Lin, C.-P., Hung, D., & Decety, J. (2008). Gender Differences in the Mu Rhythm of the Human Mirror-Neuron System. PLoS ONE, 3(5). https://doi.org/10.1371/journal.pone.0002113

Chong, T. T.-J., Cunnington, R., Williams, M. A., Kanwisher, N., & Mattingley, J. B. (2008). fMRI adaptation reveals mirror neurons in human inferior parietal cortex. Current Biology: CB, 18(20), 1576–1580. https://doi.org/10.1016/j.cub.2008.08.068

Cook, R., Bird, G., Catmur, C., Press, C., & Heyes, C. (2014). Mirror neurons: from origin to function. The Behavioral and Brain Sciences, 37(2), 177–192. https://doi.org/10.1017/S0140525X13000903

Ede, F. van, Köster, M., & Maris, E. (2012). Beyond establishing involvement: quantifying the contribution of anticipatory α- and β-band suppression to perceptual improvement with attention. Journal of Neurophysiology, 108(9), 2352–2362. https://doi.org/10.1152/jn.00347.2012

Ensenberg, N. S., Perry, A., & Aviezer, H. (2017). Are you looking at me? Mu suppression modulation by facial expression direction. Cognitive, Affective & Behavioral Neuroscience, 17(1), 174–184. https://doi.org/10.3758/s13415-016-0470-z

Enticott, P. G., Harrison, B. A., Arnold, S. L., Nibaldi, K., Segrave, R. A., Fitzgibbon, B. M., … Fitzgerald, P. B. (2012). Emotional valence modulates putative mirror neuron activity. Neuroscience Letters, 508(1), 56–59. https://doi.org/10.1016/j.neulet.2011.12.018

Everitt, B. J., Cardinal, R. N., Parkinson, J. A., & Robbins, T. W. (2003). Appetitive behavior: impact of amygdala-dependent mechanisms of emotional learning. Annals of the New York Academy of Sciences, 985, 233–250.

Ferri, F., Stoianov, I. P., Gianelli, C., D'Amico, L., Borghi, A. M., & Gallese, V. (2010). When action meets emotions: how facial displays of emotion influence goal-related behavior. PloS One, 5(10). https://doi.org/10.1371/journal.pone.0013126

Frith, C. D., & Singer, T. (2008). The role of social cognition in decision making. Philosophical Transactions of the Royal Society B: Biological Sciences, 363(1511), 3875–3886. https://doi.org/10.1098/rstb.2008.0156

Gallese, V., Fadiga, L., Fogassi, L., & Rizzolatti, G. (1996). Action recognition in the premotor cortex. Brain: A Journal of Neurology, 119 (Pt 2), 593–609.

Hajcak, G., Molnar, C., George, M. S., Bolger, K., Koola, J., & Nahas, Z. (2007). Emotion facilitates action: a transcranial magnetic stimulation study of motor cortex excitability during picture viewing. Psychophysiology, 44(1), 91–97. https://doi.org/10.1111/j.1469-8986.2006.00487.x

Hari, R. (2006). Action–perception connection and the cortical mu rhythm. In C. N. and W. Klimesch (Ed.), Progress in Brain Research (Vol. 159, pp. 253–260). Elsevier. Retrieved from http://www.sciencedirect.com/science/article/pii/S007961230659017X

Heyes, C. (2012). What's social about social learning? Journal of Comparative Psychology (Washington, D.C.: 1983), 126(2), 193–202. https://doi.org/10.1037/a0025180

Hill, A. T., Fitzgibbon, B. M., Arnold, S. L., Rinehart, N. J., Fitzgerald, P. B., & Enticott, P. G. (2013). Modulation of putative mirror neuron activity by both positively and negatively valenced affective stimuli: a TMS study. Behavioural Brain Research, 249, 116–123. https://doi.org/10.1016/j.bbr.2013.04.027

Izuma, K., Saito, D. N., & Sadato, N. (2008). Processing of social and monetary rewards in the human striatum. Neuron, 58(2), 284–294. https://doi.org/10.1016/j.neuron.2008.03.020

Jones, S. R., Kerr, C. E., Wan, Q., Pritchett, D. L., Hämäläinen, M., & Moore, C. I. (2010). Cued Spatial Attention Drives Functionally-Relevant Modulation of The Mu Rhythm in Primary Somatosensory Cortex. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 30(41), 13760–13765. https://doi.org/10.1523/JNEUROSCI.2969-10.2010

Jung, T. P., Makeig, S., Humphries, C., Lee, T. W., McKeown, M. J., Iragui, V., & Sejnowski, T. J. (2000). Removing electroencephalographic artifacts by blind source separation. Psychophysiology, 37(2), 163–178.

Keysers, C., & Gazzola, V. (2006). Towards a unifying neural theory of social cognition. Progress in Brain Research, 156, 379–401. https://doi.org/10.1016/S0079-6123(06)56021-2

Kilner, J. M., Marchant, J. L., & Frith, C. D. (2006). Modulation of the mirror system by social relevance. Social Cognitive and Affective Neuroscience, 1(2), 143–148. https://doi.org/10.1093/scan/nsl017

Kilner, J. M., Neal, A., Weiskopf, N., Friston, K. J., & Frith, C. D. (2009). Evidence of mirror neurons in human inferior frontal gyrus. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 29(32), 10153–10159. https://doi.org/10.1523/JNEUROSCI.2668-09.2009

Klein-Flügge, M. C., Kennerley, S. W., Friston, K., & Bestmann, S. (2016). Neural Signatures of Value Comparison in Human Cingulate Cortex during Decisions Requiring an Effort-Reward Trade-off. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 36(39), 10002–10015. https://doi.org/10.1523/JNEUROSCI.0292-16.2016

Kourtis, D., Sebanz, N., & Knoblich, G. (2010). Favouritism in the motor system: social interaction modulates action simulation. Biology Letters, 6(6), 758–761. https://doi.org/10.1098/rsbl.2010.0478

Lawrence, E. J., Shaw, P., Baker, D., Baron-Cohen, S., & David, A. S. (2004). Measuring empathy: reliability and validity of the Empathy Quotient. Psychological Medicine, 34(5), 911–919.

Le Bel, R. M., Pineda, J. A., & Sharma, A. (2009). Motor-auditory-visual integration: The role of the human mirror neuron system in communication and communication disorders. Journal of Communication Disorders, 42(4), 299–304. https://doi.org/10.1016/j.jcomdis.2009.03.011

Lin, A., Adolphs, R., & Rangel, A. (2012). Social and monetary reward learning engage overlapping neural substrates. Social Cognitive and Affective Neuroscience, 7(3), 274–281. https://doi.org/10.1093/scan/nsr006

Lockwood, P. L., Apps, M. A. J., Roiser, J. P., & Viding, E. (2015). Encoding of Vicarious Reward Prediction in Anterior Cingulate Cortex and Relationship with Trait Empathy. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 35(40), 13720–13727. https://doi.org/10.1523/JNEUROSCI.1703-15.2015

Marshall, P. J., Bar-Haim, Y., & Fox, N. A. (2002). Development of the EEG from 5 months to 4 years of age. Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 113(8), 1199–1208.

Mendelsohn, A., Pine, A., & Schiller, D. (2014). Between thoughts and actions: motivationally salient cues invigorate mental action in the human brain. Neuron, 81(1), 207–217. https://doi.org/10.1016/j.neuron.2013.10.019

Molenberghs, P., Cunnington, R., & Mattingley, J. B. (2012). Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies. Neuroscience and Biobehavioral Reviews, 36(1), 341–349. https://doi.org/10.1016/j.neubiorev.2011.07.004

Moore, A., Gorodnitsky, I., & Pineda, J. (2012). EEG mu component responses to viewing emotional faces. Behavioural Brain Research, 226(1), 309–316. https://doi.org/10.1016/j.bbr.2011.07.048

Mukamel, R., Ekstrom, A. D., Kaplan, J., Iacoboni, M., & Fried, I. (2010). Single-neuron responses in humans during execution and observation of actions. Current Biology: CB, 20(8), 750–756. https://doi.org/10.1016/j.cub.2010.02.045

Nogueira-Campos, Anaelli A., Saunier, G., Della-Maggiore, V., De Oliveira, L. A. S., Rodrigues, E. C., & Vargas, C. D. (2016). Observing Grasping Actions Directed to Emotion-Laden Objects: Effects upon Corticospinal Excitability. Frontiers in Human Neuroscience, 10, 434. https://doi.org/10.3389/fnhum.2016.00434

Nogueira-Campos, Anaelli Aparecida, de Oliveira, L. A. S., Della-Maggiore, V., Esteves, P. O., Rodrigues, E. de C., & Vargas, C. D. (2014). Corticospinal excitability preceding the grasping of emotion-laden stimuli. PloS One, 9(4), e94824. https://doi.org/10.1371/journal.pone.0094824

Oberman, L. M., Pineda, J. A., & Ramachandran, V. S. (2007). The human mirror neuron system: a link between action observation and social skills. Social Cognitive and Affective Neuroscience, 2(1), 62–66. https://doi.org/10.1093/scan/nsl022

Oberman, L. M., Ramachandran, V. S., & Pineda, J. A. (2008). Modulation of mu suppression in children with autism spectrum disorders in response to familiar or unfamiliar stimuli: the mirror neuron hypothesis. Neuropsychologia, 46(5), 1558–1565. https://doi.org/10.1016/j.neuropsychologia.2008.01.010

Perry, A., Stein, L., & Bentin, S. (2011). Motor and attentional mechanisms involved in social interaction--evidence from mu and alpha EEG suppression. NeuroImage, 58(3), 895–904. https://doi.org/10.1016/j.neuroimage.2011.06.060

Perry, A., Troje, N. F., & Bentin, S. (2010). Exploring motor system contributions to the perception of social information: Evidence from EEG activity in the mu/alpha frequency range. Social Neuroscience, 5(3), 272–284. https://doi.org/10.1080/17470910903395767

Pfeifer, J. H., Iacoboni, M., Mazziotta, J. C., & Dapretto, M. (2008). Mirroring others' emotions relates to empathy and interpersonal competence in children. NeuroImage, 39(4), 2076–2085. https://doi.org/10.1016/j.neuroimage.2007.10.032

Pfurtscheller, G., Brunner, C., Schlögl, A., & Lopes da Silva, F. H. (2006). Mu rhythm (de)synchronization and EEG single-trial classification of different motor imagery tasks. NeuroImage, 31(1), 153–159. https://doi.org/10.1016/j.neuroimage.2005.12.003

Pfurtscheller, G., & Neuper, C. (1994). Event-related synchronization of

mu rhythm in the EEG over the cortical hand area in man. Neuroscience Letters, 174(1), 93–96.

Pineda, J. A. (2005). The functional significance of mu rhythms: translating "seeing" and "hearing" into "doing." Brain Research. Brain Research Reviews, 50(1), 57–68. https://doi.org/10.1016/j.brainresrev.2005.04.005

Press, C., Weiskopf, N., & Kilner, J. M. (2012). Dissociable roles of human inferior frontal gyrus during action execution and observation. NeuroImage, 60(3), 1671–1677. https://doi.org/10.1016/j.neuroimage.2012.01.118

Riečanský, I., Paul, N., Kölble, S., Stieger, S., & Lamm, C. (2015). Beta oscillations reveal ethnicity ingroup bias in sensorimotor resonance to pain of others. Social Cognitive and Affective Neuroscience, 10(7), 893–901. https://doi.org/10.1093/scan/nsu139

Rizzolatti, G., Fadiga, L., Gallese, V., & Fogassi, L. (1996). Premotor cortex and the recognition of motor actions. Brain Research. Cognitive Brain Research, 3(2), 131–141.

Ruff, C. C., & Fehr, E. (2014). The neurobiology of rewards and values in social decision making. Nature Reviews. Neuroscience, 15(8), 549–562. https://doi.org/10.1038/nrn3776

Salmelin, R., & Hari, R. (1994). Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement. Neuroscience, 60(2), 537–550. https://doi.org/10.1016/0306-4522(94)90263-1

Schulte-Rüther, M., Markowitsch, H. J., Fink, G. R., & Piefke, M. (2007). Mirror neuron and theory of mind mechanisms involved in face-to-face interactions: a functional magnetic resonance imaging approach to empathy. Journal of Cognitive Neuroscience, 19(8), 1354–1372. https://doi.org/10.1162/jocn.2007.19.8.1354

Trilla Gros, I., Panasiti, M. S., & Chakrabarti, B. (2015). The plasticity of the mirror system: How reward learning modulates cortical motor simulation of others. Neuropsychologia, 70, 255–262. https://doi.org/10.1016/j.neuropsychologia.2015.02.033

Yang, C.-Y., Decety, J., Lee, S., Chen, C., & Cheng, Y. (2009). Gender differences in the mu rhythm during empathy for pain: an electroencephalographic study. Brain Research, 1251, 176–184. https://doi.org/10.1016/j.brainres.2008.11.062

JNBS 2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org

ORIGINAL ARTICLE-ARAŞTIRMA

Year (Yıl) : 2018
Volume (Cilt) : 5
Issue Number (Sayı) : 3
Doi : 10.5455/JNBS.1535643410

Received/Geliş 30.08.2018
Accepted/Kabul 08.10.2018
JNBS, 2018, 5(3):150-155

ÇOCUKLUK ÇAĞI TRAVMALARI İLE YETİŞKİN AYRILMA ANKSİYETESİ ARASINDAKİ İLİŞKİ

THE RELATIONSHIP BETWEEN CHILDHOOD TRAUMAS AND SEPARATION ANXIETY IN ADULTS

Buse Çakmak[1], Gökben Hızlı Sayar[1*], Hüseyin Ünübol[1], Hüseyin Bulut[2], Eylem Özten[3]

Özet

Çocukluk çağında deneyimlenen olumsuz yaşam olaylarının yetişkin yaşamdaki depresif bozukluk ve anksiyete bozuklukları ile ilişkisi bilinmektedir. Yetişkin ayrılma anksiyetesi DSM-5 ile anksiyete bozuklukları sınıfına alınmış, görece olarak yeni bir tanı olarak karşımıza çıkmaktadır. Çocukluk çağı travmalarının birçok anksiyete bozukluğu ile ilişkisi saptandığı için yeni tanı olarak yetişkin ayrılma anksiyetesi ile de çocukluk cağı travmatik yaşantıları arasındaki olası ilişkiyi araştırmak çalışmamızda amaçlanmıştır. Araştırmada 119 kadın, 113 erkek katılımcı yer almıştır. Sadece 20 yas ve üzerinde olan, psikiyatrik hastalık geçmişi olmayan, mental kısıtlılığı olmayan kişiler çalışmaya dahil edilmiştir. Katılımcılara Sosyodemografik Veri Formu, Ayrılma Anksiyetesi Belirti Envanteri (AABE), Yetişkin Ayrılma Anksiyetesi Ölçeği (YAAÖ), Çocukluk Çağı Travma Ölçeği verilmiştir(CTÖ). Veriler Bağımsız Örneklem t Testi, Çok Yönlü Varyans Analizi ve Tukey Testi, Pearson Korelasyon Analizi ve Ki-Kare testleri kullanılarak analiz edilmiştir. YAAÖ Toplam puanı ile Duygusal İstismar, Duygusal İhmal, Cinsel İstismar, CTÖ Toplam puanı arasında pozitif yönde anlamlı korelasyon tespit edilmiştir. Çocukluk cağında yaşanan örseleyici yaşantıların varlığı, yetişkin ayrılma anksiyetesi ile ilişkisi saptanmıştır. Ancak konuyla ilgili araştırmaların artması, daha geniş örneklemle yapılacak takip çalışmalarına ihtiyaç bulunmaktadır.

Anahtar Kelimeler: yetişkin ayrılma anksiyetesi; çocukluk çağı travmaları; ihmal; istismar

Abstract

It is known that the negative life events experienced in childhood are related to depressive disorder and anxiety disorders in adult life. Adult separation anxiety is a relatively new diagnosis classified under the title of anxiety disorders in DSM-5. The aim of this study is to investigate the possible relationship between adult separation anxiety and traumatic experiences in childhood since childhood trauma has been associated with many anxiety disorders. The study included 119 female and 113 male participants. Only individuals aged 20 years and older and who do not have a psychiatric illness history and mental limitations were included in the study. Sociodemographic Data Form, Separation Anxiety Symptom Inventory (SASI), Adult Separation Anxiety Questionnaire (ASAQ), and Childhood Trauma Scale (CTS) were given to the participants. The data were analyzed by using Independent Sample t Test, Multi-directional Variance Analysis and Tukey Test, Pearson Correlation Analysis and Chi-Square tests. A significant positive correlation was found between total score of ASAQ and Emotional Abuse, Emotional Neglect, Sexual Abuse, CTS total score. The presence of traumatic experiences in childhood was found to be associated with adult separation anxiety. However, more studies on this subject and follow-up studies with larger samples are needed.

Keywords: *adult separation anxiety; childhood trauma; neglect; abuse*

[1]Üsküdar Üniversitesi Sosyal Bilimler Enstitüsü
[2]Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi
[3]Üsküdar Üniversitesi, İnsan ve Toplum Bilimleri Fakültesi
[*]Sorumlu Yazar: Üsküdar Üniversitesi Sosyal Bilimler Enstitüsü, e-mail: gokben.hizlisayar@uskudar.edu.tr, phone: 02166330633

2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org
JNBS

1. Giriş

Dünya Sağlık Örgütü (WHO), 2002 yılında yaptığı tanımda çocuk istismarını, "Çocuğun sağlık, büyüme ve gelişmesini olumsuz yönde etkileyecek olan her türlü fiziksel, duygusal, cinsel ihmal veya ihmale neden olacak ticari reklam amaçlı ya da diğer bütün etkileme şekilleri de dahil olmak üzere her türlü tutum ve davranışlara maruz kalması." şeklinde belirlemiştir. Çocuk istismarı; fiziksel istismar, duygusal istismar, cinsel istismar olarak üç gruba ayrılmaktadır. Çocuk ihmali ise, fiziksel ihmal ve duygusal ihmal olarak iki alt türe ayrılmaktadır (Acehan ve ark., 2013). İhmal ve istismar kavramları arasındaki fark, istismar kavramının aktif, ihmal kavramının pasif olmasıdır. İstismarda, çocuğa yapılmaması gereken, çocuğun gelişimine engel olan dövme, itme, örseleme, cinsel her türlü kötüye kullanım ya da aşağılama, dışarıda çalıştırma gibi davranışlar yapılırken, ihmalde, sevgi ihtiyacını karşılama, giyinme, barınma, eğitim ihtiyaçlarını karşılama gibi çocuğa yapılması gereken ama yapılmayan davranışlar söz konusudur.

İhmal ve istismar sıklıkla gözden kaçtığı için yaygınlığını belirleme çalışmaları yapmak da güçtür. Türk toplumunda yaygınlığının kız çocuklarsa %20, erkek çocuklarda ise %30 civarında olduğu tahmin edilmektedir (Şimşek ve Gençoğlan, 2014). Duygusal istismar için kız ve erkek çocuklar arasında görülme sıklığı bakımından bir fark bildirilmemiştir (Taner ve Gökler, 2004; Şahin, 2008). Ulusal düzeyde geniş örneklemler kullanılarak yapılan çalışmalar olmamakla birlikte ülkemizde çocuklarda fiziksel istismarın %30-35, cinsel istismarın ise %13-15 civarı olduğun tahmin edilmektedir (Ayaz, 2012).

Çocukluk çağında deneyimlenen olumsuz yaşam olaylarının yetişkin yaşamdaki depresif bozukluk ve anksiyete bozuklukları ile ilişkisi bilinmektedir. Bir çalışmada panik bozukluk hastalarında çocukluk çağı travması öyküsü varlığının sağlıklı kontrollerden 8.7 kat, yaygın anksiyete bozukluğunda, sosyal fobi ve agorafobide ise 3.7 kat daha fazla bulunduğu bildirilmiştir (Brown ve Harris, 1993). Friedman ve ark. (2002), erken dönem travmatik yaşantıları panik bozukluk ile, Mathews ve ark (2008) ile obsesif kompulsif bozukluk gelişimi ile ilişkili bulmuşlardır.

Ayrılma anksiyetesi bozukluğu kişinin bağlandığı insanlardan ayrılmasıyla ilgili, gelişimsel olarak uygun olmayan ve aşırı düzeyde bir kaygı ya da korku duyması ile karakterize bir psikopatolojidir. Çocukluk çağında yaşanan kaygılar yetişkinlikte şekil değiştirmekle birlikte devam etmektedir. Yakınlarının başına kötü bir şey gelmesinden korkarlar, ayrılmaya karşı çok duyarlıdırlar ve yakın olduğu kişileri aramak gibi davranışlarla sürekli kendilerini yatıştırmaya ihtiyaç duyarlar. Çocuklukta daha ziyade gastrointestinal sistem belirtileri, uyku sorunları ya da mide bulantısı, karın ağrısı gibi somatik belirtilerle kendisini gösterirken, yetişkin ayrılma anksiyetesinde (YAA) bu somatik belirtiler daha çok bilişsel ve duygusal anlamda oluşmakta ve çoğu kez panik bozukluk, panik atağı, agorafobi, yaygın anksiyete bozukluğu ile karışabilmektedir.

Ayrılma anksiyetesinin nedeni kesin olarak bilinmemekle birlikte Bowlby (1973), aşırı korumacı anne tutumunun, ileriki yıllarda çocuğun başa çıkma becerilerini engelleyerek kaygının gelişmesine neden olabileceğini söylemektedir. Güvensiz ve ikircikli bağlanmanın ayrılma anksiyetesiyle ilgisinin olduğu birçok çalışma ile gösterilmiştir. (Dallaire ve Weinraub, 2005; Brumariu ve Kerns, 2010). Özellikle anksiyöz bağlanma biçiminin, YAA ek tanısı alan panik bozukluğu hastalarında, YAA ek tanısı almayanlara göre daha fazla olduğu tespit edilmiştir. Silove ve ark. (2007) ise travma sonrası stres bozukluğu ile YAA arasında anlamlı bir ilişki bulmuşlardır. Poulton ve ark. (2001), YAA ile düşük sosyoekonomik durum ve 3-18 yaş öncesi ebeveyn kaybı arasında anlamlı bir ilişki bildirmişlerdir. Shear ve ark. (2006) ise epidemiyolojik çalışmasında 9.282 kişi ile yaptığı çalışmada yaşam boyu YAA prevalansını %6.6 olarak bulmuşlar ve kadınlarda daha yaygın olduğunu bildirmişlerdir. Ayrıca YAA'yi işsizlik, eğitim düzeyinin düşük olması ve boşanma ile de ilişkili bulmuşlar ve kişinin günlük yaşam işlevselliğini bozduğunu bildirmişlerdir. Özten ve arkadaşları erişkin dikkat eksikliği hiperaktivite bozukluğu olan hastalarda ayrılma anksiyetesi belirtilerinin varlığını %53.3 olarak bulurken sağlıklı kontrol grubunda bu oran %11.5 olarak saptanmıştır (Özten et al, 2016).

Çeşitli araştırmalar, ilk ayrılık kaygısının yetişkinlikte de ayrılık semptomlarının sürmesi ile doğrudan ilişkili olduğunu göstermektedir (Manicavasagar ve ark., 1997). Bu açıklamalar çerçevesinde, çocukluk ve ergenlik yıllarındaki geçmiş ayrılık kaygısı yaşantılarının bireyin yetişkinlikteki kaygı düzeyinde önemli bir belirleyici faktör olabileceğini araştırma bulgularının desteklediği belirtilebilir.

Bu çalışmanın birincil amacı, genel popülasyonda çocukluk çağı travmaları ile yetişkinlik dönemi ayrılma anksiyetesi arasındaki ilişkiyi ortaya koymaktır. Bu amaçla, çocukluk çağı ihmal ve istismar yaşantılarıyla, yetişkinlik ayrılma anksiyetesinin ilişkisi incelenmiştir.

2. Yöntem ve Araçlar

Bu araştırma, n=119 kadın ve n=103 erkek toplamda N=222 katılımcı (yaş ort:32,60; ss:12,48) ile yürütülmüştür. Araştırmada klinik dışı örneklem kullanılmıştır. Katılımcılara sosyal medya platformlarındaki araştırmayı kısaca tanımlayıp gönüllüler arandığını bildiren ilanlarla ulaşılmıştır. 20 yaş ve üzerinde olan, psikiyatrik hastalık geçmişi olmayan, mental kısıtlılığı olmayanlar dahil edilmiştir. Araştırma anketi internet online formlar üzerinden gerçekleştiğinden seçkisiz ve rastgele, çok farklı gruplar ve kültürlerden kişiler katılmıştır. Araştırma desenini Üsküdar Üniversitesi Girişimsel Olmayan Araştırmalar Etik Kurulu onaylamıştır. Katılımcıların kısa bir bilgilendirme ile yönlendirildikleri online anket platformunda öncelikle bilgilendirilmiş onam formunu okumaları ve kabul etmeleri durumunda onay kutucuğunu işaretlemeleri istenmiştir. Hemen ardından yaş, geçmiş psikiyatrik hastalık sorgulanarak dışlama kriterleri kontrol edilmiştir. Mükerrer katılım olmaması online anket platformunun yaptığı IP denetlemesi ile sağlanmıştır. Araştırmada 236 kişi cevap vermiş, 14 kişinin cevapları geçersiz sayılmıştır.

3. Veri Toplama Araçları

3.1. Sosyodemografik Veri Formu

Araştırmanın değişkenlerini ölçebilmek adına araştırmacı tarafından hazırlanan sorulardan oluşmaktadır.

Katılımcılara yaş, cinsiyet, medeni durum, eğitim durumu, sosyoekonomik durum, memleket ve büyüdüğü yer, anne-baba ile ilgili faktörler, psikiyatrik bozukluklarının olup olmadığı, daha önce akranları tarafından, herhangi bir grup ya da biri tarafından şiddete maruz kalıp kalmadıkları, doğal afet, göç, kaza gibi bir durum yaşayıp yaşamadıkları sorulmuştur.

3.2. Ayrılma Anksiyetesi Belirti Envanteri / AABE (Seperation Anxiety Symptom Inventory)

Silove ve ark. (1996) tarafından, çocukluk çağında yaşanan ayrılma kaygısı belirtilerinin geçmişe yönelik olarak sorgulanması amacıyla geliştirilmiştir. 15 maddeden oluşmaktadır. 4'lü likert tipi ölçüm sağlayan kendi bildirime dayalı bir ölçektir. Maddelerin her biri, yetişkinlerde, geçmişe yönelik olarak 0 "hiç hissetmedim", 3 "çok sık hissettim" arasında dağılım gösterecek biçimde çocuklukta yaşanmış olabilecek ayrılma anksiyetesi semptomlarını sorgulamaktadır.

Türkçeye uyarlamasını, güvenirlik ve geçerlilik çalışmalarını Diriöz ve arkadaşları yapmıştır. Bulgulara göre iç tutarlılık; 410 katılımcıdan toplanan verilere göre Cronbach Alfa değeri 0,89 olarak tespit edilmiştir. ROC analizi; Ayrılma Anksiyetesi Belirti Envanteri için duyarlılığın %83, özgüllüğün %76 olduğu, "12 puan" (ham puan cinsinden) kesme noktası olarak belirlenmiştir. (Diriöz, M. ve ark., 2012).

3.3. Yetişkin Ayrılma Anksiyetesi Ölçeği YAA / (Adult Seperation Anxiety Questionnaire, ASA)

Manicavasagar ve ark. (2003) tarafından geliştirilmiş olan yetişkinlik dönemindeki ayrılma anksiyetesi belirtilerini araştıran ve self-report ölçektir. 27 maddeden oluşmaktadır. Uygulaması ortalama 10 dakika sürmektedir. 4'lü likert tipi ölçüm yapmakta, her bir madde 0 "hiç hissetmedim" ile 3 "çok sık hissettim" arasında dağılım göstermektedir. Türkçeye uyarlamasını, güvenirlik ve geçerlilik çalışmalarını Diriöz ve arkadaşları yapmıştır.

ROC analizinde, kesme noktası puanı 24.5 alındığında duyarlılığın %85 özgüllüğün %75, kesme noktası puanı 26.5 alındığında duyarlılığın %81 özgüllüğün %79 olması göz önünde tutularak "25 puan" olası kesme noktası olarak belirlenmiştir. Ulaşılan sonuca göre bu ölçekten 25 puan ve üzeri alanların Ayrılma Anksiyetesi Bozukluğu kriterlerini karşılama olasılığı fazladır.

3.4. Çocukluk Çağı Travmaları Ölçeği 2.0 (Childhood Trauma Questionnaire (CTQ)

Bu ölçek çocukluk ve ergenlikteki istismar ve ihmal yaşantılarını geçmiş yıllara dönük olarak değerlendirmeyi amaçlar. David P. Bernstein tarafından geliştirilmiştir. Ölçek ilk olarak 70 madde olarak geliştirilmiş olan bu ölçek, 1995 yılında 54 maddeye indirilmiş ve sonra yeniden düzenlenerek 28 maddelik kısa forma dönüştürülmüştür. Araştırmada kullanılan da ölçeğin 28 maddeden oluşan formudur. 5'li likert tipi bir ölçektir. Yanıtlama seçenekleri "1 hiçbir zaman" ile "5 çok sık" şeklindedir. Beş alt boyut; fiziksel istismar, cinsel istismar, duygusal istismar, fiziksel ihmal ve duygusal ihmaldir. 3 tane minimalizasyon-inkar sorusu (10, 16, 22. sorular) bulunmaktadır. Beş alt puanın toplamı CTQ toplam puanını verir. Alt puanlar 5-25, toplam puan 25- 125 arasındadır. Minimizasyon puanını hesaplamak için bu üç maddenin her birinden alınan sadece 5 puan (en yüksek) cevapları hesaba katılır ve bunları hepsi 1 puan olarak sayılır. Bunların toplanması ile 0-3 puan arasında bir minimizasyon puanı elde edilir.

Şar ve ark. (2011) tarafından yapılan çalışmanın bulguları cinsel ve fiziksel istismar için 5 puanın aşılmasının, yani sorulardan her hangi birine en alt düzeyde de olsa evet yanıtı verilmesinin pozitif bildirim olarak sayılması gerektiğini düşündürmektedir. Fiziksel ihmal ve duygusal istismar için bu sınırın 7 puan, duygusal ihmal için ise 12 puan düzeyine çekilebileceği anlaşılmaktadır. Toplam puan için bu sınırın 35 dolayında olabileceği görülmüştür.

3.5. Veri Analiz Yöntemleri

Çalışmada elde edilen verilerin değerlendirilmesinde, istatistiksel analizler için SPSS 21.0 programı kullanılmıştır. Toplanan veriler Bağımsız Örneklem t Testi, Çok Yönlü Varyans Analizi ve Tukey Testi, Pearson Korelasyon Analizi, ve Ki-Kare testleri kullanılarak analiz edilmiştir.

4. Bulgular

Bu araştırma, n=119 kadın (yaş ort:30,74; ss:11,61) ve n=103 erkek (yaş ort: 34,76; ss:13,15) toplamda N=222 katılımcı (yaş ort:32,60; ss:12,48) ile yürütülmüştür. Tablo 1'de kadın ve erkek katılımcıların çocukluk çağı travmatik deneyimlerine göre frekans dağılımları ve yüzdelikleri ile bu dağılımın anlamlılığına ilişkin ki-kare analizi bulguları verilmiştir.

En sık bildirilen çocukluk çağı travmatik deneyimi kadınların %36,1'i ve erkeklerin %37,9'unda izlenen çocukken akran tarafından şiddete uğrama olmuştur. Erkeklerin çocukken göç yaşama oranlarının kadınlara göre anlamlı şekilde yüksek; kadınların ise çocukken herhangi biri tarafından yıldırma, işkence eziyet ya da şiddete maruz kalma oranlarının erkeklere göre anlamlı şekilde yüksek olduğu gözlenmiştir ($\chi 2=8,747$; $p<0,05$).

Demografik değişkenlere ve klinik özelliklere göre ölçeklerden alınan puanların karşılaştırılması yapıldığında medeni duruma, gelir durumuna, memlekete, büyüdüğü yere, annenin sağ olup olmamasına ve anne-baba çalışma durumuna göre ölçeklerden alınan puanlar arasında anlamlı fark bulunmamıştır. Cinsiyete göre ölçeklerden alınan puanlara ilişkin ortalamalar, standart sapmalar ve bağımsız örneklem t testi bulguları Tablo 2'te yer almaktadır.

Kadınların Ayrılma Anksiyetesi puan ortalamaları erkeklerin ortalamalarından anlamlı şekilde yüksek bulunmuştur. Erkeklerin Okul Fobisi, Fiziksel İhmal, Duygusal İhmal puan ortalamaları kadınların ortalamalarından anlamlı şekilde yüksek bulunmuştur. Diğer ölçek ve alt boyutlarından alınan ortalama puanlar arasındaki farklar anlamlı bulunmamıştır.

Eğitim durumuna göre AABE "Ayrılma Anksiyetesi" alt ölçeği ortalamaları arasında istatistiksel olarak anlamlı fark bulunmuştur ($p=0,000$). Farkın kaynağının belirlenebilmesi amacıyla yapılan Tukey testinde lisans

Tablo 1. Kadın ve Erkek Katılımcıların Çocukluk Çağı Travmatik Deneyimleri Açısından Karşılaştırılması

Değişkenler	Kadın		Erkek		Toplam		χ^2	P
	n	%	n	%	n	%		
Çocukken akran tarafından şiddete uğrama (Duygusal-Fiziksel)								
Evet	43	36,1	39	37,9	82	36,9	0,071	0,449
Hayır	76	63,9	64	62,1	140	63,1		
Çocukken herhangi bir doğal afet mağduru olma								
Evet	22	18,5	15	14,6	37	16,7	0,612	0,274
Hayır	97	81,5	88	85,4	185	83,3		
Çocukken herhangi biri tarafından yıldırma, işkence eziyet ya da şiddete maruz kalma								
Evet	20	16,8	8	7,8	28	12,6	4,093	0,033*
Hayır	99	83,2	95	92,2	194	87,4		
Çocukken savaş veya terör olayı yaşama								
Evet	9	7,6	8	7,8	17	7,7	0,003	0,575
Hayır	110	92,4	95	92,3	205	92,3		
Çocukken göç yaşama								
Evet	9	7,6	22	21,4	31	14,0	8,747	0,003*
Hayır	110	92,4	81	78,6	191	86,0		
Çocukken kolektif şiddete maruz kalma								
Evet	1	0,8	3	2,9	4	1,8	1,340	0,259
Hayır	118	99,2	100	97,1	218	98,2		
Çocukken ölümcül bir hastalık geçirme ya da aileden birinin geçirdiğine şahit olma								
Evet	25	21,0	17	16,5	42	18,9	0,730	0,248
Hayır	94	79,0	86	83,5	180	81,1		
Doğuştan ya da sonradan oluşan bir sağlık sorunu								
Evet	34	28,6	21	20,4	55	24,8	1,984	0,105
Hayır	85	71,4	82	79,6	167	75,2		
Çocukken kaza geçirme								
Evet	26	21,8	32	31,1	58	26,1	2,431	0,080
Hayır	93	78,2	71	68,9	164	73,9		
Toplam	119	100,0	103	100,0	222	100,0		

** p<0.05*

Tablo 2. Cinsiyete Göre Ölçeklerden alınan puanlara ilişkin ortalama, standart sapma ve t testi bulguları

		N	Ort.	ss	t	P
AABE	Kadın	119	6,00	4,485	2,757	0,006*
"Ayrılma Anksiyetesi"	Erkek	103	4,42	3,994		
	Toplam	222	5,27	4,328		
AABE	Kadın	119	1,73	1,721	-2,525	0,012*
"Okul Fobisi"	Erkek	103	2,37	2,044		
	Toplam	222	2,03	1,900		
CTQ	Kadın	119	6,67	1,971	-4,041	0,000*
"Fiziksel İhmal"	Erkek	103	7,95	2,727		
	Toplam	222	7,27	2,432		
CTQ	Kadın	119	9,89	4,058	-2,020	0,045*
"Duygusal İhmal"	Erkek	103	11,01	4,183		
	Toplam	222	10,41	4,145		

** p<0.05*

mezunlarının Ayrılma Anksiyetesi puanları ortaokul ve lise mezunları puan ortalamalarından anlamlı şekilde yüksek bulunmuştur.

Babaları sağ olanlarla ölü olanların AABE "Ayrılma Anksiyetesi" alt ölçeği ortalamaları arasında istatistiksel olarak anlamlı fark bulunmuştur (p=0,004). Babası sağ olanların Ayrılma Anksiyetesi, Okul Fobisi ortalama puanları, babası hayatta olmayanlara göre anlamlı biçimde yüksek bulunmuştur.

Ebeveynleri akraba evliliğiyle evli olanların Okul Fobisi ve Fiziksel İhmal puan ortalamaları, ebeveynleri akraba evliliği yapmamış olanlara göre istatistiksel olarak anlamlı biçimde yüksek bulunmuştur (sırasıyla p=0.029 ve p=0.028).

Ebeveynleri boşanmış olanların Aile Üyelerinden Uzak Kalamama alt ölçeği ortalamaları boşanmamış olanların ortalamalarından anlamlı şekilde düşük (p=0.049); Duygusal İhmal puanları anlamlı şekilde yüksek (p=0.025) bulunmuştur.

Ebeveynlerinin herhangi birinden, kreş, boşanma vb. gibi sebeplerle ayrı kalmış olanların Duygusal İhmal puanları, ebeveynlerinden ayrı kalmamış olanlara göre istatistiksel olarak anlamlı biçimde yüksek bulunmuştur (p=0.034). Diğer ölçek ve alt boyutlarından alınan ortalama puanlar arasındaki farklar anlamlı bulunmamıştır.

Tablo 3. Demografik Verilerle Ölçeklerden Alınan Puanların Korelasyonları

	Kaç Kardeş	Kaçıncı Çocuk	Yaş
AABE "Ayrılma Anksiyetesi"			-,266**
AABE "Okul fobisi"			-,162*
AABE Toplam			-,242**
CTQ Minimizasyon "Travmanın inkarı"		-,140*	
CTQ "Duygusal istismar"		,133*	
CTQ "Fiziksel istismar"		,135*	
CTQ "Fiziksel ihmal"	,304**	,294**	
CTQ "Duygusal ihmal"	,144*	,183**	
CTQ Toplam	,181**	,205**	

** p<0,05 ** p<0,01*

Bu sonuca göre yaş arttıkça Ayrılma Anksiyetesi, Okul Fobisi ve AABE Toplam puanı azalmaktadır. Kardeş sayısı ile Fiziksel İhmal (r=0,304; p<0,01), Duygusal İhmal (r=0,144; p<0,05), CTQ Toplam puanı (r=0,181; p<0,01) arasında pozitif yönde anlamlı korelasyon bulunmuştur. Doğum sırası arttıkça CTQ Minimizasyon -Travmanın İnkarı azalmakta (r=-0,140; p<0,05), Duygusal İstismar (r=0,133; p<0,05), Fiziksel İstismar (r=0,135; p<0,05), Fiziksel İhmal (r=0,294; p<0,01), Duygusal İhmal (r=0,183; p<0,01) artmaktadır.

Tablo 4. Ölçekler Arasındaki Pearson Korelasyon Bulguları

	1	2	3	4	5	6
1. AABE "Ayrılma Anksiyetesi"	1					
2. AABE "Aile üyelerinden uzak kalamama"	,448**	1				
3. AABE "Okul fobisi"	,275**	,269**	1			
4. AABE Toplam	,887**	,733**	,559**	1		
5. YAA Toplam	,465**	,545**	,167*	,548**	1	
6. CTQ Minimizasyon "Travmanın inkarı"	-,117	-,015	-,075	-,102	-,046	1
7. CTQ "Duygusal istismar"	,348**	,241**	,144*	,353**	,225**	-,293**
8. CTQ "Fiziksel istismar"	,119	,130	,139*	,164*	,106	-,157*
9. CTQ "Fiziksel ihmal"	,035	,043	,075	,059	,029	-,294**
10. CTQ "Duygusal ihmal"	,162*	,142*	,108	,188**	,153*	-,498**
11. CTQ "Cinsel istismar"	,270**	,220**	,056	,271**	,159*	-,112
12. CTQ Toplam	,257**	,211**	,142*	,283**	,190**	-,418**

** p<0,05 ** p<0,01*

JNBS 2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org

Tablo 4'de araştırmada kullanılan ölçeklerden alınan puanlar arasındaki korelasyonlar bulunmaktadır. Ayrılma Anksiyetesi ile YAA, Duygusal İstismar, Duygusal İhmal, Cinsel İstismar ve CTQ toplam puanı arasında pozitif yönde anlamlı korelasyon izlenmiştir. Aile Üyelerinden Uzak Kalamama Duygusal İstismar, Duygusal İhmal, Cinsel İstismar ve CTQ Toplam puanı arasında pozitif yönde anlamlı korelasyon tespit edilmiştir. Okul Fobisi ile YAA, Duygusal İstismar, Fiziksel İstismar ve CTQ Toplam puanı arasında pozitif yönde anlamlı korelasyon tespit edilmiştir. AABE Toplam puanı ile YAA Toplam puanı, Duygusal İstismar, Fizisiksel İstismar, Duygusal İhmal, Cinsel İstismar ve CTQ Toplam puanı arasında pozitif yönde anlamlı korelasyon tespit edilmiştir. YAA Toplam puanı ile Duygusal İstismar, Duygusal İhmal, Cinsel İstismar, CTQ Toplam puanı arasında pozitif yönde anlamlı korelasyon tespit edilmiştir.

5. Tartışma

Bu araştırmada çocukluk çağında yaşanan travmalar ile yetişkinlik dönemindeki ayrılma anksiyetesi belirtileri, çeşitli sosyodemografik değişkenler açısından incelenmiştir. Araştırmada kadınların AABE puanları, erkeklere oranla daha fazla bulunmuş ancak YAA puanları açısından kadın ve erkekler arasında anlamlı bir fark bulunamamıştır. Literatüre bakıldığında, Alkan (2007), kadın ve erkek katılımcıların YAA belirtilerini kadınlarda daha fazla bulmasına rağmen anlamlı bir fark elde etmediğini bildirmiştir. Shear ve ark. (2006), çocuklukta ayrılma anksiyetesinin kız çocuklarda daha yaygınken erkeklerde YAA, yetişkinlik döneminde daha sık görüldüğünü, kısacası kadın ve erkekler arasında bir farkın olmadığını bildirmişlerdir. Mertol ve ark (2012) ise, erkeklerde YAA belirtilerinin daha düşük olduğu sonucuna ulaşmıştır. Yine cinsiyet değişkeni açısından, erkek katılımcılarda Fiziksel ve Duygusal İhmal puanları kadın katılımcılardan daha yüksek bulunmuştur. Güler (2014), erkeklerde yalnızca Duygusal İhmal puanlarının kadın katılımcıların puanlarından yüksek bulmuş, diğer bütün alt kategorilerde kadın katılımcıların puanlarını daha yüksek bulmuştur. Ayaz (2012), Cinsel İstismarı kadınlarda, Fiziksel İstismarı erkeklerde daha fazla bulmuştur.

Eğitim seviyesi arttıkça, Fiziksel İstismar puanları azalmaktadır. Bu puanın az olmasının sebebi eğitim seviyesi yüksek olan bireylerin ailelerinin de eğitimli olması ya da eğitimli olmasa bile çocuğunun okuması veya gelişimi için eğitime teşvik eden, okuması koşuluyla kendisine iyi davranan aileler olmasından olabilir. Ayrıca eğitim seviyesi arttıkça, Ayrılma Anksiyetesinin arttığı görülmüştür. Lise mezunlarının puanları, ortaokul mezunlarının puanlarından daha fazla, lisans mezunlarının ise lise mezunlarından daha fazla puan aldıkları bulunmuştur. Bunun nedeni, ülkemizdeki eğitim sistemi ve kolektif toplum olmak ile yani kültürle ilgili olabilir. Eğitim seviyesinin yükselmesi, sorumlulukları ve ayrılıkları da beraberinde getirebilmektedir. Ancak alan yazında bunun tam tersi bulgulara sahip araştırma sonuçları da mevcuttur. Alkan (2007), eğitim seviyesi arttıkça ayrılma anksiyetesi belirtilerinin düştüğünü belirtmiştir. Bunun nedenlerini de eğitimli kişilerin, kaygı ile baş etme çabalarının daha fazla gelişmiş olabileceği ya da ayrılma anksiyetesinin yoğunluğunun, kişilerin işlevselliğini etkilemiş olabileceğinden okula devam edememiş olabilecekleri şeklinde bir açıklama getirmişlerdir. Shear ve ark. (2006) da, ayrılma anksiyetesini, düşük eğitimle ilişkili bulmuştur. Mertol ve ark (2012) ise eğitim durumu ile ilgili anlamlı bir sonuca ulaşmamıştır.

YAA Toplam puanı ile Duygusal İstismar arasında pozitif yönde bir korelasyon olduğu görülmüştür. Ayrıca YAA puanları yüksek olanların Duygusal İhmal ve Cinsel İstismar puanlarının YAA olmayan gruptan yüksek olduğu bulunmuştur. Mertol ve ark (2012), Duygusal İstismar alt ölçeğini, YAA olan grupta daha yüksek bulmuş, ancak Fiziksel İhmal, Fiziksel İstismar, Duygusal İhmal ve Cinsel İstismar puanları arasında bir farklılık bulamamıştır.

Literatürde farklı sosyodemografik gruplar için farklı çocukluk çağı travmaları, farklı psikopatolojiler için risk olarak saptanmıştır. Bu araştırmanın sonuçları da, diğer bir çok araştırma gibi çocukluk çağı travmalarının yetişkin ayrılık anksiyetesi için bir risk faktörü olabileceğine işaret etmektedir. Çocukluk çağı travmaları hem bireysel hem de toplumsal bazda olumsuz etkileri gözlenmektedir. Evrensel önleme çalışmalarında ailelere yönelik eğitim verme, bilgilendirme, aile planlaması hakkında toplumun ve ailelerin bilgilendirilmesi, çocuk bakımı konusunda bilgilendirme, varsa alkol ve madde kullanımından kurtulmayla ilgili destek verilmesi, kadının güçlendirilmesi, kişilik haklarının öğretilmesi ve aile içi şiddetin önlenmesi gibi "aileye yönelik hizmetler" oldukça önemlidir. Ayrıca kişisel haklarının öğretilmesi, bedenlerinin özel olduğunu ve mahrem bölgelerinin olduğunu öğretmek, hayır demesi gerektiği ve gerektiğinde bağırması, yardım istemesi için bilinçlendirmek ve cesaretlendirmek gibi "çocuğa yönelik hizmetler" de önem taşır.

Küçük yaşta ebeveyn olma, evlilikte şiddet ve çatışma olan, maddi sıkıntılar yaşayan, göç sonucu toplumsal yalıtılma yaşayan ve içe kapanan aileler, işsizlik ve ekonomik sorun yaşayan aileler, alkol ve madde kullanımı olan, eğitim düzeyi çok düşük veya yozlaşmış çok çocuklu ailelerin çocukları her zaman daha fazla risk altında olduğundan bu çocuklara gereken ilgi ve şefkatin daha fazla verilebilmesi adına bazı önlemlerin alınması gibi "toplumsal önleme çalışmaları" artırılmalıdır.

Travma önlenememiş olsa bile en azından devam etmesini durdurmak için en büyük sorumluluk yakınlıkları sebebiyle ebeveyne ve öğretmenlere düşmektedir. İyi bir gözlemle bile bir çocuğun hayatı kurtulabilir ve hatta bu sağlıklı bireylerle sağlıklı bir toplum oluşabilir. Travmatik geçmişi olan yetişkinler, kendi çocuklarına da yaşadığı sıkıntıları ve belirtileri yansıtabilmekte veya çocuklarına da uygulayabilmektedirler. Bu da sağlıksız bir toplumu oluşturmaktadır.

Bu araştırmanın bazı sınırlılıkları bulunmaktadır. Araştırma, kesitsel olarak yapılmış, katılımcıların hatırladıkları çocukluk anıları ile ilgili verdikleri verilere ve son zamanlarda hissettikleri anksiyete seviyelerine göre sonuçlara ulaşılmıştır. Konuyla ilgili benzer araştırmaların ve bu araştırmanın sınırlılığı boylamsal olmaması olabilir. Araştırma seçkisiz olarak her yaştan, her sosyo-ekonomik ve kültürel gruptaki yetişkinin katılmasıyla yapılmış olsa da, daha fazla katılımcının olması daha faydalı sonuçlar doğurabilir. Ayrılma anksiyetesi yüksek olan bireylerin ve çocukluk çağı travmaları yaşayanların kaygı puanlarının

yüksek olabileceği hesaba katılırsa, araştırma içinde yer alan soruların bireyler için hassas ve özel olması ile araştırmanın internet ortamı üzerinden yürütülüyor olmasından, kişiler gerçekleri yansıtmaktan imtina etmiş, gerçekleri olduğu gibi göstermemiş olabilirler. Ölçekleri dolduran katılımcılara, ek olarak her hangi bir psikiyatrik hastalığı olup olmadığını ölçen bir envanter doldurtulmamıştır. Kişinin hayatında hiç psikiyatriste gitmemiş olması hasta olmadığı anlamına gelmeyebilir. Ancak sosyodemografik veri formunda yalnızca kişinin hastalığına veya sağlığına ilişkin bilgisi ve iç görüsünün olduğu varsayılarak kabul edilmiştir.

6. Sonuç

Bu araştırmanın sonuçları da, diğer birçok araştırma gibi çocukluk çağı travmalarının yetişkin ayrılık anksiyetesi için bir risk faktörü olabileceğine işaret etmektedir. Yetişkin ayrılma anksiyetesi, çocukluk çağı travmalarının tek belirtisi olmamakla birlikte, çocukluk çağı travmaları da, yetişkin ayrılma anksiyetesinin tek sebebi değildir. Ancak diğer anksiyete bozuklukları gibi özellikle belirtilerinin travmatik geçmişi olan kişilerde olduğu gözlemlenmektedir. Bu çalışma, konuyla ilgili araştırma yapacaklara sosyodemografik değişkenler açısından fikir sunmaktadır.

Kaynakça

Acehan, S., Bilen, A., Ay, M. O., Gülen, M., Avci, A., & İçme, F. (2013). Çocuk istismarı ve ihmalinin değerlendirilmesi. Arşiv Kaynak Tarama Dergisi, 22(4) 591-614.

Alkan, M. (2007). Duygudurum ve anksiyete bozukluklarında panik-agorafobik spektrumun ve erken ayrılma anksiyetesinin komorbiditesi ve etkileri (Doctoral dissertation, Ege Üniversitesi).

Ayaz, M., Ayaz, A. B., & Soylu, N. (2012). Çocuk ve ergen adli olgularda ruhsal değerlendirme. Klinik Psikiyatri Dergisi, 15(1), 33-40.

Bowlby, J. (1973). Attachment and loss: Separation: Anxiety and anger (Vol. 2).

Brown, G. W., & Harris, T. O. (1993). Aetiology of anxiety and depressive disorders in an inner-city population. 1. Early adversity. Psychological medicine, 23(1), 143-154.

Brumariu, L. E., & Kerns, K. A. (2010). Mother–child attachment patterns and different types of anxiety symptoms: Is there specificity of relations?. Child Psychiatry & Human Development, 41(6), 663-674.

Dallaire, D. H., & Weinraub, M. (2005). Predicting children's separation anxiety at age 6: The contributions of infant–mother attachment security, maternal sensitivity, and maternal separation anxiety. Attachment & Human Development, 7(4), 393-408.

Diriöz, M., Alkin, T., Yemez, B., Onur, E., & EMİNAĞAOĞLU, P. N. (2012). Ayrılma Anksiyetesi Belirti Envanteri İle Yetişkin Ayrılma Anksiyetesi Anketinin Türkçe Versiyonunun Geçerlik ve Güvenirliği. Turk Psikiyatri Dergisi, 23(2), 108-116.

Diriöz, M., Alkin, T., Yemez, B., Eminagaoglu, N., & Onur, E. (2012). Ayrılma Anksiyetesi Belirtileri Için Yapilandirilmis Klinik Görüsmesi Türkçe Versiyonunun Psikometrik Özellikleri/Psychometric Properties of the Turkish Version of the Structural Clinical Interview for Separation Anxiety Symptoms. Noro-Psikyatri Arsivi, 49(1), 6.

Friedman, S., Smith, L., Fogel, D., Paradis, C., Viswanathan, R., Ackerman, R., & Trappler, B. (2002). The incidence and influence of early traumatic life events in patients with panic disorder: a comparison with other psychiatric outpatients. Journal of anxiety disorders, 16(3), 259-272.

Güler, A. (2014). Şizofreni Tanılı hastalarda çocukluk çağı travmalarının etkileri. İstanbul. Haliç Üniversitesi Sosyal Bilimler Anabilim Dalı Uygulamalı Psikoloji Yüksek Lisans Programı Yayınlanmamış Yüksek Lisans Tezi.

Manicavasagar, V., Silove, D., Curtis, J., & Wagner, R. (2000). Continuities of separation anxiety from early life into adulthood. Journal of anxiety disorders, 14(1), 1-18.

Manicavasagar, V., Silove, D., Wagner, R., & Drobny, J. (2003). A self-report questionnaire for measuring separation anxiety in adulthood. Comprehensive Psychiatry, 44(2), 146-153.

Manicavasagar, V., Silove, D., & Curtis, J. (1997). Separation anxiety in adulthood: a phenomenological investigation. Comprehensive psychiatry, 38(5), 274-282.

Mathews, C. A., Kaur, N., & Stein, M. B. (2008). Childhood trauma and obsessive-compulsive symptoms. Depression and anxiety, 25(9), 742-751.

Mertol, S., & Alkın, T. (2012). Temperament and character dimensions of patients with adult separation anxiety disorder. Journal of affective disorders, 139(2), 199-203.

Özten, E., Tufan, A. E., Eryilmaz, G., Sayar, G. H., & Bulut, H. (2016). The prevalence of adult separation anxiety disorder in a clinical sample of patients with attention-deficit/hyperactivity disorder/Eriskin dikkat eksikligi hiperaktivite bozuklugu hastalari klinik örnekleminde eriskin ayrilma anksiyetesi bozuklugu yayginligi. Anadolu Psikiyatri Dergisi, 17(6), 459-465.

Poulton, R., Milne, B. J., Craske, M. G., & Menzies, R. G. (2001). A longitudinal study of the etiology of separation anxiety. Behaviour research and therapy, 39(12), 1395-1410.

Shear, K., Jin, R., Ruscio, A. M., Walters, E. E., & Kessler, R. C. (2006). Prevalence and correlates of estimated DSM-IV child and adult separation anxiety disorder in the National Comorbidity Survey Replication. American Journal of Psychiatry, 163(6), 1074-1083.

Silove, D., Slade, T., Marnane, C., Wagner, R., Brooks, R., & Manicavasagar, V. (2007). Separation anxiety in adulthood: dimensional or categorical?. Comprehensive psychiatry, 48(6), 546-553.

Şar, V., Öztürk, P. E., & İkikardeş, E. (2012). Çocukluk çağı ruhsal travma ölçeğinin türkçe uyarlamasının geçerlilik ve güvenilirliği. Turkiye Klinikleri Journal of Medical Sciences, 32(4), 1054-1063.

Şimşek, Ş., & Gençoğlan, S. (2014). Cinsel istismar mağdurlarında istismar süresi ve sıklığı ile travma belirtileri arasındaki ilişkinin incelenmesi. Dicle Medical Journal/Dicle Tip Dergisi, 41(1), 166-171.

Taner, Y., & Gökler, B. (2004). Çocuk istismarı ve ihmali: Psikiyatrik yönleri. Acta Medica, 35(2), 82-86.

JNBS 2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org

ORIGINAL ARTICLE-ARAŞTIRMA

Year (Yıl) : 2018
Volume (Cilt) : 5
Issue Number (Sayı) : 3
Doi : 10.5455/JNBS.1538465211

Received/Geliş 25.10.2018
Accepted/Kabul 5.11.2018
JNBS, 2018, 5(3):156-164

POSITIVE PSYCHOLOGY COURSE AND ITS EFFECT ON WELL-BEING, SOCIAL, AND EMOTIONAL INTELLIGENCE

POZİTİF PSİKOLOJİ EĞİTİMİNİN İYİ OLUŞ HALİ İLE SOSYAL VE DUYGUSAL ZEKA ÜZERİNE ETKİLERİ

Hüseyin Ünübol[1*], Gökben Hızlı Sayar[1], Kübra Ekşi[1], Zeynep Avşaroğlu[1], Büşra Barış[1], Şeyma Günaydın[1*], Fatma Nur Dolu[1], Ezgi Yıldız[1], Nevzat Tarhan[1]

Abstract

The present study examines whether the Positive Psychology course, which is given for 14 weeks and 3 hours per week to students at a university in Istanbul. 417 students participated. The study assessed pre- to post-test modifications in personal and mental well-being, happiness, satisfaction of life, emotional and social intelligence, emotional expressions and attachment styles factors. The findings showed that significant differences between male and female gender in emotional and social intelligence. Interestingly, positive psychology course effects the participants negatively in happiness, well-being, and social intelligence, unlike in emotional expression. It was necessary to discuss these results in a new perspective. The point reached at the end of the Positive Psychology course was not a happier life. Also, if the increase in awareness causes someone to find a deeper meaning, then happiness and well-being will be decreased at the beginning.

Keywords: happiness; positive psychology; emotional intelligence; social intelligence

Özet

Bu çalışmanın amacı, İstanbul'da bir üniversitede öğrencilere haftada 3 saat ve 14 hafta süreyle verilen Pozitif Psikoloji dersinin etkisinin olup olmadığını incelemektedir. 417 öğrenci katıldı. Çalışma, öznel ve mental iyi oluş, mutluluk, yaşam doyumu, duygusal ve sosyal zeka, duygudurum ve bağlanma stilleri faktörleri arasında test öncesi ve sonrası değişimleri değerlendirildi. Bulgular, duygusal ve sosyal zekâda erkek ve kadın cinsiyet arasında anlamlı farklılıklar olduğunu göstermiştir. İlginç bir şekilde, pozitif psikoloji dersi, duygusal ifadeden farklı olarak, katılımcıları mutluluğa, öznel iyi oluşa ve sosyal zekaya olumsuz yönde etki gösterdiği bulunmuştur. Bu sonuçları yeni bir bakış açısıyla tartışmak gerekiyordu. Pozitif Psikoloji dersinin sonunda ulaşılan nokta daha mutlu bir yaşam değildi. Başlangıçta ki mutluluk ve öznel iyi oluşta ki negatif etkinin, farkındalıkla kazanılan daha derin bir anlamın etkileri üzerinden değerlendirildi.

Anahtar Kelimeler: *mutluluk; pozitif psikoloji; duygusal zeka; sosyal zeka*

[1]Sosyal Bilimler Enstitüsü, Üsküdar Üniversitesi, İstanbul, Türkiye.
[*]Corresponding Author: Sosyal Bilimler Enstitüsü, Üsküdar Üniversitesi, İstanbul, Türkiye. E-mail: huseyin.unubol@uskudar.edu.tr

1. Introduction

Positive psychology includes the elements of optimism, hope, maturity, and defense mechanism in the specific structure division, (Compton & Hoffman, 2012) which is an analysis of behavior that moves the focus from the negative to the positive, from what's wrong to what's right. At present, the research of positive psychology is mainly inclined to three aspects that is emotion and experience (Vazquez, 2017), personality (Ng, 2015) and public relations in a group perspective (Kobau et al., 2011). As Seligman and Csikszentmihalyi (Seligman & Csikszentmihalyi, 2014) observed, "A science of positive, subjective experience, positive individual traits, and positive institutions promises to improve the quality of life and prevent the pathologies that arise when life is barren and meaningless." The meaning of life is not a new issue. It has been an important issue throughout human history. Human psychology is at the top of the psychological theories that are most interested in the meaning of life. Humanistic psychology assumes that the human being tries to realize his potentials best in a process called self-actualization (Wong, 2011). Self-actualization guides people's goals, their conscious awareness, and their rational choices. This provides a far different perspective than the human nature of psychoanalysts and behaviorists who represent the dominant view of psychologists in the 20th century (Criswell, 2003).

Getting the necessary perspectives to make rational choices begins at a young age. Although attending university is viewed as a positive experience, offering many new opportunities, it nonetheless sometimes involves a stressful period of adaptation for students. First-year university students face a variety of stressors that make them independent adults (Parker, Hogan, Eastabrook, Oke, & Wood, 2006) include making new relationships, modifying existing relationships with parents and family, and learning study habits for a new academic environment. The presence of these stressors often correlates with low self-confidence, anxiety and low academic performance. Consequently, In recent studies, the mental health problems of college students have increasingly interested (Afrisham et al., 2015). Experts and scholars have begun to study the problem of College Students' mental health, and struggle to change some unhealthy psychological problems of college students through research. Evidence suggests that emotion regulation has a causal role in the development of almost all mental illnesses, particularly in the disorders of mood, anxiety, substance use, eating, and personality (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Dieter et al., 2017; O'Driscoll, Laing, & Mason, 2014; Sharpe & Wallis, 2014). Longitudinal data suggest that poor emotion regulation precedes the onset of depression and not vice versa (Aldao et al., 2010; Millgram, Joormann, Huppert, & Tamir, 2015). Researchers have shown that people with positive emotions increase their tendency to involve social interaction and new experiences (Fredrickson & Branigan, 2005). People experiencing positive emotions are more likely to affiliate with others and report higher quality social interactions (Berry & Hansen, 1996; DeNeve & Cooper, 1998; Nichols & Molix, 2013), and they are more likely to be extraversion and sociability that showed in many studies (Lyubomirsky, King, & Diener, 2005). For this reason, positive emotions help us establish our social relationships when we need them ((Fredrickson, 1998)). Most young people are not equipped to manage the emotional impact of stressors. The ability to regulate emotions follows other developments in the cognitive, social, and physiological domains, from infancy to adulthood (Zeman, Cassano, Perry-Parrish, & Stegall, 2006). Adults are better equipped than younger because of their experience and practice of emotional regulation strategies (Garnefski, Legerstee, Kraaij, Van Den Kommer, & Teerds, 2002). This is why learning emotional regulation strategies are likely to benefit this population and improve the rates of mental health disorders that arise. Emotion regulation skills begin to develop first through the support mechanism in the family. Childhood attachment is probably the most important resource for improving emotional regulation strategies. Attachment contributes to how individuals learn to regulate their emotions throughout development (Contreras, Kerns, Weimer, Gentzler, & Tomich, 2000; Kerns, Abraham, Schlegelmilch, & Morgan, 2007; Mikulincer & Shaver, 2007). People with a secure attachment style seek the support of others to combat negative moods; those with insecure attachment styles use less adaptive strategies (Fraley & Shaver, 2000; Mikulincer, 1998). People with secure attachments use adaptive coping strategies that have more positive effects on their psychological health (Mikulincer, Shaver, & Pereg, 2003). More avoidant individuals tend to rely on deactivating strategies in stressful situations, which include down-regulating, suppressing emotional reactions and emotional expressivity to maintain distance from others (Laan, van Assen, & Vingerhoets, 2012).

Emotional expressivity refers to the outward display of emotion (Kring, Smith, & Neale, 1994) which can take the form of facial expressions, body postures or verbal behavior. Emotional expressivity which usually takes place in the social context is linked to positive mental states and physical health (Sloan & Marx, 2004). Expressing emotions and being aware of their emotions is one of the parts of emotional intelligence (Caruso, Salovey, Brackett, & Mayer, 2015). The emotional intelligence was characterized as the personal ability for the application of emotions in different social situations. Salovey and Mayer ((Mayer, DiPaolo, & Salovey, 1990) conceptualized that the emotional intelligence includes: (1) the ability to monitor one's own and others' emotions, (2) the capability to discriminate the types of emotions, and (3) to use the information to guide one's thinking and actions in social exchanges. Both "emotional intelligence" and "positive psychology" are rapidly becoming very visible, popular and important areas of psychology. Researchers are trying to adopt many areas such as emotional education which aims to develop emotional skills and wellbeing (Louis, 2011). It is based on the principle that well-being is one of the basic goals of personal and social life. The APA Guidelines for the Psychology Major include a call for undergraduate programs to promote students' "insight into their own and others' behavior and mental processes and apply effective strategies for self-management and self-improvement" (2007, p. 10). The course of positive psychology generally involves the evaluation of scientific findings about human welfare, longevity, creativity, positive emotions, attributions, character strengths, human protective factors, and self-actualization in improving individual well-being (Diener,

Suh, Lucas, & Smith, 1999; Emmons & McCullough, 2003; Mongrain & Anselmo-Matthews, 2012; Seligman, Steen, Park, & Peterson, 2005). In addition, the risks of the global, personal and universal self-attributes of adverse events that creating the negative mental health conditions (Seligman, Rashid, & Parks, 2006) are almost universal components of the positive psychology curriculum. Positive psychology courses, which have a unique approach to improving the condition of the human being, are increasingly being offered in university college courses (Goodmon, Middleditch, Childs, & Pietrasiuk, 2016; Magyar-Moe, 2011). Maybury (Maybury, 2013) reported that students who took a positive psychology course improve subjective well-being, subjective happiness, mindfulness, self-actualization, and hope in 14 weeks.

This study aimed to measure the effects of positive psychology course on students. Happiness, personal and mental well-being, social and emotional intelligence, attachment and life satisfaction related scales were given to students before and after the 14-week course. The data from these scales are discussed.

2.Methods

2.1.Participants

Positive psychology lessons are given to all departments in Uskudar University for the last five years. Positive Psychology course is given 3 hours a week, following a common curriculum and evaluated every year. This course is given throughout the semester as a classical university curriculum. The positive psychology course is given in the 2nd semester of the 2016-2017 academic year started with 1645 people. Eight scales and sociodemographic forms were brought together as booklets. There is a volunteer form on the first page. No extra points and prizes were awarded except for the condition of volunteering to work. Scales The first hour of the first lesson was distributed. The filling time of the scales is approximately 50-60 minutes. The number of students who come to class during the first week and voluntarily fill the scales is 1543 people. Among the non-inclusion criteria are the abandonment of the scales, the expression of psychiatric illness at this time, the lack of mention of the scales, and the physical inconvenience that causes the scales to fail to fill alone. After the evaluation, 1459 students were included in the study. Last week, 1083 students entered the class again. After the evaluation of the booklets, 1000 people were included in the study. This study was designed as a project carried out with four thesis students. Four students completed their thesis. The purpose of this project is to look at the relationships of positive psychology education to emotional and social intelligence characteristics, life satisfaction, well-being and attachment characteristics of all students.

Due to the multiplicity of data in the study, it was decided to be evaluated pre and posttest data. Only 417 students who were suitable to be evaluated as pretest and posttest were determined from those filling the scales. Evaluation of the other students as pretest and posttest was not appropriate.

2.2.Measures

2.2.1.The Bar-On Emotional Quotient Inventory (EQ-i)

The Bar-On EQ-i (1997a) has been designed to assess Bar-On's (1997a) model of emotional intelligence (EI). Consistent with Bar-On's proposed theoretical structure of EI, the EQ-i comprises 13 sub-scales about four second-order factors and an overall or total EQ score.

Acer (2001) was adapted by Turkey. The original version consists of 133 items and is reduced by Acar to 88 items. The Emotional Intelligence Scale used in the study is a total of 5 second-order factors and a total of 13 sub-dimensions after adaptation to Turkey. Personal Awareness second-factor is used, and 30 questions with 5 sub-scales are available. A 6-point Likert-type Measure.

2.2.2.The Tromso Social Intelligence Scale:

The Tromso Social Intelligence Scale (TSIS) was developed by Silvera et al. (Silvera, Martinussen, & Dahl, 2001). The scale was adapted to Turkey by Dogan (2006). Social intelligence scale is a 21-item self-report tool designed to demonstrate social intelligence. TSIS measures social intelligence in three separate areas. It also reveals the level of social intelligence as a whole. Social information processing, social skills, social awareness are the sub-dimensions of TSIS.

2.2.3.The Warwick-Edinburgh Mental Well-Being Scale (WEMWB)

The Warwick-Edinburgh Mental Well-Being Scale (WEMWB) is developed by Tennant et al. (Tennant et al., 2007) is used to assess the levels of mental well-being in the UK, including mental well-being and subjective well-being. WEMWB is composed of 14 items to assess positive mental well-being levels of individuals. WEMWB is a five-point Likert-type measure and participants rate each item of scale ranging from Negotiation Levels (1) to Strongly Agree (5). Possible points range from 14 to 70. High scores indicate subjective well-being. The reliability and validity of the scale were tested in individuals aged 16 years and over. The reliability of the Turkish version was calculated by Keldal (2015) as .92.

2.2.4.The Personal Well-being Index-Adult (PWI-A)

The personal well-being index developed by the International Wellbeing Group (2006); subjective well-being is an 11-point Likert-type (0-10) instrument measuring the level of satisfaction with the eight domains of individuals' lives by the concept's structure. These eight domains by the International Wellbeing Group (2006); quality of life, individual health, success in life, bilateral relations, personal security, social belonging, future-oriented care, and spirituality.

Adapted by Meral (2014) in Turkish, PWI-A consists of 8 items and scores of maximum 80 are scored on the scale. The Cronbach Alpha internal consistency coefficient for this scale was .89.

2.2.5.The Oxford Happiness Questionnaire (OHQ):

OHQ is a 29-item, 6-point Likert type (1-I do not agree, 6-I agree) developed by Hills and Argyle to measure happiness. Hills and Argyle (Hills & Argyle, 2002)reported the internal consistency coefficient (Cronbach alpha) of the scale as 0.91. The result of the factor analysis to determine the construct validity of the scale was a construct of 8 factors with an eigenvalue greater than 1. However, because of the problems with the interpretation and naming of the mentioned factors, they have concluded that it is appropriate to use the scale as one factor. Adapted by Doğan (2012) in Turkish.

2.2.6.The Emotional Expression Scale

The Emotional Expression Scale developed by King and Emmons (King & Emmons, 1990) and adapted to Turkish by Kuzucu (2011) has been developed to measure the extent to which university students express their feelings irrespective of interpersonal relationships, both in interpersonal relationships. The data collection tool consists of 16 items prepared in 7 "li Likert type and consists of three sub-dimensions; "Positive Emotion" " Proximity" and "Negative Emotion." The coefficient of internal consistency measured by the Cronbach Alpha coefficient of the scale is .78, and the high scores indicate that the tendency to express feelings is high (Kuzucu, 2011).

2.2.7.The Satisfaction with Life Scale (SWLS)

The SWLS (Diener et al., 1985) is a five-item self-report measure of satisfaction with one's life (i.e., a measure of global life satisfaction). Each item was scored from 1 (totally disagree) to 7 (totally agree) so that the scores ranged from 5 (low satisfaction) to 35 (high satisfaction). The coefficient an of the scale was 0.87 and the test-retest reliability conducted during a two month period was 0.82 (Diener et al., 1985).The Turkish validity and reliability study of the scale was carried out by Yetim (YetIm, 1993).

2.2.8.Experiences in Close Relationships-Revised (ECR-R)

The attachment styles of participants were measured by Experiences in Close Relationships-Revised (ECR-R) developed by Fraley, Waller, and Brennan (2000) and adapted to Turkish Selçuk, Günaydın, Sümer and Uysal (2005). The Turkish form of ECR-R consists of 36 items rated on 7 Likert scales (1=Strongly disagree, 7=Strongly agree) and two subscales. The subscales are attachment-related avoidance (18 items) and attachment-related anxiety (18 items).

2.3.Research Design

The researcher introduced himself/herself before starting the data collection process and explained the purpose and content of the research. The respondents who agreed to participate in the survey explained how to fill the questionnaire. In the demographic form, participants were asked to respond to research questions, and participation in the survey was based on volunteerism. All the answers given to the questions were kept confidential, and the scales were filled out, expressing that they could not be used except for scientific purposes. Each questionnaire was completed within 45-50 minutes. The study was approved by the ethics committee from Üsküdar Üniversity.

3.Results

To examine the effects of taking positive psychology course on General Happiness, Tromso Social Intelligence Scale, Bar-on Emotional Intelligence, Emotional Expressivity Scale, Oxford Happiness Scale, Personal Well-Being Scale, Warwick-Edinburgh Mental Well-being Scale, Life-Satisfaction Scale and Experiences in Close Relationships Inventory, paired sample t-test was conducted by gender, with pre- and postcourse conditions as paired samples.

Tablo 1. Independent t-test between genders on all assessments before the positive psychology course

Assesments	Female		Male		t	p
	M	SD	M	SD		
GH	3.35	.638	3.40	.765	-.64	.52
WEMWBS	54.56	9.27	53.96	10.03	.57	.57
OHQ	119.36	18.48	117.58	18.82	.87	.39
EES-I	28.65	5.93	25.67	5.92	4.56	.000***
EES-P	23.66	4.94	20.96	5.37	4.86	.000***
EES-N	20.02	4.28	18.65	5.01	2.78	.006**
EES-T	72.34	10.62	65.27	11.61	5.89	.000***
SWLS	23.07	7.49	20.90	6.77	2.69	.007**
PWI	60.83	12.08	57.09	13.80	2.70	.007**
ECR-Av	64.60	15.61	58.19	13.95	3.83	.000***
ECR-Anx	67.94	16.60	68.27	18.24	-.18	.86
TSIS-T	77.10	9.98	73.64	12.73	2.61	.01*
TSIS-SIP	29.43	4.92	29.32	5.96	.18	.85
TSIS-SS	21.80	4.43	20.62	5.23	2.29	.02*
TSIS-SA	25.87	4.70	23.70	5.46	3.75	.000***
EQ-i ESA	26.93	5.25	26.28	4.50	1.25	.21
EQ-i EMS	19.62	5.23	22.27	6.32	-4.35	.000***
EQ-i SM	23.09	5.11	24.86	5.57	-3.07	.002**
EQ-i E	28.11	4.37	26.66	5.36	2.82	.005**
EQ-i EMO	26.81	4.97	25.08	5.47	3.07	.002**

Note: *Two tailed *p<.05, **p<.01, ***p<.001. M=Mean; SD=Standart Deviation; GH: General Happiness; WEMWBS: Warwick-Edinburgh Mental Well-being Scale; OHQ; Oxford Happiness Questionnaire; EES-I: Intimacy Subscale of Emotional Expressivity Scale; EES-P: Positive Subscale of Emotional Expressivity Scale; EES-N: Negative Subscale of Emotional Expressivity Scale; EES-T: Total of Emotional Expressivity Scale; SWLS: Satisfaction With Life Scale; PWI: Personal Well-Being Index; ECR-Av: Avoidance Subscale of Experiences in Close Relationships Inventory; ECR-Anx: Anxiety Subscale of Experiences in Close Relationships Inventory; TSIS-T: Total of Tromso Social Intelligence Scale; TSIS-SIP: Social Information Processing Subscale of Tromso Social Intelligence Scale; TSIS-SS: Social Skills Subscale of Tromso Social Intelligence Scale; TSIS-SA: Social Awareness Subscale of Tromso Social Intelligence Scale; EQ-i ESA: Emotional Self-Awareness Subscale of Bar-on Emotional Quotient Inventory; EQ-i EMS: Emotion Management in Self Subscale of Bar-on Emotional Quotient Inventory; EQ-i SM: Self-Motivation Subscale of Bar-on Emotional Quotient Inventory; EQ-i E: Empathy Subscale of Bar-on Emotional Quotient Inventory; EQ-i EMO: Emotion Management in Others Subscale of Bar-on Emotional Quotient Inventory.*

Results of independent t-test for gender differences are shown in table 1. According to the T-test results, students were found to differ in terms of Emotional expressions all dimensions, Satisfaction with life, personal well-being, Tromso social intelligence scale scores, all subscales of Bar-on Emotional Quotient Inventory, Avoidance subscale of experiences in close relationship inventory. It was observed that the average scores of Emotional Expressions all dimensions, Satisfaction with life, Personal Well-being, Tromso Social Intelligence scale, Empathy and Emotion management in others subscale of Bar-on Emotional Quotient Inventory were significantly higher in female students while the average of Emotion management in self and Self-motivation subscales of Bar-on Emotional Quotient variable attitude scores was significantly higher in male students.

Tablo 2. Paired sample t-test for male and female students

Assesments		Precourse		Postcourse		t	p
		M	SD	M	SD		
GH	Female	3.35	.64	3.37	.72	-.54	.59
	Male	3.39	.77	3.38	.867	.11	.92
WEMWBS	Female	54.55	9.27	53.84	9.87	1.20	.23
	Male	53.95	10.03	52.47	10.61	1.41	.16
OHQ	Female	119.36	18.47	117.32	18.71	2.11	.04*
	Male	117.58	18.81	113.5	20.63	2.21	.03*
EES-I	Female	28.65	5.93	28.75	5.51	-.282	.78
	Male	25.67	5.92	27.44	5.46	-3.01	.003**
EES-P	Female	23.66	4.94	24.21	4.79	-2.05	.04*
	Male	20.95	5.36	21.80	4.73	-1.69	.09
EES-N	Female	20.02	4.28	20.58	4.31	-2.05	.04*
	Male	18.64	5.01	20.00	4.84	-2.43	.02*
EES-T	Female	72.33	10.61	73.55	11.14	1.82	.07
	Male	65.27	11.61	69.24	11.59	-3.23	.002**
SWLS	Female	23.07	7.49	23.32	6.73	-0.64	.05
	Male	20.90	6.77	21.51	7.23	-.92	.36
PWI	Female	60.83	12.08	57.52	13.24	4.65	.000***
	Male	57.09	13.8	53.89	16.34	2.22	.03*
ECR-Av	Female	64.6	15.61	64.94	15.39	-.45	.65
	Male	58.18	13.94	61.51	14.77	-2.51	.01*
ECR-Anx	Female	67.94	16.6	69.24	17.45	-1.54	.12
	Male	68.27	18.24	69.88	18.93	-.79	.43
TSIS-T	Female	77.1	9.98	75.1	10.97	3.33	.001**
	Male	73.64	12.73	71.82	12.42	1.46	.15
TSIS-SIP	Female	29.43	4.92	30.02	4.97	-2.0	.05*
	Male	29.32	5.96	29.31	5.72	.01	.99
TSIS-SS	Female	21.8	4.43	21.15	4.10	2.79	.006**
	Male	20.62	5.23	20.19	4.77	.93	.36
TSIS-SA	Female	25.87	4.695	23.93	5.87	5.62	.000***
	Male	57.09	13.8	53.89	16.34	2.09	.04*
EQ-i ESA	Female	26.93	5.25	26.38	4.73	1.63	.10
	Male	26.28	4.50	25.40	5.69	1.50	.14
EQ-i EMS	Female	19.62	5.23	20.76	5.50	-3.58	.000***
	Male	22.27	6.32	22.97	6.29	-1.06	.29
EQ-i SM	Female	23.09	5.11	23.42	5.47	-1.13	.26
	Male	24.86	5.57	24.07	5.82	1.32	.19
EQ-i E	Female	28.11	4.37	27.77	4.94	1.18	.24
	Male	26.66	5.36	25.67	6.09	1.51	.21
EQ-i EMO	Female	26.81	4.97	26.59	5.34	.69	.49
	Male	25.08	5.47	25.01	6.29	.115	.91

Note: *: Two tailed *p<.05, **p<.01, ***p<.001. M=Mean; SD=Standart Deviation; GH: General Happiness; WEMWBS: Warwick-Edinburgh Mental Well-being Scale; OHQ; Oxford Happiness Questionnaire; EES-I: Intimacy Subscale of Emotional Expressivity Scale; EES-P: Positive Subscale of Emotional Expressivity Scale; EES-N: Negative Subscale of Emotional Expressivity Scale; EES-T: Total of Emotional Expressivity Scale; SWLS: Satisfaction With Life Scale; PWI: Personal Well-Being Index; ECR-Av: Avoidance Subscale of Experiences in Close Relationships Inventory; ECR-Anx: Anxiety Subscale of Experiences in Close Relationships Inventory; TSIS-T: Total of Tromso Social Intelligence Scale; TSIS-SIP: Social Information Processing Subscale of Tromso Social Intelligence Scale; TSIS-SS: Social Skills Subscale of Tromso Social Intelligence Scale; TSIS-SA: Social Awareness Subscale of Tromso Social Intelligence Scale; EQ-i ESA: Emotional Self-Awareness Subscale of Bar-on Emotional Quotient Inventory; EQ-i EMS: Emotion Management in Self Subscale of Bar-on Emotional Quotient Inventory; EQ-i SM: Self-Motivation Subscale of Bar-on Emotional Quotient Inventory; EQ-i E: Empathy Subscale of Bar-on Emotional Quotient Inventory; EQ-i EMO: Emotion Management in Others Subscale of Bar-on Emotional Quotient Inventory.*

Results of paired sample t-test for females and males are shown in table 2. Females reported significantly greater levels of positive emotional expressiveness, negative emotional expressiveness, social information processing and emotion management in self on posttest compared to pretest. For females, significantly positive difference is found on four measures: Positive Subscale of Emotional Expressivity Scale (t=-2,05: p=0,04<0,05), Negative Subscale of Emotional Expressivity Scale (t=-2,05: p=0,04<0,05), Social Information Processing Subscale of Tromso Social Intelligence Scale (t=-2.0: p=0,005<0,01) and Emotion Management in Self Subscale of Bar-on Emotional Quotient Inventory (t=-3,58: p=0,00<0,001). Whereas, five of the measures which are Oxford Happiness Questionnaire (t=2,11: p=0,04<0,05), Personal Well-Being Index (t=4,65: p=0,00<0,001), Social Skills Subscale of Tromso Social Intelligence Scale (t=2,79: p=0,006<0,01), Social Awareness Subscale of Tromso Social Intelligence Scale (t=5,62: p=0,00<0,001) and Total of Tromso Social Intelligence Scale (t=3,33: p=0,001<0,05) indicated significantly negative difference.

Males reported significantly greater levels of intimacy expressiveness, negative emotional expressiveness, total emotional expressiveness, avoidance in close relationships on posttest compared to pretest. For males, significantly positive difference is found on four measures: Intimacy Subscale of Emotional Expressivity Scale (t=-3,01: p=0,003<0,01), Negative Subscale of Emotional Expressivity Scale (t=-2,43: p=0,02<0,05), Total of Emotional Expressivity Scale (t=-3,23: p=0,002<0,01) and Avoidance Subscale of Experiences in Close Relationships Inventory (t=-2,51: p=0,01<0,05). Three of the measures revealed significantly negative difference: Oxford Happiness Questionnaire (t=2,21: p=0,03<0,05); Personal Well-Being Index (t=2,22: p=0,03<0,05) and Social Awareness Subscale of Tromso Social Intelligence Scale (t=2,09: p=0,04<0,05).

4. Discussion

Our study aims to examine the effect of a positive

psychology course on students' emotional intelligence, social intelligence, expressing their emotions, happiness and well-being. Positive psychology course started to take place in the curriculum at the universities. There are very few universities where all departments of the Positive Psychology course are put into the curriculum. No other study measures the effects of positive psychology, many students, and many different characteristics.

1459 students were included in the study, and the post-test included 1000 people. However, only the 417 students data were evaluated because the other students did not correctly code their names on the pre and post-tests.

In the evaluation of the scale before the lesson, it was seen that the happiness of the students was on the average of 3.5. The happiness questionnaire is a 5-point Likert-type questionnaire, the 5th happiest moment, the 1st most unhappy moment. Overall, they were found to be at a level of happiness slightly above average, with no gender differences. Mental wellbeing is a measure of psychological well-being and is rated with a score of 14-70. Students' mental well-being levels show an assessment above the average. The reliability of the Oxford Happiness Scale was tested with 450 university students and found to be 118-120 on average. In our study, the average level of happiness reaches similar results. It has been observed that the personal well-being score is consistent with the general average at mean values (McGillivray, Lau, Cummins, & Davey, 2009).

According to the results of our study, it is significantly higher in favor of women regarding total and subscales of the scale of emotions, life satisfaction, personal well-being scales, Tromso social intelligence, and emotional intelligence empathy and emotional intelligence-managing feelings of others. Many studies have shown that emotional intelligence is higher in women than in men (Das & Sahu, 2015; Day & Carroll, 2004; Lumley, Gustavson, Partridge, & Labouvie-Vief, 2005). Among the most important determinants of emotional intelligence, in particular, empathy is one of the most important areas where women are better than men (Clarke, Marks, & Lykins, 2016). First focusing on Emotional Intelligence, many acknowledge that it is a distinct form of intelligence (Ciarrochi, Chan, & Caputi, 2000) and it is accepted by many researchers that Emotional Intelligence is related to Social Intelligence (Dulewicz & Higgs, 2000; Dulewicz, Higgs, & Slaski, 2003; Mayer et al., 1990; Mongrain & Anselmo-Matthews, 2012). Naturally, a good empathic ability determines social intelligence as well as a person's life satisfaction (Marilaf Caro, San-Martín, Delgado-Bolton, & Vivanco, 2017), personal well-being, and the ability to manage other people's emotions (Bos & Stokes, 2018; Grant, 2014). Despite these characteristics of women, it was found that they were significantly lower than men regarding their ability to manage their own emotions and to determine inner motivation. At some point, the relationship of people to other people can prevent them from seeing their relationship with their own emotions, and it can reduce the confrontation with own problems. It can even be shown in studies that cognitive empathy and some psychopathological processes may be positively correlated (Wai & Tiliopoulos, 2012). Especially, concerning attachment characteristics, the study showed that the avoidance dimension is higher than males. Avoidance attachment styles may also cause emotional management problems and focusing on relations with other people rather than own emotions (Fantini-Hauwel, Boudoukha, & Arciszewski, 2012; Gentzler, Ramsey, Yi, Palmer, & Morey, 2014; Liu, Ding, Lu, & Chen, 2017).

According to the results of our study, it has been determined that the personal well-being and happiness of the students have decreased in the evaluation of the last week of the positive psychology course. The results may be effected with exam week, and we cannot be able to compare with a control group as we can assess in one of the most important limitations of our study. On the other hand, some studies argue that people live happily and sadly together (Larsen & Green, 2013). It does not mean that we are not happy when we are sad, nor does it mean that if we are so happy, we are not accompanied by our unhappiness. We live most of the emotions together, and we need to evaluate the positive psychology course effects more carefully because of raising awareness. Baumeister et al. (2013) offer a different perspective on meaningful and happy life. They argued that meaningful life was related to a more anxious, more depressive and less happy life (Baumeister, Vohs, Aaker, & Garbinsky, 2013). A meaningful life is about being a giver than a taker like a happy life. The positive psychology course eventually promises a better life by increasing one's awareness. Most often awareness causes certain distress before it causes one's happiness. At the same time, the idea of creating awareness is about giving meaning to life, not a happy life.

Regarding gender variables, the proportion of female and male students is three-fold. On the other hand, it is similar to the gender ratio of the students at Uskudar University. Although there is not a big difference according to the total evaluation, there are some differences between men and women. It was seen that male participants increased their ability to express their emotions after education. On the other hand, the ability to manage own emotions significantly increase in women, unlike men. The unusual thing is that there is a significant decrease in the social intelligence characteristics of women after education. Although social intelligence represents a positive aspect of our relationships, it has been shown in many studies that social intelligence is related to aggression too (Kaukiainen et al., 1999; Kaukiainen, Björkqvist, Österman, & Lagerspetz, 1996). It has been noted that achieving goals such as being popular and manipulating people require a high level of social intelligence (Dyches & Mayeux, 2015). Need is a necessity of life. Knowledge of what is needed can be realized through self-awareness. It is the source of the basic needs and the satisfaction of it through one's own awareness. In the most basic need, one understands one's own feelings and needs. For this reason, every new awareness can cause one to turn to their own needs. Anger is a product of feelings and desires that are not even noticed. Managing their own emotions and increasing their skills may have caused the reduction of the anger and in the control of social manipulation tendencies (Björkqvist, Österman, & Kaukiainen, 2000) At the same time, more directed to their own emotions may have reduced their tendency to see the emotions of others. We can evaluate this change in the way that when we face with our own emotions, that we did not think existed before, we are not accustomed

to during our social relationships, and also it can lead to some social conflicts. In general, these kinds of changes have emerged in the short term with increased awareness in therapy, but the emotional fluctuations are mediated by the individual becoming a stronger and more durable identity. Particularly, some traumatic experiences lead to the awareness that may increase the resistance of the person (Armstrong, Galligan, & Critchley, 2011), if such events turn into an inner emotional awareness, they let to improve personal identity (Seaton & Beaumont, 2015).

5. Conclusion

In many of the other studies, the effects of positive psychology training have shown a significant improvement in the processes of personal well-being, happiness, and awareness (Shoshani & Steinmetz, 2014). However, in our work, we have observed that personal well-being and happiness have decreased significantly, especially in women. Turkey has a more alexithymic structure like in many eastern and middle east countries (Karagöl, 2017; Sayar, Kose, Grabe, & Topbas, 2005). Therefore, the effect of education we provide may have led to a different effect from the western countries. Particularly, students with less emotional awareness may have encountered new awareness, exposure of students to more emotion, and a negative impact on happiness and well-being. For this reason, the provision of positive psychology training, course content, consideration of the cultural appropriateness of subjects may also be evaluated in future studies, which may enable us to measure the effectiveness of the training much better. From another point of view, it is necessary to discuss the educational needs of the students, whether they are for the happiness of the person or their awareness. Tamir and his colleagues (Tamir, Schwartz, Oishi, & Kim, 2017) showed that happiness involves experiencing emotions that feel right, whether they feel good or not, in their work involving 2324 people from 8 different countries. It is one of the other suggestions of our studying that positive psychology course let students understand the nature of the problem first and then after let them searching the meaning their life and trying to understand the real solution for life journey is their problems as well. One of the most famous Sufistic poems from Yunus Emre was said that "I used to seek a way to solve for my nuisance, my nuisance had been my cure." Sometimes bad feelings are an opportunity of being the cure of our nuisance.

Acknowledgments

This work was supported, in part, by the Uskudar University.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

Acar, F. T. (2001). Duygusal zekâ yeteneklerinin göreve yönelik ve insana yönelik liderlik davranışları ile ilişkisi: banka şube müdürleri üzerine bir alan araştırması. Yayınlanmamış Doktora Tezi. İstanbul Üniversitesi, Sosyal Bilimler Enstitüsü, İstanbul

Afrisham, R., Sadegh-Nejadi, S., Soliemanifar, O., Abromand, M., Kooti, W., Najjar-Asl, S., & Khaneh-Keshi, A. (2015). Evaluating the salivary alpha-amylase level under psychological stress and its relationship with rumination and the five personality traits. Journal of Mazandaran University of Medical Sciences, 25(126), 22–33.

Aldao, A., Nolen-Hoeksema, S., & Schweizer, S. (2010). Emotion-regulation strategies across psychopathology: A meta-analytic review. Clinical Psychology Review, 30(2), 217–237. http://doi.org/10.1016/j.cpr.2009.11.004

American Psychological Association. (2007). APA guidelines for the psychology major. Washington, DC: Author. Retrieved from www.apa.org/ed/resources.html

Armstrong, A. R., Galligan, R. F., & Critchley, C. R. (2011). Emotional intelligence and psychological resilience to negative life events. Personality and Individual Differences, 51(3), 331–336. http://doi.org/10.1016/j.paid.2011.03.025

Bar-On, R. (1997a). The Emotional Quotient Inventory (EQ-i).Toronto, Canada: Multi-Health Systems, Inc.

Baumeister, R. F., Vohs, K. D., Aaker, J. L., & Garbinsky, E. N. (2013). Some key differences between a happy life and a meaningful life. The Journal of Positive Psychology, 8(6), 505–516. http://doi.org/10.1080/17439760.2013.830764

Berry, D. S., & Hansen, J. S. (1996). Positive Affect, Negative Affect, and Social Interaction. Journal of Personality and Social Psychology, 71(4), 796–809. http://doi.org/10.1037/0022-3514.71.4.796

Björkqvist, K., Österman, K., & Kaukiainen, A. (2000). Social intelligence - Empathy = aggression? Aggression and Violent Behavior, 5(2), 191–200. http://doi.org/10.1016/S1359-1789(98)00029-9

Bos, J., & Stokes, M. A. (2018). Cognitive empathy moderates the relationship between affective empathy and wellbeing in adolescents with autism spectrum disorder. European Journal of Developmental Psychology, 8(2), 1–14. http://doi.org/10.1080/17405629.2018.1444987

Caruso, D. R., Salovey, P., Brackett, M., & Mayer, J. D. (2015). The Ability Model of Emotional Intelligence. In Positive Psychology in Practice: Promoting Human Flourishing in Work, Health, Education, and Everyday Life: Second Edition (pp. 543–558). Wiley-Blackwell. http://doi.org/10.1002/9781118996874.ch32

Ciarrochi, J. V., Chan, A. Y. C., & Caputi, P. (2000). A critical evaluation of the emotional intelligence construct. Personality and Individual Differences, 28(3), 539–561. http://doi.org/10.1016/S0191-8869(99)00119-1

Clarke, M. J., Marks, A. D. G., & Lykins, A. D. (2016). Bridging the gap: the effect of gender normativity on differences in empathy and emotional intelligence. Journal of Gender Studies, 25(5), 522–539. http://doi.org/10.1080/09589236.2015.1049246

Compton, W., & Hoffman, E. (2012). Positive Psychology: The Science of Happiness and Flourishing. Cengage Learning.

Contreras, J. M., Kerns, K. A., Weimer, B. L., Gentzler, A. L., & Tomich, P. L. (2000). Emotion regulation as a mediator of associations between mother-child attachment and peer relationships in middle childhood. Journal of Family Psychology, 14(1), 111–124. http://doi.org/10.1037/0893-3200.14.1.111

Criswell, E. (2003). A challenge to humanistic psychology in the 21st century. Journal of Humanistic Psychology, 43(3), 42–52. http://doi.org/10.1177/0022167803043003004

Das, R. P., & Sahu, T. L. (2015). Relationship between emotional intelligence and gender difference: An empirical study. Prabandhan: Indian Journal of Management, 8(9), 15–23. http://doi.org/10.17010/pijom/2015/v8i9/77188

Day, A. L., & Carroll, S. A. (2004). Using an ability-based measure of emotional intelligence to predict individual performance, group performance, and group citizenship behaviours. Personality and Individual Differences, 36(6), 1443–1458. http://doi.org/10.1016/S0191-8869(03)00240-X

DeNeve, K. M., & Cooper, H. (1998). The Happy Personality: A Meta-Analysis of 137 Personality Traits and Subjective Well-Being. Psychological Bulletin, 124(2), 197–229. http://doi.org/10.1037/0033-2909.124.2.197

Diener, E., Suh, E. M., Lucas, R. E., & Smith, H. L. (1999). Subjective well-being: Three decades of progress. Psychological Bulletin, 125(2), 276–302. http://doi.org/10.1037/0033-2909.125.2.276

Dieter, J., Hoffmann, S., Mier, D., Reinhard, I., Beutel, M., Vollstädt-Klein, S., et al. (2017). The role of emotional inhibitory control in specific internet addiction – an fMRI study, 1–14. http://doi.org/10.1016/j.bbr.2017.01.046

Doğan, T. and Çetin B. (2009). Tromso Sosyal Zeka Ölçeği Türkçe Formunun Faktör Yapısı, Geçerlik ve Güvenirlik Çalışması. Kuram ve Uygulamada Eğitim Bilimleri, 9(2), 691-720

Doğan, T., and Sapmaz, F. (2012). "Oxford Mutluluk Ölçeği Türkçe Formunun Psikometrik Özelliklerinin Üniversite Öğrencilerinde İncelenmesi" Düşünen Adam: Psikiyatri ve Nörolojik Bilimler Dergisi, 25, 297-304.

Dulewicz, V., & Higgs, M. (2000). Emotional intelligence – A review and evaluation study. Journal of Managerial Psychology, 15(4), 341–372. http://doi.org/10.1108/02683940010330993

Dulewicz, V., Higgs, M., & Slaski, M. (2003). Measuring emotional intelligence: Content, construct and criterion-related validity. Journal of Managerial Psychology, 18(5), 405–420. http://doi.org/10.1108/02683940310484017

Dyches, K. D., & Mayeux, L. (2015). Popularity and Resource Control Goals as Predictors of Adolescent Indirect Aggression. Journal of Genetic Psychology, 176(4), 253–259. http://doi.org/10.1080/00221325.2015.1048661

Emmons, R. A., & McCullough, M. E. (2003). Counting Blessings Versus Burdens: An Experimental Investigation of Gratitude and Subjective Well-Being in Daily Life. Journal of Personality and Social Psychology, 84(2), 377–389. http://doi.org/10.1037//0022-3514.84.2.377

Fantini-Hauwel, C., Boudoukha, A. H., & Arciszewski, T. (2012). Adult attachment and emotional awareness impairment: a multimethod assessment. Socioaffective Neuroscience & Psychology, 2(1), 10744. http://doi.org/10.3402/snp.v2i0.10744

Fraley, R. C., & Shaver, P. R. (2000). Adult Romantic Attachment: Theoretical Developments, Emerging Controversies, and Unanswered Questions. Review of General Psychology, 4(2), 132–154. http://doi.org/10.1037/1089-2680.4.2.132

Fredrickson, B. L. (1998). What good are positive emotions? Review of General Psychology, 2(3), 300–319. http://doi.org/10.1037/1089-2680.2.3.300

Fredrickson, B. L., & Branigan, C. (2005). Positive emotions broaden the scope of attention and thought-action repertoires. Cognition & Emotion, 19(3), 313–332. http://doi.org/10.1080/02699930441000238

Garnefski, N., Legerstee, J., Kraaij, V., Van Den Kommer, T., & Teerds, J. (2002). Cognitive coping strategies and symptoms of depression and anxiety: A comparison between adolescents and adults. Journal of Adolescence, 25(6), 603–611. http://doi.org/10.1006/jado.2002.0507

Gentzler, A. L., Ramsey, M. A., Yi, C. Y., Palmer, C. A., & Morey, J. N. (2014). Young adolescents' emotional and regulatory responses to positive life events: Investigating temperament, attachment, and event characteristics. The Journal of Positive Psychology, 9(2), 108–121. http://doi.org/10.1080/17439760.2013.848374

Goodmon, L. B., Middleditch, A. M., Childs, B., & Pietrasiuk, S. E. (2016). Positive Psychology Course and Its Relationship to Well-Being, Depression, and Stress. Teaching of Psychology, 43(3), 232–237. http://doi.org/10.1177/0098628316649482

Grant, L. (2014). Hearts and Minds: Aspects of Empathy and Wellbeing in Social Work Students. Social Work Education, 33(3), 338–352. http://doi.org/10.1080/02615479.2013.805191

Hills, P., & Argyle, M. (2002). The Oxford Happiness Questionnaire: A compact scale for the measurement of psychological well-being. Personality and Individual Differences, 33(7), 1073–1082. http://doi.org/10.1016/S0191-8869(01)00213-6

International Wellbeing Group.(2006). Personal wellbeing index-adult (PWI-A): 4th Edition. Melbourne: Australian Centre on Quality of Life, Deakin University. Retrieved 10 September 2009 from: http://www.deakin.edu.au/research/acqol/ instruments/ wellbeing_ index.htm.

Karagöl, A. (2017). Level, prevalence and sociodemographic correlates of alexithymia in a physician population in Ankara. Anadolu Psikiyatri Dergisi, 18(3), 217–223. http://doi.org/10.5455/apd.243551

Kaukiainen, A., Björkqvist, K., Lagerspetz, K., Österman, K., Salmivalli, C., Rothberg, S., & Ahlbom, A. (1999). The relationships between social intelligence, empathy, and three types of aggression. Aggressive Behavior, 25(2), 81–89. http://doi.org/10.1002/(SICI)1098-2337(1999)25:2<81::AID-AB1>3.0.CO;2-M

Kaukiainen, A., Björkqvist, K., Österman, K., & Lagerspetz, K. M. J. (1996). Social intelligence and empathy as antecedents of different types of aggression (Vol. 794, pp. 364–366). Presented at the Annals of the New York Academy of Sciences, Wiley/Blackwell (10.1111). http://doi.org/10.1111/j.1749-6632.1996.tb32543.x

Keldalı G. (2015). Warwick-Edinburgh Mental İyi Oluş Ölçeği'nin Türkçe Formu: Geçerlik ve Güvenirlik Çalışması, The Journal of Happiness & Well-Being, 2015, 3(1): 103-115.

Kerns, K. A., Abraham, M. M., Schlegelmilch, A., & Morgan, T. A. (2007). Mother - Child attachment in later middle childhood: Assessment approaches and associations with mood and emotion regulation. Attachment & Human Development, 9(1), 33–53. http://doi.org/10.1080/14616730601151441

King, L. A., & Emmons, R. A. (1990). Conflict Over Emotional Expression: Psychological and Physical Correlates. Journal of Personality and Social Psychology, 58(5), 864–877.

Kobau, R., Seligman, M. E. P., Peterson, C., Diener, E., Zack, M. M., Chapman, D., & Thompson, W. (2011). Mental health promotion in public health: Perspectives and strategies from positive psychology. American Journal of Public Health, 101(8), e1–e9. http://doi.org/10.2105/AJPH.2010.300083

Kring, A. M., Smith, D. A., & Neale, J. M. (1994). Individual Differences in Dispositional Expressiveness: Development and Validation of the Emotional Expressivity Scale. Journal of Personality and Social Psychology, 66(5), 934–949. http://doi.org/10.1037/0022-3514.66.5.934

Kuzucu Y. , "Duyguları İfade Etme Ölçeği'nin Uyarlanması: Geçerlik Ve Güvenirlik Çalışmaları" Kastamonu Eğitim Dergisi, Cilt:19 No:3, 2011,779-792.

Laan, A. J., van Assen, M. A. L. M., & Vingerhoets, A. J. J. M. (2012). Individual differences in adult crying: The role of attachment styles. Social Behavior and Personality, 40(3), 453–472. http://doi.org/10.2224/sbp.2012.40.3.453

Larsen, J. T., & Green, J. D. (2013). Evidence for mixed feelings of happiness and sadness from brief moments in time. Cognition & Emotion, 27(8), 1469–1477. http://doi.org/10.1080/02699931.2013.790782

Liu, Y., Ding, Y., Lu, L., & Chen, X. (2017). Attention Bias of Avoidant Individuals to Attachment Emotion Pictures. Scientific Reports, 7, 41631. http://doi.org/10.1038/srep41631

Louis, M. C. (2011). Strengths interventions in higher education: The effect of identification versus development approaches on implicit self-theory. Journal of Positive Psychology, 6(3), 204–215. http://doi.org/10.1080/17439760.2011.570366

Lumley, M. A., Gustavson, B. J., Partridge, R. T., & Labouvie-Vief, G. (2005). Assessing alexithymia and related emotional ability constructs using multiple methods: Interrelationships among measures. Emotion (Washington, D.C.), 5(3), 329–342. http://doi.org/10.1037/1528-3542.5.3.329

Lyubomirsky, S., King, L., & Diener, E. (2005). The benefits of frequent positive affect: Does happiness lead to success? Psychological Bulletin, 131(6), 803–855. http://doi.org/10.1037/0033-2909.131.6.803

Magyar-Moe, J. L. (2011). Incorporating positive psychology content and applications into various psychology courses. Journal of Positive Psychology, 6(6), 451–456. http://doi.org/10.1080/17439760.2011.634821

Marilaf Caro, M., San-Martín, M., Delgado-Bolton, R., & Vivanco, L. (2017). Empathy, loneliness, burnout, and life satisfaction in Chilean nurses of palliative care and homecare services. Enfermeria Clinica, 27(6), 379–386. http://doi.org/10.1016/j.enfcli.2017.04.007

Maybury, K. K. (2013). The Influence of a Positive Psychology Course on Student Well-Being. Teaching of Psychology, 40(1), 62–65. http://doi.org/10.1177/0098628312465868

Mayer, J. D., DiPaolo, M., & Salovey, P. (1990). Perceiving Affective Content in Ambiguous Visual Stimuli: A Component of Emotional Intelligence. Journal of Personality Assessment, 54(3-4), 772–781. http://doi.org/10.1080/00223891.1990.9674037

McGillivray, J. A., Lau, A. L. D., Cummins, R. A., & Davey, G. (2009). The Utility of the Personal Wellbeing Index Intellectual Disability Scale in an Australian Sample. Journal of Applied Research in Intellectual Disabilities, 22(3), 276–286. http://doi.org/10.1111/j.1468-3148.2008.00460.x

Meral, B. F. (2014). Kişisel iyi oluş indeksi-yetişkin Türkçe formunun psikometrik özellikleri. The Journal of Happiness and Well-Being, 2(2), 119-131.

Mikulincer, M. (1998). Adult Attachment Style and Affect Regulation: Strategic Variations in Self-Appraisals. Journal of Personality and Social Psychology, 75(2), 420–435.

Mikulincer, M., & Shaver, P. R. (2007). Attachment, group-related processes, and psychotherapy. International Journal of Group Psychotherapy, 57(2), 233–245. http://doi.org/10.1521/ijgp.2007.57.2.233

Mikulincer, M., Shaver, P. R., & Pereg, D. (2003). Attachment theory and affect regulation: The dynamics, development, and cognitive consequences of attachment-related strategies. Motivation and Emotion, 27(2), 77–102. http://doi.org/10.1023/A:1024515519160

Millgram, Y., Joormann, J., Huppert, J. D., & Tamir, M. (2015). Sad as a Matter of Choice? Emotion-Regulation Goals in Depression. Psychological

JNBS 2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org

Science, 26(8), 1216–1228. http://doi.org/10.1177/0956797615583295

Mongrain, M., & Anselmo-Matthews, T. (2012). Do Positive Psychology Exercises Work? A Replication of Seligman et al. Journal of Clinical Psychology, 68(4), 382–389. http://doi.org/10.1002/jclp.21839

Ng, W. (2015). Boosting Well-Being with Positive Psychology Interventions: Moderating Role of Personality and Other Factors. Journal of Contemporary Psychotherapy, 45(2), 79–87. http://doi.org/10.1007/s10879-014-9291-y

Nichols, C. P., & Molix, L. (2013). Positive psychology as social change. The Journal of Positive Psychology, 8(2), 165–167. http://doi.org/10.1080/17439760.2012.747218

O'Driscoll, C., Laing, J., & Mason, O. (2014). Cognitive emotion regulation strategies, alexith, mia and dissociation in schizophrenia, a re, iew and meta-analysis. Clinical Psychology Review, 34(6), 482–495. http://doi.org/10.1016/j.cpr.2014.07.002

Parker, J. D. A., Hogan, M. J., Eastabrook, J. M., Oke, A., & Wood, L. M. (2006). Emotional intelligence and student retention: Predicting the successful transition from high school to university. Personality and Individual Differences, 41(7), 1329–1336. http://doi.org/10.1016/j.paid.2006.04.022

Salovey, P., & Mayer, J. d. (1990). Emotional intelligence. Imagination, Cognition, and Personality, 9, 185-211.

Sayar, K., Kose, S., Grabe, H. J., & Topbas, M. (2005). Alexithymia and dissociative tendencies in an adolescent sample from Eastern Turkey. Psychiatry and Clinical Neurosciences, 59(2), 127–134. http://doi.org/10.1111/j.1440-1819.2005.01346.x

Seaton, C. L., & Beaumont, S. L. (2015). Pursuing the good life: A short-term follow-up study of the role of positive/negative emotions and ego-resilience in personal goal striving and eudaimonic well-being. Motivation and Emotion, 39(5), 813–826. http://doi.org/10.1007/s11031-015-9493-y

Selcuk, E., Gunaydin, G., Sumer, N., & Uysal A. (2005). A new measure for adult attachment styles: The psychometric evaluation of Experiences in Close Relationships - Revised (ECR-R) on a Turkish sample. Turkish Psychological Articles, 8, 1-11.

Seligman, M. E. P., & Csikszentmihalyi, M. (2014). Positive psychology: An introduction. In Flow and the Foundations of Positive Psychology: The Collected Works of Mihaly Csikszentmihalyi (Vol. 9789401790888, pp. 279–298). Dordrecht: Springer Netherlands. http://doi.org/10.1007/978-94-017-9088-8_18

Seligman, M. E. P., Rashid, T., & Parks, A. C. (2006). Positive psychotherapy. American Psychologist, 61(8), 774–788. http://doi.org/10.1037/0003-066X.61.8.774

Seligman, M. E. P., Steen, T. A., Park, N., & Peterson, C. (2005). Positive psychology progress: empirical validation of interventions. The American Psychologist, 60(5), 410–421. http://doi.org/10.1037/0003-066X.60.5.410

Sharpe, E., & Wallis, D. J. (2014). Attitudes towards emotional expression, emotion regulation and eating psychopathology. Appetite, 83, 354. http://doi.org/10.1016/j.appet.2014.06.072

Shoshani, A., & Steinmetz, S. (2014). Positive Psychology at School: A School-Based Intervention to Promote Adolescents' Mental Health and Well-Being. Journal of Happiness Studies, 15(6), 1289–1311. http://doi.org/10.1007/s10902-013-9476-1

Silvera, D. H., Martinussen, M., & Dahl, T. I. (2001). The Tromsø Social Intelligence Scale, a self-report measure of social intelligence. Scandinavian Journal of Psychology, 42(4), 313–319.

Sloan, D. M., & Marx, B. P. (2004). A Closer Examination of the Structured Written Disclosure Procedure. Journal of Consulting and Clinical Psychology, 72(2), 165–175. http://doi.org/10.1037/0022-006X.72.2.165

Tamir, M., Schwartz, S. H., Oishi, S., & Kim, M. Y. (2017). The secret to happiness: Feeling good or feeling right? Journal of Experimental Psychology: General, 146(10), 1448–1459. http://doi.org/10.1037/xge0000303

Tennant, R., Hiller, L., Fishwick, R., Platt, S., Joseph, S., Weich, S., et al. (2007). The Warwick-Edinburgh Mental Well-being Scale (WEMWBS): development and UK validation. Health and Quality of Life Outcomes, 5, 63. http://doi.org/10.1186/1477-7525-5-63

Vazquez, C. (2017). What does Positivity Add to Psychopathology? An Introduction to the Special Issue on "Positive Emotions and Cognitions in Clinical Psychology." Cognitive Therapy and Research, 41(3), 325–334. http://doi.org/10.1007/s10608-017-9847-8

Wai, M., & Tiliopoulos, N. (2012). The affective and cognitive empathic nature of the dark triad of personality. Personality and Individual Differences, 52(7), 794–799. http://doi.org/10.1016/j.paid.2012.01.008

Wong, P. T. P. (2011). Reclaiming positive psychology: A meaning-centered approach to sustainable growth and radical empiricism. Journal of Humanistic Psychology, 51(4), 408–412. http://doi.org/10.1177/0022167811408729

YetIm, Ü. (1993). Life satisfaction: A study based on the organization of personal projects. Social Indicators Research, 29(3), 277–289. http://doi.org/10.1007/BF01079516

Zeman, J., Cassano, M., Perry-Parrish, C., & Stegall, S. (2006). Emotion regulation in children and adolescents. Journal of Developmental and Behavioral Pediatrics, 27(2), 155–168. http://doi.org/10.1097/00004703-200604000-00014

ORIGINAL ARTICLE-ARAŞTIRMA

Year (Yıl) : 2018
Volume (Cilt) : 5
Issue Number (Sayı) : 3
Doi : 10.5455/JNBS.1536676866

Received/Geliş 23.04.2018
Accepted/Kabul 28.05.2018
JNBS, 2018, 5(3):165-171

INVESTIGATION OF SERUM BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) LEVELS IN PATIENTS DIAGNOSED WITH SCHIZOPHRENIA WITHOUT ANTIPSYCHOTIC TREATMENT HISTORY

ANTİPSİKOTİK TEDAVİ ÖYKÜSÜ OLMAYAN ŞIZOFRENİ TANILI HASTALARDA SERUMDAKİ BEYİN KAYNAKLI NÖROTROFİK FAKTÖR (BDNF) DÜZEYLERİNİN ARAŞTIRILMASI

Oguzhan Bekir Egilmez[1], Mehmet Hamdi Orum[1*], Elmas Beyazyuz[2], Makbule Çiğdem Aydemir[3]

Abstract

BDNF is a member of the neurotrophic family that promotes the development, regeneration, sustaining and maintenance of neuron function in the central nervous system. BDNF modulates neurotransmitter synthesis, metabolism and neuronal activity and is also involved in the development of dopaminergic-related systems, and the mesolimbic dopamine systems. In this study we aimed to investigate the possible differences of serum brain-derived neurotrophic factor (BDNF) levels between the drug-naive patients with schizophrenia and healthy controls. Serum BDNF levels were determined in the serum of 35 drug-naive patients diagnosed as schizophrenia according to SCID-I and DSM-IV-TR criteria and 35 healthy controls subjects matched for gender and age. The schizophrenia symptomatology was assessed by the positive and negative syndrome scale (PANSS). The results showed that BDNF levels were significantly lower in drug-naive patients with schizophrenia than in healthy control subjects (p=0.000). There was a significant difference in BDNF levels between disorganized and paranoid (p = 0.000), disorganized and undifferentiated schizophrenia (p = 0.000) subtypes. There was no significant difference in BDNF levels between the undifferentiated and paranoid schizophrenia subtypes (p = 0.081). The relationship between PANSS scores and subscale scores and serum BDNF levels was not found to be significant (p>0.05). The relationship between general assessment of functionality scores and serum BDNF levels was examined and there was a positive correlation between them (p = 0.07, r = 0.445). Our findings showed decreased BDNF serum levels in a sample of drug-naive patients with schizophrenia. Lower serum levels of BDNF in a sample of drug-naive patients with schizophrenia are consistent with the hypothesis that a deficit in this neurotrophic factor may contribute to the structural and functional alterations of brain underlying in the initial phase of schizophrenia suggesting that neurodevelopmental disturbances may be involved in the pathogenesis of schizophrenia.

Keywords: brain-derived neurotrophic factor; BDNF; schizophrenia

[1]Adiyaman University Faculty of Medicine, Department of Psychiatry, Adiyaman, Turkey.
[2]Tekirdağ Namik Kemal University Faculty of Medicine, Department of Psychiatry, Tekirdağ, Turkey.
[3]Ankara University Faculty of Medicine, Department of Psychiatry, Ankara, Turkey.
[*]Corresponding Author: Adiyaman University Faculty of Medicine, Department of Psychiatry, Adiyaman, Turkey. E-mail: mhorum@hotmail.com
Phone: 04162161015

JNBS 2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org

Özet

Beyin kaynaklı nörotrofik faktör (BDNF) santral sinir sisteminde en geniş dağılımı gösteren nörotrofik faktördür. Santral sinir sistemindeki nöronların gelişimine, rejenerasyonuna ve korunmasına yardımcı olur. Nörotransmitterlerin sentezini, metabolizmasını ve nöronal aktivitesini düzenler; ayrıca dopaminle ilişkili sistemlerin ve mezolimbik dopamin sisteminin gelişimiyle ilişkilidir. Bu çalışmada daha önce tedavi almamış şizofreni hastaları ile sağlam kontrol grubunun serum BDNF düzeyleri arasındaki olası farklılıkların araştırılması amaçlanmıştır. SCID-I ve DSM-IV-TR kriterlerine göre şizofreni tanısı alan daha önce antipsikotik tedavi almamış 35 şizofreni tanılı hasta ile yaş ve cinsiyet olarak eşleştirilmiş 35 kişiden oluşan sağlıklı kontrol grubunun serum BDNF düzeyleri karşılaştırıldı. Şizofreni semptomatolojisi, pozitif ve negatif sendrom ölçeği (PANSS) ile değerlendirildi. Sonuçlar, BDNF düzeylerinin şizofreni hastalarında sağlıklı kontrol deneklerine göre anlamlı olarak daha düşük olduğunu gösterdi (p = 0.000). Dezorganize ve paranoid (p = 0.000), dezorganize ve farklılaşmamış şizofreni (p = 0.000) alt tipleri arasında BDNF düzeylerinde anlamlı bir farklılık vardı. Farklılaşmamış ve paranoid şizofreni alt tipleri arasında BDNF düzeylerinde anlamlı fark yoktu (p = 0.081). PANSS skorları ile alt ölçek puanları ve serum BDNF düzeyleri arasındaki ilişki anlamlı bulunmadı (p> 0.05). Fonksiyonel skorların genel değerlendirmesi ile serum BDNF düzeyleri arasındaki ilişki incelendi ve aralarında pozitif korelasyon bulundu (p = 0.07, r = 0.445). Bulgularımız antipsikotik tedavi almamış şizofreni hastalarının düşük BDNF seviyelerine sahip olduklarını göstermiştir. Antipsikotik ilaç öyküsü olmayan şizofreni hastalarında saptanan düşük BDNF serum düzeyleri, bu nörotrofik faktörle ilgili bir sorunun, şizofreninin başlangıç evresinde yatan beynin yapısal ve fonksiyonel değişikliklerle ilişkisi olabileceği hipotezi ile tutarlıdır.

Anahtar Kelimeler: *beyin kaynaklı nörotrofik faktör; BDNF; şizofreni*

1. Introduction

Schizophrenia; is a mental disorder that manifests symptoms and signs in almost all areas of the mental state, usually beginning in youth, leading to a significant loss of functioning and yet having no complete understanding of etiology. Although the etiology of schizophrenia has been investigated for many years, a proven hypothesis for the cause of the disease has not yet been found. The neurodevelopmental hypothesis is one of these hypotheses (Van & Kapur, 2009; Khan et al., 2013).

An abnormality in the DNA of a patient with schizophrenia can lead to the establishment of false synaptic connections during the prenatal and early childhood brain development and linkage phases. This is due to abnormalities in fetal brain development in the early stages of neuronal selection and migration (Rapaport et al., 2012). Migration begins in the weeks following fertilization and is largely completed by birth. On the other hand, various processes that affect brain structures and synaptogenesis continue throughout life. Potential changes in synaptogenesis may form the basis of learning, emotional maturity, cognitive and motor development throughout life. Periodically and under certain conditions, the neurons deactivate some connections, with apoptosis (programmed cell death) and synaptic pruning (trimming of extended dendrites and thorns) to maintain balance (Woo, 2014; Boksa, 2012). On the other hand, brain-derived neurotrophic factors play a crucial role in the survival of neurons and their ability to function. Neurotrophic factors play important roles in apoptosis programming and execution in the central nervous system. Deficiency due to endogenous or exogenous causes of neurotrophic factors specific to certain neurons is an effect that triggers a chain of biological events that will result in the death of that neuron or group of neurons. Neurons need neurotrophic factors that they secrete for living, differentiating and neuroplasticity (McAllister et al., 1995; Schuman, 1999).

Brain-derived neurotrophic factor (BDNF) is an important member of the neurotrophin family, found in the brain and peripheral tissues. BDNF is a 28-kDa basic dimeric protein consisting of 14-kDa subunits, structurally similar to nerve growth factor (NGF), linked by non-covalent bonds (Rosenthal et al., 1991). BDNF mRNA and proteins have been detected in the hippocampus, amygdala, thalamus, projection fields of the olfactory system, inner and outer pyramidal layers of the neocortex, septum, cerebellum and superior colliculus (Connor & Dragunov, 1998). Although BDNF is present in high concentrations in the nervous system, it is also present in plasma and serum (Radka et al., 1996). Platelets, neurons, and vascular endothelial cells are potential sources of BDNF. The ability of BDNF to cross the blood brain barrier has been shown and based on this it has been reported that serum BDNF levels may reflect the level of BDNF in the brain. The presence of BDNF levels in the human serum suggests that this neurotrophin plays a role in many events, including neuronal regeneration, proliferation of vascular smooth muscle in platelet activation, inflammation and cell proliferation (Shimizu et al., 2003, Pan et al., 1998). The basis of neurodevelopmental theories in schizophrenia etiology is based on neuroimaging studies and neuroimaging studies on young, first episode, non-drug psychotic patients (Bloom, 1993). There are numerous sources of evidence that BDNF levels are altered in schizophrenia brains (Buckley et al., 2007a). Post-mortem studies have shown that BDNF protein levels (measured by ELISA) increase in the cortical areas of patients with schizophrenia and decrease in the hippocampus (Durany et al., 2001). Immunohistochemical studies have shown that schizophrenia increases the expression of BDNF and TrkB-positive neurons in the hippocampus (Iritani et al., 2003), while another study reported increased hippocampal BDNF levels and decreased TrkB levels. Both BDNF and TrkB mRNA levels were found to be significantly lower in prefrontal cortexes (Hashimoto et al., 2005). Although contradictions have been found in these post-mortem studies, all of them point out that schizophrenia BDNF levels have changed (Pillai, 2008). Several studies have shown that BDNF levels in patients with schizophrenia change. There was a decrease in serum BDNF levels in schizophrenia (Tan et al., 2005). In a study by Buckley and colleagues (2007b), the first episode psychosis patients were compared with a normal

healthy control group, and plasma BDNF levels were significantly lower in psychotic patients. The low level of BDNF at the onset of psychosis suggests that BDNF contributes to the pathogenesis of schizophrenia and may be a neurobiological marker to assist in intervention for possible early treatment (Buckley et al., 2007b).

In various studies, the effects of antipsychotic drugs on BDNF levels were assessed using serum or plasma samples from schizophrenia patients and control groups. Serum BDNF levels of schizophrenia patients using clozapine were higher than those using risperidone, but no statistically significant difference was found when compared with patients using typical antipsychotics (Tan et al., 2005). Another study (Hori et al., 2007) reported that eight weeks of olanzapine use did not affect serum BDNF levels prior to olanzapine use. In a study (Rizos et al., 2010), baseline BDNF levels of patients with schizophrenia who did not receive antipsychotic treatment and BDNF levels after six weeks of antipsychotic treatment were compared; it was found that olanzapine-treated patients had a greater increase in serum BDNF levels compared to patients receiving risperidone, haloperidol, and amisulpride. In another study (Xiu et al., 2009), serum BDNF levels of schizophrenia patients using risperidone, clozapine and typical antipsychotics were compared; serum BDNF levels were higher in patients using clozapine and typical antipsychotics compared to those using risperidone. Man et al. (Man et al., 2018) demonstrated that serum BDNF levels in first-episode drug-naïve patients with schizophrenia is significantly low. Heitz et al. (2018) stated that the lower peripheral BDNF levels in at-risk mental state for psychosis compared to first-episode psychosis and chronic schizophrenia might point towards an important drop of this neurotrophin prior to the onset of psychosis. The number of studies involving non-drug users or first-episode schizophrenia patients is increasing. It is thought that it is important to make new studies in terms of providing contribution to the literature and providing data to systematic reviews. In this study, we aimed to compare the BDNF levels of healthy control group with those who did not use any medication for psychotic symptoms before.

2. Material and Methods

2.1. Participants

This is a prospective and analytical case-control study. Between March 2009 and September 2009, patients who were admitted to the Ankara Numune Training and Research Hospital psychiatry clinic (ANTRH) for inpatient or outpatient treatment were taken. According to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR) criteria, diagnosis of schizophrenia was made. Patients were selected from those who did not use drugs before. A total of 35 cases were included in the study. Patients and their relatives accepted to study were informed and approved. Other inclusion criteria were age between 18-55, no physical or organic disease, no menopausal or post-menopausal symptoms, symptoms continued for 6 months or longer. Exclusion criteria were use of other medications (antidepressant, mood stabilizer, thyroid hormone, corticosteroid) for any reason, patients with mental retardation, another Axis-I diagnosis, and substance use. The control group consisted of volunteers age and gender matched to the patients, physically and mentally healthy, and volunteers who did not have schizophrenia or psychotic disorder trait in the first degree relatives.

2.2. Data Collection and Laboratory Analysis

2.2.1. Sociodemographic Data Form

It is a semi-structured form used to identify the sociodemographic characteristics of the cases participating in the study. After the psychiatric interview, the sociodemographic information form was filled. In this form, questions such as age, gender, marital status, educational status, occupation, income level, duration of illness, family history of illness, drug or drug use, smoking are included.

2.2.2. Structured Clinical Interview for DSM-IV Axis-I Disorder (SCID-I)

It is a structured clinical interview scale developed by First et al. (1996) for the establishment of DSM-IV Axis-I diagnoses. The structured interview has been developed to apply the diagnostic evaluation in a standardized manner, to improve the reliability and to systematize it. The validity and reliability study of SCID-I for Turkey was made by Ozkurkcugil et al. (1999).

2.2.3. Positive and Negative Symptom Scale (PANSS)

This scale was developed by Kay et al. (1987) to measure the level, distribution, and severity of positive and negative symptoms of schizophrenia in the subject. The validity and reliability study of the Turkish version of this test was performed by Kostakoglu et al. (1999). The interviewer evaluates the patient. Totally 3 subscales and 30 items. These subscales are positive symptoms, negative symptoms and general psychopathology. The filling of the scale is based on interviews with the patient, observations during interviews, and information from people around the patient (relatives, treatment team, etc.). The rating of each item ranges from 0-7. The subscale total scores are obtained by the sum of subscale items. The total score of the scale is obtained by summing the subscale total scores. The total score ranges from 0-210. The cut-off score was not calculated in the validity and reliability study for the Turkish form of the scale. For this reason, it is used commonly in comparative studies.

2.2.4. Measurement of BDNF Levels

BDNF levels were determined by micro-ELISA method based on sandwich enzyme immunoassay. Quantikine Human BDNF kit was used in the study. Test kit was run in accordance with the principle of kit.

2.2.5. Implementation of Method

All patients were evaluated by the same physician

(OBE). Physical examination of the cases that met the criteria for taking the study was done. An information form containing sociodemographic characteristics has been completed. The PANSS scale was used to assess the clinical status of the cases and the General Assessment of Functionality (GAF) as outlined in Axis-V was performed according to the DSM-IV diagnostic system to assess patients' functionality. Venous blood samples were obtained from antecubital vein of both patient and control group between 8 and 9 a.m. after at least 8 h of starving.

2.3. Statistical Analysis

SPSS for Windows statistical package version 15.0 was used for all statistical analyses. The numerical data were expressed as means and standard deviations, and the categorical data were expressed as frequencies and percentages. The Mann-Whitney test was used to compare the two groups. The Kruskal-Wallis test was used to compare the values of more than one group; the differences between the groups were tested in duplicate using the Tukey's multiple comparison test for significant groups according to the results of this analysis. In addition, Spearman correlation test was used to determine the relationship between variables. The level of significance was taken as 0.05 and the value of "ρ" was compared with the level of significance as calculated in SPSS.

3. Results

Both the patient and control group consisted of 19 (54.3%) women and 16 (45.7%) men. The mean age of the patient group was 37.03 ± 12.70 and the mean age of the control group was 38.65 ± 12.50 (p = 0.540). Other sociodemographic data of the patient and control group are shown in Table 1.

Tablo 1. Sociodemographic Variables of the Patient and Control Group

		Patient N (%) or Mean ± SD	Control N (%) or Mean ±
Gender	Male	16 (45.7%)	16 (45.7%)
	Female	19 (54.3%)	19 (54.3%)
Age (years)		37.03 ± 12.70	38.65 ± 12.52
Marital Status	Married	14 (40.0%)	27 (77.2%)
	Single	17 (48.6%)	4 (11.4%)
	Divorced	4 (11.4%)	4 (11.4%)
Education (years)		9.57 ± 4.80	9.68 ± 4.51
Income Rate	Low (0-1000)	14 (40.0%)	8 (22.8%)
	Moderate (1000-2000)	5 (14.3%)	10 (28.6%)
	Medium-High (2000-3500)	6 (17.1%)	10 (28.6%)
	High (3500 and above)	10 (28.6%)	7 (20.0%)
Number of Siblings		4.23 ± 1.81	3,12 ± 1.25
Psychiatric	First-Degree Relative	11 (31.4%)	0 (0.0%)
History of Family	Distant Relative	9 (25.71%)	0 (0.0%)
Smoking Use		14 (40.0%)	7 (20.0%)

The time from the onset of illness symptoms to the time of admission to the hospital for treatment was questioned. The results are shown in Table 2. The vast majority applied after 5 years (45.7%).

Tablo 2. Time to First Application From the Onset of Disorder-Symptoms

Time-Interval (month)	N	%
6-12	3	8.6
13-24	8	22.9
25-36	4	11.4
37-48	3	8.6
49-60	1	2.9
61 and above	16	45.7
Total	35	100.0

SCID-I was applied to 35 patients who were studied and diagnosed as schizophrenia according to DSM-IV-TR. The schizophrenia subtypes of the cases were identified by SCID-I. According to these results, 17 patients were diagnosed as paranoid schizophrenia, 10 patients were undifferentiated schizophrenia, and 8 patients were diagnosed as disorganized schizophrenia. There were no cases with catatonic and residual schizophrenia subgroups meeting the diagnostic criteria (Table 3).

Tablo 3. Case Distribution According to Schizophrenia Subtypes

Subtype	N (%)	BDNF (ng/ml) ± SD
Paranoid	17 (48.6)	22.44 ± 8.91
Undifferentiated	8 (22.8)	21.18 ± 7.48
Disorganized	10 (28.6)	13.32 ± 5.73

When the mean serum BDNF levels of the patient group and the control group were compared, it was found that there was a significant difference between the two groups (p = 0.000). As a result, mean serum BDNF levels in the patient group were lower than in the control group. In the patient group, there was no significant difference in serum BDNF levels between the sexes (p = 0.660) (Table 4).

Tablo 4. BDNF Levels (ng/ml) of Patient and Control Group

	BDNF Level (ng/ml)		SD	p value	
Patient	17.55 ± 9.48	20.00	8.53	0.660	0.000*
	Male (Mean ± SD)	Total Mean			
	22.90 ± 6.38				
	Female (Mean ± SD)				
Control	43.37	14.67			
Total	31.68	16.74			

**p<0.005*

Notes: *BDNF: Brain-Derived Neurotrophic Factor; SD: Standard Deviation*

Serum BDNF levels of schizophrenia subtypes were calculated. There was a significant difference between mean serum prolactin levels of paranoid, undifferentiated and disorganized schizophrenia subtypes (p = 0.046). There was a significant difference in BDNF levels between disorganized and paranoid (p = 0.000), disorganized and undifferentiated schizophrenia (p = 0.000) subtypes. There was no significant difference in BDNF levels between

the undifferentiated and paranoid schizophrenia subtypes (p = 0.081) (Table 3).

In our study, all patients with schizophrenia were administered PANSS and mean PANSS scores and PANSS subscale scores were calculated. The relationship between PANSS scores and subscale scores and serum BDNF levels was not found to be significant (p = 0.990 for PANSS negative subscale scores, p = 0.546 for PANSS positive subscale scores, p = 0.116 for PANSS general psychopathology sub scores, p = 0.113 for PANSS total scores). The relationship between GAF scores and serum BDNF levels was examined and there was a positive correlation between them (p = 0.07, r = 0.445).

4. Discussion

Neurotrophins are the main proteins responsible for the development, differentiation and migration of cells in the central nervous system during organogenesis and embryogenesis. In adult life these proteins are responsible for regeneration of neurons and regulation of synaptic activity. Thus, neural plasticity in the brain is maintained (Reis et al., 2008). BDNF is the most widely distributed neurotrophic factor in the central nervous system. It helps the development, regeneration and protection of neurons in the central nervous system. It regulates the synthesis, metabolism and neuronal activity of neurotransmitters; as well as the development of dopamine-related systems and the mesolimbic dopamine system (Rizos et al., 2008).

In our study, we compared the serum BDNF levels of schizophrenia patients without antipsychotic use history with the serum BDNF levels of the healthy control group from the neurodevelopmental hypothesis of schizophrenia. As a result of comparison of schizophrenia cases and control group serum BDNF levels, the mean serum BDNF level of schizophrenia group was found to be lower than control group. Findings obtained from our study are consistent with the literature. In the study of Rizos et al. (2008), serum BDNF levels were compared in 14 patients with schizophrenia and 15 healthy controls without antipsychotic treatment. According to the results of this study, the serum BDNF level of the schizophrenia group was statistically significantly lower than the control group. In a study conducted by Chen et al. (2009) serum BDNF levels were compared in 88 patients with schizophrenia who did not receive antipsychotic treatment and 90 control group, and the relationship between schizophrenia subtypes and BDNF was investigated. According to the results of this study, the serum BDNF levels of schizophrenia patients were significantly lower than the control group. In the study of Jindal et al. (2010), Serum BDNF levels of patients diagnosed with schizophrenia were found to be significantly lower than the serum BDNF levels of healthy control group and psychotic patients not diagnosed with schizophrenia. In a study conducted by Pirildar et al. (2004) in our country, the serum BDNF levels of schizophrenia patients were found to be significantly lower than the healthy control group. In recent studies, Man et al. (2018) demonstrated that serum BDNF levels in first-episode drug-naïve patients with schizophrenia is significantly low. In another recent study, Heitz et al. (2018) stated that the lower peripheral BDNF levels in at-risk mental state for psychosis compared to first-episode psychosis and chronic schizophrenia might point towards an important drop of this neurotrophin prior to the onset of psychosis.

There are also studies in the literature comparing the serum BDNF levels of schizophrenia patients receiving antipsychotic treatment with healthy control group. Xiu et al. (2009) found that the serum BDNF levels of schizophrenia patients receiving antipsychotic treatment were significantly lower than the control group. Grillo et al. (2007) compared the serum BDNF levels of schizophrenia patients using clozapine or typical antipsychotic with healthy controls. As a result, they stated that serum BDNF levels of schizophrenia patients in both groups were significantly lower than the control group. There are also studies that find results in the opposite direction. Reis and colleagues (2008) compared serum BDNF levels of schizophrenia patients using antipsychotic with BDNF levels of healthy control group. BDNF levels of schizophrenia patients were significantly higher than the control group. Gama et al. (2007) compared the serum BDNF levels of patients with schizophrenia receiving antipsychotic treatment with healthy control group and euthymic bipolar disorder patients. Serum BDNF levels of schizophrenia patients were found to be significantly higher in both control group and bipolar disorder patients. Patients taking antipsychotics were taken in these studies. In our study, patients who had not used antipsychotic before were taken. These last two studies were also done in Brazil. Genetic differences and the effect of drug use may be the main reason for the differences in the findings of studies.

Chen et al. (2009) found that serum BDNF levels in paranoid schizophrenia patients were significantly higher than other schizophrenia subtypes. In our study, serum BDNF levels of paranoid schizophrenia patients were significantly higher than disorganized schizophrenic patients. Although serum BDNF levels of paranoid schizophrenia patients were higher than those of undifferentiated schizophrenia patients, the difference was not statistically significant. The reason for this may be the inadequate number of patients in our study. Huang and Lee (2006) found that serum BDNF levels of catatonic schizophrenia patients were significantly lower than those of residual and paranoid schizophrenia patients. These results suggest that the subtypes of schizophrenia may be source from different biological bases. However, there is a need for more research to be able to put this out more precisely.

Studies in which the relationship between serum BDNF levels and PANSS scores were investigated in the literature revealed different results. Chen et al. (2009) found a positive correlation between PANSS positive subscale scores and BDNF, but not between PANSS negative subscale scores and BDNF. Rizos et al. (2008) found a negative correlation between both positive and negative subscale scores and serum BDNF levels. Reis et al. (2008) found no positive correlation between serum BDNF level and PANSS positive subscale scores, but found a positive correlation between PANSS negative subscale scores and BDNF. Huang and Lee (2006) found

JNBS 2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org

a significant relationship between serum BDNF and PANSS subscale scores consistent with our results. The reasons for these differences that arise in studies are not known precisely. However, these differences may be due to differences in the clinical status of the patients, the duration of the disease, or the frequency of alleles due to BDNF gene polymorphism (Chen et al., 2009). GAF scores of schizophrenia patients were compared with serum BDNF levels and positive correlations were found between them. When serum BDNF levels of schizophrenia patients were lowered, GAF scores were also found to decrease. A positive correlation between GAF scores and BDNF may reflect a relationship between BDNF and disease severity.

The most important limitation of our study is that our sample size is low. We also do not know how long the stress level affects the BDNF measurement. It has been shown that different stress sources may reduce BDNF levels during studies. The stress they experience due to the symptoms of schizophrenia patients may be affecting BDNF levels (Smith et al., 1995). In conclusion, our findings show that schizophrenia patients without antipsychotic treatment have low BDNF levels. This may be a reflection of the impaired neurodevelopmental process in schizophrenia patients. Enlightening the role of BDNF in schizophrenia can help to develop new therapeutic strategies in the treatment of schizophrenia. In order to better understand the role of BDNF in schizophrenia, we need to conduct research on larger groups of patients.

Competing interests

The authors declare that they have no competing interest.

Financial Disclosure

The financial support for this study was provided by the investigators themselves.

Acknowledgements

This study is the dissertation thesis in medicine of Oguzhan Bekir Egilmez dated 2017 from the authors. The thesis study was approved by the Ankara Numune Training and Research Hospital Psychiatry Clinic under the name (in Turkish) "Daha önce hiç antipsikotik tedavi kullanmamış şizofreni hastalarında serum BDNF düzeylerinin araştırılması: Karşılaştırmalı bir çalışma". Associate Prof. Dr. Makbule Cigdem Aydemir was supervisor of the thesis.

References

Bloom, F. E. (1993). Advancing a neurodevelopmental origin for schizophrenia. Archives of general psychiatry, 50(3), 224-227.

Boksa, P. (2012). Abnormal synaptic pruning in schizophrenia: Urban myth or reality?. Journal of psychiatry & neuroscience: JPN, 37(2), 75-77.

Buckley, P. F., Mahadik, S., Pillai, A., & Terry Jr, A. (2007). Neurotrophins and schizophrenia. Schizophrenia research, 94(1-3), 1-11.

Buckley, P. F., Pillai, A., Evans, D., Stirewalt, E., & Mahadik, S. (2007). Brain derived neurotropic factor in first-episode psychosis. Schizophrenia research, 91(1-3), 1-5.

Wang, J., Wang, B., Yang, S. C., Zhang, C. X., Zheng, Y. L., Li, Y. L., ... & Zhang, X. Y. (2009). Decreased levels of serum brain-derived neurotrophic factor in drug-naïve first-episode schizophrenia: relationship to clinical phenotypes. Psychopharmacology, 207(3), 375-380.

Connor, B., & Dragunow, M. (1998). The role of neuronal growth factors in neurodegenerative disorders of the human brain. Brain Research Reviews, 27(1), 1-39.

Durany, N., Michel, T., Zöchling, R., Boissl, K. W., Cruz-Sánchez, F. F., Riederer, P., & Thome, J. (2001). Brain-derived neurotrophic factor and neurotrophin 3 in schizophrenic psychoses. Schizophrenia research, 52(1-2), 79-86.

First, M. B., Gibbon, M., Spitzer, R. L., & Williams, J. B. (1996). User's guide for the structured clinical interview for DSM-IV axis I Disorders—Research version. New York: Biometrics Research Department, New York State Psychiatric Institute.

Gama, C. S., Andreazza, A. C., Kunz, M., Berk, M., Belmonte-de-Abreu, P. S., & Kapczinski, F. (2007). Serum levels of brain-derived neurotrophic factor in patients with schizophrenia and bipolar disorder. Neuroscience letters, 420(1), 45-48.

Grillo, R. W., Ottoni, G. L., Leke, R., Souza, D. O., Portela, L. V., & Lara, D. R. (2007). Reduced serum BDNF levels in schizophrenic patients on clozapine or typical antipsychotics. Journal of psychiatric research, 41(1-2), 31-35.

Hashimoto, T., Bergen, S. E., Nguyen, Q. L., Xu, B., Monteggia, L. M., Pierri, J. N., ... & Lewis, D. A. (2005). Relationship of brain-derived neurotrophic factor and its receptor TrkB to altered inhibitory prefrontal circuitry in schizophrenia. Journal of Neuroscience, 25(2), 372-383.

Heitz, U., Papmeyer, M., Studerus, E., Egloff, L., Ittig, S., Andreou, C., ... & Riecher-Rössler, A. (2018). Plasma and serum brain-derived neurotrophic factor (BDNF) levels and their association with neurocognition in at-risk mental state, first episode psychosis and chronic schizophrenia patients. The World Journal of Biological Psychiatry, 1-10.

Hori, H., Yoshimura, R., Yamada, Y., Ikenouchi, A., Mitoma, M., Ida, Y., & Nakamura, J. (2007). Effects of olanzapine on plasma levels of catecholamine metabolites, cytokines, and brain-derived neurotrophic factor in schizophrenic patients. International clinical psychopharmacology, 22(1), 21-27.

Huang, T. L., & Lee, C. T. (2006). Associations between serum brain-derived neurotrophic factor levels and clinical phenotypes in schizophrenia patients. Journal of psychiatric research, 40(7), 664-668.

Iritani, S., Niizato, K., Nawa, H., Ikeda, K., & Emson, P. C. (2003). Immunohistochemical study of brain-derived neurotrophic factor and its receptor, TrkB, in the hippocampal formation of schizophrenic brains. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 27(5), 801-807.

Jindal, R. D., Pillai, A. K., Mahadik, S. P., Eklund, K., Montrose, D. M., & Keshavan, M. S. (2010). Decreased BDNF in patients with antipsychotic naive first episode schizophrenia. Schizophrenia research, 119(1-3), 47-51.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia bulletin, 13(2), 261-276.

U Khan, Z., Martin-Montañez, E., & Chris Muly, E. (2013). Schizophrenia: causes and treatments. Current pharmaceutical design, 19(36), 6451-6461.

Kostakoğlu, A.E., Batur, S., Tiryaki, A. (1999). Pozitif ve Negatif Sendrom Ölçeğinin (PANSS) Türkçe uygulamasının geçerlik ve güvenirliği. Türk Psikoloji Dergisi, 14, 23–32.

Man, L., Lv, X., Du, X. D., Yin, G., Zhu, X., Zhang, Y., ... & Zhang, X. Y. (2018). Cognitive impairments and low BDNF serum levels in first-episode drug-naive patients with schizophrenia. Psychiatry research, 263, 1-6.

McAllister, A. K., Lo, D. C., & Katz, L. C. (1995). Neurotrophins regulate dendritic growth in developing visual cortex. Neuron, 15(4), 791-803.

Özkürkçügil, A., Aydemir, Ö., Yıldız, M., Esen Danacı, A., & Köroğlu IV, E. DSM-IV eksen I bozuklukları için yapılandırılmış klinik görüşmenin Türkçe'ye uyarlanması ve güvenilirlik çalışması.[Structured clinical interview for DSM-IV axis I disorders-clinical version (SCID-CV) in Turkish: study of reliability] İlaç ve Tedavi Dergisi. 1999; 12 (3): 233–236.

Pan, W., Banks, W. A., Fasold, M. B., Bluth, J., & Kastin, A. J. (1998). Transport of brain-derived neurotrophic factor across the blood–brain barrier. Neuropharmacology, 37(12), 1553-1561.

Pillai, A. (2008). Brain-derived neurotropic factor/TrkB signaling in the pathogenesis and novel pharmacotherapy of schizophrenia. Neurosignals, 16(2-3), 183-193.

Pırıldar, Ş., Gönül, A. S., Taneli, F., & Akdeniz, F. (2004). Low serum levels of brain-derived neurotrophic factor in patients with schizophrenia do not elevate after antipsychotic treatment. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 28(4), 709-713.

Radka, S. F., Hoist, P. A., Fritsche, M., & Altar, C. A. (1996). Presence

of brain-derived neurotrophic factor in brain and human and rat but not mouse serum detected by a sensitive and specific immunoassay. Brain research, 709(1), 122-130.

Rapaport, J.L., Giedd, J.N., Gogtay, N. (2012). Neurodevelopmental model of schizophrenia: update 2012. Mol Psychiatry, 17(12), 1228–1238. http://dx.doi.org/10.1038/mp.2012.23.

Reis, H.J., Nicolato, R., Barbosa, I.G., Teixeira do Prado, P.H., Romano-Silva, M.A., Teixeira, A.L. (2008). Increased serum levels of brain-derived neurotrophic factor in chronic institutionalized patients with schizophrenia. Neurosci Lett, 439(2), 157–159. http://dx.doi.org/10.1016/j.neulet.2008.05.022.

Rizos, E.N., Rontos, I., Laskos, E., Arsenis, G., Michalopoulou, P.G., Vasilopoulos, D., Gournellis, R., Lykouras, L. (2008). Investigation of serum BDNF levels in drug-naive patients with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry, 32(5), 1308–1311. http://dx.doi.org/10.1016/j.pnpbp.2008.04.007.

Rizos, E.N., Papadopoulou, A., Laskos, E., Michalopoulou, P.G., Kastania, A., Vasilopoulos, D., Katsafouros, K., Lykouras, L. (2010). Reduced serum BDNF levels in patients with chronic schizophrenic disorder in relapse, who were treated with typical or atypical antipsychotics. World J Biol Psychiatry, 11(2 Pt 2), 251–255. http://dx.doi.org/10.3109/15622970802182733.

Rosenthal, A., Goeddel, D.V., Nguyen, T., Martin, E., Burton, L.E., Shih, A., Laramee, G.R., Wurm, F., Mason, A., Nikolics, K., et al. (1991). Primary structure and biological activity of human brain-derived neurotrophic factor. Endocrinology, 129, 1289–1294. http://dx.doi.org/10.1210/endo-129-3-1289.

Schuman, E.M. (1999). Neurotrophin regulation of synaptic transmission. Curr Opin Neurobiol, 9, 105–109.

Shimizu, E., Hashimoto, K., Okamura, N., Koike, K., Komatsu, N., Kumakiri, C., Nakazato, M., Watanabe, H., Shinoda, N., Okada, S., Iyo, M. (2003). Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Society of Biological Psychiatry, 54, 70–75.

Smith, M.A., Makino, S., Kvetnansky, R., Post, R.M. (1995). Effects of stress on neurotrophic factor expression in the rat brain. Ann N Y Acad Sci, 771, 234–239.

Tan, Y.L., Zhou, D.F., Cao, L.Y., Zou, Y.Z., Zhang, X.Y. (2005). Decreased BDNF in serum of patients with chronic schizophrenia on long-term treatment with antipsychotics. Neurosci Lett, 382, 27–32..

Van Os, J., Kapur, S. (2009). Schizophrenia. Lancet, 374(9690), 635–645.

Woo, T.U. (2014). Neurobiology of schizophrenia onset. Curr Top Behav Neurosci, 16, 267–295.

Xiu, M.H., Hui, L., Dang, Y.F., Hou, T.D., Zhang, C.X., Zheng, Y.L., Chen, D.C., Kosten, T.R., Zhang, X.Y. (2009). Decreased serum BDNF levels in chronic institutionalized schizophrenia on long-term treatment with typical and atypical antipsychotics. Prog Neuropsychopharmacol Biol Psychiatry, 33(8), 1508–1512.

REVIEW ARTICLE-DERLEME

Year (Yıl) : 2018
Volume (Cilt) : 5
Issue Number (Sayı) : 3
Doi : 10.5455/JNBS.1528214611

Received/Geliş 05.06.2018
Accepted/Kabul 12.08.2018
JNBS, 2018, 5(3): 172-176

KUSHMANDA GRAHONMADA: PARANEOPLASTIC NEUROLOGICAL SYNDROME WITH TESTICULAR CANCER

KUSHMANDA GRAHONMADA: TESTİS KANSERİ İLE PARANEOPLASTİK NÖROLOJİK SENDROMLAR

Kshama Gupta[1], Prasad Mamidi[1*]

Abstract

Unmada (is a broad term which includes various psychiatric conditions) is characterized by deranged mental functions. 'Bhutonmada' (psychiatric conditions of idiopathic nature) is a type of unmada caused by affliction of 'bhuta' / 'graha' (evil spirits or super natural powers). Kushmanda grahonmada (KG) is one among 18 types of bhutonmada. Till date there were no studies have been conducted on KG and the present study aims at better understanding of this condition (KG) along with its clinical utility. KG is characterized by various signs and symptoms like Bahu pralaapam (excessive talking / irrelevant speech / logorrhoea), Ugra vaakyam (verbal abuse / aggression / irritability), Vilambita gatim (slow movements / hypokinesia), Krishna vadanam (hyperpigmentation of face) and Shoona pralamba vrishanam (huge scrotal / testicular swelling). It is very difficult to understand KG based on these few lakshana's (signs & symptoms) described in Ayurvedic texts. KG is a psychiatric condition associated with huge scrotal swelling. Various conditions like 'Paraneoplastic neurological syndromes' (PNS), 'Testicular adrenal rest tumors' (TART), Testicular cancer with brain metastasis', 'Paraneoplastic limbic encephalitis' (PLE), 'Paraneoplastic cerebellar ataxia' (PCA) and other scrotal swellings with psychiatric manifestations resembles with KG.

Keywords: paraneoplastic limbic encephalitis; testicular adrenal rest tumors; paraneoplastic cerebellar ataxia

Özet

Unmada (çeşitli psikiyatrik koşulları içeren geniş bir terimdir), dengesiz zihinsel işlevlerle vasıflandırılmıştır. 'Bhutonmada' (idiyopatik doğanın psikiyatrik koşulları), bhuta' / 'graha' (kötü ruhlar ya da süper doğal güçler) 'in neden olduğu bir unmada türüdür. Kushmanda grahonmada (KG), 18 çeşit bhutonma'nın arasında bulunmaktadır. KG üzerine bugüne kadar herhangi bir çalışma yapılmamıştır ve bu çalışma, klinik durumu ile birlikte bu durumun (KG) daha iyi anlaşılmasını amaçlamaktadır. KG, Bahu pralaapam (aşırı konuşma / ilgisiz konuşma / logorrhoea), Ugra vaakyam (sözlü istismar / saldırganlık / sinirlilik), Vilambita ağ geçidi (yavaş hareketler / hipokinezi), Krishna vadanam (yüzün hiperpigmentasyonu) ve Shoona gibi çeşitli belirtiler ve semptomlarla ilişkilendirilmektedir. Ayurvedik metinlerde anlatılan bu birkaç laksanaya (işaret ve semptom) bakarak KG'yi anlamak çok zordur. KG, büyük skrotal şişlik ile ilişkili bir psikiyatrik durumdur. 'Paraneoplastik nörolojik sendromlar' (PNS), 'Testis adrenal rest tümörleri' (TART), beyin metastazı ile Testis kanseri ',' Paraneoplastik limbik ensefalit '(PLE),' Paraneoplastik serebellar ataksi '(PCA) ve diğer skrotal şişlikler gibi çeşitli durumlar psikiyatrik belirtileri olmaktadır. KG, "PLE"yi özel referans vererek "PNS" ile benzerlik göstermektedir.

Anahtar Kelimeler: *paraneoplastik nörolojik sendromlar; paraneoplastik limbik ensefalit; paraneoplastik serebellar ataksi*

[1]Department of Kayachikitsa, Abhilashi Ayurvedic College & Research Institute, Abhilashi University, Mandi, Himachal Pradesh, India
[*]Corresponding Author: Associate Professor, Department of Kayachikitsa, Abhilashi Ayurvedic College & Research Institute, Abhilashi University, Mandi, Himachal Pradesh, India

1. Introduction

Ayurveda possesses eight specialities among them, 'Bhuta vidya' (Ayurvedic psychiatry) deals with diagnosis and management of various psychiatric conditions. The word 'bhuta' has different meanings such as 'super natural power' / 'demon' / 'extra terrestrial force' / 'paranormal force' / 'popular 'mythological personality' etc in different contexts of various classical Ayurvedic texts. 'Bhutonmaada' is a broad term and is characterized by various abnormal behaviours and psychomotor activity seen in a person with insidious onset and idiopathic in nature (Mamidi & Gupta, 2015). Bhutonmada is a type of unmada (psychosis) caused by affliction of 'bhuta' / 'graha'. There are 18 types of bhutonmada's explained in Ayurvedic texts and 'Kushmanda grahonmada' (KG) is one among those (Prasad & Kshama, 2015).

Description of KG is not available in Charaka samhita (Agnivesha, 2008), Sushruta samhita (Sushruta, 2009) and Madhava nidana (Madhavakara, 2012). Only lakshana's (signs and symptoms) of KG are explained in Ashtanga samgraha (Vriddha Vagbhata, 2012) and Ashtanga hridaya (Vagbhata, 2005). The description of KG is similar in both texts (Ashtanga samgraha and Ashtanga hridaya). KG is characterized by the features like Bahu pralaapam (excessive talking / irrelevant speech / logorrhoea), Ugra vaakyam (verbal abuse / aggression / irritability), Vilambita gatim (slow movements / hypokinesia), Krishna vadanam (hyperpigmentation of face) and Shoona pralamba vrishanam (huge scrotal / testicular swelling) (Vriddha Vagbhata, 2012; Vagbhata, 2005). 'Kushmanda' is a Sanskrit word referring to a fruit of the plant 'Benincasa hispida' (ash gourd). KG is named as such due to the huge scrotal swelling which resembles with the size of the ash gourd. Till date no studies have been conducted on KG and it is an unexplored concept of Ayurvedic psychiatry. The present study is focused at better understanding of KG and its clinical utility. KG has shown similarity with various psychiatric / neuropsychiatric conditions like 'Paraneoplastic neurological syndromes' (PNS), 'Testicular adrenal rest tumors' (TART), Testicular cancer with brain metastasis', 'Paraneoplastic limbic encephalitis' (PLE), 'Paraneoplastic cerebellar ataxia' (PCA) and other scrotal swellings with psychiatric manifestations.

2. Paraneoplastic Neurological Syndromes

PNS is a condition which is defined as remote effects of cancer and they should not caused by the tumor itself and its metastasis, or by infection, by ischemia or by metabolic disruptions. Central & peripheral nervous system, neuromuscular junction and muscles can be affected by PNS. PNS can be seen as an isolated condition or it can occur in association also. In most of the patients, the neurological disorder develops before the cancer becomes clinically overt. The most common PNS are Lambert-Eaton myasthenic syndrome (LEMS), limbic encephalitis (LE), retinopathies, sensory neuronopathy (SSN), stiff-person syndrome (SPS), encephalomyelitis (EM), chronic gastrointestinal pseudo-obstruction (CGP), subacute cerebellar ataxia, opsoclonus-myoclonus (OM), and dermatomyositis. PNS are generally caused by various autoimmune processes triggered by the cancer. A subacute progressive clinical course and a severe disability are highly indicative of PNS (Honnorat & Antoine, 2007).

Limbic encephalitis (LE) is one of the PNS and is characterized by confusion, marked reduction of the short term memory, seizures, depression, hallucinations etc which mimics a psychiatric illness. Among LE patients, 20% have a testicular tumor. Ma2-Ab (Ma 2 antibodies) are present in the most of the patients with LE and testicular cancer. LEMS is an autoimmune disorder of the neuromuscular junction which is characterized by muscle weakness and autonomic dysfunction. Opsoclonus is defined by the spontaneous, arrhythmic and large amplitude conjugate saccades occurring in all directions of gaze. It is usually associated with myoclonus of the limbs, trunk, and with encephalopathy. Patients with Ma2-Ab generally develop limbic and brainstem encephalitis with tumors of testes and also with some additional cerebellar symptoms (Honnorat & Antoine, 2007).

3. Testicular Adrenal Rest Tumors

TART's are benign in nature and generally they are bilateral. The location of TART's is within the rete testis. Histologically, TART resembles adreno-cortical tissue. TART's arise from aberrant adrenal cells descended during embryological period along with the testes. TART has the similar histological and functional features of adreno-cortical tissue and growth can be stimulated by increased ACTH (adreno-cortico trophic hormone) (Claahsen-van der Grinten et al., 2009). Bilateral testicular tumors (adrenal rests) may occur in untreated or poorly controlled congenital adrenal hyperplasia (CAH). Psychological abnormalities can be produced by abnormal adrenal or adrenal rest tissue (Keely et al., 1993). CAH is an autosomal recessive disorder occurs due to 21-hydroxylase deficiency. Increased psychiatric morbidity like drug and / or alcohol abuse as well as suicidal tendency was found in CAH patients (Falhammar et al., 2014).

4. Other Scrotal Swellings with Psychiatric Manifestations

Scrotal swellings are common problem among men of all ages. The cause of scrotal swellings may be benign or malignant. Most of the testicular tumors (95%) are germ cell in origin, 4% lymphomas, and 1% other rare histological types (Bromby & Cresswell, 2014).

4.1. Hydrocoele

It is a collection of fluid between the parietal and visceral layers of the tunica vaginalis around the testis. Hydrocoele in adults usually occurs due to the result of imbalance between absorption and secretion of fluid by the tunica. Hydrocoele may be secondary to an underlying testicular tumour. Scrotal swellings can cause considerable anxiety to the patient (Bromby & Cresswell, 2014).

4.2. Scrotal elephantiasis

It is an endemic in tropical regions due to 'filariasis' (Wucheria bancrofti). Scrotal elephantiasis is a condition

characterized by huge scrotal lymphedema with gross deformation of genitals. Even though it is not a life-threatening condition, chronic lymphedema is a disabling with significant physical and psychological morbidity. Scrotal elephentiasis leads to various complications, impaired hygiene, urinary incontinence and also immobility (Brotherhood et al., 2014).

4.3. Giant scrotal lymphedema

It can be caused by obstruction, aplasia / hypoplasia of lymphatic vessels. Most cases of lymphedema are usually caused by an infection. Scrotal lymphedema is due to abnormal accumulation of lymphatic fluid in subcutaneous tissue of the scrotum. Lymphedema is of two types; primary and secondary. Primary lymphedema can be congenital-inherited (Milroy's), praecox / tarda. Secondary lymphedema has three origins, obstructive, phlebitial and angio-neurotic. Peno-scrotal lymphedema generally occurs following an infection or as a reaction to injury. It is a condition leading to progressive enlargement of the scrotum and penis (Rahman et al., 2009).

Inflammatory conditions of the testes like orchitis, epididimitis, epididymo-orchitis; non inflammatory conditions like varicocele, testicular torsion, hydrocele and inguinal hernia are the causative factors of various scrotal swellings (Sehgal et al., 2016). Conditions like hydrocele, scrotal elephantiasis, scrotal lymphedema due to inflammatory origin have not shown any similarity in the signs and symptoms of KG (except scrotal swelling). There is no evidence of presence of psychiatric features in hydrocele, scrotal elephantiasis & scrotal lymphedema etc conditions in literature.

5. Etiology, Pathogenesis, Course and Prognosis of KG & PNS

Bhutonmada is idiopathic in nature and causative factors are untraceable. Pragyaparaadha (intellectual blasphemy) or karma (idiopathic) plays a significant role in the pathogenesis as well as in prognosis of bhutonmada. The onset of bhutonmada is sudden or insidious, without significantly affecting the physiology of the body. The signs and symptoms of bhutonmada is variable and the nature of the condition is multi factorial. The course and prognosis of bhutonmada is unpredictable in nature (Prasad & Kshama, 2015). There is no special description regarding etiology, pathogenesis, course and prognosis of KG described in Ayurvedic texts. The common etiology, course and prognosis mentioned for bhutonmada is applicable for KG also (Agnivesha, 2008; Sushruta, 2009; Madhavakara, 2012; Vriddha Vagbhata, 2012; Vagbhata, 2005).

Para-neoplastic antibodies are the only marker of autoimmunity and they generally do not produce the disease. Cellular immune mechanisms play a crucial role in the pathogenesis of PNS. Till date, no studies have proved that paraneoplastic antibodies are pathogenic. The hypothesis that PNS are immune-mediated remains to be proved yet (Honnorat & Antoine, 2007). PLE is an under diagnosed due to its variability of symptoms and lack of specific diagnostic markers (Voltz et al., 1999). PNS are a heterogeneous group of disorders with huge variability in clinical presentation. The psychiatric characterizations of PNS syndromes remain relatively cursory (Kayser et al., 2010). Thus, variable clinical presentation, uncertain prognosis, idiopathic pathological processes of PNS shows similarity with the etiopathology, course and prognosis explained in the context of grahonmada / bhutonmada.

6. Similarity of Clinical Picture in Between KG and PNS / PLE

Various lakshana's of KG like Bahu pralaapam, Ugra vaakyam, Vilambita gatim, Krishna vadanam and Shoona pralamba vrishanam etc features resembles with PNS and especially with PLE. The similarity in between the signs and symptoms of these two conditions (KG and PNS / PLE) is as follows;

6.1. Bahu pralaapam (excessive speech / irrelevant speech / logorrhoea)

The word 'bahu pralaapam' denotes either excessive speech or irrelevant speech or logorrhoea. There is no evidence of association of scrotal swelling with excessive, irrelevant speech or logorrhoea. Confusion, dementia, psychomotor seizures and hallucinations are the features of PLE (Gultekin et al., 2000) which may cause 'bahu pralaapa'. Autoimmune encephalitis clinically manifests with neurological symptoms such as seizures, psychiatric symptoms, such as anxiety, agitation, hallucinations and psychosis. According to a case report, autoimmune encephalitis clinically manifested with the symptoms of bipolar disorder (Choe et al., 2013). 'Pressure of speech' is one of the characteristic features of 'mania' / 'bipolar disorder' which are similar to 'bahu pralaapa'.

PNS generally involves the central or peripheral nervous systems, resulting in various symptoms ranging from sensory neuropathies to severe and diverse neuropsychiatric disturbances, such as dysfunction in consciousness, cognition, behavior, mood, and perception. Psychiatric changes such as irritability, hallucinations, depression, personality disturbances, and cognitive changes etc are found in PNS. Additionally patients may experience confusion, sleep disturbances, and seizures. Patients with LE have been described various myriad symptoms, ranging from delusional thought content & paranoid ideation to obsessive-compulsive behaviour (Kayser et al., 2010). Mild to moderate dysarthria is found in anti-Ta (Ma 2) syndrome (testicular cancer with PNS) (Somnier, 2017). Even though there is no direct evidence of 'excessive speech' or 'irrelevant speech' in PNS, it seems that the underlying central nervous system pathology and associated psychiatric or neuropsychiatric features of PNS / PLE may cause 'bahu pralaapa' associated with testicular tumors.

6.2. Ugravaakyam (agitation / aggression / verbal abuse)

PNS associated with anti-Ma2 antibodies is characterized

by nervousness and behavioural distrubances (Suero et al., 2017). LE is an autoimmune neuropsychiatric condition, which affects the medial temporal lobe of the brain and is characterized by sub acute cognitive symptoms, seizures, short-term memory loss, and mood disturbances (Neto et al., 2016). According to a case report, a patient of testicular cancer with anti-Ma2 encephalitis and PNS has shown irritability and anxiety (Matsumoto et al., 2007). Mood disturbances such as irritability & depression, panic attacks, hallucinations, unexplained fear, confusion and obsessive-compulsive behaviour etc are seen in anti-Ma2 LE. The association of testicular cancer and anti-Ma2 limbic encephalitis in very strong and due to this strong association orchiectomy or testicular irradiation is suggested even if a tumor cannot be found. LE is characterized by personality changes, cognitive changes, irritability, delusions, hallucinations, paranoid ideations, temporal lobe seizure / psycho-motor seizures and dementia (Kayser et al., 2010). The verbal abuse / irritability / agitation seen in PLE are similar to 'Ugravaakyam' of KG.

6.3. Vilambita gatim (slow movements / hypokinesia)

'Vilambita gati' denotes slowness of movements, which may be due to the huge scrotal swelling or hypokinesia seen in PNS. LEMS is characterized by muscle weakness and autonomous dysfunction (Honnorat & Antoine, 2007). The huge scrotal lymphedema or scrotal elephantiasis causes impairment of free movement due to progressive enlargement of scrotum and penis (Rahman et al., 2009). Gait disturbances and hypokinesis are found in PLE (Kayser, 2010; Gultekin, 2000; Choe, 2013; Somnier, 2017; Suero, 2017). Impaired gait, rigidity of limbs and hypokinesis are found in PNS associated with testicular cancer and anti-Ma2 antibodies. Severe hypokinesis with reduced verbal output has been found in some cases with anti-Ma2 encephalitis. Severe hypokinesis is a very rare phenomenon of para-neoplastic encephalitis. In these patients (with hypokinesis), multifocal abnormalities in substantia nigra or globus pallidus or both has been seen in MRI (Magnetic resonance imaging). Bilateral lesions of globus pallidus can cause Parkinsonism. The hypokinesis and slowness of initiation or completion of movement may be due to the damage of globus pallidus (major output structure of basal ganglia) (Matsumoto et al., 2007).

The clinical clues for Ma2 antinbodies with testicular cancer and PNS are the presence of both hypothalamic (daytime sleepiness, cataplexy, narcolepsy, hormonal deficits and hyperphagia) and brainstem dysfunction (Machado et al., 2012). Atypical Parkinsonism with severe akinesia, facial masking, tremors and rigidity are seen in anti-Ta (Ma 2) syndrome (Somnier, 2017). PCA or subacute cerebellar ataxia is one of the PNS, which may manifests with gait disturbances and hypokinesia (Honnorat & Antoine, 2007). The 'vilambita gati' of KG denotes hypokinesis or atypical Parkinsonism or cerebellar ataxia of PNS or impaired movement due to huge scrotal swelling.

6.4. Krishna vadanam (hyper pigmentation of face)

The word 'Krishna vadanam' denotes either hyper pigmentation of face or dark complexion of face due to underlying disease. In 1% of internal malignancies, skin provides the first clue for diagnosis. Skin manifestations of internal malignancies may be due to direct effects (due to the invasion of the skin by a tumor or its metastases) or to indirect effects (which triggers the cutaneous signs or symptoms). Some of the skin manifestations occur as a part of complex PNS. PNS affecting the skin may precede the manifestation of the tumor, but sometimes they may also manifest at much later time. Malignancy is one of the multiple causes which cause diffuse or focal darkening (which is a distinctive skin sign) of the skin. The hyper pigmentation in such cases is diffuse and profound in exposed areas such as face, neck, back of hands, areas affected by trauma, areas subjected to slight pressure, and mucous membranes. Pigmentary changes have been linked to the production of the polypeptide lipotropin, which can induce the production of MSHs (melanocyte stimulating hormone), which in turn, stimulates the production of melanocytes in the skin. Association of ACTH syndrome and reproductive organ tumors is well known. Elevated plasma cortisol and corticotropin levels indicates ACTH syndrome. Hyperpigmentation is a nonspecific cutaneous manifestation of leukemia, Hodgkin and non-Hodgkin lymphomas (Yuste-Chaves & Unamuno-Pérez, 2013). Based on these findings it seems that 'krishna vadana' mentioned in KG can be seen in a case of testicular cancer with PNS.

6.5. Shoona pralamba vrishanam (scrotal swelling)

As discussed in the previous sections, the scrotal swelling may be due to various inflammatory and non-inflammatory causes. Scrotal lymphedema or scrotal elephantiasis, hydrocele, inguinal hernia, testicular tumors (malignant or benign) and TART etc are the causes for scrotal swellings. 'Shoona pralamba vrishana' denotes painless scrotal swelling which indicates towards a non-inflammatory (tumor or lymphedema) pathology. By considering all the above facts it seems that the lakshana's explained in KG denotes a scrotal swelling (mostly tumors) with associated psychiatric features (PNS or PLE or PCA). No other bhutonmada (except KG) is associated with scrotal swelling.

7. Conclusion

'Kushmanda grahonmada' is one among 18 types of bhutonmada. KG is a psychiatric condition associated with huge scrotal swelling. The signs and symptoms of KG have shown similarity with various conditions like 'Paraneoplastic neurological syndromes' (PNS), 'Testicular adrenal rest tumors' (TART), Testicular cancer with brain metastasis', 'Paraneoplastic limbic encephalitis' (PLE), 'Paraneoplastic cerebellar ataxia' (PCA) and other scrotal swellings with psychiatric manifestations. Among these conditions, KG has shown striking similarity with 'PNS' with special reference to 'PLE'.

JNBS 2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org

References

Agnivesha, C. (2008). Elaborated by Charaka and Dridhabala commentary by Chakrapani. Charaka samhita, Chikitsa sthana, Unmada chikitsitam adhyaya, 9/20, edited by vaidya Jadavji Trikamji Acharya. Chaukhambha Surabharati Prakashana, Varanasi, 469.

Bromby, A., & Cresswell, J. (2014). Differential diagnosis of a scrotal mass. Trends in Urology & Men's Health, 5(1), 15-18.

Brotherhood, H. L., Metcalfe, M., Goldenberg, L., Pommerville, P., Bowman, C., & Naysmith, D. (2014). A surgical challenge: Idiopathic scrotal elephantiasis. Canadian Urological Association Journal, 8(7-8), E500.

Choe, C. U., Karamatskos, E., Schattling, B., Leypoldt, F., Liuzzi, G., Gerloff, C., ... & Mulert, C. (2013). A clinical and neurobiological case of IgM NMDA receptor antibody associated encephalitis mimicking bipolar disorder. Psychiatry research, 208(2), 194-196.

Claahsen-Van der Grinten, H. L., Hermus, A. R. M. M., & Otten, B. J. (2009). Testicular adrenal rest tumours in congenital adrenal hyperplasia. International journal of pediatric endocrinology, 2009(1), 624823.

Falhammar, H., Butwicka, A., Landén, M., Lichtenstein, P., Nordenskjöld, A., Nordenström, A., & Frisén, L. (2014). Increased psychiatric morbidity in men with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. The Journal of Clinical Endocrinology & Metabolism, 99(3), E554-E560.

Gultekin, S. H., Rosenfeld, M. R., Voltz, R., Eichen, J., Posner, J. B., & Dalmau, J. (2000). Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. Brain, 123(7), 1481-1494.

Honnorat, J., & Antoine, J. C. (2007). Paraneoplastic neurological syndromes. Orphanet journal of rare diseases, 2(1), 22.

Kayser, M. S., Kohler, C. G., & Dalmau, J. (2010). Psychiatric manifestations of paraneoplastic disorders. American Journal of Psychiatry, 167(9), 1039-1050.

Machado, S., Pinto, A. N., & Irani, S. R. (2012). What should you know about limbic encephalitis?. Arquivos de neuro-psiquiatria, 70(10), 817-822.

Madhavakara, (2012). Rogavinischaya / Madhava Nidana, Unmada nidana, 20/18-25, commentary 'Madhukosha' by Vijayarakshita & Shrikanthadatta, edited by Dr. Brahmananda tripathi. Varanasi: Chaukhamba surbharati prakashan; 1st edition, 487-492.

Mamidi, P., & Gupta, K. (2015). Guru, vriddha, rishi and siddha grahonmaada: Geschwind syndrome?. International Journal of Yoga-Philosophy, Psychology and Parapsychology, 3(2), 40.

Mamidi, P., & Gupta, K. (2015). Obsessive compulsive disorder–'Sangama graha': An ayurvedic view. J Pharm Sci Innov, 4, 156-64.

Matsumoto, L., Yamamoto, T., Higashihara, M., Sugimoto, I., Kowa, H., Shibahara, J., ... & Dalmau, J. (2007). Severe hypokinesis caused by paraneoplastic anti□Ma2 encephalitis associated with bilateral intratubular germ□cell neoplasm of the testes. Movement disorders, 22(5), 728-731.

Matwijiw, I., Thliveris, J. A., & Faiman, C. (1993). Congenital adrenal hyperplasia with testicular tumors, aggression, and gonadal failure. Urology, 41(4), 346-349.

Neto, S., Ribeiro, H., Cavalcante, W. C. P., Martins Filho, S. N., Smid, J., & Nitrini, R. (2016). Capgras syndrome associated with limbic encephalitis in a patient with diffuse large B-cell lymphoma. Dementia & Neuropsychologia, 10(1), 63-69.

Rahman, G. A., Adigun, I. A., Yusuf, I. F., Aderibigbe, A. B., & Etonyeaku, A. C. (2009). Giant scrotal lymphedema of unclear etiology: a case report. Journal of medical case reports, 3(1), 7295.

Sehgal, V. N., Sehgal, R., Sehgal, D., Pandey, S. S., Amin, S. S., Bhattacharya, S. N., & Oberai, R. (2016). Scrotal Swellings Synopsis of Differential Diagnosis (Part III). Investigative Dermatology and Venereology Research, 2(3), 1-7

Somnier, F. E. Paraneoplastic neurological and muscular syndromes. Available at: http://www.ssi.dk/~/media/Indhold/DK%20%20dansk/Diagnostik/DiagnostiskHaandbog/Paraneoplastic%20neurological%20and%20muscular%20syndromes%2045.ashx

Suero, G. O., Sola-Valls, N., Escudero, D., Saiz, A., & Graus, F. (2018). Anti-Ma and anti-Ma2-associated paraneoplastic neurological syndromes. Neurología (English Edition), 33(1), 18-27.

Sushruta, (2009). Sushruta samhita, commentary by Dalhana. Uttara tantra, Amanusha upasarga pratishedha adhyaya, 60/7-16, edited by vaidya Jadavji Trikamji Acharya and Narayana Ram Acharya. Varanasi: Chaukhamba orientalia, 794-795.

Vagbhata, (2005). Ashtanga Hridaya, Commentary by Arunadatta and Hemadri, Uttara tantra, Bhoota vigyaneeyam adhyaya, 4/39, edited by Bhishagacharya Harishastri Paradkara Vaidya. Varanasi: Chowkhamba Sanskrit series office; Ninth edition, 792.

Voltz, R., Gultekin, S. H., Rosenfeld, M. R., Gerstner, E., Eichen, J., Posner, J. B., & Dalmau, J. (1999). A serologic marker of paraneoplastic limbic and brain-stem encephalitis in patients with testicular cancer. New England Journal of Medicine, 340(23), 1788-1795.

Vriddha Vagbhata, (2012). Ashtanga Sangraha, commentary by Indu, Uttara tantra, Bhoota vigyaneeyam adhyaya, 7/22, edited by Dr. Shivprasad sharma. Varanasi: Chowkhamba Sanskrit series office; Third edition, 670.

Yuste-Chaves, M., & Unamuno-Pérez, P. (2013). Cutaneous alerts in systemic malignancy: Part I. Actas Dermo-Sifiliográficas (English Edition), 104(4), 285-298.

Year (Yıl) : 2018
Volume (Cilt) : 5
Issue Number (Sayı) : 3
Doi : 10.5455/JNBS.1532253525

Received/Geliş 22.06.2018
Accepted/Kabul 12.08.2018
JNBS, 2018, 5(3): 177-183

DİKKAT EKSİKLİĞİ HİPERAKTİVİTE BOZUKLUĞUNDA SIK GÖRÜLEN KOMORBİD DURUM VE HASTALIKLAR, ORTAK GENETİK ETKENLER

COMORBID SITUATIONS, COMORBID PSYCHIATRIC DISORDERS AND COMMON GENETIC FACTORS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER

Hesna Gül[1*], Bedriye Öncü[2]

Özet

Dikkat eksikliği hiperaktivite bozukluğu (DEHB), dikkatsizlik, aşırı hareketlilik ve dürtüsellik belirtileriyle seyreden nörogelişimsel bir bozukluktur. DEHB'nin etiyolojisinde genetik, sosyal ve fiziksel faktörlerin etkili olduğu düşünülmektedir.

Bu yazıda DEHB ile komorbiditesi yüksek olan durum ve hastalıklar ve DEHB etiyolojisindeki genetik faktörler- komorbidite ilişkisinin ele alınması hedeflenmiştir. Bu amaçla Pubmed, Google Akademik ve diğer çevrimiçi arama motorları taranmış, elde edilen veriler temel bilgilerle birleştirilerek sunulmaya çalışılmıştır. DEHB'den sorumlu olduğu öne sürülen genetik faktörlerle ilgili çalışmaların sonuçlarının çelişkili olması, bozukluğun heterojenliğine, genetik ve çevresel etkenlerin oluşturduğu epigenetik değişikliklerin etkisine ve çalışmalardaki istatistiksel kısıtlılığa bağlı görünmektedir. Bu sınırlılıkların aşılabilmesi için, daha büyük örneklemlerde genetik ve çevresel faktörlerin aynı anda ele alındığı çalışmaların gerekliliği açıktır.

Anahtar Kelimeler: dikkat eksikliği hiperaktivite bozukluğu; DEHB; genetik; etiyoloji; komorbidite

Abstract

Attention deficit hyperactivity disorder (ADHD) is a heterogeneous neurodevelopmental disorder characterized by inattention, hyperactivity and impulsivity. Genetic, social and physical factors are thought to be influential in the etiology of ADHD. In this review, we focus on diseases with high comorbidities with ADHD, study results on genetic factors in the etiology of ADHD, and the relationship between genetic factors and comorbidities. The challenges of the results on genetical factors could be related with the heterogeneity of the disorder, the effects of epigenetic changes caused by genetic and environmental factors, and the statistical limitations of the studies. In order to overcome these limitations, it is clear that the larger studies should address genetic and environmental factors at the same time.

Keywords: *attention deficit hyperactivity disorder; ADHD; genetic; etiology; comorbidity*

[1]Ankara Universitiy School of Medicine, Ankara, Turkey
[2]Gülhane Training and Research Hospital, Istanbul, Turkey
[*]Sorumlu Yazar: Ankara University School of Medicine E-mail: drhesnagul@gmail.com

1. Giriş ve Amaç

Dikkat eksikliği hiperaktivite bozukluğu (DEHB), dikkatsizlik, aşırı hareketlilik ve dürtüsellik belirtileriyle seyreden nörogelişimsel bir bozukluktur (Association, 2013a). Tüm dünyada çocuk ve ergenlerdeki DEHB prevalansı %5.0-7.1, erişkinlerdeki prevalansı ise %2.5 olarak belirlenmiştir (Gallo & Posner, 2016; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Simon, Czobor, Bálint, Mészáros, & Bitter, 2009; Willcutt, 2012). DEHB tanısının erkeklerde kızlardan 2-4 kat daha fazla konduğu bilinmektedir. Ancak bu durumun kızlarda daha geç yaşlarda tanı konması ile ilişkili olduğu düşünülmektedir çünkü çocukluk dönemi sonrasında cinsiyetler arasındaki farkın azaldığı gözlenmektedir (Davies, 2014). DEHB belirtilerinin şiddeti ve görülme sıklığında yaşam evreleri boyunca değişiklikler olsa da, çoğunlukla belirtilerin okul öncesi dönemde bile var olduğu (Daley, Jones, Hutchings, & Thompson, 2009) ve %50'ye varan oranlarda erişkinlik döneminde de devam ettiği saptanmıştır (Geissler & Lesch, 2011; Spencer, Biederman, & Mick, 2007).

DEHB, yapılan tüm araştırmalara rağmen halen nedenleri tam olarak anlaşılamamış, genetik, sosyal ve fiziksel faktörlerin etkili olduğu düşünülen heterojen bir bozukluktur (Thapar, Cooper, Eyre, & Langley, 2013). Bu hastalık sıklıkla diğer psikiyatrik hastalıklar ve fonksiyonel bozukluklarla birliktelik gösterir. Tedavinin etkin şekilde planlanabilmesi için hem DEHB'nin hem de komorbid durumların bütüncül bir yaklaşımla ele alınması gerekmektedir. Bu yazıda DEHB ile sık görülen komorbid durumlar ve fonksiyonel sorunların gözden geçirilmesi, DEHB etiyolojisini aydınlatmaya yönelik genetik çalışma sonuçlarının komorbiditelerle/ diğer psikiyatrik hastalıklarla ilişkisinin ele alınması planlanmıştır.

Bu yazıda çocuklar ve erişkinlerde yapılan çalışmalar ışığında aşağıdaki konu başlıkları ele alınacaktır.

i. DEHB'de sık görülen komorbid durumlar,

ii. Etiyolojide yer alan genetik faktörlerin komorbiditeler/ diğer psikiyatrik hastalıklarla ilişkisi

2. Yöntem

Bu derleme için Pubmed ve Google Akademik arama motorları ''attention deficit hyperactivity disorder'', ''ADHD'', ''genetic, ''etiology'', '' comorbidity'' terimleri kullanılarak taranmıştır. Elde edilen veriler temel kitaplardaki bilgilerle birleştirilerek sunulmaya çalışılmıştır. Tarama sırasında tarih sınırlaması yapılmamış, tam metinlerine ulaşılabilen tüm araştırmalar/ derlemeler gözden geçirilmiş ve herhangi bir dışlama ölçütü kullanılmamıştır.

3. DEHB'de Sık Görülen Komorbid Durumlar

3.1. Nöropsikolojik İşlevsellikle İlgili Sorunlar

DEHB de görülen davranışsal ve bilişsel sorunları açıklamak üzere birçok nöropsikolojik model öne sürülmüştür. Bunlardan en çok kabul görenleri yürütücü işlevlerde bozulma (executive dysfunction) (Barkley, 1997; Castellanos & Tannock, 2002), ertelemeye katlanamama durumu (delay aversion) (E. Sonuga-Barke, Taylor, Sembi, & Smith, 1992), ve temporal işlemleme sorunlarıdır (temporal processing deficits)(E. Sonuga-Barke, Bitsakou, & Thompson, 2010). DEHB'li bireylerde yapılan fMRI çalışmaları, yürütücü işlevlerin merkezi olan frontal lobda hipoaktivasyon olduğunu ortaya koymaktadır (Cortese et al., 2012; Seidman, 2006; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Yürütücü işlev bozukluğunun kliniğe yansımaları, unutkanlık, plan yapamama ve günlük işleri organize etmede (örneğin sabahları okula gitmek için zamanında hazırlanmak) zorluk yaşama şeklindedir. Ancak yakın dönemde DEHB li bireylerle yapılan ve farklı nöropsikolojik işlevleri de araştıran çalışmalar bu kişilerdeki nöropsikolojik sorunların heterojen bir yapıda olduğunu(Coghill, Seth, & Matthews, 2014), yalnızca yürütücü işlev bozukluğu değil, ertelemeye katlanamama, daha sonra elde edilecek büyük bir ödül yerine yakın dönemdeki daha küçük bir ödülü tercih etme gibi pek çok farklı sorunu da ortaya koymuştur (E. J. Sonuga-Barke, 2002; E. J. Sonuga-Barke & Halperin, 2010). Motivasyonel farklılıklar, DEHB'li bireylerde sık görülen emosyonel labilitenin kaynağı olarak gösterilmektedir (Shaw, Stringaris, Nigg, & Leibenluft, 2014; Tripp & Wickens, 2009).

3.2. Emosyonel İşlevsellikle İlgili Sorunlar

Emosyonel disregulasyon DEHB li bireylerde çok sık görülen bir klinik problemdir. Bir çok ebeveyn çocuklarının emosyonel kontrolde zorlandıklarını ve DEHB olmayan akranlarından daha sık negatif duygulanım yaşadıklarını belirtmektedir (Anastopoulos et al., 2011). Yakın dönem klinik çalışma derlemelerinde, emosyonel disregulasyon prevalansı çocuk ve ergen yaştaki DEHB'lerde %25-45, erişkin DEHB'lerde ise %30-70 olarak saptanmıştır (Posner, Kass, & Hulvershorn, 2014; Shaw et al., 2014). Emosyonel disregulasyonun en sık klinik görünümü agresif davranışlar, düşük engellenme eşiği ve artmış eksitabilitedir (çabuk uyarılma). Vakaların çocukluktan erişkinliğe kadar izlendiği bir çalışma emosyonel disregulasyonun dikkat eksikliği ve hiperaktivite/dürtüsellik belirtilerinden bağımsız olarak sosyal ve mesleki açıdan olumsuzluklara yol açtığını ortaya koymaktadır (Barkley & Fischer, 2010).

Emosyonel işlevsellikle ilgili diğer bir sorunda DEHB'li çocuk ve ergenlerde duygu tanıma ve duyguları regule etme sorununun yalnızca negatif duygularla sınırlı olmamasıdır. Yakın dönemde yapılan bir çalışmada DEHB'li çocuklarda pozitif duyguları (mutluluk, coşku gibi) tanıma ve regule etmeyle ilgili sorunlar da saptanmıştır (Da Fonseca, Seguier, Santos, Poinso, & Deruelle, 2009; Sjöwall, Roth, Lindqvist, & Thorell, 2013). Kontrol grubuyla yapılan çalışmalar emosyonel disregulasyon ve artmış uyarılabilirliğin fizyolojik yönüne de dikkat çekmektedir. Bu sorunları yaşayan DEHB'li çocuklarda sempatik/ parasempatik sistem aktivasyonun daha yüksek olduğu saptanmıştır.(Musser, Galloway-Long, Frick, & Nigg, 2013)

3.3. Sosyal İlişkiler ve Akran İlişkilerindeki Sorunlar

DEHB'li çocuk, ergen ve erişkinler arkadaşlık açısından daha az tercih edilen bireylerdir (Harpin, Mazzone, Raynaud, Kahle, & Hodgkins, 2016; Hoza, 2007; Hoza et al., 2005). Sosyal ilişkilerdeki sorunlar DEHB belirtilerinin

tipi ve şiddetine bağlı farklılıklar içermektedir. DEHB kombine tip çocuk ve ergenlerde (hem dikkat eksikliği hem hiperaktivite/ dürtüsellik semptomları olan), agresif ve intrusiv davranışların sıklığı, dikkat eksikliği ön planda olan tipte ise çekingenlik ve hafıza problemleri en sık tercih edilmeme nedenleridir (García-Castellar, Jara-Jiménez, Sánchez-Chiva, & Mikami, 2015; Hoza, 2007; Mikami, Huang-Pollock, Pfiffner, McBurnett, & Hangai, 2007). Sosyal ilişkilerde özgüven ve yüksek sosyal işlevsellikle ilgili 127 çalışmanın gözden geçirildiği ve 150 sonucun değerlendirildiği bir derlemede, tedavi edilmeyen DEHB'li bireylerin DEHB olmayan bireylere göre daha fazla özgüven eksikliği ve sosyal işlev kaybı yaşadıkları belirlenmiştir. Ayrıca tedavi alan DEHB'li grupların (ilaç tedavisi ve/veya terapi yöntemleri), özgüvende %89, sosyal işlevsellikte %77 oranında almayan gruplara göre daha iyi durumda oldukları da ortaya konmuştur (Harpin et al., 2016).

3.4. Akademik İşlevsellikle İlgili Sorunlar

Akademik işlevsellikteki sorunlar çocuk ve ergenlerde tedavi arayışının en önemli nedenlerinden biridir. Yapılan çalışmalar bu alandaki sorunların okul öncesi dönemde başladığını (DuPaul, McGoey, Eckert, & VanBrakle, 2001) ve ergenlik dönemi sonrasına kadar devam ettiğini göstermektedir (Frazier, Youngstrom, Glutting, & Watkins, 2007). Hastalığın özellikle dikkat eksikliği ve yürütücü işlev bozukluğu ile ilgili belirtilerinin bu alanda etkili olduğu düşünülmektedir (Daley & Birchwood, 2010).

3.5. Yıkıcı Davranım Bozuklukları

DEHB ile en sık komorbid psikiyatrik hastalık grubu yıkıcı davranım bozukluklarıdır. Yapılan çalışmalar Karşı Olma Karşıt Gelme Bozukluğu (KOKGB) ve Davranım Bozukluklarının yaklaşık %50 oranında DEHB'ye eşlik ettiğini (Biederman, Newcorn, & Sprich, 1991; S. Faraone, Biederman, & Monuteaux, 2002; Spencer et al., 2007), uzun dönemde farklı alanlarda işlev kaybı ve diğer kötü sonuçların ortaya çıkmasında etkili olduğunu (Connor, Steeber, & McBurnett, 2010), ve sadece DEHB belirtilerine sahip bireylere göre tedavi uyumsuzluğu ve tedaviye direncin bu grupta daha yüksek olduğunu ortaya koymaktadır (Villodas, Pfiffner, & McBurnett, 2012).

3.6. Duygudurum ve Kaygı Bozuklukları

DEHB ile birlikteliği en sık olan duygudurum bozuklukları major depresyon, distimi ve bipolar bozukluk; kaygı bozuklukları ise yaygın anksiyete bozukluğu, ayrılma anksiyetesi bozukluğu ve panik bozukluktur (Tarver, Daley, & Sayal, 2014). DEHB tanısı konmuş 381 okul çocuğuyla yapılan bir çalışmada, çocukların %50'sinde duygudurum bozukluğu, %33'ünde ise en az bir kaygı bozukluğu olduğu saptanmıştır(Wilens et al., 2002). Anksiyete, duygudurum bozuklukları ve DEHB ilişkisinin nörobiyolojisini inceleyen yeni bir derlemede ise bu komorbiditenin farklı bir yönüne dikkat çekilmektedir. Bilindiği gibi anhedoni (pozitif duyguları hissetmedeki azalma, yetersizlik) depresyonun önemli semptomlarından biridir. Anhedoninin kişilik özelliği haline geldiği durum ise hedonik ton olarak adlandırılmaktadır. Bu derlemede hedonik tona sahip bireylerde, emosyonel afektin azalmasına neden olan limbik - kortikal - striatal - pallidal - talamik yolaklardaki sorunların, DEHB, anksiyete ve duygudurum komorbiditesinin temel nedeni olduğu öne sürülmektedir. Dopamin sistemi ve ödül yolaklarındaki sorunlar nedeni ile özellikle SSRI tedavisinden fayda görmeyen anksiyete/ depresyon hastalarında DEHB'nin mutlaka akılda tutulması gerektiği de vurgulanmaktadır(Sternat & Katzman, 2016).

Tedavinin bu grup komorbiditeler üzerindeki etkisini araştıran çalışmalar ise, stimulan tedavilerin uzun dönemde duygudurum ve anksiyete bozukluğu riskini azalttığını (Biederman, Monuteaux, Spencer, Wilens, & Faraone, 2009), kullanılan davranışsal yöntemlerin de DEHB' li çocuklardaki içe yönelim ve anksiyete belirtileri üzerinde olumlu etkilerinin olduğunu göstermektedir (Jensen et al., 2001; Van Den Hoofdakker et al., 2007).

3.7. Nörogelişimsel Bozukluklar

Nörogelişimsel bozukluklardan otizm ve tik bozuklukları DEHB ile birlikteliği sıkça karşımıza çıkan hastalıklardır (Gallo & Posner, 2016). Son dönemde yapılan nörobiyolojik, genetik ve görüntüleme çalışma sonuçları bu hastalıkların bir bütünün farklı parçaları olduğu görüşünün ortaya atılmasına neden olmuştur (Kern et al., 2015). Bu görüşe göre, çeşitli etiyolojik nedenler (nörotoksisite, nöroinflamasyon, eksitotoksisite, kronik mikroglial aktivasyon, proinflamatuar sitokinler, toksik madde maruziyeti, oksidatif stres gibi) nöron hücrelerinde uzun süreli eşik değerin altındaki iletim ve/ veya kısa süreli eşik değeri aşan iletime neden olmakta ve otizm, DEHB, tik bozukluğu semptomlarının tamamını farklı derecelerde ortaya çıkarmaktadır (Aoki, Abe, Nippashi, & Yamasue, 2013; Cao, Shu, Cao, Wang, & He, 2014; Casanova et al., 2009; Keown et al., 2013; Kern et al., 2015; Liu, Chen, Lin, & Wang, 2014; Peters et al., 2013).

Klinik çalışma sonuçları da bu görüşü destekler niteliktedir. Otizmin temel belirtileri olan ilişki kurmada zorluk ve sosyal işlevsellikte bozulma ile sınırlı davranış kalıpları ve tekrarlayan davranışlar, DEHB ve tik bozukluğunda en sık rapor edilen sorunlar arasındadır (Grzadzinski et al., 2011; Hattori et al., 2006). DEHB'nin çekirdek belirtilerinden olan dikkat, dürtüsellik ve kendini kontrol edebilme becerisi ile ilgili sorunlar ve hiperaktivite, hem otizmli hem tik bozukluğu olan bireylerde sıklıkla tedavi gerektiren klinik problemleri oluşturmaktadır (Association, 2013b; Banaschewski, Poustka, & Holtmann, 2011). Anksiyete- korku belirtileri, davranım sorunları, obsesif kompulsif davranışlar, duyusal girdilerle ilişkili aşırı duyarlılık, depresyon ve uyku sorunları da başta tik bozukluğu olmak üzere her üç hastalıkta da çok sık görülen klinik tablolardır (Geier, Kern, & Geier, 2012; Ghosh et al., 2014; Hodge, Carollo, Lewin, Hoffman, & Sweeney, 2014; Hvolby, 2015; Ozsivadjian, Hibberd, & Hollocks, 2014).

4. DEHB ile Komorbiditesi Yüksek Psikiyatrik Bozukluklar ve Ortak Genetik Faktörler

4.1. Bipolar Bozukluk-DEHB

Erişkinlerde DEHB-BAB birlikteliği şansla açıklanamayacak kadar yüksektir. Bipolar Bozukluk

JNBS 2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org

tanısı konmuş vakalardaki DEHB oranı %9.5-28, erişkin DEHB tanısı konmuş vakalardaki Bipolar Bozukluk oranı ise %20 civarında görünmektedir. Meta analizlerde bu komorbiditenin yüksekliğini desteklemektedir (S. V. Faraone et al., 2015; Ryden et al., 2009; Wingo & Ghaemi, 2007). Tüm bu sonuçlara rağmen moleküler genetik çalışmalarında komorbidite ile ilgili yeterli kanıta ulaşılamamıştır (Landaas et al., 2011; Lee et al., 2013; Schimmelmann et al., 2013). 2017 yılında yapılan bir çalışma 4609 DEHB, 9650 BAB ve 21,363 sağlıklı bireyin GWAS (genom boyu ilişkilendirme çalışması genetik varyasyonları tanımlamak, bu varyasyonların hastalıkların etiyolojisi veya patofizyolojisindeki etkisini araştırmak amacıyla hasta ve kontrol gruplarının bütün genomlarının analiz edilmesini içeren çalışmalardır) çalışma sonuçlarıyla analizleri tekrarlamış ve DEHB-BAB arasındaki genetik ortaklıkta anlamlı olabilecek SNP'lere (single nükleotid polimorfizm) ulaşılmıştır. Bu SNP lerin 6. Kromozom üzerindeki CEP85L, 10. Kromozom üzerindeki TAF9BP2, ve sadece erken başlangıçlı BAB vakaları analiz edildiğinde de 5. Kromozom üzerindeki ADCY2 geni ile ilişkili olduğu belirlenmiştir (van Hulzen et al., 2017).

4.2. Tourette Sendromu- DEHB

Tourette Sendromu-DEHB arasındaki güçlü komorbiditeye rağmen bu durumun genetik alt yapısı da maalesef yeterince aydınlatılamamıştır. Her iki durumunda poligenik-heterojen yapıda olması etiyolojiyi aydınlatmaya yönelik çalışmalar karşısındaki en önemli zorluk gibi görünmektedir. Bu güne kadar ulaşılabilmiş sonuçlar, DEHB-Hiperaktivite/Dürtüsellik ön planda olan tip ve Tourette komorbiditesinde COMT, DRD2, MAOA ve SLC6A4 ; DEHB-Dikkatsizlik ön planda olan tip ve Tourette komorbiditesinde ise MOBP, DRD1 ve FASD2 genleri ile ilgili polimorfizmlerin etkili olduğunu göstermektedir (Diaz-Anzaldua et al., 2004; El Malhany, Gulisano, Rizzo, & Curatolo, 2015; Tian et al., 2012; Yoon, Gause, Leckman, & Singer, 2007; Yoon, Rippel, et al., 2007)

4.3. SNARE Kompleksi ve DEHB- Diğer Psikiyatrik Hastalıklar

SNARE kompleksi, nörogelişim esnasında etkili olan hücre içi veziküler salınımın önemli bir parçasıdır. Bu kompleksi oluşturan temel proteinler SNAP-25 (synaptosomal- associated protein 25), VAMP (vesicule-associated membrane protein), Syntaxin ve düzenleyici olarak rol alan Sinaptotagmindir. Bu proteinleri kodlayan genlerden SNAP25, VAMP1, VAMP2, STX1A, SYT1, SYT2 genleri DEHB dışında 4 önemli psikiyatrik hastalıkta daha çalışılmış bazı çalışmalarda ilişki saptanmazken, bazılarında pozitif ilişki ortaya konmuştur. Daha ayrıntılı ifade edecek olursak SNAP 25 geni erişkin DEHB (Herken et al., 2014), Major depresif bozukluk (Kim et al., 2007; Wang et al., 2015), Bipolar bozukluk (Etain et al., 2010) ve şizofrenide (Carroll, Kendall, O'Donovan, Owen, & Williams, 2009; Dai et al., 2014; Fanous et al., 2010; Lochman, Balcar, Šťastný, & Šerý, 2013; Wang et al., 2015); VAMP2 geni erişkin DEHB'de (Kenar, Ay, Herken, & Erdal, 2014), STX1A geni erişkin DEHB (Kenar et al., 2014; Sánchez-Mora et al., 2013), Otizm Spektrum Bozukluğu (Durdiaková, Warrier, Banerjee-Basu, Baron-Cohen, & Chakrabarti, 2014; Roberts, Hovanes, Dasouki, Manzardo, & Butler, 2014; Tordjman et al., 2013) ve Şizofrenide (Mulle et al., 2014; Wong et al., 2004) ve SYT1 geni Otizm spektrum bozukluğunda etkili bulunmuştur (Szatmari et al., 2007).

4.4. DEHB ve Diğer Psikiyatrik Hastalıklarda Ortak CNV'ler (Kopya Sayısı Varyantı)

Nöropsikiyatrik hastalıkların etiyolojisinde etkili olduğu düşünülen diğer alan genomik hastalıklar ve CNV'lerdir. Bu hastalıklardan özellikle 22q11.2 delesyonu (Di-George Sendromu), 16 p 11.2 duplikasyonu, 1q21.2 delesyonu, ve 16p11.2 delesyonunun DEHB ile ilişkili olabileceği, aynı genomik sorunların Bipolar Bozukluk, Şizofreni, OSB ve Mental Retardasyonda da değişen derecelerde ilişkili olduğu belirlenmiştir (J Elia et al., 2010; Josephine Elia et al., 2012; Langley et al., 2011; Lionel et al., 2011; Lowther, Costain, Baribeau, & Bassett, 2017).

4.5. BDNF-DEHB ve Diğer Hastalıklar

BDNF santral sinir sisteminde yer alan ve beyin fizyolojisinde önemli görevleri olan bir nötrofindir. Özellikle öğrenme ve hafıza, ödülle ilgili süreçler, bilişsel işlevler gibi nörogelişimsel süreçlerde etkilidir. BDNF sentezinin bozulması ve /veya bağlandığı reseptörlerdeki sorunlar (tropomiyozin kinaz B-TrkB ve p 75) DEHB de dahil birçok psikiyatrik hastalıkla ilişkili görünmektedir. Bu hastalıklardan en çok ele alınan ve sistematik derlemeler/ metaanalizler ile etiyolojideki etkisi araştırılan başlıca psikiyatrik hastalıklar majör depresyon (Hing, Sathyaputri, & Potash, 2017; Hosang, Shiles, Tansey, McGuffin, & Uher, 2014; Molendijk et al., 2014), otizm spektrum bozukluğu (Hellings, Arnold, & Han, 2017; Spratt et al., 2015), şizofreni ve bipolar bozukluktur (Ahmed, Mantini, Fridberg, & Buckley, 2015; Notaras, Hill, & Van den Buuse, 2015; Reinhart et al., 2015). Bu çalışmaların sonuçları da çelişkili görünmektedir.

4.6. Çalışma Belleği ile İlgili Genetik Faktörler- DEHB ve Diğer Psikiyatrik Hastalıklar

Önemli nörogelişimsel/nöropsikiyatrik hastalıklardan şizofreni, bipolar bozukluk, DEHB, otizm ve major depresif bozuklukta ortak sorunlardan biri de çalışma belleği ile ilgilidir. Çalışma belleğindeki bozuklukların genetik etiyolojisi ile ilgili çalışmalar, COMT, DAT1, D1,D2, metabotropik glutamat reseptörü mgluR3 (GRM3), DISC1, Neurogulin 1 (NRG1), Voltaj bağımlı kalsiyum kanalı (CACNA1C), Reelin glikoproteini geni (RELN), ve BDNF geni ile ilgili farklılıkların etkisine dikkat çekmektedir (Schwarz, Tost, & Meyer-Lindenberg, 2016). Farkedilebileceği gibi, DEHB etiyolojisiyle ilişkili bulunmuş genlerden bazıları da çalışma belleği ile ilgilidir ve komorbidite/ genetik ortak altyapı ihtimalini desteklemektedir.

5. Sonuç

DEHB yaygınlığı ve yaşam kalitesine olumsuz etkileri açısından oldukça önemli bir psikiyatrik bozukluktur.

Geçmiş yıllardaki çalışmalarda DEHB'nin ailesel ve kalıtımsal geçiş gösterdiği saptanmışsa da, diğer çoğu psikiyatrik bozuklukta olduğu gibi, epigenetik değişiklikler ve etnik köken farklılıklarının etkisiyle kliniğe yansımada ciddi farklılıklar görülmekte ve bu durum hastalığın tanı, tedavi ve önlenmesinde önemli zorluklara neden olmaktadır. Çalışmalarla elde edilen veriler, DEHB'nin pek çok diğer psikiyatrik bozuklukla klinik ve etiyolojik açıdan ortak özelliklere sahip olduğunu, bu nedenle çok yönlü ele alınmasının gerekliliğini vurgulamaktadır.

Kaynakça

Ahmed, A. O., Mantini, A. M., Fridberg, D. J., & Buckley, P. F. (2015). Brain-derived neurotrophic factor (BDNF) and neurocognitive deficits in people with schizophrenia: a meta-analysis. Psychiatry research, 226(1), 1-13.

Anastopoulos, A. D., Smith, T. F., Garrett, M. E., Morrissey-Kane, E., Schatz, N. K., Sommer, J. L.,... Ashley-Koch, A. (2011). Self-regulation of emotion, functional impairment, and comorbidity among childrenwith AD/HD. Journal of attention disorders, 15(7), 583-592.

Aoki, Y., Abe, O., Nippashi, Y., & Yamasue, H. (2013). Comparison of white matter integrity between autism spectrum disorder subjects and typically developing individuals: a meta-analysis of diffusion tensor imaging tractography studies. Molecular autism, 4(1), 1.

Association, A. P. (2013a). Diagnostic and statistical manual of mental disorders (DSM-5®): American Psychiatric Pub.

Association, A. P. (2013b). DSM 5: American Psychiatric Association.

Banaschewski, T., Poustka, L., & Holtmann, M. (2011). [Autism and ADHD across the life span. Differential diagnoses or comorbidity?]. Der Nervenarzt, 82(5), 573-580.

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychological bulletin, 121(1), 65.

Barkley, R. A., & Fischer, M. (2010). The unique contribution of emotional impulsiveness to impairment in major life activities in hyperactive children as adults. Journal of the American Academy of Child & Adolescent Psychiatry, 49(5), 503-513.

Biederman, J., Monuteaux, M. C., Spencer, T., Wilens, T. E., & Faraone, S. V. (2009). Do stimulants protect against psychiatric disorders in youth with ADHD? A 10-year follow-up study. Pediatrics, 124(1), 71-78.

Biederman, J., Newcorn, J., & Sprich, S. (1991). Comorbidity of attention deficit hyperactivity disorder. Am J Psychiatry, 148(5), 564-577.

Cao, M., Shu, N., Cao, Q., Wang, Y., & He, Y. (2014). Imaging functional and structural brain connectomics in attention-deficit/hyperactivity disorder. Molecular neurobiology, 50(3), 1111-1123.

Carroll, L., Kendall, K., O'Donovan, M., Owen, M., & Williams, N. (2009). Evidence that putative ADHD low risk alleles at SNAP25 may increase the risk of schizophrenia. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 150(7), 893-899.

Casanova, M. F., El-Baz, A., Mott, M., Mannheim, G., Hassan, H., Fahmi, R.,... Farag, A. (2009). Reduced gyral window and corpus callosum size in autism: possible macroscopic correlates of a minicolumnopathy. Journal of autism and developmental disorders, 39(5), 751-764.

Castellanos, F. X., & Tannock, R. (2002). Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nature Reviews Neuroscience, 3(8), 617-628.

Coghill, D., Seth, S., & Matthews, K. (2014). A comprehensive assessment of memory, delay aversion, timing, inhibition, decision making and variability in attention deficit hyperactivity disorder: advancing beyond the three-pathway models. Psychological medicine, 44(09), 1989-2001.

Connor, D. F., Steeber, J., & McBurnett, K. (2010). A review of attention-deficit/hyperactivity disorder complicated by symptoms of oppositional defiant disorder or conduct disorder. Journal of Developmental & Behavioral Pediatrics, 31(5), 427-440.

Cortese, S., Kelly, C., Chabernaud, C., Proal, E., Di Martino, A., Milham, M. P., & Castellanos, F. X. (2012). Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. American Journal of Psychiatry.

Da Fonseca, D., Seguier, V., Santos, A., Poinso, F., & Deruelle, C. (2009). Emotion understanding in children with ADHD. Child psychiatry and human development, 40(1), 111-121.

Dai, D., Wang, Y., Yuan, J., Zhou, X., Jiang, D., Li, J.,... Duan, S. (2014). Meta-analyses of 10 polymorphisms associated with the risk of schizophrenia. Biomedical reports, 2(5), 729-736.

Daley, D., & Birchwood, J. (2010). ADHD and academic performance: why does ADHD impact on academic performance and what can be done to support ADHD children in the classroom? Child: care, health and development, 36(4), 455-464.

Daley, D., Jones, K., Hutchings, J., & Thompson, M. (2009). Attention deficit hyperactivity disorder in pre-school children: current findings, recommended interventions and future directions. Child: care, health and development, 35(6), 754-766.

Davies, W. (2014). Sex differences in attention Deficit Hyperactivity Disorder: candidate genetic and endocrine mechanisms. Frontiers in neuroendocrinology, 35(3), 331-346.

Diaz-Anzaldua, A., Joober, R., Riviere, J., Dion, Y., Lesperance, P., Richer, F.,... Rouleau, G. (2004). Tourette syndrome and dopaminergic genes: a family-based association study in the French Canadian founder population. Molecular psychiatry, 9(3), 272-277.

DuPaul, G. J., McGoey, K. E., Eckert, T. L., & VanBrakle, J. (2001). Preschool children with attention-deficit/hyperactivity disorder: impairments in behavioral, social, and school functioning. Journal of the American Academy of Child & Adolescent Psychiatry, 40(5), 508-515.

Durdiaková, J., Warrier, V., Banerjee-Basu, S., Baron-Cohen, S., & Chakrabarti, B. (2014). STX1A and Asperger syndrome: a replication study. Molecular autism, 5(1), 14.

El Malhany, N., Gulisano, M., Rizzo, R., & Curatolo, P. (2015). Tourette syndrome and comorbid ADHD: causes and consequences. European journal of pediatrics, 174(3), 279-288.

Elia, J., Gai, X., Xie, H., Perin, J., Geiger, E., Glessner, J.,... Lantieri, F. (2010). Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes. Molecular psychiatry, 15(6), 637-646.

Elia, J., Glessner, J. T., Wang, K., Takahashi, N., Shtir, C. J., Hadley, D.,... Robison, R. (2012). Genome-wide copy number variation study associates metabotropic glutamate receptor gene networks with attention deficit hyperactivity disorder. Nature genetics, 44(1), 78-84.

Etain, B., Dumaine, A., Mathieu, F., Chevalier, F., Henry, C., Kahn, J.-P.,... Jamain, S. (2010). A SNAP25 promoter variant is associated with early-onset bipolar disorder and a high expression level in brain. Molecular psychiatry, 15(7), 748-755.

Fanous, A., Zhao, Z., Van Den Oord, E., Maher, B., Thiselton, D., Bergen, S.,... O'Neill, F. (2010). Association study of SNAP25 and schizophrenia in irish family and case–control samples. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 153(2), 663-674.

Faraone, S., Biederman, J., & Monuteaux, M. (2002). Further evidence for the diagnostic continuity between child and adolescent ADHD. Journal of attention disorders, 6(1), 5-13.

Faraone, S. V., Asherson, P., Banaschewski, T., Biederman, J., Buitelaar, J. K., Ramos-Quiroga, J. A.,... Franke, B. (2015). Attention-deficit/hyperactivity disorder. Nature reviews disease primers, 1, 15020.

Frazier, T. W., Youngstrom, E. A., Glutting, J. J., & Watkins, M. W. (2007). ADHD and achievement meta-analysis of the child, adolescent, and adult literatures and a concomitant study with college students. Journal of learning disabilities, 40(1), 49-65.

Gallo, E. F., & Posner, J. (2016). Attention-deficit hyperactivity disorder 1 Moving towards causality in attention-deficit hyperactivity disorder: overview of neural and genetic mechanisms. Lancet, 3, 555-567.

García-Castellar, R., Jara-Jiménez, P., Sánchez-Chiva, D., & Mikami, A. Y. (2015). Social Skills Deficits in a Virtual Environment Among Spanish Children With ADHD. Journal of attention disorders, 1087054715591850.

Geier, D. A., Kern, J. K., & Geier, M. R. (2012). A prospective Cross-sectional Cohort Assessment of Health, Physical, and Behavioral Problems in Autism Spectrum Disorders. Maedica-a Journal of Clinical Medicine, 7(3).

Geissler, J., & Lesch, K.-P. (2011). A lifetime of attention-deficit/hyperactivity disorder: diagnostic challenges, treatment and neurobiological mechanisms. Expert review of neurotherapeutics, 11(10), 1467-1484.

Ghosh, D., Rajan, P. V., Das, D., Datta, P., Rothner, A. D., & Erenberg, G. (2014). Sleep disorders in children with Tourette syndrome. Pediatric neurology, 51(1), 31-35.

Grzadzinski, R., Di Martino, A., Brady, E., Mairena, M. A., O'Neale, M., Petkova, E.,... Castellanos, F. X. (2011). Examining autistic traits in children with ADHD: does the autism spectrum extend to ADHD? Journal of autism and developmental disorders, 41(9), 1178-1191.

Harpin, V., Mazzone, L., Raynaud, J.-P., Kahle, J., & Hodgkins, P. (2016). Long-Term Outcomes of ADHD A Systematic Review of Self-Esteem and Social Function. Journal of attention disorders, 20(4), 295-305.

Hattori, J., Ogino, T., Abiru, K., Nakano, K., Oka, M., & Ohtsuka, Y. (2006).

JNBS 2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org

Are pervasive developmental disorders and attention-deficit/hyperactivity disorder distinct disorders? Brain and Development, 28(6), 371-374.

Hellings, J. A., Arnold, L. E., & Han, J. C. (2017). Dopamine antagonists for treatment resistance in autism spectrum disorders: review and focus on BDNF stimulators loxapine and amitriptyline. Expert Opinion on Pharmacotherapy, 18(6), 581-588.

Herken, H., Erdal, M. E., Kenar, A. N. İ., Ünal, G. A., Çakaloz, B., Ay, M. E.,... Şengül, C. (2014). Association of SNAP-25 Gene Ddel and Mnll Polymorphisms with Adult Attention Deficit Hyperactivity Disorder. Psychiatry Investigation, 11(4), 476-480.

Hing, B., Sathyaputri, L., & Potash, J. B. (2017). A comprehensive review of genetic and epigenetic mechanisms that regulate BDNF expression and function with relevance to major depressive disorder. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics.

Hodge, D., Carollo, T. M., Lewin, M., Hoffman, C. D., & Sweeney, D. P. (2014). Sleep patterns in children with and without autism spectrum disorders: developmental comparisons. Research in developmental disabilities, 35(7), 1631-1638.

Hosang, G. M., Shiles, C., Tansey, K. E., McGuffin, P., & Uher, R. (2014). Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis. BMC medicine, 12(1), 7.

Hoza, B. (2007). Peer functioning in children with ADHD. Journal of pediatric psychology, 32(6), 655-663.

Hoza, B., Gerdes, A. C., Mrug, S., Hinshaw, S. P., Bukowski, W. M., Gold, J. A.,... Elliott, G. R. (2005). Peer-assessed outcomes in the multimodal treatment study of children with attention deficit hyperactivity disorder. Journal of Clinical Child and Adolescent Psychology, 34(1), 74-86.

Hvolby, A. (2015). Associations of sleep disturbance with ADHD: implications for treatment. ADHD Attention Deficit and Hyperactivity Disorders, 7(1), 1-18.

Jensen, P. S., Hinshaw, S. P., Kraemer, H. C., Lenora, N., Newcorn, J. H., Abikoff, H. B.,... Conners, C. K. (2001). ADHD comorbidity findings from the MTA study: comparing comorbid subgroups. Journal of the American Academy of Child & Adolescent Psychiatry, 40(2), 147-158.

Kenar, A. N. I., Ay, Ö. İ., Herken, H., & Erdal, M. E. (2014). Association of VAMP-2 and Syntaxin 1A Genes with Adult Attention Deficit Hyperactivity Disorder. Psychiatry Investigation, 11(1), 76-83.

Keown, C. L., Shih, P., Nair, A., Peterson, N., Mulvey, M. E., & Müller, R.-A. (2013). Local functional overconnectivity in posterior brain regions is associated with symptom severity in autism spectrum disorders. Cell reports, 5(3), 567-572.

Kern, J. K., Geier, D. A., King, P. G., Sykes, L. K., Mehta, J. A., & Geier, M. R. (2015). Shared brain connectivity issues, symptoms, and comorbidities in autism spectrum disorder, attention deficit/hyperactivity disorder, and Tourette syndrome. Brain connectivity, 5(6), 321-335.

Kim, J., Biederman, J., Arbeitman, L., Fagerness, J., Doyle, A., Petty, C.,... Faraone, S. (2007). Investigation of variation in SNAP-25 and ADHD and relationship to co-morbid major depressive disorder. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 144(6), 781-790.

Landaas, E., Johansson, S., Halmøy, A., Oedegaard, K., Fasmer, O., & Haavik, J. (2011). Bipolar disorder risk alleles in adult ADHD patients. Genes, Brain and Behavior, 10(4), 418-423.

Langley, K., Martin, J., Agha, S. S., Davies, C., Stergiakouli, E., Holmans, P.,... Thapar, A. (2011). Clinical and cognitive characteristics of children with attention-deficit hyperactivity disorder, with and without copy number variants. The British Journal of Psychiatry, 199(5), 398-403.

Lee, S. H., Ripke, S., Neale, B. M., Faraone, S. V., Purcell, S. M., Perlis, R. H.,... Witte, J. S. (2013). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nature genetics, 45(9), 984.

Lionel, A. C., Crosbie, J., Barbosa, N., Goodale, T., Thiruvahindrapuram, B., Rickaby, J.,... Wang, Z. (2011). Rare copy number variation discovery and cross-disorder comparisons identify risk genes for ADHD. Science translational medicine, 3(95), 95ra75-95ra75.

Liu, T., Chen, Y., Lin, P., & Wang, J. (2014). Small-world brain functional networks in children with attention-deficit/hyperactivity disorder revealed by EEG synchrony. Clinical EEG and neuroscience, 1550059414523959.

Lochman, J., Balcar, V. J., Šťastný, F., & Šerý, O. (2013). Preliminary evidence for association between schizophrenia and polymorphisms in the regulatory Regions of the ADRA2A, DRD3 and SNAP-25 Genes. Psychiatry research, 205(1), 7-12.

Lowther, C., Costain, G., Baribeau, D. A., & Bassett, A. S. (2017). Genomic Disorders in Psychiatry—What Does the Clinician Need to Know? Current psychiatry reports, 19(11), 82.

Mikami, A. Y., Huang-Pollock, C. L., Pfiffner, L. J., McBurnett, K., & Hangai, D. (2007). Social skills differences among attention-deficit/hyperactivity disorder types in a chat room assessment task. Journal of abnormal child psychology, 35(4), 509-521.

Molendijk, M., Spinhoven, P., Polak, M., Bus, B., Penninx, B., & Elzinga, B. (2014). Serum BDNF concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analyses on 179 associations (N= 9484). Molecular psychiatry, 19(7), 791-800.

Mulle, J. G., Pulver, A. E., McGrath, J. A., Wolyniec, P. S., Dodd, A. F., Cutler, D. J.,... Conrad, D. F. (2014). Reciprocal duplication of the Williams-Beuren syndrome deletion on chromosome 7q11. 23 is associated with schizophrenia. Biological psychiatry, 75(5), 371-377.

Musser, E. D., Galloway-Long, H. S., Frick, P. J., & Nigg, J. T. (2013). Emotion regulation and heterogeneity in attention-deficit/hyperactivity disorder. Journal of the American Academy of Child & Adolescent Psychiatry, 52(2), 163-171. e162.

Notaras, M., Hill, R., & Van den Buuse, M. (2015). A role for the BDNF gene Val66Met polymorphism in schizophrenia? A comprehensive review. Neuroscience & Biobehavioral Reviews, 51, 15-30.

Ozsivadjian, A., Hibberd, C., & Hollocks, M. J. (2014). Brief report: the use of self-report measures in young people with autism spectrum disorder to access symptoms of anxiety, depression and negative thoughts. Journal of autism and developmental disorders, 44(4), 969-974.

Peters, J. M., Taquet, M., Vega, C., Jeste, S. S., Fernández, I. S., Tan, J.,... Warfield, S. K. (2013). Brain functional networks in syndromic and non-syndromic autism: a graph theoretical study of EEG connectivity. BMC medicine, 11(1), 54.

Polanczyk, G., de Lima, M. S., Horta, B. L., Biederman, J., & Rohde, L. A. (2007). The worldwide prevalence of ADHD: a systematic review and metaregression analysis. American journal of psychiatry.

Posner, J., Kass, E., & Hulvershorn, L. (2014). Using stimulants to treat ADHD-related emotional lability. Current psychiatry reports, 16(10), 1-8.

Reinhart, V., Bove, S. E., Volfson, D., Lewis, D. A., Kleiman, R. J., & Lanz, T. A. (2015). Evaluation of TrkB and BDNF transcripts in prefrontal cortex, hippocampus, and striatum from subjects with schizophrenia, bipolar disorder, and major depressive disorder. Neurobiology of disease, 77, 220-227.

Roberts, J. L., Hovanes, K., Dasouki, M., Manzardo, A. M., & Butler, M. G. (2014). Chromosomal microarray analysis of consecutive individuals with autism spectrum disorders or learning disability presenting for genetic services. Gene, 535(1), 70-78.

Ryden, E., Thase, M., Stråht, D., Åberg-Wistedt, A., Bejerot, S., & Landen, M. (2009). A history of childhood attention-deficit hyperactivity disorder (ADHD) impacts clinical outcome in adult bipolar patients regardless of current ADHD. Acta Psychiatrica Scandinavica, 120(3), 239-246.

Sánchez-Mora, C., Cormand, B., Ramos-Quiroga, J. A., Hervás, A., Bosch, R., Palomar, G.,... Corrales, M. (2013). Evaluation of common variants in 16 genes involved in the regulation of neurotransmitter release in ADHD. European Neuropsychopharmacology, 23(6), 426-435.

Schimmelmann, B., Hinney, A., Scherag, A., Pütter, C., Pechlivanis, S., Cichon, S.,... Albayrak, Ö. (2013). Bipolar disorder risk alleles in children with ADHD. Journal of neural transmission, 120(11), 1611-1617.

Schwarz, E., Tost, H., & Meyer-Lindenberg, A. (2016). Working memory genetics in schizophrenia and related disorders: An RDoC perspective. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 171(1), 121-131.

Seidman, L. J. (2006). Neuropsychological functioning in people with ADHD across the lifespan. Clinical psychology review, 26(4), 466-485.

Shaw, P., Stringaris, A., Nigg, J., & Leibenluft, E. (2014). Emotion dysregulation in attention deficit hyperactivity disorder. American Journal of Psychiatry.

Simon, V., Czobor, P., Bálint, S., Mészáros, Á., & Bitter, I. (2009). Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. The British Journal of Psychiatry, 194(3), 204-211.

Sjöwall, D., Roth, L., Lindqvist, S., & Thorell, L. B. (2013). Multiple deficits in ADHD: executive dysfunction, delay aversion, reaction time variability, and emotional deficits. Journal of Child Psychology and Psychiatry, 54(6), 619-627.

Sonuga-Barke, E., Bitsakou, P., & Thompson, M. (2010). Beyond the dual pathway model: evidence for the dissociation of timing, inhibitory, and delay-related impairments in attention-deficit/hyperactivity disorder. Journal of the American Academy of Child & Adolescent Psychiatry, 49(4), 345-355.

Sonuga-Barke, E. J. (2002). Psychological heterogeneity in AD/HD—a dual pathway model of behaviour and cognition. Behavioural brain research, 130(1), 29-36.

Sonuga-Barke, E., Taylor, E., Sembi, S., & Smith, J. (1992). Hyperactivity and delay aversion—I. The effect of delay on choice. Journal of Child

Psychology and Psychiatry, 33(2), 387-398.

Sonuga-Barke, E. J., & Halperin, J. M. (2010). Developmental phenotypes and causal pathways in attention deficit/hyperactivity disorder: potential targets for early intervention? Journal of Child Psychology and Psychiatry, 51(4), 368-389.

Spencer, T. J., Biederman, J., & Mick, E. (2007). Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. Journal of pediatric psychology, 32(6), 631-642.

Spratt, E. G., Granholm, A.-C., Carpenter, L. A., Boger, H. A., Papa, C. E., Logan, S.,... Brady, K. T. (2015). Pilot study and review: physiological differences in BDNF, a potential biomarker in males and females with autistic disorder. International neuropsychiatric disease journal, 3(1), 19.

Sternat, T., & Katzman, M. A. (2016). Neurobiology of hedonic tone: the relationship between treatment-resistant depression, attention-deficit hyperactivity disorder, and substance abuse. Neuropsychiatric Disease and Treatment, 12, 2149.

Szatmari, P., Paterson, A. D., Zwaigenbaum, L., Roberts, W., Brian, J., Liu, X.-Q.,... Senman, L. (2007). Mapping autism risk loci using genetic linkage and chromosomal rearrangements. Nature genetics, 39(3), 319.

Tarver, J., Daley, D., & Sayal, K. (2014). Attention-deficit hyperactivity disorder (ADHD): an updated review of the essential facts. Child: care, health and development, 40(6), 762-774.

Thapar, A., Cooper, M., Eyre, O., & Langley, K. (2013). Practitioner review: what have we learnt about the causes of ADHD? Journal of Child Psychology and Psychiatry, 54(1), 3-16.

Tian, Y., Stamova, B., Ander, B. P., Jickling, G. C., Gunther, J. R., Corbett, B. A.,... Sharp, F. R. (2012). Correlations of gene expression with ratings of inattention and hyperactivity/impulsivity in tourette syndrome: a pilot study. BMC medical genomics, 5(1), 49.

Tordjman, S., Anderson, G. M., Cohen, D., Kermarrec, S., Carlier, M., Touitou, Y.,... Verloes, A. (2013). Presence of autism, hyperserotonemia, and severe expressive language impairment in Williams-Beuren syndrome. Molecular autism, 4(1), 29.

Tripp, G., & Wickens, J. R. (2009). Neurobiology of ADHD. Neuropharmacology, 57(7), 579-589.

Van Den Hoofdakker, B. J., Van der Veen-Mulders, L., Sytema, S., Emmelkamp, P. M., Minderaa, R. B., & Nauta, M. H. (2007). Effectiveness of behavioral parent training for children with ADHD in routine clinical practice: a randomized controlled study. Journal of the American Academy of Child & Adolescent Psychiatry, 46(10), 1263-1271.

van Hulzen, K. J., Scholz, C. J., Franke, B., Ripke, S., Klein, M., McQuillin, A.,... Andreassen, O. A. (2017). Genetic overlap between attention-deficit/hyperactivity disorder and bipolar disorder: Evidence from genome-wide association study meta-analysis. Biological psychiatry, 82(9), 634-641.

Villodas, M. T., Pfiffner, L. J., & McBurnett, K. (2012). Prevention of serious conduct problems in youth with attention deficit/hyperactivity disorder. Expert review of neurotherapeutics, 12(10), 1253-1263.

Wang, Q., Wang, Y., Ji, W., Zhou, G., He, K., Li, Z.,... Shen, J. (2015). SNAP25 is associated with schizophrenia and major depressive disorder in the Han Chinese population. The Journal of clinical psychiatry, 76(1), e76-82.

Wilens, T. E., Biederman, J., Brown, S., Tanguay, S., Monuteaux, M. C., Blake, C., & Spencer, T. J. (2002). Psychiatric comorbidity and functioning in clinically referred preschool children and school-age youths with ADHD. Journal of the American Academy of Child & Adolescent Psychiatry, 41(3), 262-268.

Willcutt, E. G. (2012). The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. Neurotherapeutics, 9(3), 490-499.

Willcutt, E. G., Doyle, A. E., Nigg, J. T., Faraone, S. V., & Pennington, B. F. (2005). Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. Biological psychiatry, 57(11), 1336-1346.

Wingo, A. P., & Ghaemi, S. N. (2007). A systematic review of rates and diagnostic validity of comorbid adult attention-deficit/hyperactivity disorder and bipolar disorder. The Journal of clinical psychiatry.

Wong, A. H., Trakalo, J., Likhodi, O., Yusuf, M., Macedo, A., Azevedo, M.-H.,... Pato, C. N. (2004). Association between schizophrenia and the syntaxin 1A gene. Biological psychiatry, 56(1), 24-29.

Yoon, D. Y., Gause, C. D., Leckman, J. F., & Singer, H. S. (2007). Frontal dopaminergic abnormality in Tourette syndrome: a postmortem analysis. Journal of the neurological sciences, 255(1), 50-56.

Yoon, D. Y., Rippel, C. A., Kobets, A. J., Morris, C. M., Lee, J. E., Williams, P. N.,... Singer, H. S. (2007). Dopaminergic polymorphisms in Tourette syndrome: association with the DAT gene (SLC6A3). American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 144(5), 605-610.

CASE REPORT-VAKA ÇALIŞMASI

Year (Yıl) : 2018
Volume (Cilt) : 5
Issue Number (Sayı) : 3
Doi : 10.5455/JNBS.1537169385

Received/Geliş 17.09.2018
Accepted/Kabul 09.10.2018
JNBS, 2018, 5(3): 184-186

A RARE CAUSE OF ACUTE HYPONATREMIA: PSYCHOGENIC POLYDIPSIA

AKUT HİPONATREMİNİN NADİR NEDENİ: PSİKOJENİK POLİDİPSİ

Mahmut Tas[1*], Mehmet Tahir Gokdemir[1], Abdullah Şen[1], Öner Avınca[1], Mehmet Serdar Yıldırım[2]

Abstract

Psychogenic polydipsia is a psychiatric condition characterized by excessive drinking of water. In studies conducted regarding psychogenic or primary polydipsia, it's been reported in patients with psychiatric disorders. Excessive drinking of water can lead to excessive fluid loading and electrolyte imbalance. We aimed to present a patient case with psychotic disorder who developed hyponatremia due to extreme water drinking and applied to emergency service with loss of consciousness. Case Presentation: Thirty-four-year-old male, secondary school graduate, single, living with his family was applied to emergency room clinically unconscious. In physical examination, general situation was bad, glasgow coma scale score point was 8. Minimal brain edema was detected in cranial computed tomography (CT). In laboratory tests Na: 109 mmol / L (136-145 mmol / L). The patient who was diagnosed with schizophrenia used drugs he could not remember its name. For the past 3 years, the patient has been using amylsulpride 1200 mg / day, valproic acid + sodium valproate 1000 mg / day and clozapine 600 mg / day. The patient was treated in emergency room with 150 ml 3% hypertonic infusion twice in 20 minutes to increase the Na concentration in the first hour by 5 mmol / L and to relieve symptoms. As conclusion, hyponatremia patients may apply to emergency room with nonspecific symptoms such as nausea and vomiting at the onset and consciousness changes that may progress to coma. Psychogenic polydipsia-associated hyponatremia should be considered in patients with similar clinical findings and psychiatric history admitted to emergency room.

Keywords: Hyponatremia; psychogenic polydipsia; water intoxication

Giriş

Psikojenik polidipsi, aşırı su içme ile karakterize bir psikiyatrik durumdur. Yapılan çalışmalarda Psikojenik veya primer polidipsi psikiyatrik bozukluğu olan hastalarda bildirilmiştir. Aşırı su içilmesi sıvı yüklemesine ve elektrolit dengesizliğine yol açabilir. Bizler, psikotik bozukluğu olan Aşırı su içilmesi nedeniyle hiponatremi ve bilinç kaybı gelişmesi sonucu acil servise başvuran bir olgu sunmayı amaçladık.Vaka sunumu: Otuz dört yaşında, ortaokul mezunu, bekâr, ailesi ile beraber yaşayan erkek hasta acil servis kliniğimize bilinci kapalı vaziyette getirildi. Yapılan muayenesinde genel durum kötü, bilinç kapalı Glasgow Koma Skalası (GKS) 8, kranial bilgisayarlı tomografi (BBT)'sinde minimal beyin ödemi değerlendirildi. Laboratuvar tetkiklerinde Na:109 mmol/L (136-145 mmol/L), tespit edildi. Şizofreni tanısı alan hasta bu süre zarfında ismini hatırlayamadığı ilaçlar kullanmış. Son 3 yıldır amilsulprid 1200 mg/gün,valproik asit+sodyum valproat 1000 mg/gün ve klozapin 600 mg/gün ilaçlarını kullanıyormuş. Hastaya Acil serviste, ilk 1 saatte Na konsantrasyonunu 5 mmol/l artırmak ve semptomların gerilemesini sağlamak amacıyla 150 ml %3'lük hipertonik infüzyonunu 20 dakikada gidecek şekilde 2 defa uygulandı. Sonuç olarak, hiponatremi hastaları, başlangıçta bulantı kusma ve tablo komaya kadar ilerleyebilen bilinç değişikliği gibi nonspesifik klinik bulgularla acil servise başvurabilirler. Benzer klinik bulgularla acil servise başvuran psikiyatrik öyküsü olan hastalarda psikojenik polidipsiye bağlı gelişen hiponatremi akla gelmelidir.

Anahtar Kelimeler: *hiponatremi; psikojenik polidipsi; su zehirlenmesi*

[1]Health Sciences University, Gazi Yasargil Research and Training Hospital, Emergency Department, Diyarbakır, Turkey.
[2]Health Sciences University, Gazi Yasargil Research and Training Hospital, Department of Internal Medicine Diyarbakır, Turkey.
[*]Corresponding Author: Health Sciences University, Gazi Yasargil Research and Training Hospital, Emergency Department, Diyarbakır, Turkey.
E-mail: drmahmuttas@gmail.com

1. Introduction

Psychogenic polydipsia is a psychiatric condition characterized by excessive drinking of water. (Cronin RE.,1987). For the first time, in 1933, Hoskins and Sleeper described polyuria in schizophrenic patients. Then, in 1938, a 31-year-old female schizophrenic patient who had undergone convulsions after excessive water consumption was published by Baharal (Illowsky BP.et al., 1988;Bremner AJ.et al.,1991). In studies conducted regarding psychogenic or primary polydipsia, it's been reported that about 6-20% of psychiatric patients could be affected .(Verghese C.et al.,1996).

Fatal water intoxication has been described in many different clinical situations in the literature. The most common being the term "psychogenic polydipsia" while others as; Polydipsia-hyponatremia syndrome (PHS), hysterical polydipsia, compulsive polydipsia, primer polydipsia, dipsomania, potomania, water poisoning, psychogenic water poisoning and spontaneous water poisoning. Unspecific symptoms such as nausea and vomiting may be seen early in patients, and there may be changes in mental and psychotic symptoms. This may cause delay in the diagnosis. Early diagnosis is very important to prevent severe hyponatremia that can result seizures, coma and death (Farrell DJ.et al., 2003) In this article, we aimed to present a patient case with psychotic disorder who developed hyponatremia due to extreme water drinking and applied to emergency service with loss of consciousness.

2. Case Report

Thirty-four-year-old male, secondary school graduate, single, living with his family was applied to emergency room clinically unconscious. In physical examination, general situation was bad, glasgow coma scale score point was 8. Minimal brain edema was detected in cranial computed tomography (CT). In laboratory tests Na: 109 mmol / L (136-145 mmol / L), Urea: 6 mmol / L, Creatine: 0,52 mmol / L, Potassium 4,42 mmol / L, Chlorine 69,9 mmol / L, Glucose 109 mmol / L. Arterial blood gas analysis pH: 7,49, pCO2: 25,7 pO2: 60,3. In urine analysis, a density of 1001 mg / dL (1005-1030 mg / dL) was detected.

In the archive review of the patient, he first applied to the psychiatric outpatient clinic in 2003 for aggressive behavior, percussion delusions, anger explosions, and delusions. The patient who was diagnosed with schizophrenia used drugs he could not remember its name. For the past 3 years, the patient has been using amylsulpride 1200 mg / day, valproic acid + sodium valproate 1000 mg / day and clozapine 600 mg / day. The patient's general condition was good until last week; the patient was admitted to the emergency department after worsening of consciousness after agitation and aggressive behaviors developed in the last 2 days. According to the information from the family of the patient, they said that he drank a lot of water and made urine very often and that he drank a lot of water in the last week. In other examinations, no pathology was found and the patient was diagnosed as psychogenic polydipsia due to excessive water intake and acute hyponatremia due to it.

The patient was treated in emergency room with 150 ml 3% hypertonic infusion twice in 20 minutes to increase the Na concentration in the first hour by 5 mmol / L and to relieve symptoms. The patient's level of conscious was improved during the treatment in emergency room, and then he was transferred to intensive care unit for follow-up and treatment. Treatment was continued with sodium chloride and water restriction. He was discharged with the recommendation to apply to the psychiatric outpatient clinic after the sodium value increased to 137 mEq/L and the general condition improved.

3. Discussion

Excessive water drinking in our case was diagnosed as psychogenic polydipsia based on the history and the examinations of the results. Excessive intake of polydipsia or fluids is often seen in patients with psychiatric disorders, particularly schizophrenia, when in fact there is no need for water. Sudden and / or severe hyponatremia that develops as a result of a condition defined as water intoxication may lead to brain edema leading to neurological and psychiatric symptoms. For this reason, continuous ingestion of fluids in large quantities may result in a potentially fatal medical problem .(De Leon J.et al.,1994).

Polydipsia, which develops in psychiatric patients, is totally voluntary in some cases. Excessive water intake of patients with hypersensitivity to vasopressin is caused by an increase in the dopaminergic activity and consequently the elevated dopamine level stimulating the thirst center. The etiopathogenesis of psychogenic polydipsia remains uncertain despite this theories .(Dundas B.et al.,2007). An organic cause was not found as a result of the examinations performed in our case. The fact that the patient was treated for a long period due to schizophrenia in the archive scan was consistent with the literature in that the vast majority of psychogenic polydipsia cases occurred in chronic schizophrenic patients.

Psychogenic polydipsia or primer polydipsia is characterized by low plasma sodium. Hyponatremia may exacerbate psychotic symptoms, sodium deficiency may imitate early symptomatic psychosis or bipolar disorder. (Dundas B.et al.,2007). Acute-onset hyponatremia may induce delirium and behavioral changes that may resemble psychomotor agitation or retardation. Our patient initially showed agitation and aggressive behavior, and then the consciousness was closed. We think that the cause of acute hyponatremia due to excessive water intake is the rapid change of consciousness that develops within a few days.

Early diagnosis is important in reducing morbidity and mortality associated with hyponatremic encephalopathy. Prior symptoms in the hyponatremic clinic include nausea, vomiting, disorientation, headache, fatigue, numbness, confusion and muscle cramps. Most patients do not show symptoms until serum [Na +] <125 mEq / L8. Patients with chronic hyponatremia may exhibit nonspecific symptoms at lower serum [Na +] levels, usually up to <120 mEq / L. As hyponatremia progresses, patients

JNBS 2018 Published by Üsküdar University / 2018 Üsküdar Üniversitesi tarafından yayımlanmaktadır www.jnbs.org

may react improperly to verbal and painful stimuli and may exhibit bizarre behavior or psychiatric symptoms such as auditory or visual hallucinations may be observed. Cerebral edema progression may lead to supratentorial cerebral herniation, which may lead to seizures, or may result in respiratory arrest due to compression of the brainstem (Siegel AJ, 2008). The serum sodium level of the patient was measured as 109 mEq / L.

Treatment should aim to increase the Na level rapidly in cases of acute hyponatremia. It is known that hyponatremia is a risk of osmotic demyelination when corrected very fast. However, in the hyponatremic guideline of 2014, it was underlined that the brain edema caused by hyponatremia should be eliminated immediately. Inadequately treated hyponatremia due to slow infusion may result in permanent damage due to brain edema, herniation or even death. Therefore, the 2014 hyponatremia guide takes rapid treatment of hyponatremia as priority, despite the risk of osmotic demyelination (Spasovski G.et al., 2014). Encephalopathy may progress to seizure and coma, which require aggressive correction with hypertonic solutions such as 3% saline, to reduce neurological morbidity and death risk with respiratory arrest (Nzerue CM.et al., 2003). An aggressive treatment protocol was applied to prevent complications of hyponatremia in our case.

4. Conclusion

Hyponatremia patients may apply to emergency room with nonspecific symptoms such as nausea and vomiting at the onset and consciousness changes that may progress to coma. Psychogenic polydipsia-associated hyponatremia should be considered in patients with similar clinical findings and psychiatric history admitted to emergency room.

References

Cronin, R. E. (1987). Psychogenic polydipsia with hyponatremia: report of eleven cases. American Journal of Kidney Diseases, 9(5), 410-416.

Illowsky, B. P., & Kirch, D. G. (1988). Polydipsia and hyponatremia in psychiatric patients. The American journal of psychiatry, 145(6), 675-683.

Bremner, A. J., & Regan, A. (1991). Intoxicated by water: polydipsia and water intoxication in a mental handicap hospital. The British Journal of Psychiatry, 158(2), 244-250.

Verghese, C., de Leon, J., & Josiassen, R. C. (1996). Problems and progress in the diagnosis and treatment of polydipsia and hyponatremia. Schizophrenia Bulletin, 22(3), 455-464.

Farrell, D. J., & Bower, L. (2003). PMCID: PMC1770067. J Clin Pathol, 56(10), 803-804.

De Leon, J., Verghese, C., Tracy, J. I., Josiassen, R. C., & Simpson, G. M. (1994). Polydipsia and water intoxication in psychiatric patients: a review of the epidemiological literature. Biological psychiatry, 35(6), 408-419.

Dundas, B., Harris, M., & Narasimhan, M. (2007). Psychogenic polydipsia review: etiology, differential, and treatment. Current psychiatry reports, 9(3), 236-241.

Siegel, A. J. (2008). Hyponatremia in psychiatric patients: update on evaluation and management. Harvard review of psychiatry, 16(1), 13-24.

Spasovski, G., Vanholder, R., Allolio, B., Annane, D., Ball, S., Bichet, D., ... & Joannidis, M. (2014). Clinical practice guideline on diagnosis and treatment of hyponatraemia. Nephrology Dialysis Transplantation, 29(suppl_2), i1-i39.

Nzerue, C. M., Baffoe-Bonnie, H., You, W., Falana, B., & Dai, S. (2003). Predictors of outcome in hospitalized patients with severe hyponatremia. Journal of the National Medical Association, 95(5), 335-343.

Year (Yıl) : 2018
Volume (Cilt) : 5
Issue Number (Sayı) : 3
Doi : 10.5455/JNBS.1534601834

Received/Geliş 18.08.2018
Accepted/Kabul 08.10.2018
JNBS, 2018, 5(3):187-189

TO WHAT EXTENT ANTIDEPRESSANT MONOTHERAPY STROLL UPON THE PINSTRIPE BETWEEN STANDARD OF CARE AND PSYCHIATRIC MALPRACTICE IN BIPOLAR DEPRESSION?: A COMMENTARY FROM THE VIEWPOINT OF SUICIDE

BİPOLAR DEPRESYONDA ANTİDEPRESAN MONOTERAPİSİ STANDART TEDAVİ İLE PSİKİYATRİK MALPRAKTİS ARASINDAKİ İNCE ÇİZGİDE NEREDE DOLAŞIR?: İNTİHAR BAKIŞ AÇISINDAN BİR AÇIMLAMA

Yasin Hasan Balcioglu*

Abstract

Psychiatry is one of the least facing profession to malpractice claim in medicine. Misevaluation of suicide risk is one of the most frequent issues for litigation in the practice of psychiatry. Psychiatrists are expected to foresee and prevent suicidality by the law, although suicide has an unpredictable diagnostic nature. Bipolar disorder (BPD) is an affective disorder associated with elevated rates of suicidal behaviour, particularly in depressive episodes. Therefore, the main target of standard therapeutic approaches in BPD depression is the reduction of suicide risk. Treatment options ought to be carefully formed by the clinician, in light of the determination of clinical severity and suicidal risk in bipolar depression. This article aimed to discuss to what extent use of antidepressants is appropriate in bipolar depression regarding possible malpractice in line with evidence-based clinical guidelines and actual literature.

Keywords: bipolar disorder; depression; malpractice; suicide

Özet

Tıpta malpraktis iddialarıyla en az karşı karşıya kalan branşlardan biri psikiyatridir. İntihar riskinin değerlendirilmesindeki hatalar psikiyatri uygulamalarında en sık karşılaşılan dava konularındandır. İntiharın tahmin edilmesi güç tanısal doğasına rağmen hukuk, psikiyatristlerden intiharı öngörebilmesini ve önlemesini bekler. Bipolar bozukluk, özellikle depresif hecmedeki yüksek intihar davranış oranlarıyla ilişkili bir affektif bozukluktur. Bu yüzden bipolar depresyonda standart terapötik yaklaşımların ana amacı intihar riskini azaltmaktır. Bipolar depresyonda tedavi seçenekleri klinisyen tarafından hastalığın şiddeti ve intihar riski göz önünde bulundurularak dikkatlice şekillendirilmelidir. Bu yazı, bipolar bozuklukta antidepresan kullanımının olası malpraktis açısından ne ölçüde uygun olduğunu kanıta dayalı klinik kılavuzlar ve güncel literatür ışığında tartışmayı amaçlamıştır.

Anahtar Kelimeler: *bipolar bozukluk; depresyon; intihar; malpraktis*

[1]Forensic Psychiatry Unit, Bakirkoy Training and Research Hospital for Psychiatry, Neurology and Neurosurgery, Istanbul, Turkey
*Corresponding author: Forensic Psychiatry Unit, Bakirkoy Training and Research Hospital for Psychiatry, Neurology and Neurosurgery, Istanbul, Turkey.
E-mail: yhasanbalcioglu@gmail.com Mobile: 905365477147

Common recognition and the literature indicate that psychiatry is one of the least facing profession to malpractice claim in medicine. Psychiatry ranked 22nd in the number of malpractice charges among 28 medical specialities with a prevalence of 2.6% in a retrospective 15-year follow-up study (Jena, Seabury, Lakdawalla, & Chandra, 2011). Unfavourably, while Turkish literature lacks on actual malpractice statistics, nine of the 931 malpractice claims admitted to the Ministry of Health between 1994 – 1999, were cases of psychiatry; however, the numbers are estimated to be increasing in Turkey (Ertem, Oksel, & Akbıyık, 2009; Ozver et al., 2013). Misevaluation of suicide risk is one of the most frequent issues for litigation in the practice of psychiatry. A comprehensive examination is the sole and essential diagnostic instrument to estimate the risk. Regardless of the physician's appropriate efforts for prevention, patients inevitably commit suicide in some occasions which may result in a lawsuit for psychiatric malpractice. 14% of lawsuits are related to a failure in preventing suicide/homicide (Meyer, 2006). Psychiatric liability regarding suicide includes inexperience, misdiagnosis, erroneous treatment, lack of surveillance and underestimation of the risk (Terranova & Sartore, 2013).

Patients with affective disorders are at a very high risk of death by suicide, approximately 20 times higher than in the general population, particularly when remained untreated. Bipolar disorder (BPD) is a lifelong affective disorder characterized by manic, hypomanic, depressive and euthymic episodes and associated with elevated rates of suicidal behaviour. About a third to a half of bipolar patients attempt suicide at least once in their lifetime, and roughly 15–20% of attempts are completed, particularly patients with depressive predominant polarity or in depressive episode (Grande, Berk, Birmaher, & Vieta, 2016). Due to its episodic nature, treatment options may vary from each episode in BPD. Mood stabilizers, antipsychotics, antidepressants, electroconvulsive therapy and psychotherapy are used in BPD. Nevertheless, the severity of the prognosis in BD is mainly linked to the high rate of suicide, especially in depressive episodes. Hence, treatment of depression in BPD requires more specific and structured medication procedures with strict follow-ups. Mood-stabilizing pharmacotherapy is a cornerstone of BPD treatment. Lithium is strongly recommended lone or in combination with other psychotropic medication, as a first- or second-line pharmacotherapy for the treatment of mania and bipolar depression, as well as a first-line maintenance treatment option for BPD (Toffol et al., 2015). Growing body of evidence has indicated that with lithium reduces the risk of suicide and suicide attempts in patients suffering from affective disorders (Baldessarini & Tondo, 2008). Apart from the fact that lithium has a significant decreasing impact on suicidal attempt risk in BPD, other mood-stabilizers such as valproate are also found to be associated with a reduction of suicide risk (Søndergård, Lopez, Andersen, & Kessing, 2008).

Suicide is a major worldwide public health concern. Almost one million lives are lost each year to suicide, and between 3%–5% of adults attempt suicide at least once in their life. The most powerful predictor, major precursor and risk factor of attempted and completed suicide is a previous suicide attempt (Pompili et al., 2008). A psychiatrist is expected to be able to evaluate the risk on the basis of all available information, including patient responses in a proper psychiatric interview, known risk factors and history. "Foreseeability" is a legal term defines reasonable expectation that some damage is likely to arise from certain acts or omissions, and the law seeks for it in order to conclude a suicide lawsuit as misdiagnosis or negligent treatment (Sher, 2015).

Depression in bipolar disorder is a major therapeutic challenge associated with disability and excess mortality. Prompt and comprehensive assessment and management of suicidal ideation in patients with bipolar depression are needed (Grande et al., 2016). In the presence of suicidal risk in BPD depressive episode, treatment alternatives ought to be paid more attention. Various pharmacotherapeutic interventions are available and published in the literature in BPD depression; however, to avoid legislative acts due to inappropriate medication leading to suicide, physicians should ground their medication on universal evidence-based clinical guidelines. The relative usefulness of standard antidepressants in BPD remains controversial due to their propensity to induce cycling, mania or hypomania, they are often enhanced by a combination with mood-stabilizer in the first line treatment of bipolar depression (Sadock, Sadock, & Ruiz, 2015).

As one of the most recognized, American Psychiatric Association (APA) guideline on BPD suggests lithium and lamotrigine to prevent any mood episode, lamotrigine is an effective preventer for depressive episode. Medications having the strongest evidence for efficacy for acute treatment of depression in patients with bipolar disorder are the olanzapine-fluoxetine combination, quetiapine and lamotrigine. Prescription of antidepressants in the absence of a mood stabilizer is not recommended for bipolar patients according to APA guideline (Hirschfeld, 2005). The National Institute for Health and Care Excellence (NICE) guideline offers lithium as a first-line maintenance therapy in BPD. If lithium is ineffective adding valproate or poorly tolerated switching valproate with or without olanzapine are the alternatives. In BPD depression, NICE guideline suggests checking lithium blood level if the patient is taking lithium, if it is inadequate, increase the dose of lithium; if it is at maximum level, add either fluoxetine combined with olanzapine or quetiapine on its own. If the patient is not taking any mood-stabilizer, guideline suggests olanzapine with/without fluoxetine, or lamotrigine, or quetiapine on its own (NICE, 2014). Canadian Network for Mood and Anxiety Treatments (CANMAT) guideline suggest lithium, lamotrigine, valproate, olanzapine, quetiapine, risperidone or aripiprazole monotherapy in BPD maintenance, antidepressants are not recommended. In BPD depression first-line treatment options are lithium, lamotrigine, quetiapine monotherapy or, lithium/valproate combined with antidepressants, olanzapine combined with antidepressants, lithium - valproate combination. CANMAT guideline considers management of a bipolar depressive episode with antidepressants controversial (Yatham et al., 2013). According to Consensus Group of the British Association for Psychopharmacology (BAP)

guideline, lithium or lamotrigine is recommended as a first-line agent in bipolar depression. Lithium is also considered as a risk-reducing agent for suicide. Quetiapine also suggests convincing efficacy in BPD depression (Goodwin & Psychopharmacology, 2009). Antidepressants are probably effective for treating depression in bipolar disorder; however, should be combined with antimanic agents in order to prevent manic switches. The association between suicidal behaviour and antidepressants are needed to be clarified by the means of further studies. Aforementioned guidelines are based on randomized double-blind clinical trials, systematic reviews and meta-analyses (Table 1).

Tablo 1. Evidence-based clinical guidelines on bipolar depression

Guideline	First-line	Recommended	Not recommended / Controversial
APA	Lithium	Lamotrigine Quetiapine Olanzapine+Fluoxetine	Antidepressants without mood stabilizors
NICE	Lithium	Valproate Olanzapine Quetiapine Olanzapine + Fluoxetine Lamotrigine	-
CANMAT	Lithium Lamotrigine Quetiapine	Lithium + Valproate Lithium/Valproate + antidepressants Olanzapine + Antidepressants	Antidepressants alone
BAP	Lithium	Lamotrigine Quetiapine Olanzapine+Fluoxetine	Antidepressants without mood stabilizors

Despite one can find various treatment options in the literature regarding BPD depression, none of the guidelines encourages antidepressant monotherapy. Any intolerance or side effect of lithium or valproate occurs, substitutional options are available in guidelines. Assesment of suicide risk is a subjective matter that protects psychiatrist facing to legislation; nevertheless, medication preference in ought to be compatible with the evidence-based literature in order to fit standard of care.

References

Baldessarini, R. J., & Tondo, L. (2008). Lithium and suicidal risk. Bipolar disorders, 10(1), 114-115.

Ertem, G., Oktem, E., & Akbiyik, A. (2009). A retrospective review about the malpractice applications in medicine. Dirim, 84(1), 1-10.

Goodwin, G. O., & Consensus Group of the British Association for Psychopharmacology. (2009). Evidence-based guidelines for treating bipolar disorder: revised second edition—recommendations from the British Association for Psychopharmacology. Journal of Psychopharmacology, 23(4), 346-388.

Ertem, G., Oktem, E., & Akbiyik, A. (2009). A retrospective review about the malpractice applications in medicine. Dirim, 84(1), 1-10.

Goodwin, G. O., & Consensus Group of the British Association for Psychopharmacology. (2009). Evidence-based guidelines for treating bipolar disorder: revised second edition—recommendations from the British Association for Psychopharmacology. Journal of Psychopharmacology, 23(4), 346-388.

Grande, I., Berk, M., Birmaher, B., & Vieta, E. (2016). Bipolar disorder. Lancet (London, England), 387(10027), 1561–72.

Hirschfeld, R. M. (2005). Guideline watch: Practice guideline for the treatment of patients with bipolar disorder. Arlington, VA: American Psychiatric Association.

Jena, A. B., Seabury, S., Lakdawalla, D., & Chandra, A. (2011). Malpractice risk according to physician specialty. New England Journal of Medicine, 365(7), 629-636.

Meyer, D. J. (2006). Psychiatry malpractice and administrative inquiries of alleged physician misconduct. Psychiatric Clinics, 29(3), 615-628.

NICE CG185, S. (2014). Bipolar disorder: the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care. Commissioned by the National Institute for Health and Care Excellence. Leicester and London: The British Psychological Society and the Royal College of Psychiatrists, (April 2007).

Ozver, I., Sahin, E., Sevindir, E., Demirel, O. F., Emul, M., & Ozen, S. (2013). Malpractice Claims against Psychiatrists Related to Psychopharmacologic Agents: File series. Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology, 23(4), 320-325.

Pompili, M., Innamorati, M., Raja, M., Falcone, I., Ducci, G., Angeletti, G., ... & De Pisa, E. (2008). Suicide risk in depression and bipolar disorder: Do impulsiveness-aggressiveness and pharmacotherapy predict suicidal intent?. Neuropsychiatric disease and treatment, 4(1), 247.

Sadock, B. J., Sadock, V. A., & Ruiz, P. (2015). Mood Disorders. In B. J. Sadock, V. A. Sadock, & P. Ruiz (Eds.), Kaplan & Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry 11th Edition (pp. 347–387). Philedelphia: Wolters Kluwer.

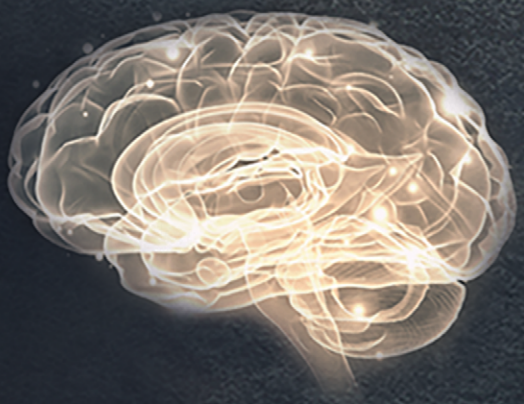
Sher, L. (2015). Suicide medical malpractice: an educational overview. International journal of adolescent medicine and health, 27(2), 203-206.

Søndergård, L., Lopez, A. G., Andersen, P. K., & Kessing, L. V. (2008). Mood-stabilizing pharmacological treatment in bipolar disorders and risk of suicide. Bipolar disorders, 10(1), 87-94.

Terranova, C., & Sartore, D. (2013). Suicide and psychiatrist's liability in Italian law cases. Journal of forensic sciences, 58(2), 523-526.

Toffol, E., Hätönen, T., Tanskanen, A., Lönnqvist, J., Wahlbeck, K., Joffe, G., ... & Partonen, T. (2015). Lithium is associated with decrease in all-cause and suicide mortality in high-risk bipolar patients: A nationwide registry-based prospective cohort study. Journal of affective disorders, 183, 159-165.

Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Beaulieu, S., Alda, M., ... & Ravindran, A. (2013). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar disorders, 15(1), 1-44.



TO HAVE A "BETTER" FUTURE

WITH ÜSKÜDAR UNIVERSITY'S MASTER'S AND DOCTORATE PROGRAMS

Recently Opened Master's and Doctorate Programs

Institute of Health Sciences

Master's Degree Programs

- Addiction Counselling and Rehabilitation (Thesis - Non Thesis)
- Child Development (Thesis - Non Thesis)
- Health Informatics (Thesis - Non Thesis)
- Health Management (Thesis - Non Thesis)
- Occupational Health and Safety (Thesis - Non Thesis)
- Neuroscience (Thesis - Non Thesis)
- Nursing (Thesis - Non Thesis)
- Physiotherapy and Rehabilitation (Thesis)
- Social Work (Thesis - Non Thesis)
- Speech and Language Therapy (Thesis)

Doctorate Degree Programs

- Health Management
- Speech and Language Therapy
- Molecular Neuroscience
- Neuroscience
- Nursing

Institute for Sufi Studies

Master's Degree Programs

- Sufi Culture and Literature (Thesis - Non Thesis)

Institute of Social Sciences

Master's Degree Programs

- Applied Psychology (Thesis - Non Thesis)
- Clinical Psychology (Thesis - Non Thesis)
- Media and Cultural Studies (Thesis - Non Thesis)
- Neuromarketing (Thesis - Non Thesis)
- New Media and Journalism (Thesis - Non Thesis)

Doctorate Degree Program

- Psychology

Institute of Addiction and Forensic Sciences

Master's Degree Programs

- Forensic Sciences (Thesis - Non Thesis)
- Criminal Justice (Thesis - Non Thesis)

Master's Degree Programs

- Forensic Sciences

Institute of Sciences

Master's Degree Programs

- Biotechnology (Thesis - Non Thesis)
- Bioengineering (Thesis - Non Thesis)
- Electrical-Electronics (Thesis – Non Thesis)
- Molecular Biology (Thesis - Non Thesis)

Spring Term online applications continue!

ÜSKÜDAR UNIVERSITY
ISTANBUL 2011

Turkey's Brain Base

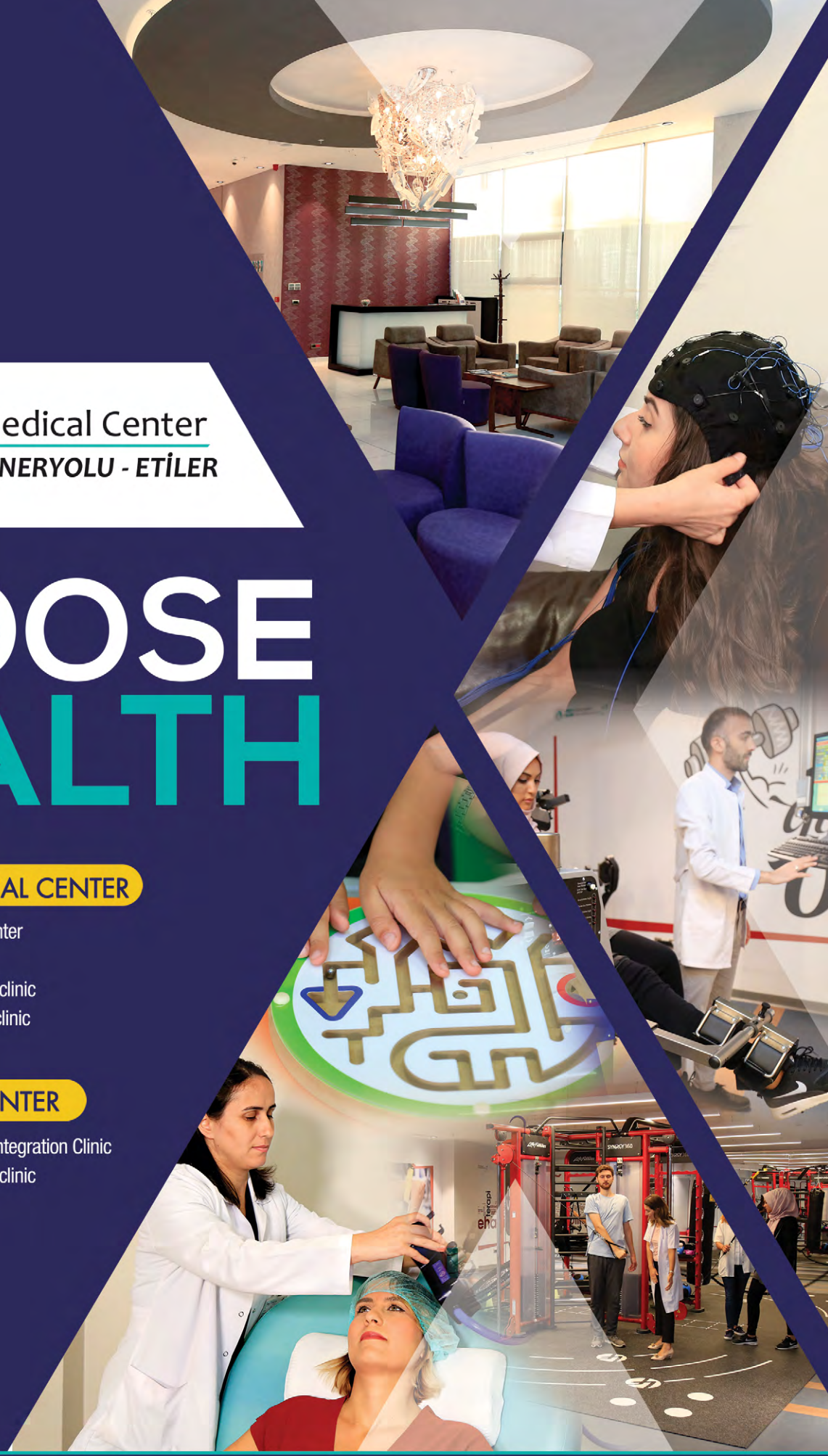
+90 216 400 22 22 Üsküdar University uskudaruni_en

www.uskudar.edu.tr/en

ÜSKÜDAR UNIVERSITY
İSTANBUL 2011

NP Medical Center
FENERYOLU - ETİLER

CHOOSE HEALTH



NP FENERYOLU MEDICAL CENTER

Physiotherapy and Rehabilitation Center
Adult Psychiatry Polyclinic
Child and Adolescent Psychiatry Polyclinic
Speech and Language Therapy Polyclinic
Otorhinolaryngology

NP ETİLER MEDICAL CENTER

Occupational Therapy and Sensory Integration Clinic
Child and Adolescent Psychiatry Polyclinic
Adult Psychiatry Polyclinic

20th YEAR
NP İSTANBUL Brain Hospital
Neuropsychiatry | Addiction | Neurosurgery

İNSANİ DEĞERLER VE RUH SAĞLIĞI VAKFI
www.ider.org

Management System ISO 9001:2015

www.nptipmerkezi.com

nptipmerkezi NPİSTANBULBeyinHastanesi **Feneryolu Medical Center Tel: +90 216 418 15 00** **Etiler Medical Center Tel: +90 212 270 12 92**

Turkey's first and only brain hospital...

Neurosurgery

Full-Fledged
General Hospital

1A Operating Rooms

Fully-Equipped
Intensive Care Unit

Child Psychiatry,
Neurology, Neurosurgery

Neuromodulation
Center

Psychology,
Psychiatry, Neurology

Private 7 / 24 Psychiatric
Intensive Care Unit

NPAMATEM
Addiction Center

Personalized
Pharmacogenetic
Treatment

Üsküdar University
Science Partner

20th YEAR 1998

NP İSTANBUL Brain Hospital

Neuropsychiatry | Addiction | Neurosurgery

We are inspired by the brain to achieve excellence

npistanbulbrainhospital www.npistanbul.com/en

Saray Mah. Ahmet Tevfik İleri Cad. No:18, 34768 Ümraniye / İstanbul TURKEY
T: +90 216 633 06 33 F: +90 216 634 12 50

Üsküdar University *Science Partner*

Organization Accredited by Joint Commission International

Management System ISO 9001:2008

T.C. ÜSKÜDAR UNIVERSITY

One more step in understanding human nature