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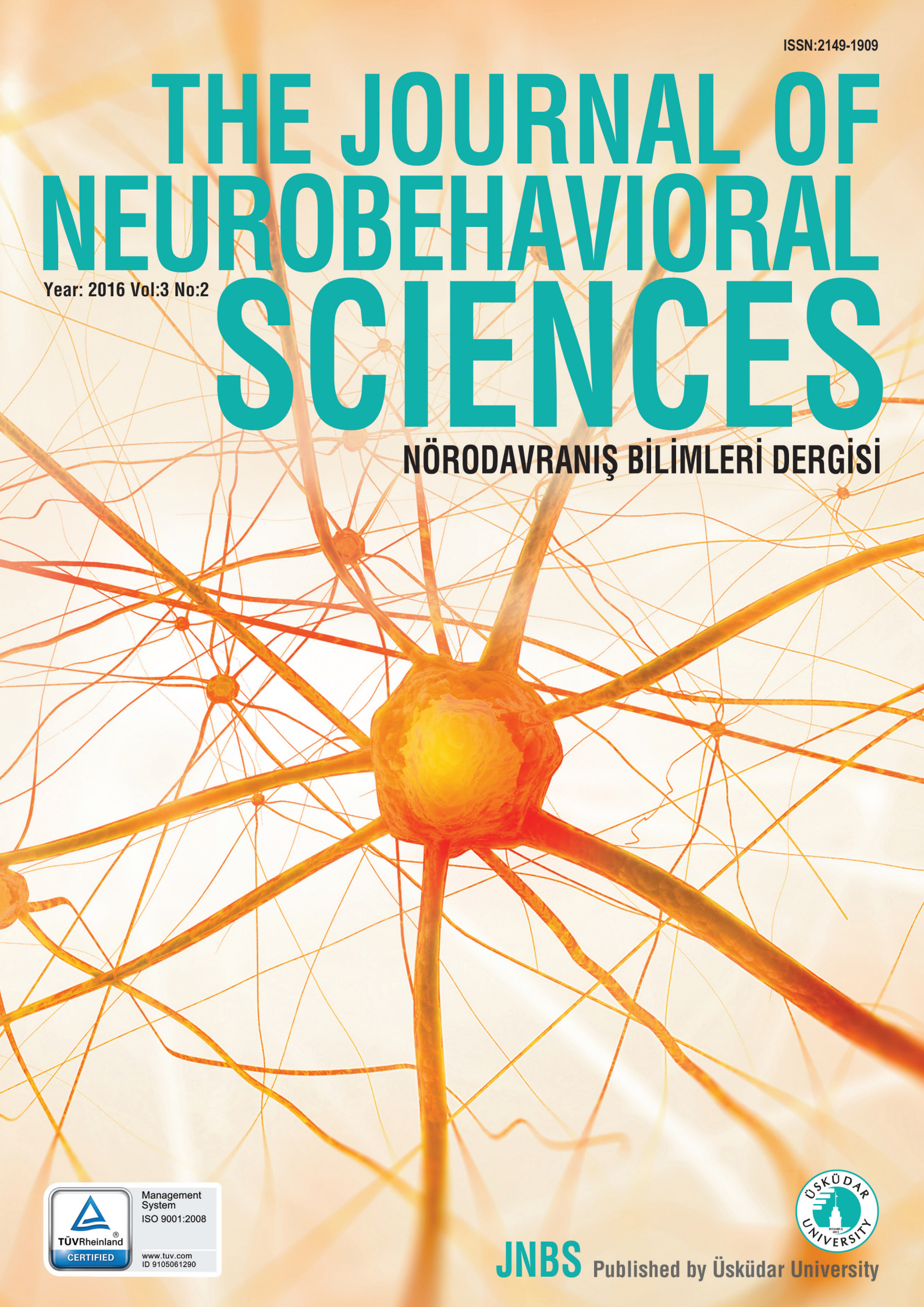

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JOURNAL OF NEUROBEHAVIORAL SCIENCES ADVISORY COMMITTEE

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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 language of JNBS is in English. However, our editorial office provide Turkish abstracts in addition to English for each article.

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)

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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
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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.

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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.

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PREFACE

We would like to present, with great pleasure, the second issue of JNBS in 2016. This journal is a publication of Üsküdar University, and is devoted to the neurobehavioral sciences in a wide range, from theoretical aspects to clinical studies. JNBS is envisioned and founded to represent the growing needs of neurobehavioral sciences as an emerging and increasingly vital field.

This issue is devoted to the application of neurobehavioral research in different areas. In this spirit, the editorial by Arıkan and Artukoğlu is titled as "What Does the Brain Mapping Tell the Psychiatrist in Daily Practice?"

The original researches of this volume comprise three manuscripts: "Patient-derived Stem Cells as New Frontiers for Disease Modelling with Focus on Neurodegenerative Diseases" by Kuldip S. Sidhu; "Immune-Behavioral Changes After Pregestational Psychological Stress" by Meriem Haloui; and "Comparison of Wavelet Families for Mental Task Classification" by Uyulan and Ergüzel. These articles exemplify the application of neuroscience in various domains of science.

This issue also includes four review papers which provide insights into the clinical problems and use of neurobehavioral science in clinical applications. The four papers comprising this part are: "Nonpharmacological Treatment Approach to Pain" by Özcan et al., "A speculation on the mechanisms of ECT, TMS, tDCS and similar techniques" by Antikacioglu and Tarhan; "Future of Psychiatry: Mobile Health and Social Sensing" by Hızlı Sayar et al; and "Somatic Diseases in Psychiatry" by Evrensel et al.

"Sertraline induced tremor" by Uvais et al; and "Functional MRI in feigned visual loss" by Antonio-Santos are the two case reports of the present issue which provide a contribution to literature. Aslan and Ulucan's letter "Can we consider SLC2A1 polymorphisms as a genomic diagnostic marker for cognitive problems?" supports the idea of creating a genomic diagnostic marker for cognitive functions. We are very thankful to everybody who supported the JNBS. This issue would not have been possible without the great support of the Editorial Board members, and we would like to express our sincere thanks to all of them. It is our hope that this fine collection of articles will be a resource for Neurobehavioral Sciences and will stimulate further research.

Best Regards,

Nevzat Tarhan, MD.

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Farmakogenetik Laboratuvarı

Beyin Fonksiyonlarını Ölçerek Tedavi

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EDITORIAL

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
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WHAT DOES THE BRAIN MAPPING TELL THE PSYCHIATRIST IN DAILY PRACTISE?

Kemal Arıkan[*1], Bekir B. Artukoglu[2]

In order for the brain mapping to be useful for the psychiatrist in daily practice, it should reveal a Z Score Mapping which would allow the clinician to make a comparison with the normal age group. The brain mapping should also reveal a regional interconnectivity map. Production of the brain mapping is also a crucial point: it should imitate the reading of a standard EEG. Frequency analysis should be favored since other analysis methods may be out of a standard clinician's comfort zone.

One significant area where brain mapping is expected to bring revolutionary advances is the diagnosis of psychiatric disorders. 4 major patterns have been detected in 4 major psychiatric syndromes: Alpha wave increase in the frontal lobe is significant in depression. Generalized increase of beta waves in anxiety disorders may be informative for the clinician. An increase in delta and theta waves is seen in dementia. An intermixed increase of slow, very slow and fast waves is valuable as a diagnostic tool for schizophrenia.

Brain mapping may be an improvement on DSM diagnosis since it has the potential to enable the psychiatrist to identify the pathological electrophysiological activities in a psychiatric disorder. (McLoughlin et al., 2014; Miller, 2010). Studies of the biomarker trait of brain mapping in various psychiatric disorders has been promising so far. Significant progress have been made in disorders such as depression (Eyre et al., 2015; Leaver et al., 2015) , autism (Jann et al., 2015) and schizophrenia. (Taylor & Macdonald, 2012; Gur et al., 2002; Turetsky et al., 2007)

Regional connectivity put forward by statistical methods may reveal patterns that have genetic correlations. These potential endophenotypes will allow the psychiatrist to devise personalized treatment plans. (Moseley et al., 2015; Gardner et al., 2014; Di Martino et al., 2014) For instance, whole brain functional connectivity changes in children with Autism Spectrum Disorders and their healthy siblings point to the fact that brain mapping is one promising approach to detect endophenotypes of psychiatric disorders. (Moseley et al., 2015)

Using a test dose and observing the effect of a drug via brain mapping may predict the success of a treatment modality. (Arns & Olbrich, 2014; Mucci et al., 2006; Saletu et al., 2006) Bioavailability of a drug is made up of components such as crossing the blood brain barrier, binding its receptor and causing the desired effect. Brain mapping and test dose studies together can give the clinician an accurate idea of the bioavailability of a drug. Previous studies indicate that changes in EEG waves and brain morphometry may be used as predictors of clinical response to interventions against ADHD (Arns & Olbrich, 2014) , depression (Wade et al., 2015; Arns & Olbrich, 2014).

Finally, brain mapping may evolve into an objective method for the monitoring of psychiatric patients. The psychiatrist could observe the prognosis of a disorder in an evidence based fashion by using brain mapping at regular intervals.

In conclusion, brain mapping has implications for the diagnosis of psychiatric disorders, the detection of endophenotypes, predicting clinical response to therapeutic interventions and the monitoring of psychiatric patients. Further research is necessary to better determine the potentials of brain mapping and make full use of brain mapping in the aforementioned areas of daily practice.

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PATIENT- DERIVED STEM CELLS AS NEW FRONTIERS FOR DISEASE MODELLING WITH FOCUS ON NEURODEGENERATIVE DISEASES

NÖRODEJENERATİF HASTALIKLAR ÜZERİNE ODAKLANAN HASTALIK MODELLEMELERİ İÇİN YENİ SINIRLAR OLARAK HASTA-KAYNAKLI KÖK HÜCRELERİ

Kuldip S. Sidhu*

Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder and represents the most common form of dementia, affecting over 46.9 million people worldwide. AD is characterized by the progressive loss of specific neurons in the brain, which leads to gradual loss of bodily functions, long term memory loss and eventually death. The pathology of AD remains elusive due to the lack of appropriate animal and/or in vitro models, which recapitulate the human AD. The induced pluripotent stem (iPS) cells derived from patient's somatic cells and thus patient-specific and disease-specific iPS cells offer great potential in regenerative medicine, in drug discovery and modelling disease processes in vitro. Here we report the first generation of feeder-free iPS cells from Alzheimer's patients with an early onset of disease using a polycistronic lentiviral vector containing four pluripotent genes, Oct4, Sox2, Klf4 and cMyc. These iPS cells are pluripotent as demonstrated by both the in vitro and in vivo assays i.e. stem cell surface markers, gene expressions and teratomas formation after injecting these cells into the SCID mice. These iPS cells from patients that are predisposed to Alzheimer's disease have been analyzed by using the microarray chip and the computation of data is assisting in developing the in vitro models for this disease and for future regenerative medicine. Genome-wide microarray analysis revealed that AD-iPS cells are similar to control iPS cells and hESC lines; however, eight candidate genes differentially expressed between familial iPS cells and sporadic iPS cells. Some Alzheimer's specific genes and pathways were overrepresented in these cells hence in vitro disease modelling possible.

Keywords: Alzheimer's disease, neurodegenerative disorder

Özet

Alzheimer Hastalığı(AH) nörodejeneratif bir bozukluktur ve dünya çapında 46.9 milyonun üzerinde insanı etkileyen demans hastalığının en yaygın şeklini temsil eder. Alzheimer Hastalığı(AD), beyindeki spesifik nöronların artan kaybı sonucu uzun süreli hafıza kaybı ile başlayan, vücut fonksiyonlarının yavaş ve sürekli olarak yitirildiği, ve en sonunda ölüm ile neticelenen ciddi bir hastalıktır. Alzheimer Hastalığı'nın patolojisi, Alzheimer Hastalığı'nı yeniden özetleyen uygun hayvan ve/ya da deney ortamındaki modellerin eksikliği nedeniyle tarif edilmesi zor bir hastalık olarak kalmıştır. Hastanın somatik hücrelerinden edinilen uyarılmış pluripotent kök hücreleri(iPS) ve dolayısıyla hasta-özgü ve hastalık-özgü iPS hücreleri rejeneratif tıpta, ilaç keşfetmede ve deney ortamında hastalık modellemede büyük bir potansiyel arz eder. Bu çalışmada, 4 pluripotent geni olan Oct4, Sox2, Klf4 ve cMyc'i içeren polycistronic lentiviral vektörü kullanan erken hastalık başlangıcı olan Alzheimer hastalarından besleyici eksik İPS hücrelerinin ilk jenerasyonunu raporladık. Bu İPS hücrelerinin SCID farelerine enjekte edilmesinden sonra kök hücresi yüzey yapıcıları, gen ifadeleri ve teratoma formasyonu gibi hem deney ortamlarında hem yaşayan organizma denemelerinde gösterildiği gibi İPS hücreleri pluripotenttir. Alzheimer hastalığına yatkınlığı olan hastalardaki bu İPS hücreleri mikroçipler kullanılarak analiz edilmiştir ve data ölçümü bu hastalık ve gelecek rejeneratif tıp için deney ortamındaki modellerin gelişimine yardımcı olacaktır. Genom-kapsamlı mikroçip analizi ortaya çıkarmıştır ki; Alzheimer hastalığıİPS hücreleri İPS hücrelerinin ve hESC yollarının kontrolüne benzerdir. Ancak, 8 aday gen ailevi ve sporadik hücreler arasında farklılar ortaya koymuştur. Bazı Alzheimer'a özgü genler ve yolları, bu hücrelerde ve bunun sonucu olarak deney ortamında hastalık modellemede fazla temsil edilmiştir.

Anahtar Kelimeler: *Alzheimer hastalığı, nörodejeneratif bozukluk*

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1. Introduction

Our interest is in Alzheimer's and Parkinson's diseases they both come under a broader term, dementia. As it on 2015 now there are 46.9 million people living with dementia worldwide, 342, 800 Australian. This number will be double in 2030 and triple in 2050. These people are and will continue to populate mostly the low and middle income countries. The current cost to manage this disease is around 818 billion, soon will be 1 trillion in 2018 worldwide and about 4.9 billion in Australia. If dementia was a country, it would be the 18th largest economy of the world with budget as good as of Apple and Google combined. There are 23 million residing in Asia-Pacific. There is no cure but only the management and hence growing burden. It is a gigantic problem to sustain unless we do something about it.

There is a strong need to bring in focus the need of the Brain Initiative. This is because 1/3 of world population is inflicted with some sort of mental and psychiatric illnesses including neurological disorders like Alzheimer's, Parkinson etc.These all account for 13% of disease burden that surpasses cancer (10%) and cardiovascular (5%) diseases Worldwide funding is not in commensurate with disease burden. Majority goes to cancer and cardiovascular. This inequality is imposing a huge in balance & impact on quality of human life Medical funding is required to increase globally to offset this in balance & improve quality of life.

2. What is an Alzheimer's disease

There are over 100 billion neurons in a normal human brain and each neuron makes about 15 000 connections (synapses) with other neurons. This massive network of neurons is responsible for the cognition, reasoning, language, and storage and retrieving of information and all that is affected in AD patients

There are two major hall marks of AD – extracellular Amyloidal plaques probably caused by mutations in APP, PS1/PS2 genes and intracellular neural fibrillar tangles in the brain in addition to oxidative stress, mitochondrial dysfunction, neuroinflammation, co-morbidity with PD all appear to be contributing pathological factors.

The traditional route for drug discovery is a long and expensive journey. Each new drug discovery costs around 1.5 billion US$. A part of the reason is that it involves using preclinical animal trials and modelling. Animal models of diseases are invaluable often do not faithfully mirror human pathophysiology. We have an alternative, with the advent of patient-derived induced pluriptoent stem cells technology (Takahashi & Yamanaka, 2006) we can turn the clock back on these diseases by reproducing these diseases in the Petri dish that is discussed here. The iPS cells obtained by reprogramming from patients promise unique insights into the disease modelling, & development of customized cellular therapies (Sidhu, 2015).

The primary source of pluripotent stem cells has been the embryos, however, due to ethical issues involved, in 2006 a remarkable discovery by Yamanaka from Japan that an adult somatic cell can be reprogrammed to its pluripotent state by simply transducing with four pluripotent genes, Oct4, Sox2, Klf4, c-Myc either by viral or protein transduction has taken the debate away from human embryos. There is a paradigm shift with the birth of iPSC technology. Such pluripotent cells called as induced pluripotent stem cells though can generate different lineages all derived from three germ layers for future regenerative medicine, but has limitations because of transgenes and these as such as currently being developed for drug discovery and disease modelling. There are advances now to produce non-integrating iPSC that can be converted to relevant neurons, probably that will move towards custom-made cell therapies for such patients a whole new world of regenerative medicine.

In Alzheimer's patients, there is extensive loss of specific neurons in the brain called basal forebrain cholinergic neurons (BFCN) that leads to shrinkage of the brain. In our lab we have used iPSC derived from such patients and converted these into BFCN using our optimised protocols. The major question now is to fully understand and characterise these cells before they can used for therapy for example study their electric conductivity through synapses called electrophysiology. We have done that though in individual cells in a Petri dish, but in the real world million of these neurons in the brain talk to each other and that we want to simulate in the Petri dish, I called human brain in the Petri dish. So that we can understand their function in totality more specifically so for example n AD, how they fire together and produce response and how that is affected under disease situation. This has relevance in studying disease pathophysiology and disease modelling. As there is a latency of 10-15 years in AD before symptoms appear and this technology can recapitulate human development in the Petri dish, and hence the disease process and we can reset the clock from numbers of years to number of days by this technology.

3. Disease Modelling

3. 1. Production of iPS cells & Characterisation

We used Yamanaka cocktail consisting of four pluripotent markers, Oct2, Sox2, Klf4 and c-Myc using a stem cell lentiviral cassette with a constitutive promoter EF-1alpha. With experience on iPSC technology, we have now produced patient-specific iPSC from AD (Chung et al., 2015). We recruited a cohort of 12 patients both sporadic and familial cases of AD including age and sex-matched control and have produced > 100 iPSC clones that are a various stages of characterisation

These clones express pluripotent surface markers i.e Oct4, Nanog, SSEA4, TRA-160. These cells do undergo spontaneous differentiation to three germ layers i.e. ecto- endo-, meso- with specific immunostaining. In vitro pluripotency is also matched with that seen in in vivo after injecting these cells into SCID mice and formation of solid teratomas (Figure)

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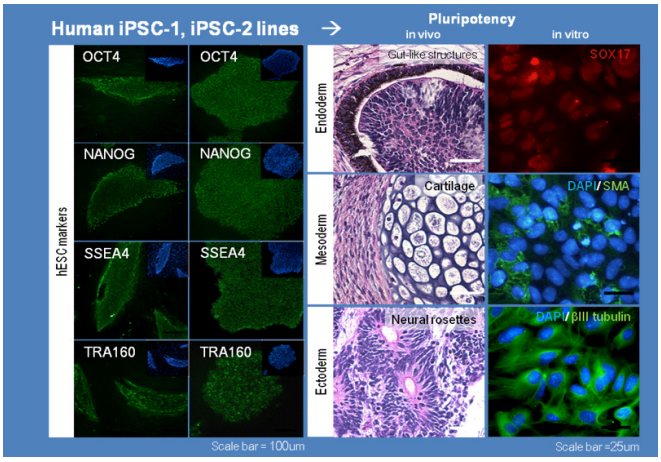


Figure 1: In vitro and in vivo analysis of pluripotency of iPSCs. Surface markers for pluripotency, Oct4, Nanog, SSEA4 and TRA160 in iPSC 1&2 lines. In vivo teratoma formation assays were performed by intratesticular injection of AD-iPSCs into SCID mice. In vitro Immunofluorescence staining of early lineage markers after in vitro differentiation.
Representative tissues of the 3 embryonic lineages were observed. (From Chung et al. 2011)

Microarray analyses and annotation of differentially expressed genes indicated that cell cycle and DNA replication that are indicated of pluripotency are over expressed in ff-iPSCs (figure2).

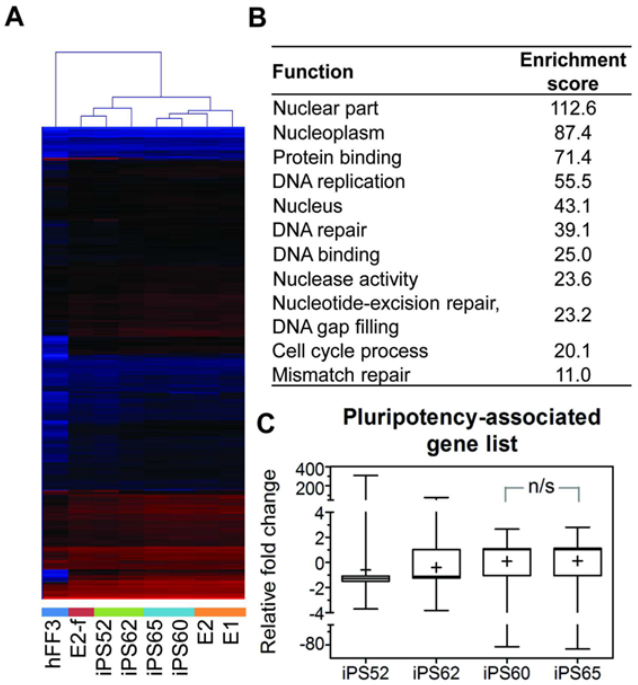


Figure 2: A. Heatmap of 951 pluripotency-associated genes across all cell lines. ff-iPSC lines (iPS60 and iPS65) were tightly clustered to hESCs (E1, E2), whereas f-iPSCs (iPS52 and iPS62) clustered separately. B, GO enrichment analysis of these 951 genes reveals they are highly related to DNA metabolic processes and mostly occur within the nucleus. C, Quantitative fold changes of these genes in all iPSC lines relatively to hESCs. Only ff-iPSCs were not significantly (n/s) different (from Chung et al. 2011).

3. 2. Production of Basal Forebrain Cortical Neurons (BFCN)

In AD there is a substantial loss of BFCN in addition to other clinical symptoms. Therefore, following ontological approach we produced BFCN from pluripotent stem cells using BMP9 signalling. BFCN is 36 days protocol consisting of first generating NPC by neural rosettes assay for 15 days followed by specific BFCN induction using BMP9 signalling after traditional neural patterning with FGF8/SHH for 21 days followed by maturation.

We followed through the rigour of these protocols and shown by gene and protein expression that the relevant cells can be produced. There is down regulation of NPC markers i.e. PAX6 and SOX1 with concomitant up regulation of BFCN markers i.e. CHAT and VCHAT. There are significant differences between control and AD patients in terms of expression of BFCN markers (Figure 3).

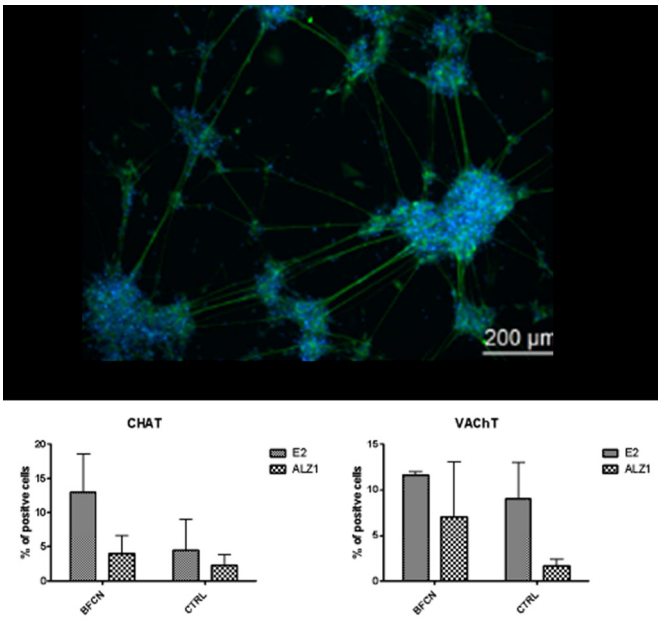
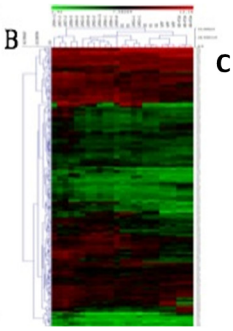


Figure 3: Production of Chat and VChat positive cells from AD-iPSC. Immunolocalisation and specific gene expression analysis.

3. 3.Characterisation of iPSC from AD Patients

We have produced iPSC from a cohort of AD patients both sporadic and familial with age-sex matched controls. We have carried out a comprehensive transcriptomics on these clones by microarray analyses. The principal component analyses clearly separated out AD clones both familial and sporadic from controls groups.

In particular our interest is in sporadic patients who far more in numbers and our Heat map analyses (B) indicated that 293 genes were differentially expressed significantly among control (CO-iPS) and sporadic cases (SAD-iPS). Gene ontology studies demonstrated the following keg pathways were significantly affected in these groups (figure 4).



C *Gene ontology enrichment analysis*

Pathway Name	Database	Enrichment Score	Enrichment p-value
Axon guidance	kegg	8.8592	0.000142068
Staphylococcus aureus infection	kegg	7.50233	0.000551799
Asthma	kegg	7.49542	0.000555622
Systemic lupus erythematosus	kegg	7.02695	0.000887632
Allograft rejection	kegg	6.75396	0.00116625
Graft-versus-host disease	kegg	6.39368	0.00167209
Type I diabetes mellitus	**kegg**	**6.30944**	**0.00181906**

Figure 4: Trasncriptomic analysis of iPS cell lines from sporadic AD cases and controls. B. Heat map showing the 293 genes differentially expressed between sporadic AD and control lines; green = downregulated and red = upregulated. C. Summarisation of these differentially expressed genes shows that the KEGG Type 1 diabetes is among the most significantly different pathways.

In particular the following genes came out interesting out of these data, **MAPK10** -mitogen-activated protein kinase **(2.5 fold change)** - We predict that changes in the level of this protein would have implications in the regulation of the beta-amyloid precursor protein/APP signalling during neuronal differentiation by phosphorylating APP formation. **PIK3R1** - phosphoinositide-3-kinase, regulatory subunit 1 (alpha) **(1.6 folds change)** may be involved in insulin resistance. **GPX2** -glutathione peroxidase 2 **(-1.7 fold change)**- could possibly explain the increased susceptibility to oxidative stress (Chung et al. 2015).

These data conform with our in vitro phenotyping of these clones where we have shown that AD-specific iPSC clones were more susceptible to oxidated stress (Figure 5).

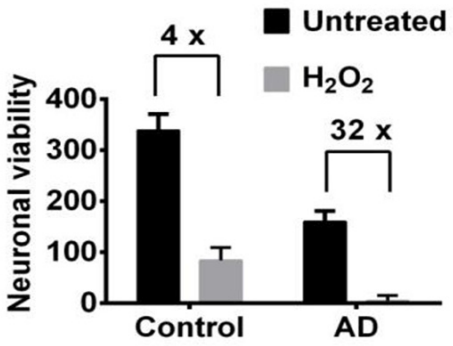


Figure 5: AD neurons showed increased susceptibility to oxidative stress. Neurons were generated from iPSCs from a familial AD patient carrying a PSEN1 P117R mutation or an age-matched control. Data shown are mean ± standard error of the mean from 3 independent experiments. Neurons were treated ± 100 μM H2O2 for 24 hours and viability of AD or control neurons was measured (from ooi & Sidhu unpublished).

Another important genotype relevant to sporadic forms of AD is the APOE. Individuals with APOE 4/4 are more susceptible than APOE3/3. The data from one of an another collaborator, Prof Brett's lab indicated recently that a protective form of protein APOE-25 is significantly expressed more in APOE3/3 than in APOE4/4 in the brain (Hippocampus extracts from post mortem patients). We carried out similar analyses in our iPSC clones derived from these patients. Although there was no significant difference between APOE-25 in the conditioned media from iPSC-derivd neurons, however, neuronal extract brought out significant differences in APOE3/3 and 4/4 iPSC clones, the former produced more and thus may be providing protection. This is a very important validation of these in vitro model based on patient-derived iPSC technology.

3.4. Mechanism of AD

To understand the mechanisms of these differences between groups, we also carried out meta-analyses of transcriptomics from other studies. A number of go terms related to various biological phenomenons like amyloid precursor protein metabolic, apolipoprotein binding, sterol and cholesterol homomeostasis, MAPK cascade, and ageing emerged all relevant to AD disease. MAPK cascade was interesting as it related to cell cycle regulation that also emerged in our transcriptomics data. Briefly this cartoon (Figure 6) explains the role of MAPK cascade in regulating cell cycle and its implication in AD. Under normal circumstances with optimal growth factors and adhesion molecules (extracellular matrix), Raf, MEK, ERK pathways are activated and that brings about transition in cell cycle from gap phase to synthesis and mitosis in cells by derepressing transcription factor, E2F through phosphorylating various cyclin proteins (A, D, E). However, in the presence of stress factors like in AD caused by MAPK, and oxidative stress by Akt (As shown by our microarray and phenotype data) that derepression of E2F is blocked and that leads to cell cycle arrest and apoptosis in cells. However, there are other factors that may impact cell cycle directly.

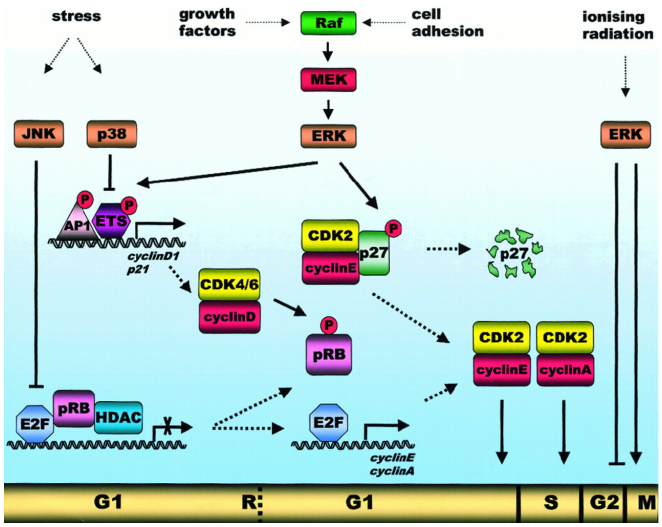


Figure 6: Mechanism of Alzheimer's disease (see text for explanation – figure taken from website)

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IMMUNE-BEHAVIORAL CHANGES AFTER PREGESTATIONAL PSYCHOLOGICAL STRESS

PROJESTASYONEL PSİKOLOJİK STRES SONRASI BAĞIŞIKLIĞA DAYALI DAVRANIŞSAL DEĞİŞİKLİKLER

Meriem Haloui[*1], Fatiha Bououza[2], Abdelkrim Tahraoui[1]

Abstract

Gestational stress has been extensively studied in order to clarify its effects on behavioral and neurodevelopmental in both mother and offspring. Our study was deflected to investigate the pregestational psychological stress, the relationship between parameters of the immune system and the neurobehavioral changes (spatial memory).

The stress was applied in female albino wistar rats, were submitted to chronic restraint stress for 1h/day for 4 days a week during 5 weeks before gestation. The behavior of rats and offspring was assessed in the Morris water maze test and the immune system by measuring the plasma concentration of IgG, which are the only immunoglobulin able to cross the placenta. Our results showed a change in the concentration of IgG, immune system cells and disturbance of spatial memory (Morris water maze).

Keywords: pregestational stress, immune parameters, spatial memory.

Özet

Jestasyonel stres, hem annedeki hem de anne karnındaki bebekteki davranışsal ve nörogelişimsel etkileri açıklamak için kapsamlı bir şekilde çalışılmaktadır. Bu çalışma, projestasyonel psikolojik stres ve bağışıklık sistemi parametreleri ve nörodavranışsal değişimler(uzamsal hafıza) arasındaki ilişkiyi incelemek için oluşturulmuştur.

Stres, hamilikten önce 5 hafta boyunca haftada 4 gün birer saat olmak üzere kronik kısıtlayıcı strese maruz bırakılan dişi albino wistar sıçanlarında denenmiştir. Sıçanların ve yavruların davranışları, Morris su labirenti testiyle ve plasentayı geçebilen tek immunoglobulin olan IgGnin plazma konsantrasyonunu ölçen bağışıklık sistemiyle değerlendirilmiştir. Çalışmamızın sonuçları IgG'nin konsantrasyonunda, bağışıklık sistemi hücrelerinde ve uzamsal hafıza bozulmasında(Morris su labirenti) bir değişiklik göstermiştir.

Anahtar Kelimeler: *Projestasyonel stres, bağışıklık parametreleri, uzamsal hafıza.*

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1. Introduction

Stress is an inevitable experience in life that can disrupt cognitive processes, neuroplasticity, endocrine and immune system in animals and humans (Dantzer and Mormede, 1995).

Chronic restraint stress models are the most popular for studying the mechanisms of impairments or cognitive disturbances (Chen et al., 2010; Yi et al.,2013). Glucocorticoids are able to modulate many cellular processes such as energy and neurotransmitter metabolism (Datson et al., 2008) which are all the intervening elements in response to stress in the restoration of homeostasis. Authors have shown that the mother of both human and animals exposed to environmental factors such as emotional stress (Dudley et al., 2011; Yong et al., 2012; Neigh et al. , 2013) can influence the behavior and development of the offspring (Mychasiuk et al., 2011; Inhasz Kiss et al., 2012; Huang et al., 2013). These changes may be mediated by intrauterine exposure to glucocorticoids secreted during activation of the HPA axis of the mother by stress. These can pass through the placenta, thereby enriching the fetal brain development (charil et al., 2010).

Other studies have shown a relationship between maternal anxiety in late pregnancy and the emotional and behavioral difficulties, persisting after six years, and are observed in both boys and girls during four years. This leads us to think about the quality of the mother - child relationship that plays an important role in the harmonious development and the subsequent balance of that individual. Disturbances of this relationship can lead to such serious emotional disorders.

To evaluate the concept of stress, we should see the life events that have long occupied a central place and that would likely be a source of stress. These correspond to significant events that occur in the life of the subjects stressing, the assumption that the stress resulting from the accumulation of changes that require an adaptation (Graignic-Philippe et al., 2005).

In order to clarify the effects of chronic restraint stress in rats applied before mating, we proceeded to study the immune system and trying to find relationships that may exist with the endocrine and nervous system and the neurodevelopment of the offspring. This was facilitated by the establishment of animal models of behavioral disorders such as the Morris water maze What could contribute to a better understanding of the physiological mechanisms and neurobiological disturbances.

2. Methods

2.1. Animals

Albino Rats coming from Pasteur Institute of Algiers were used during this study.

The animals were housed in specific cages maintained in natural photoperiod temperature with standard conditions: an average temperature of 22 ± 4 º C and a relative humidity of 50-70%. After a three weeks of adaptation , we selected 34 females according to the weight with an average weight of (140-170) grams then we divided them into 2 experimental batches: each batch of 17 rats.

2.2. Induction of Stress

The model of restraint stress in this study according the method of Bardin et al. in (2009). It involves placing the rats in a cylindrical bottle perforated plastic one hour in the morning at the same time for 4 days a week, for 5 weeks in the same animal room. When the restraint stress procedure was finished (24 h after the last day), all female rats were housed in pairs with a male for 6 days for mating, after-parturition, 15 male and 15 female were randomly selected pups from each batch to study the effects of this type of stress on mothers and neurodevelopment of the offspring. The experimental procedures were carried out according the National Institutes of Health (USA) and the Declaration of Helsinki.

2.3. IgG Analyses (Whicher et al., 1983)

The blood collection is done starting from the lacrimal vein at the end of the application of chronic restraint stress. The blood samples are collected in the heparinized tubes then centrifuged at 5000 rpm for 05 minutes. The IgG assay was performed by the immunoturbidimetric method. The latter is based on determining the endpoint IgG concentration by photometric measurement of an antigen- antibody reaction between anti- IgG antibodies present in the sample. The measurement is done using an OLYMPUS player on a wavelength 570 nm, and it equipped with computer software that automatically calculates the calibration range and gives us direct value to the desired unit.

2.4. Behavioral Tests

2.4.1. Morris Water Maze

Apparatus

The Morris Water Maze is used to identify and assess spatial learning and memory in rodents (Morris, 1981). Morris tank is a circular pool of 120 cm diameter and 60 cm depth, made of polypropylene and installed on a support. It is divided into four quadrants; one of the latter comprises a slightly submerged platform; 1 cm below the water surface (the target quadrant). Extra- maze cues were geometric located around the pool to provide a spatial configuration of the task. It is filled with water to 30 cm deep. The water temperature is maintained between 22 and 32 °C.

Maternal Study

The Morris test includes four days of trial with five passages per day (3 days with platform (learning) and the 4th day 2 passages with platform and 3 without platform (memorizing). The rat is placed in the water to the periphery different places, she swims to find the platform and then it is removed from the water. The test is redone with only a 60 second pass. If the rat is not the

platform after 60 seconds the transition is complete and the experimenter places the animal on the platform for ten seconds. The platform is removed on the 4th day of the test and the test lasts 60 seconds. All tests are filmed and the three parameters register are: the time spent in the target quadrant and the number of entries in the same quadrant.

Offspring Study (Adolescence age in postnatal days 50 and 51)

The test was according to the method of Morris in 1981. Offspring were subjected to the test for two consecutive days. The first test session (Day 50) includes five trials with a platform for the acquisition and familiarization tours where the animal learns to locate the location of the platform and take refuge there. The second test session (Day 51) includes two tests without the platform for retention. The parameters measured are: the time needed to find the submerged platform in the quadrant designated as target (latency) and the time spent in the same quadrant.

3.Data Analysis

All results were expressed as Mean ± Standard Deviation (M ± SD) and analyzed using Student's t-test with the Minitab program (version13) comparing between the different groups. The significance level of P ≤ 0.05 was considered.

• Differences are considered statistically significant at $p < 0.05$.

4. Results

4.1. Plasma IgG Concentration (g/l)

Statistical analysis of these results showed a highly significant increase in IgG of stressed rats (** 4.36 ± 0.06 g/l) compared with control rats (3.35 ± 0.12 g/l). Figure 1.

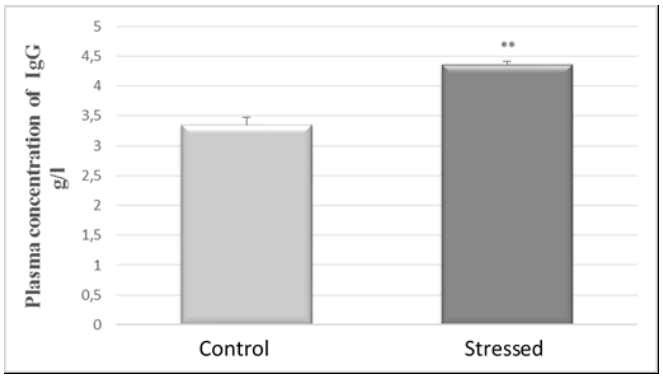

Figure 1: Changes in plasma concentration of IgG (ng / ml). (m ± s; Ns: non-significant difference p > 0.05; *p <0.05; **p < 0.01; ***p < 0.001)

4.2. Immune System Cells

Immune cells are divided into innate immunity cells (GB, MONO, PLQ) that are able to capture, present the antigen and destroy foreign elements and adaptive immunity cells (LYMPH). Figure 2 .

The results show a decrease in the rate of white blood cells (8.22 ± 0.60 µl) and monocytes (0.57 ± 0.12 µl) of stressed rats relative to white blood cell rate (9.56 ± 1.28 µl) and monocytes (0.86 ± 0.10 µl) in control rats. However, we did not find differences in the rate of lymphocytes (5.63 ± 0.77 µl) and platelets (705.33 ± 138.16 µl) of stressed rats compared to lymphocyte ratio (5.89 ± 0.84 µl) and platelet (599 ± 124.30 µl) in control rats.

Statistical analysis showed a significant decrease in the rate of white blood cells and monocytes in stressed rats compared to control rats (p * <0.05). However, the rates of lymphocytes and platelets showed no significant difference in the stressed rats compared with the control rats (p > 0.05). Figure 2.

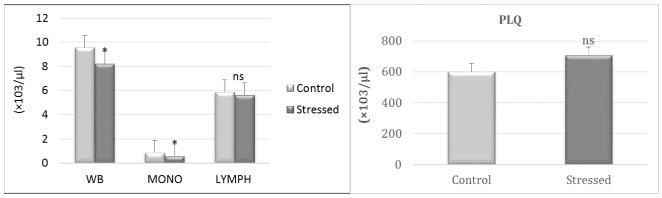

Figure 2: Cells of the innate and adaptive immune system in control and stressed rats. (m ± s, n = 17 control, n = 17 stressed). (Ns: non- significant difference p > 0.05; *p <0.05; **p < 0.01; ***p < 0.001).

4.3. Morris Water Maze of Mothers

The results in figure 3 show a significant decrease in the number of entries figure 03(A) (D3 : 12.64 ± 4.33 s *; D4 : 8.72 s ± 3.98 s*), and the time spent in the target quadrant figure 03(B) (D 3 : 20.5 * ± 2.08 s; D 4 : 14.5 * s ± 3.11) in the third (learning) and fourth (memorizing) days in stressed rats compared to the number of entries (D3 : 21.3 ± 4.52 s; D 4 : 16.30 ± 4.38 s) and the time spent in the target quadrant (D3 : 25.75 ± 1.71 s; D 4 : 25.25 ± 5.56 s) in control rats.

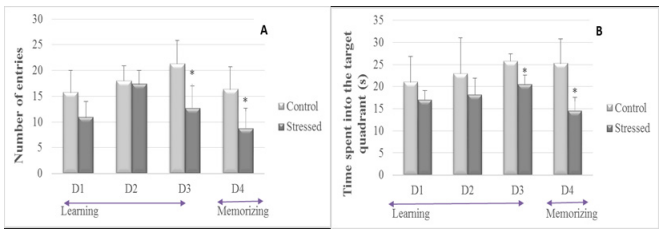

Figure 3: Morris water maze test parameters in control and stressed rats. (A) The number of entries in the target quadrant. (B) The time spent in the target quadrant. (m ± s, n = 17 control, n = 17 stressed). (Ns: non- significant difference p > 0.05; *p <0.05; **p < 0.01; ***p < 0.001).

4.4. Morris water maze of offspring

Adolescence Age (postnatal days 50 and 51)

Within two days of the Morris water maze test, we have seen remarkable difference in latency to find the submerged platform and the time spent in the target

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quadrant but insignificant between groups coming from control and stressed mothers in 51 days. Figure 4.

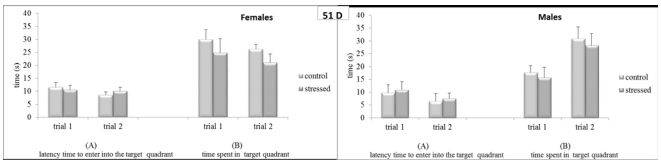

Figure 4: Latency time in the target quadrant in PND 51 (A). Time spent in the same quadrant (B) of males and females offspring. (m ± s , n of the offspring from control mothers (15 males, 15 females) and stressed mothers (15 males, 15 females).(Ns : non-significant difference p <0.05; *p <0.05; **p < 0.01; ***p < 0.001)

5. Discussion

In this study, the significant increase in latency time with decrease of the time spent in the target quadrant in the Morris water maze of rats subjected to chronic restraint stress. Which is explained by the disruption and weakening of learning and memory abilities (Xu et al., 2009). Because the main physiological responses of chronic stress include activation of the hypothalamic-pituitary - adrenal (HPA) axis and the medulla Sympatico-system , by which the levels of corticosterone and catecholamines may be modified (Cohen and Hamrick, 2003; Yi et al., 2013),induced a change in cognitive functions including learning and spatial memory. These are linked with specific alterations of the hippocampus which depend largely on these behavioral tasks (Yi et al., 2013; Vann and Albasser, 2011).

In stressful situations, the hypothalamus receives direct stimulation of the limbic system and noradrenergic stimulation from the locus coeruleus and nucleus of the solitary tract (Carrasco and Van De Kar, 2003; Itoi, 2008). In response to these stimuli hypothalamus releases CRH activates the adenohypophysis in turn secrete ACTH. It induces the synthesis of glucocorticoids by the adrenal glands. These hormones are involved in the stress in many functional regulations in the metabolism and the central nervous system (Morilak, 2005). So there is evidence that emotional stress can affect many integrator circuits between the immune, nervous and endocrine system in animals and humans (Dantzer and Mormede, 1995). As shown in our study, when we explored the immune system by studying immunoglobulin (IgG).These molecules are the first that would be released into the blood stream and they are the most abundant of the five classes of immunoglobulins. They are the only ones that are able to pass from mother to child during pregnancy through the placenta . In several studies, these molecules have demonstrated neuroprotective effects (Hulse et al., 2008; Zhang et al., 2012). The human immunoglobulin (IgG) is the main component of the protection against lesions of dopaminergic neurons from 6 - hydroxydopamine (6- OHDA) (Zhang et al., 2012). IgG has traditionally been thought to be produced by mature B cells only , but recently has been shown to be produced by neuronal cells. Huang et al en (2008) showed that IgG can be produced by the central neurons in rats and has previously been shown that IgG are abundantly produced by neurons in the cerebral cortex , hippocampus, dentate gyrus , cerebellum, the pons, the medulla and spinal cord , it is synthesized by the same intraocular eye cells in human (Niu et al., 2011). Although the function of the neurons immunoglobulins IgG is poorly understood, it has been suggested that IgG neurons are involved in maintaining the stability of the nervous system. These molecules become toxic to dopaminergic neurons when released in large quantities. Oxidative stress due to changes in the concentration of IgG under the influence of physiological glucose concentrations (Newkirk et al., 2003).

The decrease in white blood cells after restraint stress may be caused by their redistribution in peripheral tissues, such as skin and lymph nodes, where the destruction of the stem cells and exerted immunosuppression by glucocorticoids and even by catecholamines (anti activity -inflammatory and immunomodulatory). By inhibiting T cell proliferation, decrease the bactericidal activity of macrophages and suppress the cytotoxic activity of natural killer (NK) cells. However, glucocorticoids may also exert immunostimulatory properties of B cells play sometimes a role of immunostimulant and sometimes immunosuppressive (Steele, 2002). Leukocytes possess receptors for adrenaline, sex steroids, insulin, prolactin, growth hormone and thyroxine. Monocytes from bone marrow have not been only a phagocytic activity but also secrete enzymes , proteins , prostaglandins , cytokines and even ROS (reactive oxygen species) and NO (reactive nitrogen species) (Pereira et al., 1996). Which are important in the defense against pathogens and tumor cells. (Hibbs et al., 1988; Macmicking et al., 1997). High levels of cortisol stimulate apoptosis of thymocytes and can cause lymphopenia and monocytopenia (Nascimento et al., 2004).

The immune system in turn also incorporates neural information. Because primary and secondary lymphoid organs are innervated by sympathetic and cholinergic nerve endings. Leukocytes have receptors for most neurotransmitters released by these nerve endings, which explains the impairment of the immune system and its relationship with the nervous and endocrine system (Besedovsky and Del Rey, 1996). The biochemistry of neuronal dysfunction was also demonstrated in the Morris water maze test in which we also found changes in capacity memorizing of the offspring but still meaningless. These were demonstrated by the number of entries in the target quadrant and the time spent in the same quadrant (Leslie et al., 2000; Takuma et al., 2012). On the other hand, in our previous studies we have shown that this type of stress has contributed to the emergence and development of neurobehavioral disorders such as depression and anxiety in the mothers and their descendants (Haloui and Tahraoui, 2014). The hyper activation of the HPA axis of mothers activates the HPA axis of the offspring that affects the mother-child relationship and influencing the development of the embryonic brain and changing the behavior of the offspring permanently (Mychasiuk et al., 2011; Baibazarova et al.,2013; Haloui and Tahraoui, 2014; Baquedano et al., 2011).

5. Conclusion

The quality of relationships between a –mother-child plays an important role in the harmonious development and the subsequent balance of that individual. Disturbances of these relationships can lead to such serious emotional disorders. These are dependent on the timing and the type of stressor (Kapoor et al., 2009).

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COMPARISON OF WAVELET FAMILIES FOR MENTAL TASK CLASSIFICATION

ZİHİNSEL GÖREV SINIFLANDIRMA İÇİN DALGACIK DÖNÜŞÜMÜ FONKSİYONLARININ KARŞILAŞTIRMASI

Çağlar Uyulan[*1], Türker Tekin Ergüzel[2]

Abstract

Wavelet theory is a widely used feature extraction method for raw electroencephalogram (EEG) signal processing. The nature of the EEG signal is non-stationary, therefore applying wavelet transform on EEG signals is a valuable process for extraction promising features. On the other hand, determining the proper wavelet family is a challenging step to get the best fitted features for high classification accuracy. In this paper, therefore, we focused on a comparative study of different Discrete Wavelet Transform (DWT) methods to find the most convenient wavelet function of wavelet families for a non-stationary EEG signal analysis to be used to classify mental tasks. For the classification process, four different mental tasks were selected to and we grouped each with another one to set dual tasked sets including all possible combinations. Feature extraction steps are performed using wavelet functions haar, coiflets (order 1), biorthogonal (order 6.8), reverse biorthogonal (order 6.8), daubechies (order 2) and, daubechies (order 4). Later, a specific feature reduction formula is applied to the extracted feature vector. Generated feature vector is then split into train and test data before the classification. Artificial neural network was used for classification of the extracted feature sets. From the result of the repeated analysis for each DWT methods, Coiflets performed relatively better compared to other wavelet families.

Keywords: Discrete Wavelet Transform, mental task classification, coiflet wavelet, daubechies wavelet, wavelet families

Özet

Dalgacık dönüşümü, ham EEG (elektroensefalografi) verilerinden öznitelik çıkartma yöntemi olarak yaygın şekilde kullanılmaktadır. EEG sinyalleri doğası gereği durağan değildir, dolayısıyla dalgacık dönüşümü, sınıflandırma performansına katkıda bulunacak özniteliklerin çıkartılması sürecinde oldukça etkili bir yöntemdir. Diğer taraftan, uygun dalgacık fonksiyonunun seçimi de en iyi sınıflandırma performansını elde edebilmek için önem arz etmektedir. Bu sebepten dolayı, bu çalışmada, ayrık dalgacık dönüşümü yöntemlerinin karşılaştırılması üzerinde durarak, zihinsel görevlerin sınıflandırılmasına ilişkin en iyi sınıflandırma performansını gösteren dalgacık fonksiyonunu bulmayı amaçladık. Sınıflandırma süreci için dört farklı zihinsel görev seçildi ve her birinin, diğerleri ile ikili-üçlü kombinasyonları ve tüm durumlara ilişkin karşılaştırılmalı sonuçları elde edildi. Öznitelik çıkartma aşamalarında sırasıyla, haar, coiflets (seviye 1), biortogonal (seviye 6.8), ters biortogonal (seviye 6.8), daubechies (seviye 2) ve daubechies (seviye 4) kullanılmıştır. Sonrasında, elde edilen öznitelik kümesine, öznitelik indirgeme formülü uygulanmış ve elde edilen öznitelik vektörü, eğitim ve test veri kümesi olarak sınıflandırma öncesinde ayrılmıştır. Çıkartılan öznitelik kümeleri, yapay sinir ağı ile sınıflandırılmıştır. Ayrık dalgacık dönüşümü fonksiyonlarından coiflets'in, diğer fonksiyonlara göre daha iyi sonuç verdiği gözlenmiştir.

Anahtar Kelimeler: *Ayrık dalgacık dönüşümü, zihinsel görev sınıflandırma, coiflet dalgacık, daubechies dalgacık, wavelet fonksiyonları*

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1.Introduction

The wavelet transform were used to be a powerful and efficient time-frequency analysis method for analyzing non-stationary signals like EEG. In order to determine the features in the frequency bands of related potential recorded by EEG, various methods are used for the spectral and spatial analysis including Wavelet Filter Bank (Robinson et al., 2012). Wavelet filter bank decomposes the transient EEG signal into different frequency bands and every frequency band is figured out by their scaling function (Gandhi et al., 2011). By using this method, the most important step is to choosing a proper wavelet family including the mother wavelet function for signal characterization. It is also important to decide the optimal wavelets and the appropriate number of decomposition levels (Sonia et al.,2013).

A set of features, which contain sequence of wavelet coefficient vectors can be obtained after this process, which decomposes the signal into its wavelets at the specific sub-band frequencies. By using this method, called as feature extraction, the discrimination of the mental tasks becomes applicable. The dimension of the extracted features should also be reduced and made in compact form. The reduced feature vectors are evaluated as the inputs to the classification stage. In this study, an artificial neural network (ANN) with back propagation algorithm was employed. In order to acquire a satisfactory classification performance, the design process and parameters such as the number of neurons in each layer and the number of layers, of the classifier is important to be taken into consideration. The main objective of this paper is determining the most appropriate wavelet function to extract features from raw EEG signals for mental task classification combining a learning algorithm to be able to make classification prediction. The outline of this study is as follows; in section 2.1, we will explain about the experimental system for data collection and filtering stage. In section 2.2, the theory and application of feature extraction method used is reviewed followed by the concepts of discrete wavelet transforms. In section 2.3, the theoretical basis of the wavelet mother functions of DWT are explained in details. In section 2.4, the classification stage using ANN is described. The analysis of the experiments done and results obtained in Section 3 and conclusions are given in the last section.

2.Material and Methods

2.1. Data Acquisition and Preprocessing Stage

All training and testing data were collected from a healthy subject, 28 year old male. The subject focused on each mental task for 10 consecutive seconds. The sampling time of the neuroheadset is 128 samples/second for all channels. 40 different epochs were assigned for training and 10 epochs were used for test data collection. Therefore, we had in total 1600 train and 400 test dataset matrix in association with 4 mental tasks for each 14 sensor channels respectively. After performing the feature extraction process, a valuable reduced feature is evaluated. The dimension of the input training matrix and input test matrix for each feature was set as 14x1600 and 14x400 before the training process. Here, we propose a discrete wavelet transform based feature extraction method by using various wavelet mother functions to investigate the dominant frequency band and timing in EEG signals and compare with each other functions classification accuracy for all combinations of 2 mental task groups of 4 pre-defined mental tasks which are; a) Reciting the alphabet backwards, b) Imagination of rotation of a cube, c) Imagination of left arm movements (open/close) and d) Mentally performing mathematical operation. All dataset were collected from the Emotive EPOC Neuroheadset that it is available to save the EEG signals from 14 channels of the Emotiv-Headset (AF3-F7-F3-FC5-T7-P7-O1-O2-P8-T8-FC6-F4-F8-AF4). The headset samples from all channels at 128 samples/second. The EEG signals were filtered with band pass filter between 0.5 and 45 Hz. using a 6th order butterworth band pass filter to remove the artifacts.

2.2.Discrete Wavelet Transform

The wavelet term indicates to a wave based window function of the main frequency f_0. The wavelets are classified with its wavelet window. The continuous wavelet transform is given as:

$$W_c(\tau,\mu)=\frac{1}{\sqrt{\mu}}\int_{-\infty}^{\infty}x(t)\psi(t)\left\{\frac{t-\tau}{\mu}\right\}dt$$

where $\psi(t)$ refers to the mother wavelet function, the factor $\frac{1}{\sqrt{\mu}}$, normalizes the energy of the signal.

The scale factor μ is the inverse of frequency. If this scaling factor has a small value, the wavelet corresponds to high frequencies of the EEG signal. If this scaling factor is larger, then the wavelet is expanded and refers to low frequencies. τ is the translation factor and corresponds to the position of the center of window while it is shifted by the signal (Tobin, 2007).

The CWT is inefficient for ANN classification, because of the generation of redundant information. For this reason, discrete wavelet transform (DWT) was used which is implemented using sub-band coding method as filter bank (Kannan et al., 1996). The multi-rate filter bank has a series of high-pass and low-pass FIR filter and decimation factors are shown in Figure 1.

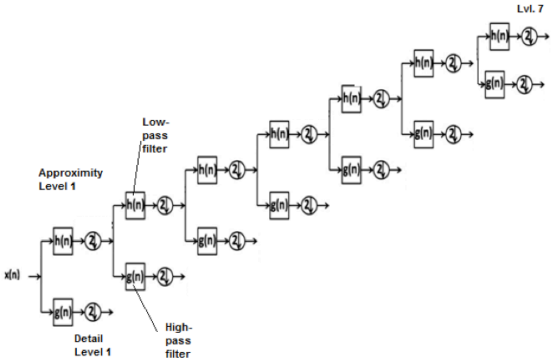


Figure 1: Filter bank representation up to seventh level.

The discrete wavelet transform is defined by the following equation (Mallat, 2008).

$$W_d(j,k) = \sum_j \sum_k x(k) 2^{-j/2} \psi\left(2^{-j} n - k\right)$$

In DWT, the original signal passes through two complementary filters, named low-pass and high-pass filters, and emerges as two signals, called approximation coefficients and detail coefficients (Weeks, 2010). DWT is convenient for processing signals like EEG, since it is very effective in time-frequency localization and multi-scale resolution (Sonia et al., 2013). The low frequency components, h[n] "approximations" are most important than high frequency components, g[n] "detail" in characterizing EEG signals. The consecutive low and high pass filtering can be evaluated by the following equations:

$$Y_{high}[k] = \sum_n x[n] g[2k - n]$$

$$Y_{low}[k] = \sum_n x[n] h[2k - n]$$

Where, Y_{high} and Y_{low} are the outputs of high pass and low pass filters respectively. The filters have a function of sub-sampling the input signal by 2. DWT has varying window size at low and high frequencies, which scans both spatial and spectral domains in order to resolve all frequencies optimally (Mallat, 2008). The wavelet coefficients (or scales) displayed in Figure 2 is in expanded time format. This is difficult format to interpret from a time-frequency point of view since both are embedded in the display. Each of the levels are concatenated in time and displayed as amplitude versus time. Applying the DWT to EEG signals yields the frequency spectrum for each sub-band.

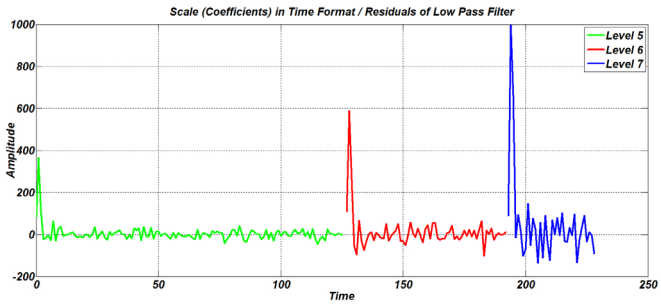


Figure 2: DWT coefficients in time format

$$\beta_i = sqrt\left(abs\left(sum\left(diff\left(fft\left(\lambda_i\right)\right)\right)\right)\right)$$

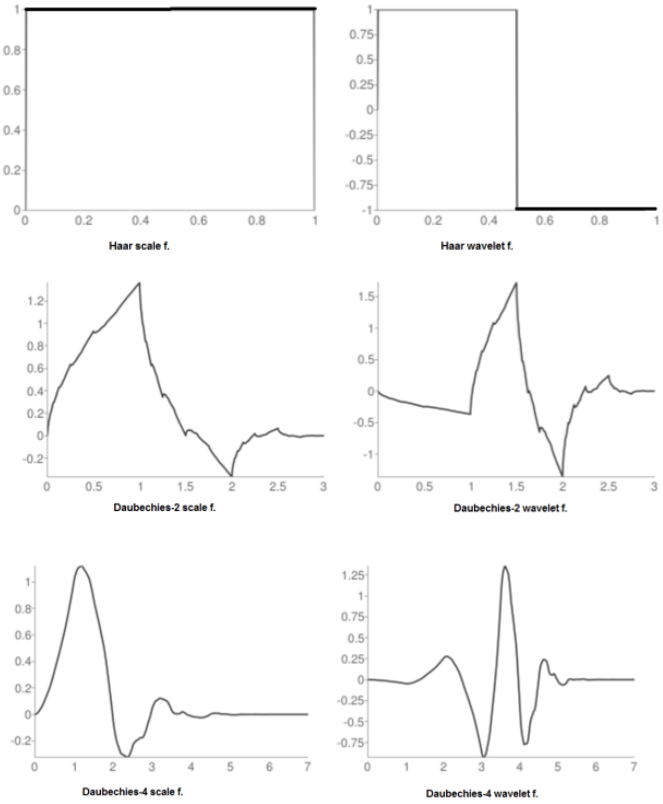
Here, λ_i denotes the node vector, which is the output of the i.th level low-pass filter and β_i is the specific feature for this level.

2.3.Neural Network Classifier

A neural network contains highly interconnected, complex nodes in order to model biological neurons. It works as a parallel processor composed of simple processing units in order to deal with uncertain, fuzzy data sets. Each neuron acquires a weighted input vector or matrix and produces an output vector (Freeman, 2006). Multi-Layer Perceptron NN supported by back-propagation training algorithm are very convenient for brain computer interface (BCI) and pattern recognition applications. MLP's are designed with an input, one or more hidden and an output layer. Multi-layer feed forward NN was applied to our data set for the classification process. The weights on the network are adjusted applying deeply training, the error is minimized based on the gradient descent algorithm. Hereafter the NN was tested with the test dataset by means of performance criteria. After making some heuristic trials, we have set the optimal configuration for the NN parameters as; number of hidden layers (1 or 2), number of neurons in each layer (50) and the maximum number of iterations in the learning process (1000), the learning rate 0.035, the momentum rate 0.2, performance criteria "mse", training algorithm "scaled conjugate gradient".

2.4 Explanation of DWT Basis Functions

Unfolding the information, localized within the signal, is based upon the structural basis function. The information hidden in the signal can be obtained through dilation and shifting procedure. It is essential to select the correct and efficient wavelet function for specific applications. In this paper, we explain a frequently used DWT basis function analysis (Kuzu et al., 2013). The scale and mother wavelet functions of the haar, daubechies-2, daubechies-4, coiflets-1, biorthogonal-6.8, reverse biorthogonal-6.8 are depicted in Figure 3, respectively.



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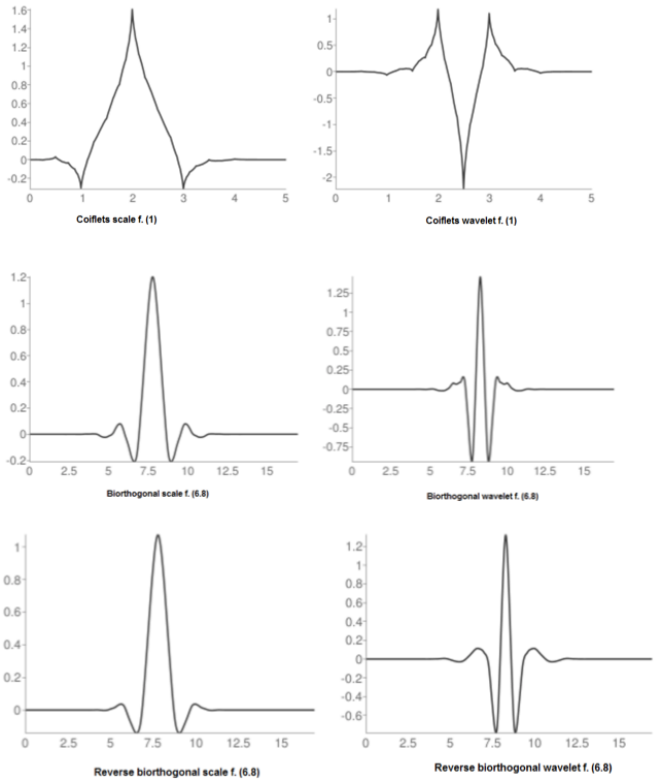

Figure 3: Wavelet shapes of different wavelet functions and their scale functions

2.4.1.Haar

Haar wavelet is a row of rescaled "square-shaped" functions. Take that $\phi(t)$ is a scaling function (Daniel, 1994; Stoloescu et al., 2010).

$$\phi(t)=\begin{cases}1\rightarrow 0\le t\le 1\\ 0\rightarrow otherwise\end{cases}$$

The haar mother wavelet function can be obtained by the following function:

$$\psi(t)=\begin{cases}1\rightarrow 0\prec t\le \frac{1}{2}\\ -1\rightarrow \frac{1}{2}\prec t\le 1\\ 0\rightarrow otherwise\end{cases}$$

Haar wavelet is orthogonal to its own translations and dilations and not continuous.

2.4.2.Daubechies

Daubechies wavelets are similar to the haar wavelet transform by evaluating the averages and difference through the scalar production with scaling and wavelets (Mohammed et al., 2009). The orthonormal wavelets are established with arbitrary number N of vanishing wavelet moments and minimal length of support 2N-1 (Cerna et al., 2008). Daubechies wavelet can be evaluated by using following mother and scaling functions:

$$\psi(t)=\sqrt{2}\sum_{m=0}^{2N-1}(-1)^m h_{2N-1-m}\phi(2t-m)$$

$$\phi(t)=\sqrt{2}\sum_{m=0}^{2N-1}h_m\phi(2t-m)$$

Where $h_0,h_1,h_2,\ldots,h_{2N-1}$ are the constant coefficients of the filter.

2.4.3.Coiflets

Coiflet wavelet function and its scaling function have 2N and 2N-1 moments equal to 0, respectively. The two functions have a support of length 6N-1. The main indicative feature of coiflet wavelet is to have highest number of vanishing moments for both scaling and wavelet function for any given support width (Majumdar et al., 2013). The approximation properties depend on the number of vanishing wavelet moments (Cerna et al., 2008). Let $P_k f$ be an approximation of $f\in L^2(\mathbb{R})$ on level k.

$$P_k f=\sum_{q\in\mathbb{Z}}\langle f,\phi_{k,q}\rangle\phi_{k,q}$$

and for J < k

$$P_k f=\sum_{q\in\mathbb{Z}}\langle f,\phi_{J,q}\rangle\phi_{J,q}+\sum_{l=J}^{k-1}\sum_{q\in\mathbb{Z}}\langle f,\psi_{l,q}\rangle\psi_{l,q}$$

where

$$\phi_{l,q}=2^{l/2}\phi(2^l.-q)$$

$$\psi_{l,q}=2^{l/2}\psi(2^l.-q)$$

The wavelet coefficients are evaluated by following formula:

$$\langle f,\psi_{l,q}\rangle=\int_{-\infty}^{\infty}f(t)2^{l/2}\psi(2^l t-q)dt$$

2.4.4.Biorthogonal

Two wavelets are used for decomposition and reconstruction. Biorthogonal wavelets are not based on vahishing moment and all wavelets referred to its family have a symmetric structure. For orthogonal wavelets, the scaling function and mother wavelet are presented by the recursive relationship (Fritz, 1994).

$$\psi(t)=\sqrt{2}\sum_m g_m\phi(2t-k)$$

$$\phi(t)=\sqrt{2}\sum_m h_m\phi(2t-m)$$

Their scaled translates are denoted by;

$$\phi_m^n(t) = 2^{n/2}\phi\left(2^n t - m\right)$$

$$\psi_m^n(t) = 2^{n/2}\psi\left(2^n t - m\right)$$

2.4.5.Reverse biorthogonal

Reverse biorthogonal wavelet family is obtained from the biorthogonal wavelet coupled. Reverse biorthogonal wavelet families are guided by biorthogonal spline wavelets, therefore the symmetrical condition and reconstruction can be assured (Varuneshkumar et al., 2015).

3.Results and Discussion

Feature vectors were created from the extracted nodes of decomposed wavelet coefficients of EEG signals at the 7th level. Our approach is to find out a proper mother wavelet function based on extracted feature set to get satisfactory classification accuracy. We investigated the effect of various wavelet functions whose filter lengths are different from each other. The EEG signals collected for 4 mental tasks were decomposed into coarse approximation and detailed information. DWT employs its set of scaling functions and wavelet functions, which are associated with low-pass and high-pass filters respectively. The EEG signals collected from each electrode channel were decomposed up the 7th level in the case of wavelet filter bank decomposition. Extracted feature vectors from both the methods were fed into the ANN for classification step. We divided the feature vector set into three sets, 70% of which is the data is used for training, 15% for validation and 15% for the testing processes respectively. ANN uses one input layer, one hidden layer and one output layer. Working with this network structure, the feature vector set obtained were first trained and then their performance were tested accordingly. The corresponding accuracies of each mental task were evaluated after testing processes. The classification performance results obtained using DWT for different wavelet functions are listed in table 1.

Table 1: The classification accuracies obtained for 4 mental task subsets by using different wavelet basis function as feature extraction method on test data

Class \ Mother Wavelet	hear	coiflets 1	biorthogonal 6.8	reverse biorthogonal 6.8	db2	db4
Alphabet-Cube	91.4%	99.6%	95.6%	95.4%	97.8%	99.4%
Alphabet-LeftArm	60.3%	64.2%	61.1%	61.0%	62.5%	63.5%
Alphabet-MathOp	62.5%	68.2%	65.1%	65.4%	67.0%	68.0%
Cube-LeftArm	90.3%	98.5%	94.3%	94.1%	96.5%	98.0%
Cube-MathOp	91.0%	99.7%	95.3%	95.2%	97.5%	99.3%
LeftArm-MathOp	73.0%	80.0%	76.5%	76.4%	78.3%	79.6%
Alphabet-Cube-LeftArm-MathOp	77.5%	85.3%	81.5%	81.2%	83.2%	84.5%

Since there are different mother wavelets of different wavelet families available, the choice of the wavelet family and the mother wavelet plays an important role in terms of classification accuracies. The results clearly underline that coiflets1 type of mother wavelet performs better than the other members of its wavelet family with its 85.3% classification performance for 4 mental task classification and higher accuracies for all other dual task classifications. Dual task performance of the proposed methods verifies the better performance of coiflet1. Besides it is also possible to deduce that, the performance of each method is good enough to work on. For the following studies, especially real time BCI design, real time response is crucially important and the response time is to be considered and has much more importance.

4. Conclusion

In this paper, a comparative study of wavelet based feature extraction methods such as discrete wavelet transform based wavelet filter bank decomposition are performed. These methods are combined with neural networks for classification purpose. The performance of both these techniques are tested and evaluated. Both the techniques are found to be efficient in EEG signal processing. The most suitable mother wavelet for feature extraction and classification of EEG signals was found. The features were extracted from the 4 different mental task performed after the decomposition by each of the wavelet family and ANN was employed to classify the cases. Based on the classification accuracy rate obtained, it was found that Coiflet of order 1 mother wavelet function, whose general classification performance for 4 mental tasks is 85.3%, is the best wavelet family for analysis of EEG signal. The computational complexity and the feature vector size were also reduced by using DWT. Provided that the experimental results done, a wavelet transform is an elegant tool for the analysis of non-stationary signals like EEG. The experimental results show that this hybrid architecture using DWT and ANN could effectively extract the features from the EEG signal for various applications. Coiflets1 as a feature extraction method achieve higher classification accuracy compared to other wavelet functions.

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NONPHARMACOLOGIC TREATMENT APPROACH TO PAIN

AĞRIYA FARMAKOLOJİK OLMAYAN TEDAVİ YAKLAŞIMI

Selin Özcan[1], Gökben Hızlı Sayar[*2], Nevzat Tarhan[1]

Abstract

Chronic pain has various forms such as inflammatory pain, visceral pain, headache, disk-related pain, neuropathic pain, cancer pain. Although the biological basis of chronic pain is related to vulnerability, it continues with behavioral and psychological components. In the context of multimodal interventions, interventions other than systemic pharmacologic treatments for chronic pain are also present. Besides interventional approaches; there are several noninvasive options including cognitive behavioral therapy, biofeedback, relaxation therapy, physical therapy, thermal applications, transcutaneous electrical stimulation and spinal cord stimulation. The neuroscientific approach to pain can only be achieved by combining physical and mental components of the pain with neuroscience

Keywords: pain, neuroscience, treatment

Özet

Kronik ağrının, enflamatuar ağrı, visseral ağrı, baş ağrısı, disk ilişkili ağrı, nöropatik ağrı, kanser ağrısı gibi çeşitli biçimleri bulunmaktadır. Her ne kadar kronik ağrının biyolojik temeli yatkınlık ile ilişkili olsa da, davranışsal ve psikolojik bileşenleri de bulunmaktadır. Ağrıya çok yönlü müdahaleler kapsamında, sistemik farmakolojik tedaviler dışında müdahale seçenekleri de mevcuttur. Kronik ağrı tedavisinde girişimsel yaklaşımların yanı sıra; bilişsel davranışçı terapi, biofeedback, gevşeme terapisi, fizik tedavi, termal uygulamalar, transkütanöz elektrik stimülasyonu ve spinal kord stimülasyonu dahil olmak üzere birçok invaziv olmayan seçenekler bulunmaktadır. Ağrıya sinirbilimsel yaklaşım, sadece ağrının fiziksel ve ruhsal bileşenlerini nöröbilim çerçevesinde ele alarak elde edilebilir

Anahtar Kelimeler: *ağrı, sinirbilim, tedavi*

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1. Introduction

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience related toa ctual or potential tissue damage " (IASP Task Force on Taxonomy, 1994). Acute pain is an essential, protective mechanism alerting about potential dangers (Woolf, 2004).

The biopsychosocial model consists of whole biological, psychological, social and behavioral factors that affect perception mechanism. In Turkey, %30 of the population which are over 18-year-old adults have pain depends on any problem, %9,5 have chronic pain. The mean persisting duration of pain is five years; chronic pain is eight years (Tulunay & Tulunay, 2000). To prevent delays in management of pain, the health professionals should present a multidimensional approach to pain as a part of a modern biopsychosocial concept.

Pain can be adaptive or maladaptive. Adaptive pain contributes to survival by protecting the organism from injury or promoting healing. Maladaptive or chronic pain represents pathologic functioning of the nervous system.

It is critical to identify the type of pain; acute or chronic. Acute pain appears as a symptom of body injury, and it does not last more than three months. However, chronic pain is a condition. It lasts more than three months with known or unknown reasons. The number of research focusing on a broad range of aspects of pain, from the molecular biology of pain pathways to the psychosocial aspects are growing. Such studies have resulted in notable gains in pain management and quality of life of patients (Dworkin et al., 2007).

Chronic pain has various forms such as inflammatory pain, visceral pain, headache, disk-related pain, neuropathic pain, cancer pain. Biological basis of chronic pain begins with vulnerability and then it continues with behavioral components. Treatment categories are very variable such as medications, chemotherapeutic agents, invasive options (such as nerve blocks or epidural steroid injections, physical therapy, biofeedback, acupuncture, and relaxation training. Emotion status, anxiety, catastrophizing (it will never stop), depression, cognition about pain (e.g. negative beliefs), active and passive coping strategies, significant others, are the psychological, behavioral and social factors related to pain (Stewart et al., 2015).

The neuroscientific approach to pain is possible with understanding of cortical association with sensorial, motor and cognitive pathways, plasticity, mirror neurons is essential while focusing on pain. Different related brain regions are affected in chronic pain. Studies demonstrate that dorsolateral prefrontal cortex, substantia nigra, brain reward system and neurotransmitter mechanisms' circuits are altered. One of the cortical areas affected by the mechanism of pain is the dorsolateral prefrontal cortex that is responsible for cognition, analyzing, motor planning and working memory. Thereby chronic pain may disrupt the cognitive and emotional process and led to anxiety, depression, mood disturbances. Brain imaging techniques demonstrated loss of the amount of substantia nigra and the association between chronic pain and brain reward system (Borsook, 2012).

There is another subject which is needed to be thought about pain is mirror neuron effect. Mirror neurons translate the sensorial perception to behavior. Mirror neurons in the human brain are identified in the premotor cortex, posterior parietal lobe and visual cortex of temporal lobe. In a study that investigates the subjects' fMRI while they are observing faces from chronic pain patients, anterior insula, left anterior cingulate cortex, left inferior parietal cortex were found to be activated while watching (Craig et al., 2000). We know that anterior insula and anterior cingulate cortex are responsible for social learning. A meta-analysis study revealed that anterior cingulate cortex, anterior insulate cortex, somatosensorial cortex (S1-2) and brainstem's neuro-hemodynamic responses were restricted. These regions are activated in acute physical pain, called pain-matrix (Fan et al., 2016).

Decreasing pain and enhancing the quality of life is the primary focus of pain medicine (McGuigan, 2014). Nonpharmacological options that have support in patients with chronic pain include neurostimulation, physical therapy, acupuncture, massage, biofeedback and the cognitive-behavioral therapy, psychotherapy, and patient education.

The goal of treatment may not necessarily be to cure pain, but to manage it and restore functionality.

2. Nonpharmacologic Therapies

In the context of multimodal interventions, interventions other than systemic pharmacologic treatments for chronic pain are also present. Besides interventional approachessuch as ablative techniques, botulinum toxin injections, nerve blocks and trigger point injections; there ara several noninvasive options including cognitive behavioral therapy, biofeedback, relaxation therapy, acupuncture, physical therapy, thermal applications, spinal cord stimulation and transcutaneous electrical stimulation.

3. Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) is the most commonly used behavioral medicine approach for pain patients. CBT focuses simultaneously on the environment, behavior, and cognition. Cognitive behavioral therapy is structured, goal-directed, problem focused, and time limited (often 10 to 20 sessions) (Beck, 2006). Emotion status, anxiety, catastrophizing (it will never stop), depression, cognition about pain (e.g. negative beliefs), active and passive coping strategies, significant others, are the psychological, behavioral and social factors related to pain (Stewart et al., 2015).

CBT for pain incorporates three components: patient education, behavioral skill training, and cognitive skill training (Okifuji et al., 2007). Behavioral skill training involves education related to the behavioral principles, such as conditioning, reinforcement, pain/illness behaviors, and attentional training, and how do they interact with pain and disability.

Cognitive training for pain management begins with discovering the situational factors that trigger their pain. CBT can be used with meditation. Instead of challenging the content of the thoughts, the patient learns to disassociate from them. Relaxation, meditation, acupuncture, and hypnosis might also be used. This eclectic form of psychotherapy is called Third-Wave CBT (Hanscom et al., 2015).

Although often delivered as a structured course of one-on-one sessions with a therapist, it appears that CBT can be effectively administered in a variety of other formats, including in a group, via the computer, or by telephone. In a randomized trial of subjects with chronic widespread pain, symptom improvement at six months was reported in 8 percent of patients assigned to usual care, 35 percent allocated to CBT via telephone, and 37 percent designated to a combination of telephone CBT and exercise (McBeth et al., 2012)..

Stress management is also an critical factor in the treatment of pain. Stress has a significant role in exacerbation of chronic pain. Linton performed a meta-analysis and reported a significant connection between stress and pain (Linton, 2000). A review reported the relationship between depression and catastrophizing in patients with pain disorders (Edwards et al., 2011). Catastrophizing is related to amplified pain and diminished effectiveness of biomedical interventions.

4. Biofeedback

Biofeedback is the process of earning elevated awareness of several physiological processes such as brainwaves, muscle tone, skin conductance, heart rate and pain perception primarily using instruments that give information on the activity of those systems, with a purpose of being capable of manipulating them at will (Nestoriuc& Martin, 2007).

Biofeedback has been observed to be effective for the treatment of chronic pain (Ma et al., 2011). Voluntary control of physiological functions using biofeedback may be also used in modulating pain perception (Ladouceur et al.,2012). When participants are exposed to pictures of different emotional valence (pleasant, neutral or unpleasant), pain perception and the spinal nociceptive flexion reflex are also modulated (Arsenault et al, 2013).

5. Physical medicine approaches

An exercise regimen specifically tailored to the patient is at the core of a physical or occupational therapy program. Stretching is a fundamental component to restoring normal range of motion. After range of motion is normalized, muscle conditioning is addressed to improve stability, function, and pain. Muscle conditioning focuses on three areas: strength, endurance, and re-education (Stanos et al., 2007).

6. Transcutaneous Electrical Stimulation

Transcutaneous Electrical Stimulation (TENS) requires the delivery of a low voltage electrical current from a small battery-operated equipment to the skin via surface electrodes for pain relief. It is a harmless, noninvasive treatment that can be self-applied (Walsh et al., 2009). Conventional TENS produces paresthesia in the area under the electrodes.

Research on TENS for pain relief has suffered from a lack of randomized controlled trials, and systematic reviews have found variable and uncertain results related to the efficacy of TENS in chronic pain management (Nnoaham & Kumbang, 2008).

7. Spinal cord stimulation

Spinal cord stimulation, a spinal neuromodulation analgesic system, is an option for chronic neuropathic pain which can arise from nerve or nervous system injury. It is a minimally invasive and reversible treatment option which can be permanently implanted after an appropriately conducted temporary screening trial with an external pulse generator to assess therapeutic efficacy and adverse effects. The technique inhibits chronic pain by stimulating the large diameter afferent nerve fibers in the spinal cord. Spinal cord stimulation remains to be a relevant tool in the treatment of chronic disabling pain (Cruccu et al., 2007; Jeon, 2012).

8. Deep brain stimulation

Deep brain stimulation (DBS) is a neurosurgical intervention reported to improve symptoms of Parkinson disease, epilepsy, Tourette's syndrome, depressive disorder, obsessive-compulsive disorders and cluster headache. Since the 1950s, DBS has been used as a treatment to relieve the intractable pain of several aetiologies including post-stroke pain and neuropathic pains. However, this technique remains "off label" in the USA as it does not have Federal Drug Administration approval (Boccard et al., 2015).

9. Conclusion

There is a growing recognition of the neuroscience of pain and its management. Psychological factors are also important in the assessment of pain patients. Optimal patient outcomes for chronic pain often emerge from a combination of multiple approaches such as pharmacologic, physical medicine, behavioral medicine and neuromodulation utilized in accord. Medication should not be the single focus of treatment but should be used in combination with other treatment modalities to increase the quality of life.

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A SPECULATION ON THE MECHANISM OF ECT, TMS, TDCS and SIMILAR TECHNIQUES

EKT, TMU, TDCS VE BENZER TEKNİKLERİN ALTINDA YATAN MEKANİZMALAR ÜZERİNE BİR SPEKÜLASYON

Levon Antikacıoğlu[*1], Nevzat Tarhan[2]

Abstract

In this paper, we tried to explain, what can eventually be the underlying mechanisms of ECT, TMS, tDCS and similar techniques. And tried to explain how, by making some slight changes in the use of the EMW (electromagnetically induced wave) devices, and by integrating them with psychotherapies and pharmacotherapies, we can either better understand their real effectiveness and, design better therapeutic strategies, and increase their positive results. So far, it seems that because of the implemented insufficient designs, either in evaluating the results or, in planning their applications, their positive effects, do not seem to be fully discovered yet.

Keywords: ECT, TMS, tDCS, electromagnetic wave therapy underlying mechanism, EMW

Özet

Bu çalışmada, EKT, TMU, tDCS ve benzer tekniklerin altında yatan muhtemel mekanizmalarının, ne olabileceklerinin açıklanmasına çalışılmıştır. Ve elektromanyetik dalgaların kullanımına paralel olarak, önerdiğimiz bazı ayrıntıların ilavesi ve bunların, psikoterapi, psikofarmakoterapi ve öğrenme prensipleri ile harmanlanmasıyla, nasıl daha iyi sonuçların elde edilebileceği, ve terapi stratejilerinin yapılandırılabileceği, tartışılmıştır. Çünkü görüldüğü kadarıyla EMD (Elektromanyetik Dalga) kullanımı ile yapılan; onların uygulanmasını ve/veya etkinlik derecelerini araştıran çalışmaların verimlilik oranları aslında, bazı metodolojik yetersizliklerden kaynaklı olarak, ihtimal ki gözden kaçmış olup, henüz tam anlamıyla keşfedilememişlerdir.

Anahtar Kelimeler: *EKT, TMU, tDCS, elektromanyetik dalga terapilerinin mekanizması, EMD*

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1. Introduction

Since decades varieties of psychopharmacotherapies and psychotherapies, either alone or in combined forms are both administrated on mild or severe psychiatric problems, depending on the diseases or preferences of the practitioners by taking in consideration the needs of the patients.

There is a third agent, the ECT (Electro Convulsive Therapy), which in the course of the history, generally by the layman, has always been considered as a controversial treatment. Nevertheless, by considering its efficiency, it is still implemented particularly in drug-resistant and persistent cases. Additionally, in these last years the variations - variations because after all, are all acting through electromagnetic (EMW) waves - like TMS (Trans Magnetic Stimulation) or tDCS (Transcranial Direct Current Stimulation), are all welcomed, because they are not as brusque as ECT.

In this manuscript we tried to discuss, on the probable "mechanism of action" of ECT, TMS, tDCS, namely the "electromagnetically induced waves" therapies and, re-evaluate some issues concerning the methodological problems, either in studying their effects or in determining strategies to empower their not yet fully discovered, efficiencies.

2. Discussion

2.1. Psychopharmacotherapies

The actual psychopharmacological agents, are primarily acting on the,

a) pre-synaptic axon terminals' neurotransmitters' production and release and re-up taking,

b) postsynaptic receptors' reception, or

c) the biochemical interactions within the synaptic cleft.

These are the actual scientific paradigms for the chemical neurons.

Their commonly shared factor is that all the strategies are organized to facilitate or inhibit the neuronal transmission; thus in a way "to manipulate the learning process" too. In other terms "all is done to loosen up the stabilized ties and/or strengthen the desired ones".

2.2. Psychotherapies of any kind

Since the beginning of the human history, several strategies have been used to persuade, impress and heal people. The first practitioners were the tribe's leaders, priests, shamans, highly prestigious governors, senior wise people etc. Nowadays psychotherapists are nothing more than the institutionalized and trained forms of their archaic predecessors.

Needless to say that all the hundreds of therapeutic strategies, are all targeted to loosen up and/or erase the undesired learned ties and/or strengthen the desired ones, indisputably "are, all targeting the manipulation of learning principles and mechanisms".

2.3. Are the above mentioned treatments working?

The truth is that all the statistical data, reveals that the actually applied psychotherapies or/and pharmacotherapies in some cases-diseases-individuals, are perfectly working. But, in some others instead, are ineffective.

At this point our question should be;

- "Why in similar clinical cases, some of the treatments are effective, instead some others, are not at all"?

And immediately after, another question should be,

- "Why in some patients even only a few psychotherapeutic procedures or small doses of medications are able to obtain satisfactory results, but in some others, even the maximum medications or repetitive therapies do not work"?

2.3.1. Which of our steps are hitching?

Whatever we do either by psychological therapy or/and pharmacotherapy, first of all, the patients must possess a neuro-anatomo-physiologically "somehow, healthy and efficiently functioning" neuronal integrity.

Thus at the background of our mind should always be a judgment like these;

a) "If we ameliorate % 100 the patient by psychopharmacological agents", it means that the broken segment was "only" the one which we affected; practically, the "pre" or "post" synaptic metabolism or synaptic "cleft's" biochemical or mechanical problems.

b) "If we ameliorate % 100 the patient by any kind of psychotherapy, training, rehabilitation, education"; it means that there was an "erroneous learning" of some behavior or just "a lack of knowledge" and we helped the patient to correct it.

c) Or if we ameliorate the patient % 100, by the combination of both of the above mentioned ways, no matter which part, and, up to what extend was not working properly, because at the end of the day, the two problematic aspects of the patient, in a combined form, have been treated.

d) "If we do not ameliorate the patient in none of the above mentioned ways" or ameliorate only "partially", we inevitably have to suppose that "there is some other problem in the rest of the neuron"; in its "nucleus" or "metabolism" or "dendritic" or "axonal" neuroanatomical "constitution" etc. which, in some way are impeding the "electro conductivity" of the neuron/s.

Thus, at this point, our opinion is that, are exactly the ECTs (and successively TMS, tDCS etc.) or better if we express in general terms, the electromagnetically induced waves, that are acting on the neuron to correct the dysfunctional remnants, mentioned at the above last clause.

2.3.2. ECT – TNS – tDCS and similars

It is still unclear the mechanism of ECT (Fosse, R., & Read, J., 2013). At the beginning has been widely used in wide ranges of clinical cases, but now, considering its some side effects, its use is limited to, especially severe cases of drug or/and therapy-resistant morbidities, like major depression or severe OCD. Nevertheless, in general terms it is accepted that "the efficiency of electroconvulsive therapy in major depression is established, but the importance of the electrical dosage and electrode placement in relation to efficacy and side effects is uncertain" (Sackeim, H.A. at al., 1993). On the other hand, it is an empirically documented fact that, the seizures' intensity, threshold, duration, ECT's unilateral or bilateral applications are all variables changing the outcomes (Sackeim, H. A., Devanand, D. P., & Prudic, J., 1991). However, it is since long time accepted and documented even on text books that, ECT at least in many cases, situations and diseases is working, especially in delusional depression and, in comparison to other combined treatments (Kroessler, D., 1985).

The relatively modern TMS, given its more "human" applicability and, apparently less adverse effects, conceded a more extensive usability in a variety of morbid entities. Also in TMS there are different studies, sometimes contradictory, are documenting its positive effects on cognition, memory and effect's durability beyond the applied times (Thut, G., & Pascual-Leone, A., 2010). etc. For instance, TMS is used in rehabilitation, brain injuries, and depression with relatively fewer side effects (Nielson, D. M., 2015). There are researches which are dealing with the orientation-positioning of the coils; Opitz, A. at al. (2016) pointed the fact that "Three distinct DLPFC stimulation zones were identified, differing with respect to the network to be affected (default, frontoparietal) and sensitivity to coil orientation (Opitz, A. at al., 2016). Carni, L. at al (2015) by conducting a treatment program by TMS (Deep Cranial Magnetic Stimulation) on OCD, concluded; "lacking the ability to target the CSTC circuit directly, standard TMS treatment protocols for OCD showed diversified results. But concluded that the stimulation of targeted deeper neuronal pathways by dTMS, is a promising therapeutic intervention on OCD" (Carmi, L. at al., 2015).

tDCS seems even safer, hence is used more extensively. A well guided mapping is necessary to be able to target the exact points and is used in perceptual, cognitive, and behavioral functions (Nitsche, M. A. at al., 2008). It is very remarkable the summative opinion made by Li (Li, L. at all. 2015); "With the slew of studies reporting 'promising results' for everything from motor recovery after stroke to boosting memory function, one could be easily seduced by the idea of tDCS being the next panacea for all neurological ills. However, huge variability exists in the reported effects of tDCS, with great variability in the effect sizes and even contradictory results reported. In this review, we consider the interindividual factors that may contribute to this variability" (Li, L. M. At al., 2015). Brunoni, A.R. at al. (2016) concluded that tDCS has mixed results, probably caused by heterogeneity of the studied groups (Brunoni, A. R. At al., 2016). Kekic, M. at al (2016) concluded that in "Overall, data suggested that tDCS interventions comprising multiple sessions can ameliorate symptoms of several major psychiatric disorders, both acutely and in the long-term. Nevertheless, the tDCS field is still in its infancy" (Kekic, M. At al., 2016).

Up to this point, the only exact words we can spell are "all of the above mentioned electromagnetically induced, wave therapies" have "different effects" on "different diseases" and "patients", in "different degrees". Nevertheless, the general opinion, though cautiously, is that TMS (Kimiskidis, V. K., 2016; Oliveira, J. at al., 2016) and tDCS (Marriage, A. P., 2016; Nitsche, M. A. at al., 2009; Nitsche, M. A., & Paulus, W., 2000; Gandiga, P. C. At al., 2006; Tortella, G. at al., 2015; Hone-Blanchet, A. at al., 2015; Vanderhasselt, M. A. at al., 2015) are promising tools for the future.

2.4. Aproposal on the probable neuro-anatomo-physiological mechanism of electromagnetically induced, wave therapies

In principle, during any kind of conditioning and/or, operational excitatory and/or inhibitory activity, along the chemical neurons, the electrical currents flow only unidirectionally; "toward the axonal terminal buttons". By nature, under normal physiological circumstances any electrical flow occurring toward opposite direction of the neuron (from terminal buttons toward dendrites) can't exist at all. This is all the necessary backbone to keep in mind to base the entire mechanism that we will now propose below.

2.4.1. Facilitated flow

By applying the electromagnetic therapy device's electrodes to the scalp, we discharge the current from one electrode, toward the other one, across the brain; from a point A, up to a point B.

The same is valid also in TMS; although it does not possess any electrodes, its pulses' waves are going from a source point A, which is the magnetic source's center, toward the point B, which is its, virtually unlimited, natural spherical three-dimensional axial distributions.

If we induce to the scalp an "electromagnetic discharge", headed for instance from the electrode A, toward the electrode B, all those neurons on its course, having the same polarity orientation ("soma→terminal button") and aligned in a "parallel" or "quasi parallel" or at most "oblique" position, in respect to the orientation of the current, those neurons inevitably will be stimulated-facilitated (Figure 1); for they have the same polarity with the applied EMW.

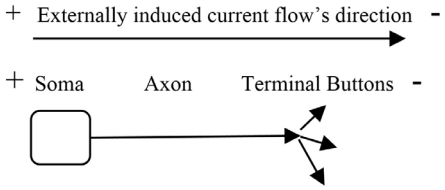

Figure 1: The External current flow, in case of having the same direction, in respect to the neuronal natural current flow.

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Let's assume that this "pushed neuronal current", or in other terms, "the current, dragged from the direction of the soma and, dropped toward the axonal terminal button" (from the "+" pole, to the "–"one), by this externally induced stronger wave/energy, in addition to the fact that will promote-facilitate an stimulus, will not do any considerable harm to the neurons, provided it remains within the safe power and duration limits. At most, they will be activated-facilitated.

2.4.2. Obstructed flow

If along the course of the externally applied electrical discharges, there are neurons lined-up toward "opposite directions – polarities", inevitably those neurons, will get some "nano-scale electric shock" and will be obstructed and, (Oppositely oriented currents will clash with each other's.) will be hurt; because the externally applied stronger current, will force the neurons to carry the current toward opposite direction, which is contrary to their innate morpho-physiology (Figure 2).

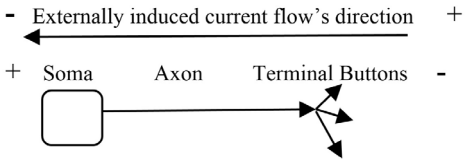

Figure 2: The External current flow, in case of having an opposite direction, in respect to the neuronal natural current flow.

Not only, but, after all, the clusters of neurons are wet environments; and if remained in between two electrodes, they will serve as just conductors. As a natural consequence, either the neuronal soma, or its nuclear functions, or the pre-post synaptic functions or cleft's physiologic bio-mechanisms, all will be stunned; vesicles, receptors, neurotransmitters and every micro or nano system in them, will suffer and their functions will be diverted, overstimulated or over inhibited.

But as long as the implemented currents remain within safe biological limits, obviously, these adverse effects will be reversible. We will get permanent side effects only if the externally induced waves are higher than the biologically tolerable threshold, or, the durations are longer, up to the point of creating structural damage on the neurons and/or on their synaptic connections. These damages don't need to be necessarily at visible scales; changes at nano-scales also, can perfectly be sufficient to spoil the integrity of the neuro-anatomo-physiological functionality. As a consequence, after the sessions, the patient will express some "side effects-negative feelings and experiences" etc.

2.4.3. Neurons and their connections are not aligned along a straight-line

The brain is a mess of anatomical (hard wired) connections and plus, with unlimited fCs (functional connectomes-connections created by personal experiences), oriented virtually toward any direction, depending on the individuals' own brainprint. And it is almost impossible to meet any functional or anatomical connection overlapping with the externally induced, quasi straight-line current trajectory; for the neuronal connections quite likely, are in form of labyrinths, zigzags and curves.

Thus any externally induced current along its course will "contemporarily" encounter neurons, either of the same or, opposite polarity.

As a final sum, the externally induced waves eventually, along their own trajectory (from "+" toward "-". Figure 3), will encounter the curved and zigzagged continuations of the same neurons too; of which, some of the segments having the same polarity will be facilitated, but instead the parts having the opposite polarity, will be obstructed (Figure 3). Needless to say, the final outcome will be a micro-shock and consequentially will result in an obstruction.

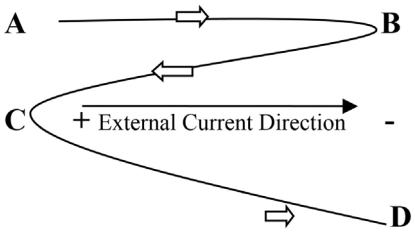

Figure 3: The External current flow which on its way, along the same neuronal axon, encounters, some segments with the same and, some other segments, with oppositely oriented neuronal current flows, just because the axon is not a straight line, instead, has some snake-like shape.

A→B segment is facilitated, B←C segment is obstructed, and C→D segment is facilitated.

2.4.4. Nano-Neurophysiotherapy and/or Neuroplasticity?

We know that in any cerebral location related to, overused organs or faculties, becomes more developed. Conversely, lessened functions are sign of diminished brain volume in the respective areas.

There is no reason to not accept that TMS application also, creates similar consequences; In fact, Bohning (Bohning, D. E. at all. 2000) reported that "Single TMS pulses applied over the motor cortex with sufficient intensity to induce thumb movement produced BOLD-fMRI responses detectable in both the ipsilateral motor cortex" (Bohning, D. E. at al., 2000). In other words, they detected an augmentation of blood flow; hence we would propose that this data gives us a possibility to conclude; that probably its repetitive applications can create a massage-like effect to the neurons and then, an upcoming neuroplasticity.

There are other researches that sustain; "Despite the fact that different studies have been performed using transcranial direct current stimulation (tDCS) in aphasia, so far, to what extend the stimulation of a cerebral region may affect the activity of anatomically connected regions remain unclear" (Cipollari, S. at al., 2015). But this interpretation pertains to the specific condition of aphasia. For other conditions can perfectly be invalid.

In short, we would propose that externally induced EMWs, eventually are acting like a nano-physiotherapy and, at least promoting blood circulation or, revitalizing for some reason the grown lazy neurons or, mobilizing inert neuronal clusters and giving some form of push or, making a massage-like stimulation or, something else and "making the neurons participate to the integrity of the cerebral functionality".

2.5. Reinterpretation of the literature and proposal of a different model

If we sum up all of the abovementioned facts, the somehow conflicting results, of researches done by "electromagnetic wave therapies", became clearer and understandable; it seems highly probable that in reality they are not conflicting at all, and are working better than we think.

The problem stands only in the fact that, in clinical researches it is very difficult to control the variables as much as in the experimental conditions. We need, to find new methodological strategies, to adequately split conditions, to keep under strict control the independent variables and, to better understand the EMWs' therapy effects.

We know that old memories are more deeply rooted; our ancestors probably new it since the beginning of the human history but since some decades ago, we also have scientifically documented, thanks to Ebbinghouse's colossal and ingenious experiments (Ebbinghaus, H., 1913).

Needless to mention that either our everyday experiences or clinical (for instance in senile dementia or alzheimer), psychopathological observations, confirm that the old personal memories, having strong ties with each other's, are the best conserved and, last deteriorated ones. It seems that the old memories have the same resistance against ECT sessions too. In fact, Squire et al. (Squire, L.R. et al., 1981) documented that after ECT, older memories have been more easily recovered (Squire, L. R. at al., 1981).

But how can we know which patient's which memory, we mean psychopathological symptom or syndrome, is deeper or shallower then the other's one? It is impossible to arrive to a healthy conclusion, within the limited methodological designs and conditions of clinical applications. As a consequence, we can neither understand what a patient's older/newer memory is, or compare the patients, with each other's psychopathological conditions and, arrive to results. This is more than enough to see conflicting results after EMW applications.

On the other hand, it is a very well-known reality that the older diseases are difficultly cured. So how it is possible to say 1-year-old OCD is an old or new one, and, standardize a group by such a criterion? Will not it depend of course on the patients' age? Another problem is that not only the durations, but also the severities, intensities, undoubtedly are important dimensions, variables and cannot be easily measured. It is hypothesized that the "strength or weakness of a learned material is directly proportional to the quantity, quality and intensity of the ties made within the entire Central Nervous System Network" (Antikacioglu, L., 2015).

All the above mentioned facts can perfectly explain why, "the efficiency of electroconvulsive therapy in major depression is established, but the importance of the electrical dosage and electrode placement, in relation to efficacy and side effects, is uncertain" (Sackeim, H. A. at al.,1993). Or why ECT seizures' intensity, threshold, duration, ECT's unilateral or bilateral applications are all variables changing the outcomes (Sackeim, H. A. at al.,1991). Why there are researches which are dealing with the orientation-positioning of the coils; Opitz, A. at al. (2016) pointed the fact that "Three distinct DLPFC stimulation zones were identified, differing with respect to the network to be affected (default, frontoparietal) and sensitivity to coil orientation (Opitz, A. at al., 2016). Why Carni, L. at al. (2015) by conducting a treatment program by TMS (Deep Cranial Magnetic Stimulation) on OCD, concluded; "lacking the ability to target the CSTC circuit directly, standard TMS treatment protocols for OCD showed diversified results. But concluded that the stimulation of targeted deeper neuronal pathways by dTMS, is a promising therapeutic intervention on OCD (Carmi, L. at al., 2015). Why Nitsche, M. A. at al. (2008) proposes that a well guided mapping is necessary to be able to target the exact points and is used in perceptual, cognitive, and behavioral functions (Nitsche, M. A. at al., 2008). Why Brunoni, A.R. at al. (2016) concluded that tDCS has mixed results, probably caused by heterogeneity of the studied groups. Why Kekic, M. at al (2016) concluded that in "Overall, data suggested that tDCS interventions comprising multiple sessions can ameliorate symptoms of several major psychiatric disorders, both acutely and in the long-term. Nevertheless, the tDCS field is still in its infancy".

In short, the above outcomes are endlessly diversified, because in our opinion, along the course of the externally applied waves, are paved neurons either of the same (and can be facilitated) or, opposite (and can be obstructed) polarity. As a natural consequence at the end, all of them will be shocked. These clashing currents cause what we call "side effects", that are consequences of the "neuro-anatomophysiological traumatic micro-shacks". And in turn are also effects of the loosening memory ties.

Probably, "simultaneously and paradoxically" the so called "side effects" generated by flatterings created by the shocks, which manifest themselves in form of attention difficulty, memory loss, concentration impossibilities, dizziness or other similar problems, "will also be the initiator of the awakening, revitalization, blood supply, neurophysiological reanimation, activation and neuroplastic changes of the inert neurons" (along with the facilitation or obstruction effects which they have got) provided they, genetically or neuro-anatomically are not totally handicapped.

Which of the above agents to what extend will be effective, depends on the individuals' brainprints. And in order to achieve improvements, we need both; slacking off the old memories and promoting new connections too, through psychotherapies and pharmacotherapies.

Now let's us concentrate on some preliminary factors which can be useful either in "designing researches to measure the effectiveness of the EMW treatments" or/ and, in "designing the treatments" themselves.

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2.6 Better strategies for research and therapy purposes

2.6.1 Early intervention

Probably the first step to take in consideration should be an "early intervention".

As the main principle of the EMW therapies is to loosen the memories connections and if possible to erase them, our primary goal must urgently be, an early intervention. Old memories are the least forgotten. The sooner the intervention the better is the result.

2.6.2. Duration of sessions

After all, EMW therapies are unnatural interventions. Just to prevent any predictable or unpredictable permanent side effects, we should suggest personalized durations. Hypothetically every individual has his own resistance threshold. The best length is, neither a longer nor a shorter than the "necessary" duration. Unnecessarily long durations can make more harm than benefit. Shorter than the optimum degree, cannot do any good. To adequately tailor flexible and optimum session durations, the patient need to be carefully and continuously observed.

2.6.3. Intensity of EMWs

Perhaps to standardize the wave intensities we should better create some kind of "resistance index" in base of body weight or some other criteria. If we exceed the necessary threshold of the individual, probably it augments the loosening process of the memories (or symptoms, syndromes etc.) but then, renders difficult to build up new ones or, harms in some other form.

2.6.4. Direction of waves

We have to continuously change the position of the electrodes. Probably the more parts are multidirectionally affected and stimulated, the better are the results.

Probably in affecting the brain throughout multiple EMW axial orientations, TMS has a remarkably superior manageability, in respect tDCSs. But by continuously changing electrodes' positions, and systematically moving them, tDCS also, can have the advantage of reaching to sufficiently remote brain points.

2.6.5. Multi-Device Intervention

Every device, has its own advantages and limits. Thus perhaps, instead of being stuck to one device only, it is better to intervene to the patient with different EMW devices.

2.6.6. Unilateral versus Bilateral

Undoubtedly both unilateral and bilateral sessions should be made. As our end goal is, nothing more than massaging and revitalizing the "entirety" of the brain, and make it function in "integrity", we have to reach every deep cerebral locality as far as the technology permits.

2.6.7. Whatever the intervention is for, in order to relocate desired habits, practices are a must

The mission of loosening the old ties and revitalizing the lazy neurons is just the half of the job. We still need to teach and solidify the adaptive behavioral patterns. Between the sessions, we must achieve, an intense and multidimensional psychotherapeutic approach, tailored to the individual. This last rule, in our opinion, should be our primary importance.

Just EMWs alone, cannot work to any full extend. Or at least, cannot have a lasting effect.

The total absence or, a weak support of psychotherapies and psychopharmacotherapies explains perfectly, why EMWs' constructive effects become disputable. The over helming majority of researches and treatments done by using EMWs, are concentrated solely on variables like ages, strokes' localities, morbidities, sessions' frequencies, intensities and durations. Of course by default they are all necessary, but are not enough. The primary target must be, to intensively plan the patient's life, between his/her EMW therapy sessions. In other words, the EMW applications, should not be our final target, but just an "intermediary tool" in reassessing, the mental-physical rehabilitation.

2.6.8. How to implement our proposal either in designing researches or intervening sessions?

We would propose that probably, by taking in consideration the above mentioned few simple rules and by using them as independent variables, we can both "design, better experimental and research models, to prove the efficacy of EMV therapies", and to obtain better results during treatments.

Our opinion about the controversy of the researches' results is that, with a very high probability, the ones which obtained better results are the ones which willingly / unwillingly or knowingly / unknowingly, have met the abovementioned criteria. Or vice versa, the ones who didn't obtain desirable results, are the ones that didn't met the above simple rules.

3. Conclusion

Our opinion simply is, that applying EMWs to the scalp; giving them micro-shacks, stunning the neurons' functions and, by this way loosening neural old ties-memories and, simultaneously revitalizing the lazy ones, are all, simply a preparation to a new mind-state and, are only half of the way.

In order to obtain curative results instead, between the sessions of the EMW therapies, by taking advantage of learning mechanisms, we must plan adequately personalized, extensive and intensive psychotherapies supported by pharmacotherapies. For the final target is the rehabilitation. Using only EMW does not rehabilitate but, it can be used as a preparative therapeutic milieu, in other words all the EMW therapy devices, can only be an intermediary tool.

Not just, but by planning efficient psycopharmacotherapies between the EMW therapy sessions, by taking in better control the EMWs' timings, durations, intensities, directions and laterality as above discussed, and by tailoring all of them in relation to the patients'/subjects' personal conditions, it is very highly probable that we will obtain better evaluative research designs, therapeutic outcomes and, the apparent controversies will fade.

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FUTURE OF PSYCHIATRY: MOBILE HEALTH AND SOCIAL SENSING

PSİKİYATRİNİN GELECEGİ: MOBİL SAĞLIK VE SOSYAL ALGILAMA

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Abstract

Mobile technologies are transforming our lives. Utilizing the mobile technologies in health care has developed into a new interdisciplinary field called mobile health (mHealth). Data about an individual's moods, cognitions, physical and social activities can be collected and can be used to track mental health of individuals, or make other predictions about their lifestyle such as eating habits and obesity. The smartphone accelerometers and GPS localization systems give information on the overall level of activity. The microphone is used for activity recognition, based on the sound sensed. The social interaction can be tracked by the log of calls, the number of people contacted. Voice analysis is a way of tracking the mood by analyzing the patient's speech during voice calls. The mental health professional must recognize the increasing availability of mobile phones however patient's motivation to use the applications must also be taken into account. Mobile sensors can assist users to monitor their emotions and behaviors. Mobile technology has the potential to transform mental health care.

Keywords: mobile health, m-Health, technology, social sensing, smartphones

Özet

Mobil teknolojiler hayatımızı değiştirmektedir. Sağlık alanında mobil teknolojilerin kullanımı "mobil sağlık" (mHealth) adlı yeni bir disiplinler arası bir alan haline gelmiştir. Bireyin ruh halleri, kognisyonları, fiziksel ve sosyal faaliyetleri hakkında veri toplanabilir ve veriler bireylerin ruh sağlığını izlemek, ya da beslenme alışkanlıkları ve obezite gibi kendi yaşam tarzı ile yakından ilişkili durumları tahmin ve takip etmek için kullanılabilir. Akıllı telefonlarda yerleşik bulunan akselerometre ve GPS gibi sistemler kişinin genel fiziksel aktivite genel düzeyi hakkında bilgi verebilir. Mikrofon sistemi, algılanan sesi analiz ederek kişinin sosyal etkileşimini ve sosyal temas düzeyini takip edebilir.. Ses analizi sesli aramalar sırasında kişinin konuşmasını analiz ederek duygulanımı izlemenin bir yolu olarak kullanılabilir. Her ne kadar cep telefonları toplumda yaygın olarak kullanılıyor olsa da bu mobil uygulamaları kullanmak için hastanın motivasyonu da dikkate alınmalıdır. Mobil sensörler duygularını ve davranışlarını izlemek için kullanıcılara yardımcı olabilir. Mobil teknoloji ruh sağlığı hizmetlerini geliştirme potansiyeline sahiptir.

Anahtar Kelimeler: *Mobil sağlık, teknoloji, sosyal algılama, akıllı telefonlar*

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1. Introduction

The smartphones and other communication technologies have impacted all our lives. We all have a rich set of options for broadcasting information, like Facebook, Twitter, YouTube, Instagram, and Foursquare. Our smartphones are other wearable technologies are equipped with cameras, accelerometers, compasses. All data from various sources are interconnected or interact with each other and form numerous, large-scale, and sophisticated networks, e.g. World Wide Web and social networks. With the aid of technology in almost everyone's pocket, scientists now have the capacity to track self-reported or automatically captured behaviors. Optimal mental health care necessitates early detection of mental health problems. Behavioral factors in severe mental illnesses can also be monitored with mobile sensing. Today, combining the Internet capabilities with the proliferation of sensors is producing a new revolution, called social sensing (Wang et al., 2015).

Mental illness is becoming a challenge in modern societies. With the widespread adoption of social media and mobile devices, a unique opportunity arises for tracking mental health problems. For tracking physical activity, sedentary versus non-sedentary activities can be followed by accelerometers, GPS devices and gyroscopes. This helps to increase physical activity and maintaining body mass index in a healthy level. For tracking social engagement, one can use social encounters, conversational turn-taking, speech volume, speaking rate and intonation via social media channels, microphones and cameras that will increase the frequency of social encounters. Sleep patterns can also be tracked for disrupted versus continuous sleep and time of sleep. Microphones, accelerometers, and even phone usage can be used to detect sleep problems, regulate sleep patterns and synchronize with internal body clock.

Traditional methods of monitoring mental health are expensive and intrusive. More importantly, these methods do not scale to large populations and not sensitive to the symptoms in the early stages of psychiatric problems. Advances in technology and machine learning, combined with the widespread use of the Internet and enactment of social media, now there is an easy way to tracking mental health (Zhou et al., 2015).

2. mHealth

Mobile phones are increasingly being advocated for innovation in psychosocial and behavioral health research and interventions as part of mobile health,"mHealth". mHealth is moving forward rapidly in research and commercial applications (Swendeman et al., 2015). Health apps have the potential to modify healthcare and health promotion. The apps comprise many topics, including smoking cessation, obesity and weight management, personal health records, pain management, fitness and physical activity, medication management and adherence, depression and many others (Nasser et al., 2015). However, although hundreds of health apps exist, very few are evidence-based, and numerous are with low-quality content.

Recently, mHealth technologies present the opportunity for scientists to collect information about the individual's biology, cognitions, emotions, behavior and social life in the real-world via wearable sensors (Wiederhold et al., 2015). mHealth technologies produce continuous streams of data, however, ethical, and security issues remain as a source of a problem, especially in areas involving sensitive behavior or treatment (e.g., alcohol use) (Arora et al., 2014).

Several internet-based self-help and treatments were developed as an attempt to give information, assessment, support, or adjunctive treatment for people with substance use disorders or behavioral addictions. A cross-sectional online survey was administered to users of an application, namely "Stop-cannabis". Users were encouraged to participate in the survey via a message sent to the app. The app was used daily by 348 of the participants (around 70%) and almost 80% of the users regarded the app to have helped them to stop or reduce cannabis consumption (Monney et al., 2015).

There is also currently growing interest in using mobile phones to support the treatment of psychotic disorders, such as schizophrenia. Firth et al recently conducted a systematic review and meta-analysis to assess mobile phone ownership and interest in mHealth among patients with psychosis (Firth et al., 2015). Their literature search yielded data from 12 samples of psychiatric patients (n = 3227). The overall mobile phone ownership percentage was 66.4%. The authors reported that having a mobile has been significantly increasing since 2007. Moreover, in studies of mHealth acceptability, the majority of patients acknowledged that they use mobile phones to contact with services and support self-management.

In another study feasibility and validity of a mHealth system for tracking mood-related symptoms after traumatic brain injury (TBI) is assessed (Juengst et al., 2015). A mobile system was developed specifically for individuals with TBI. The authors also developed a clinical patient safety management mechanism for the individuals with risk of suicidality. Participants completed 73% of all assessments which took daily less than 2 minutes to perform. Subjects described high satisfaction with applications (6.3 of 7) and found them simple to use (6.2 of 7).

Controlled breathing is vital as a behavioral intervention for panic disorder. A randomized controlled research assessed the feasibility and clinical efficacy of a mobile game called "Flowy" that digitally delivered breathing exercises for anxiety and panic management. Patients perceived "Flowy" acceptable as an anxiety control intervention. Intent-to-treat analyses exhibited a decline in anxiety and self-report hyperventilation scores. Participants perceived "Flowy" as an entertaining and beneficial intervention (Pham et al., 2015).

Wang et al reported that the smartphone intervention was a completely or at least partially effective tool to assist in managing several chronic diseases. With the help of health-related smartphone apps, patients with chronic conditions felt secure in the knowledge that their illnesses were closely monitored, participated in their own health

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management more effectively, and perceived that they had not been neglected by their doctors and were taken good care of even they are outside the hospital (Wang et al., 2014).

3. Social Sensing

Social sensing has arisen as a new paradigm for collecting sensory measurements from the human population. Humans can serve as sensor carriers (e.g., carrying GPS devices that share location data), sensor operators (e.g., taking pictures with smartphones), or as sensors themselves (e.g., sharing their observations on Twitter). We can obtain real-world data via wearable sensing technology that give clues related to interaction patterns, speaking patterns, motion, and location. The phone camera can provide measures related to body orientations. The accelerometer can be used to detect chest wall vibrations and speech activity. Wi-Fi can be used for distance calculation (Macias et al., 2013).

A recent study investigated the impact that social interactions in the real world have on weight changes in student communities (Madan et al., 2010). The researchers tried to understand the role of exposure to different types of peers– those that are obese, overweight, have unhealthy dietary habits, and inactive lifestyles. They used the measures of Bluetooth proximity to peers that are overweight or that have unhealthy dietary practices or inactive lifestyles to examine the impact of social acquaintances on weight changes. The greatest correlations noted are with social exposure to peers with weight gains during the same period. These results suggest that subjects affected by the behaviors of the peers that they interact.

A recent study examines whether the information captured with multi-modal smartphone sensors can serve as behavioral markers for one's mental health (Ben-Zeev et al., 2015). The researchers hypothesized that smartphone sensor data would be associated with individuals' daily levels of stress, changes in depression, and personal loneliness over time. Participants used smartphones with sensors and software that facilitated continuous tracking of their geospatial activity (using GPS and Wi-Fi), kinesthetic activity (using accelerometers), sleep duration (using device use data, accelerometer, sound features, and light levels), and time spent proximal to human speech (i.e., microphone and speech detection algorithms). Participants performed daily ratings of stress. Results suggest that sensor-derived geospatial activity and sleep duration were associated with daily stress levels. Changes in loneliness were associated with the sensor-derived physical activity. They suggested that smartphones could be used as instruments for tracking several behavioral indicators of mental health.

4. Tracking Sleep

To explain the interaction between sleep, depressive symptoms, and electronic media use at night, a study investigated changes in adolescents' electronic media use at night and sleep associated with smartphone ownership (Lemola et al., 2015). Owning a smartphone was found to be related to more electronic media use in bed, later sleep times and more sleep problems compared to youngsters owning standard mobile phones. Given the high usage of smartphones, mobile phone usage data may give clues on several behavioral signals of mental health problems, for example, an increased frequency of searching for information using the phone's browser might correspond to a manic episode of bipolar disorder (Matthews et al., 2014).

5. Tracking Diet

Rich user interfaces make manual logging of users' behaviors easier and more pleasant, and sensors make tracking effortless. To date, several applications use machine-learning models to create personalized recommendations based on the individual's physical activity and dietary intake. "MyBehavior" is one of them. It was created to process data related to physical activity and eating behavior and provides personalized suggestions to the user. It uses automatic and manually recorded data related to physical activity, location, and food consumption. A recent study investigated the impact of the suggestions on user physical activity and eating behavior (Rabbi et al., 2015). Users described MyBehavior suggestions to be extremely feasible and stated that they appointed to follow the advice of the application. MyBehavior users exercised significantly more than the control group over the three weeks of the study. Users considered MyBehavior's personalized recommendations more positively than the non-personalized, generic suggestions built by professionals.

6. Tracking Mood and Cognition

E-health includes multiple tools to assess and document mood symptoms, particularly mood charts. Although these approaches are popular, many of them lack the studies to evaluate validity and efficacy (Parikh & Huniewicz, 2015) Massey et al. recently described a mobile health system for mood disorders where they introduce different possible sensors for mood detection with optimal coverage and optimal placement of on-body sensors (Massey et al., 2010).

Early identifying the social media users with depressive symptoms is an aim of several research groups. In a study, authors focused used on Facebook to discern any correlations between the platform's features and users' depressive symptoms (Park et al., 2013). Facebook features found to held predictive power in identifying depressed individuals. Participants' number of viewed app tips and app points had a positive correlation with depression scales. The number of friends and location tags held a negative correlation with the depression scales. The results also suggested that depressed individuals had less intercommunication with others. Current prospective studies are examining the possibility of detecting manic episodes in bipolar disorder using changes in Facebook use.

The effectiveness of treatment in bipolar disorder

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the strongly depends on the timing. Thus, therapeutic measures can be very effective if administered at the beginning of a patient's transition into a different mood episode. Education patients about early warning signs are vital. Grunebl et al. introduce a system, which, based on smartphone-sensing can recognize mood state changes of patients with bipolar disorder. They reported that the system could recognize the episodes with 76% accuracy and state change detection precision was 97% (Grunerbl et al., 2015).

Daily tracking of mood and physical activities helps bipolar disorder patients notice how changes in their routines affect how they feel. Smartphone sensing capabilities are uniquely adapted to monitor key bipolar disorder parameters: the nature and frequency of social interaction, and sleep/wake activity (Matthews et al., 2014). The current literature reports several studies that explored how the social activity affects the mood states during the day. It was shown that different types of social encounters provoke diverse emotional effects while there is also an association between the overall amount of social interactions and responses in positive affect. A study demonstrates the use of low-cost sensing technologies for monitoring speech activity as one aspect of social behavior, which according to the previous studies, has an impact on the emotional response of individuals. The researchers used the accelerometer based speech detection method to investigate the correlation between the amount of speech and mood changes (Mukhopadhyay & Postolache, 2013).

Patients encountering a manic episode usually talk very fast, sleep very little, and are hyperactive. On the contrary, depressive people tend to move and speak slowly, sleep a lot, and gain weight. The smartphone accelerometer and GPS provide information on the overall level of activity. The microphone is used for fine activity recognition, based on the sound sensed. The social interaction is also an important factor in determining the patient's state. When in a manic phase, people tend to spend much of the day outside, moving from place to place. The type of places visited and their relative distance from the patient's home changes. In the manic phase, the patients are much engaged in making calls and sending SMS and e-mails, however, the social activity decreases significantly during the depressive episode. A log of calls, SMS and e-mails provide information related to the social activity. Voice analysis may give clue related to the mood, and this is possible by acquiring and consequently analyzes the patient speeches during voice calls. A research evaluated a wearable system, "Monarca", had the aim of recognizing early warning signs and predicting manic or depressive episodes. The system is a smartphone centered and minimally invasive wearable sensors network. The system recognizes both physical activity and social activity (Puiatti et al., 2011).

7. Conclusion

Mobile technologies are reconstructing the way in which people interact with each other. It also changes the way mental health professionals track behavior, cognition and mood changes of the patients. Mental health professional must consider the increasing availability of mobile phones however patient's motivation to use the applications must be taken into account. Mobile sensors can assist users to monitor their emotions and behaviors. Mobile technology has the potential to revolutionize mental health care.

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SOMATIC DISEASES IN PSYCHIATRY: A PHILOSOPHICAL OVERVIEW

PSİKİYATRİDE SOMATİK BOZUKLUKLAR: FELSEFİ BİR BAKIŞ

Alper Evrensel[*1] , Mehmet Emin Ceylan[2]

Abstract

Psychiatric disorders are often reflected in physical symptoms. However, nearly all physical illnesses are accompanied by mental symptoms. Also, it is generally argued that mental function disorders and stress underlie the etiology of physical illnesses. Although modern science has defined in details all the functions of the body including the brain, some areas are not fully understood yet. Philosophical answers may shed light into those dark areas while trying to understand the entity and human.

Keywords: Psychosomatic, philosophy, dualism, mind-body, existentialism

Özet

Psikiyatrik bozukluklar sıklıkla bedensel belirtilerle yansır. Bununla beraber neredeyse bütün bedensel hastalıklara ruhsal belirtiler eşlik eder. Bedensel hastalıkların etiyolojisinde ruhsal işlev bozukluklarının ve stresin yattığını savunanlar da çoğunluktadır. Modern bilim, beyin dâhil tüm beden işlevlerini ayrıntılarıyla anlamış olsa da henüz aydınlanmamış alanlar bulunmaktadır. Felsefî yanıtlar, varlığı ve insanı anlamaya çalışırken bu karanlık alanlara ışık tutabilir.

Anahtar Kelimeler: *Psikosomatik, felsefe, düalizm, zihin-beden, varoluşçuluk*

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"Mind-body" issue puzzles physicians and philosophers at least for 2500 years. Whether humans are composed of 2 substances, namely a material substance that is body and a non-material substance that is soul, or of material substance solely or of non-material substance solely is one of the important discussion topics of Philosophy (Taslaman 2007). Also, there are some that argue that this may not be the real issue, and there may be a more fundamental issue of existence.

According to historical records, existence and human's place in existence has been firstly questioned in Anatolia, by Ancient Greek philosophers. Idealism has been based on the idea that the most important task in the world is a reality based on consciousness or mind. The foundation of idealism has been laid by Plato's "Theory of Ideas", it then reinforced by various philosophers. According to the idealism, the entity does not change and is one; subject and object are one and the same (Taslaman 2007).

Materialist philosophy has emerged as a reaction to idealist philosophy that argues non-material (mental) powers determine basically all processes in the universe. The root of materialism is based on atomism. Although Leucippus pitched this idea as an ontology theory, Democritus is considered to be the first person who systematically put forth the theory. According to this, atoms are eternal; each formation and change is composed of unification and separation of atoms. The diversity of the objects arises from the differences in number, size, shape, and arrangement of atoms. Democritus claimed that the soul was composed of thin, flat, round atoms similar to fire atoms. Ultimately, although the soul is composed of different kind of atoms than the body, it is not a distinct substance, and the approach of Democritus to the soul is compatible with the understanding of materialist universe (Taslaman 2007).

With a view of the entity that cannot be explained solely by the matter, materialist philosophy has received rationalist objections. According to Parmenides the founder of rationalist philosophy, nothing changes in the universe. Reality, that is entity, is one being in the absolute sense, permanent, constant, uncreated, indestructible, eternal, and it won't move or change (Taslaman 2007). Descartes is one of the most powerful advocates of rationalism in the West. Seeking the information he wanted to be sure about the source and accuracy, Descartes objected to skepticism, the widespread understanding of the period, by using methodological doubt. He argues that we can't be sure of the accuracy of sensory information, "whatness" of the external world, and the accuracy of mathematical truth. But in the end, he puts the claim in the center of Philosophy that he can't doubt whether he doubts and even if he doubts, it requires the existence of something doubting. "I think, therefore I am" (cogito ergo sum) argument refers to that. His presence obtained by a rational intuition is the only thing known with certainty (Altuner 2013). Descartes explains the reality of thinking as follows: A person looking at a tree may suspect whether he is looking at a real tree or not. What he thinks as a tree may be another physical object or everything may be a dream. But according to Descartes, it can't be suspected that this person has thought about a tree. Although the thought of a Pegasus has a representational reality in our minds, objectively a Pegasus does not really exist. In this sense, we can't know whether Pegasus actually exists as an object, we can only have its thought. Therefore, according to Descartes, reality is the thoughts being actual and direct objects of our minds. (Önal 2014).

Throughout the 17th and 18th century, predictability of the human nature has been focused. "Substance", that is "the sum of the invariant properties of human", defines human before existence. Although the dualism argument is directly relevant to the issue of substance, it argues that human is composed of two substances, namely mind and body, and the issue is whether these two substances can be reducible to each other. Mind-body dualism argument of Descartes still continues today. Descartes defines mind and body as two distinct substances. According to him, mind does not have any features of an object. Because it cannot be parted by its nature, but objects in three dimensional space can. So, the body can always be parted. Because the body is an entity that has a shape and dimensions, but mind doesn't have any shape or dimension, and does not occupy a place (Altuner 2013, Durakoğlu and Ay 2012).

According to Descartes, when we review what we are, we become aware that we don't need any space, shape and body to exist. Hence, our knowledge of the existence of the thought or the mind precedes our knowledge of the existence of the body. Because we know that we are thinking during the period of suspicion, even if we have doubts about existence of objects belonging to the eternal world, including our bodies. Thus we come to the conclusion that a thinking "self" exists. Then, "self" with its essence and nature to think is a substance that requires neither a place nor a material. In other words, "self" is quite different than the body and is identical with the mind. Descartes is aware of the impact of the brain on mental phenomena. He claims that the body-mind relationship is established through the pineal gland (Altuner 2013).

Descartes argues that mind and body come from two different substances, and unite or stick together in the pineal gland. According to this idea, psychosomatic symptoms indicate that mind is trying to cling to the body. Phantom pain is reflected to the body from the mind and thus the mind tries to cling to the body. Also, panic symptoms such as tachycardia, nausea, vomiting result from this. Depersonalization and derealization as a result of quadriplegia can be interpreted as efforts of the mind to cling to the body.

The most basic criticisms on rationalism come from Kant who is a rationalist. According to Kant, reality consists of judgments instead of the consciousness of being able to think as Descartes claims. Judgments alone produce the information. Impressions perceived through space and time—pure forms of sensory perception—are converted to judgment through categories-- pure concepts of understanding. What we get as a result of this information is the world of appearances (phenomena) or universe. We are unable to know the objective world apart from this. Judgments which are the products of the human mind embody the object and the concept. In this sense, object

or concept is available as long as a thinking entity exists. (Önal 2014).

Through thinking and questioning, humans improve their capacity and become mature. According to Kant, depression and somatization are caused by the weakness of the capacity and maturation deficiency. People who improve their mental functioning and exist with their thoughts won't develop somatization. In humans with maturation deficiency, entity is expressed through somatic way.

Sartre says "Existence precedes essence". Sartre claims that predetermined human nature does not exist, and human essence does not exist as from the beginning of existence. Through the birth of human without substance a "conscious entity" (l'en-soi) is born just like other living things. "Conscious entity" consists of attributes specific to the type of entity. That is a reflection of the fullness of the entity. It doesn't contain any other specific thing than this fullness. (Aşar 2014). While evolving, conscious entity firstly opts to exist with its spirit. The spirit cannot evolve, and if it fails to make adequate progress, it tends to exist physically. That is, if it cannot exist spiritually, it tries to come into being as a somatic reflection by uniting its spirit and body. If a person is primitive and doesn't have the potential to experience depression, he/she will have psychosis or will somatize.

According to Sartre, there is no other phenomenon than the phenomenon of existence. This phenomenon of the existence creates the entity; we cannot think that there is another entity that is essential to this entity. Solution to all problems is found according to this basic understanding. Existential entity is everywhere embracing everything. It is unique and covers everything. According to this, it is not from anything, not from self, not from God through creation; because there is nothing except self. This existential entity gives a sense of nausea. Nausea allows us to discern entity as a "conscious thing" (Aşar 2014). Therefore, the sense of nausea is the result of existential questioning, even unconsciously, and it is almost the most common symptom of psychosomatic disorders.

According to Heidegger, the founder of existentialist philosophy, human being (Dasein) is thrown into the world, is grounded in the state of Being. Heidegger's main purpose has been to get over the Cartesian mind-brain dichotomy by formulating human existence as "Being-in-the-world" and by emphasizing mainly "to-be-in-the-world". According to Heidegger: "Beings as a whole are the ones that always exist before us and around us … Being as a whole always has the complementarity to a certain extent; everything around us is connected to every other thing. All things have the quality of belonging together" (Önal 2014).

After Dasein has been thrown to the world like a seed, it may not have been planted, may not have blossomed. Unplanted Dasein makes a move to the object, but it is repulsed by the object. These repulses cause the emergence of somatic symptoms. So, if we look at it from an existential perspective, the failure of establishing a healthy subject-object bond, the subject being insufficiently expressed underlies somatic symptoms. Dasein in its immature world adhering tightly to its narcissistic core feels its existence through its body.

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CASE REPORT

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SERTRALINE INDUCED TREMOR

SERTRALİNE BAĞLI TREMOR

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Abstract

Specific serotonin reuptake inhibitors have been associated with extrapyramidal dysfunction manifesting as parkinsonism, dystonia, tremor, and akathisia. Here, we describe an old female patient with a diagnosis of moderate depressive episode who developed tremor with sertraline in the absence of concurrent prescription of medications, which have potential action on the dopaminergic system and whose symptoms resolved after the drug was discontinued.

Keywords: Sertraline, Tremor, Agomelatine, Adverse drug reactions

Özet

Belirli serotonin gerialım inhibitörüleri; parkinsonizm, distoni, tremor ve akatizi olarak ortaya çıkan ekstrapiramidal bozukluklarla ilişkilidir. Bu çalışmada, ilaçların eş zamanlı preskripsiyonunun eksikliğinde sertraline bağlı tremor geliştiren, dopaminerjik sistem üzerinde işlem potansiyeli olan ve ilaç kesildikten sonra semptomları ortadan kalkmış orta şiddetli depresyon teşhisi olan yaşlı bir kadın hasta değerlendirilmiştir.

Anahtar Kelimeler: *Sertralin, Tremor, Agomelatin, Olumsuz ilaç reaksiyonları*

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1. Introduction

Selective serotonin reuptake inhibitors (SSRI) are widely used antidepressants due to their high index of therapeutic efficacy and safety. However, there are reports indicating that it can precipitate extrapyramidal dysfunction as an undesirable side effect manifesting as tremor, akathisia, dystonia and parkinsonism (Di Rocco, Brannan, Prikhojan and Yahr, 1998). We report a patient who developed tremor while using sertraline, whose symptom resolved after the drug was stopped.

2. Case report

A 68-year-old widowed female presented with low mood, reduced interest, somatic symptoms, disturbed sleep and decreased appetite of one month duration precipitated by death of her husband. On mental status examination depressed affect and depressive cognitions were elicited. A diagnosis of moderate depressive episode according to ICD 10 was made and she was prescribed Tab. Sertraline 50 mg/day and Tab. Clonazepam 0.25 mg/day. Patient came for first follow up after 2 weeks reported improvement. But, she started having tremors of both hands while keeping hands in air or when catching some objects with hand, but not during resting her arms on her knee. There was no history of tremors before starting the current treatment. She was diagnosed with hypertension years back and was on Tab. Amlodipin 5 mg/day. A medical evaluation done and other possible causes of tremor ruled out. Sertraline was stopped and Tab. Agomelatine 25 mg/day started. Tremor resolved over a period of 2 weeks and mental state remained better.

3. Discussion

The present case suggests the precipitation of tremors after starting sertraline. The occurrence of tremor when patient was on sertraline and resolution after stopping the drug rules out other alternative explanations. According to Naranjo Algorithm (Naranjo et al., 1981) with a score of 6, the tremors occurring in our case was probably due to sertraline.

Selective serotonin reuptake inhibitors (SSRIs) cause a variety of drug induced movement disorders, among which tremor is probably the most common. The tremors induced by SSRIs were typically postural or action in nature, as in our case (Serrano-Dueñas, 2002). The possible mechanism could be the action of SSRIs on the serotonergic receptors at the inferior olivary nucleus and sigma 2 receptors of the red nucleus. These two structures may stimulate the thalamus and cortical neurons thereby activating spinal cord and the peripheral arch resulting in a state of rhythmical tremogenic over excitement that causes tremor (Serrano-Dueñas, 2002). Agomelatine, an antidepressant with more of melatoninergic and less of serotoninergic activity (Kasper, and Hamon, 2009), was found as an alternative drug in the present case in controlling depression without precipitating tremor.

Thus, the present case describes tremor, a rare but important side effects associated with the use of SSRIs and suggest that agomelatine could be a safe and effective alternative drug in patients with depression sensitive to serotoninergic EPS.

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FUNCTIONAL MRI IN FEIGNED VISUAL LOSS

YAPAY GÖRME KAYBINDA İŞLEVSEL MR GÖRÜNTÜLEME

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Abstract

This single-subject study studied the ability of functional magnetic resonance imaging (fMRI) to discern normal visual condition compared to feigned visual loss and induced-refractive blur condition. Under the normal binocular vision condition, activation of the parieto-occipital area reflected normal patterns of blood oxygenation level-dependent (BOLD) signals in the visual pathway. During the feigned/functional visual loss and refractive-induced blur condition, there was hypoactivation in the parieto-occipital visual pathway. This study showed that the subject could strongly influence the fMRI results, thus, further investigation and protocol refinement are needed to maximize the ability of fMRI to reliably serve as a clinical diagnostic tool in individual functional patients.

Keywords: functional MRI, feigned visual loss, functional visual loss

Özet

Tek denekli bu çalışma, normal görme durumuyla yanıltıcı görme kaybı ve yapay-refraktif bulanıklık durumunu ayırt etmek için fonksiyonel magnetik resonans görünteleme(fMRI) kullanmıştır. Normal binoküler görüş durumunda, parietooksipital alanının aktivasyonu görme yolunda kan oksijenizasyonu bağımlılık düzeyi(BOLD) sinyallerinin normal örneklerini yansıtmıştır. Yanıltıcı/ fonksiyonel görme kaybı ve yapay-refraktif bulanıklık durumu esnasında parietooksipital görme yolunda hipoaktivasyon vardı. Bu çalışma göstermiştir ki; denek, fMRI sonuçlarını ciddi derecede etkileyebilir. Bu nedenle, bireysel fonksiyonel hastalarda güvenilir bir şekilde kliniksel bir teşhis aracı olarak hizmet etmesi için fMRI kullanımının yükseltilmesi amacıyla daha fazla araştırma ve protokol gelişimine ihtiyaç duyulmuştur.

Anahtar Kelimeler: *Fonksiyonel MRI, yanıltıcı görme kaybı, foksiyonel görme kaybı*

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1. Introduction

Functional visual loss refers to asserted decreased acuity, dyschromatopsia, or visual field abnormalities with normal demonstrable visual function. Functional visual loss is present in up to 4% of cases seen in neuro-ophthalmology clinics (Bengtzen et al., 2008).

We studied the ability of functional magnetic resonance imaging (fMRI) to discern normal visual condition compared to feigned visual loss and induced refractive blur condition.

2. Case Report

A healthy 53-year-old male with normal binocular vision underwent fMRI viewing pictures of either objects or scenes (Figure 1a and 1b) under three visual conditions: (1) the normal binocular vision condition with the subject focused on the image, (2) the feigned/functional visual loss condition, wherein the subject intentionally de-focused, but maintained gaze on the image, and (3) the refractive-induced blur condition, wherein the subject attempted to focus on the image while looking through +7.00-diopter lenses.

Figure 1: Examples of object and scene stimuli shown during image acquisition

2.1. fMRI Acquisition Parameters

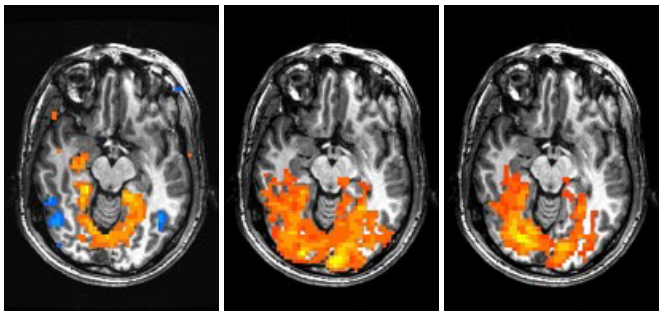
The parameters for the fMRI scan were: gradient-echo EPI, 36 contiguous 3-mm axial slices in an interleaved order, time of echo (TE) = 27.7 ms, time of repetition (TR) = 2500 ms, flip angle = 80°, field of view (FOV) = 22 cm, matrix size = 64 × 64, ramp sampling, and with the first four data points discarded. On each subject condition, each volume of images were acquired 192 times (8 minutes) while a subject was presented with 12 blocks of visual stimulation after an initial 10-second "resting" period. In a predefined randomized order, scenery images were presented in 6 blocks and object images were presented in the other 6 blocks. All pictures were unique. In each block, 10 pictures were presented continuously for 25 seconds (2.5 second for each picture), followed with a 15-second baseline condition (a white screen with a black fixation cross at the center). The subject pressed his right index finger once when the screen was switched from the baseline to picture condition. Stimuli were projected on a back screen in color with a 1024×768 resolution and a visual angle of 23°×30°. After the above functional data acquisition, 180 T1-weighted 1-mm^3 isotropic volumetric inversion recovery fast spoiled gradient-recalled images (10 minute scan time), with cerebrospinal fluid (CSF) suppressed, were obtained to cover the whole brain. These images were used to identify anatomical locations.

2.2 fMRI Data Processing and Analysis

All stimulus fMRI data pre-processing and analysis were conducted with the AFNI software (Cox, 1996) as described in Henderson (Henderson et al., 2011). Essentially, slice-timing correction and rigid-body motion correction were carried. Spatial blurring with a full width half maximum of 4 mm was applied to reduce random noise. Multiple linear regressions (using the "3dDeconvolve" routine in AFNI) were applied on a voxel-wise basis to find the magnitude change when each picture condition was presented, followed with general linear tests, to find the statistical significances between stimulus conditions.

2.3 fMRI Results

Under the normal binocular vision condition, the visual pathway had normal patterns of blood oxygenation level-dependent (BOLD) signals with primary activation of the parieto-occipital area; when viewing scene pictures, additional activation in the parahippocampal regions was present (2a). Figure 2b depicts comparison between normal viewing of scene minus +7.00 lens viewing scene; much less activation is present under the +7.00 lens condition. Figure 2c depicts scene viewing under normal conditions minus scene viewing under feigned defocusing condition and demonstrates less activation with feigned defocusing.



a. b. c.

Figure 2: The parahippocampal place area (in red and yellow) comparing the activation between scene and object pictures under normal viewing condition (a). The activation from viewing scenery pictures was much stronger under normal condition comparing to wearing +7.00 lens (b), and to when purposely feigned defocusing eyes (c).

3. Discussion

fMRI has shown promise in the investigation of patients with functional visual loss. Werring et al. looked at 5 patients with functional vision loss compared to 7 normal subjects (Werring et al., 2004). There was significantly reduced activation of primary visual cortex areas during photic stimulation and greater response in the left inferior frontal cortex, left insula, left corpus striatum, bilateral thalami, limbic structures, midbrain, and left posterior cingulated cortex compared to normals.

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Becker et al. imaged a 25-year-old subject during functional bilateral visual loss and upon spontaneous remission of symptoms 5 days later (Becker et al., 2013). During the episode of functional blindness, basic visual cortex responses were unaltered to checkerboard stimulation; however, emotion-specific pictures produced increased activity in the fronto-parietal areas and hypofunction in the occipital cortex. Bobrow et al. looked at 2 subjects with functional tunnel vision and compared them to 1 subject with an organic constricted vision (Bobrow et al., 2010). Blocks of 6-Hz expanding and contracting checkerboard ring stimuli were presented to the subjects. Subjects with functional tunnel vision showed activation to stimuli beyond their apparent field of view and in non-visual cortical areas, while the subject with organic restricted field had limited activation corresponding to their constricted visual fields.

The primary finding in the feigned/functional visual loss arm of this fMRI study is consistent with other functional imaging studies in functional visual loss, revealing hypoactivation of the primary visual regions; however, the frontoparietal and other non-primary cortical activation seen in functional patients with visual, motor, or sensory symptoms (Werring et al, 2004; Becker et al., 2013; Bobrow et al., 2010; Mailis-Gagnon et al., 2013) was not clearly replicated in our study. This perhaps emphasizes the difference between intentional feigned versus functional visual loss. It has been postulated that activation of the frontal and other non-visual areas in functional patients may reflect strategic cognitive function, and perhaps inhibits the normal visual cortical activation (Werring et al., 2004).

3. Conclusion

The subject was able to strongly influence the fMRI results, and accordingly fMRI need further refinement to reliably serve as a clinical diagnostic test in individual functional patients. More precise stimuli-driven areas with specific regional activation, such as the parahippocampal activation when viewing scenery pictures, demonstrate the potential of this technology for use as a valuable individual patient diagnostic test pending further investigation and protocol refinement (Henderson et al., 2011).

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CAN WE CONSIDER SLC2A1 POLYMORPHISMS AS A GENOMIC MARKER FOR COGNITIVE PROBLEMS?

BİLİŞSEL PROBLEMLERDE SLC2A1 POLİMORFİZMLERİNİ GENETİK BELİRTEÇ OLARAK DİKKATE ALABİLİR MİYİZ?

Kadir Sinan Arslan[1], Korkut Ulucan[*2]

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To Editor;

Glucose is the most important carbon source and energy supplier molecule for almost every cell in our body. It is very important not only for muscle cells, but also for neurons, especially the neurons of central nervous system. Its availability influences the cellular metabolism and physiological processes of the cells and tissues. Its distribution through blood and transportation from cell membrane to cells are important for aerobic capacity of the cell. All animal cells contain a plasma membrane protein involved in transporting glucose into the cell (Elbrink et al.,1975).

GLUT1 or glucose transporter 1 (OMIM 138140), also known as solute carrier family 2 facilitated glucose transporter member 1 (SLC2A1), is a uniporter carrier protein encoded by SLC2A1. GLUT1 exist in two isoforms, one with 45 kDa in astrocytes and 55 kDa in brain endothelial cells (Simpson., 2007). It mediates the basal level cellular uptake of glucose into many tissues (Mueckler et al., 1985) as well as into the brain tissue. GLUT1 has important roles in the endothelial cells of the blood brain barrier (BBB) for transporting glucose to brain (Maher et al., 1994), but its expression is not seen in neurons (Zlokovic et al., 2008). The BBB acts as a boundary between capillaries and the surrounding brain; also protects the nerve tissue by preventing different types of hazardous molecules from entering the brain. The GLUT1 protein also moves glucose between cells in the brain called glia, which protect and maintain neurons.

SLC2A1 is located at 1p34.2 and has 10 exons (Figure 1). It has over 50 variations, some of which are associated with diseases like type 2 diabetes mellitus (T2DM), diabetic nephropathy (DN), diabetic retinopathy, renal cell carcinoma, and, more recently, breast cancer and age-related macular degeneration. Mutations in the SLC2A1 are responsible for GLUT1 deficiency (de Vivo disease), which is a rare autosomal dominant disorder. This disease is characterized by a low cerebrospinal fluid glucose concentration (hypoglycorrhachia), neuroglycopenia, which results from unbalanced glucose transport across the blood–brain barrier (Seidner et al., 1998). These individuals generally have frequent seizures (epilepsy), and the probable first signs of the disorder are the involuntary eye movements, which are mainly irregular and rapid. Babies with common GLUT1 deficiency have a normal head size at birth, but due to slow development of the brain and skull, microcephaly may be seen in these individuals. As they mature, developmental delays or intellectual disabilities, some neurological problems like spasticity, ataxia and dysarthria may be observed. Episodes of confusion, lethargy, headaches, or muscle twitches (myoclonus) are the other important features of the anomaly (Pearson et al., 2013).

One of the widely analyzed polymorphism in SLC2A1 is the Variant rs841853 (also termed SLC2A1 XbaI G>T polymorphism). This polymorphism is located approximately 4.5 kbp upstream of exon 3 and affects the glucose transport ability of GLUT1, and in conjunction with the neighboring SNPs, these variations form haplotype groups. Several studies have indicated that significant association exists between rs841853 polymorphism and increased risk in Type-2 diabetes, but this association is population-specific and varied, which generated some controversies (Du, 2013). There are other case-control studies that have investigated the association between

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the diabetes-related complications, such as nephropathy, and the XbaI polymorphism in the SLC2A1, but their results were inconclusive. Some studies urge that this polymorphism is a risk factor for developing diabetic nephropathy (Liu et al., 1999; Hodgkinson et al., 2001; Ng et al., 2002), but other studies report no genetic association (Gutierrez et al., 1998;Tarnow et al., 2001) and other studies suggest the protection role of this polymorphism against diabetic nephropathy (Grzeszczak et al., 2001). To date, no study associated the related polymorphism with any kind of neurological and physiological conditions, if any, no significant associations were hold.

Another important polymorphisms is the variant rs1385129 (also termed SLC2A1 HaeII T>C polymorphism). This variation is located at the exon 2 of the GLUT1 gene (Tao et al., 1995). Like SLC2A1 XbaI polymorphism, this variation was analyzed in diabetes, but the results were not adequate to associate the polymorphism and the related disease.

There are other variations within the gene, which are considered to be an important biomarker for certain diseases and SLC2A1. As this protein is important in glucose balance through BBB, we consider that variation within the gene encoding GLUT1 may be associated with development and structure of the brain tissue. By affecting the neuro-developmental process, these variations could effect cognitive functions, which later may have an impact on physiological problems. With the help of these information, we can suggest the potential role of GLUT1 protein and its coding gene, SLC2A1, as a biomarker for cognitive problems.

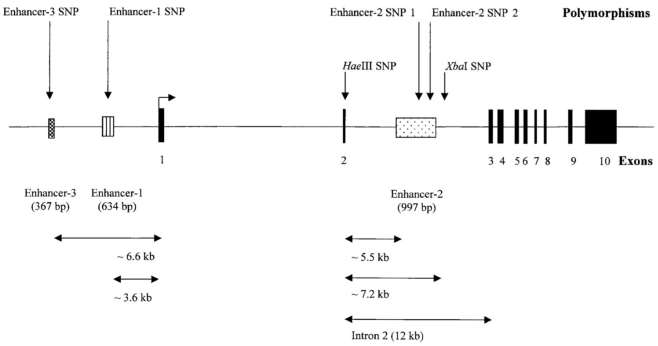

Figure 1: Structure, 5'-UTR, exons and putative enhancers (1, 2 and 3) of GLUT1. Vertical arrows indicate the important polymorphism in the gene (Ng. et al., 2002)

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