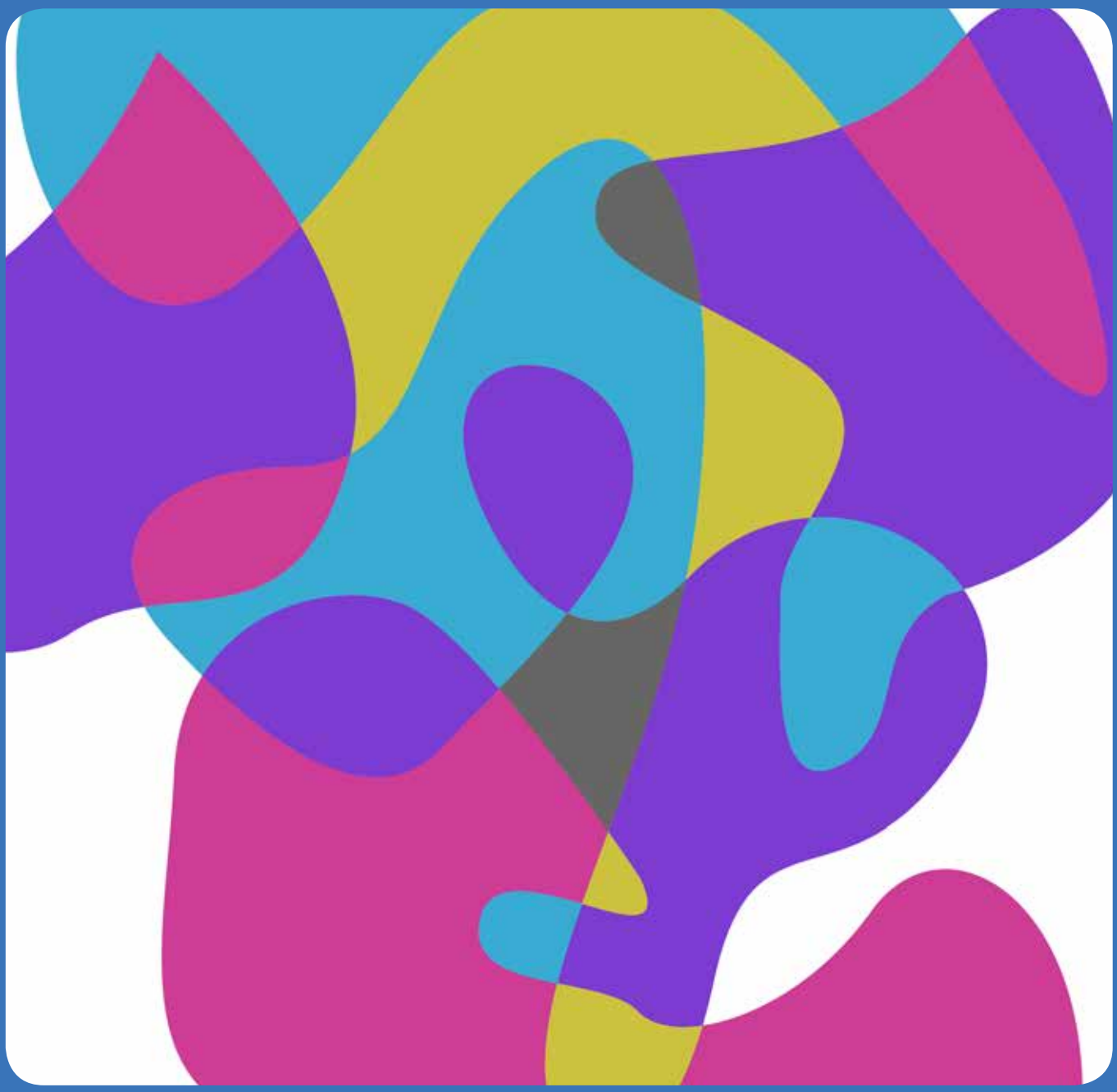
Dialogues in Clinical Neuroscience & Mental Health

Volume 1, Issue 2, April 2018

ISSN: 2585-2795



Dialogues in Clinical Neuroscience & Mental Health is an open-access, peer reviewed, international online Journal, published by the non-profit organization "obrela", www.obrela-journal.gr, www.obrela.gr, info@obrela.gr

Dialogues in Clinical Neuroscience & Mental Health

ISSN 2585-2795
https://www.obrela-journal.gr

Dialogues in Clinical Neuroscience & Mental Health (***Dialogues Clin Neurosci Ment Health,*** **DCNMH) is a quarterly issued, open-access, peer reviewed, international online journal, published by the non-profit organization "obrela". It aims to publish high quality articles in the areas of Psychiatry, Mental Health, Clinical Neuroscience, Medical Psychology, Neuropsychology and Neurology. The DCNMH welcomes varied article types such as Original Submissions, Research Articles, Review Articles, Short Reports, Case Reports, Letters to the Editor, Editorials and Guest Editorials. The DCNMH also features studies that focus on negative results, failure to reproduce, tools and methods, as well as on new theories or hypothesis.**

The *Dialogues in Clinical Neuroscience & Mental Health Journal* welcomes manuscripts on the following fields:
Brain Research, Addiction, Adolescent Development, Anxiety and Depression, Aging, Alzheimer's Disease & Other Dementias, Brain Plasticity, Brain and Evolution, Biological Rhythms and Sleep, Brain Wellness, Demyelinating Disorders, Developmental Disorders, Drug Discovery and Development, Drugs of Abuse and Addiction, Emotion, Epilepsy, Ethical and Policy Issues in Neuroscience, Food Intake and Energy Balance, Games and mental health, Psychiatric Genetics, Glial Mechanisms, History of Neuroscience, Memory Formation, Motivation and Emotion, Network Interactions, Neuroimaging, Neuroimmunology, Neuroendocrinology, Neurotoxicity, Neuroprotection, Pain, Public Awareness of Neuroscience, Stress and the Brain, Schizophrenia & Bipolar Disorder, Pharmacology, TeleCare, e-Health, m-Health, Virtual reality therapy, Pharmacoeconomics, Pharmaceutical Innovation, Rehabilitation, Prevention programs, Psychoeducation, Psychometrics, Trauma therapy.

Contact
Editorial management & manuscript submission
Email: editor@obrela-journal.gr
Editorial office:
Obrela, 2 Erifilis, 11634 Athens, Greece,
tel: 0030 210 7290496
www.obrela-journal.gr, www.obrela.gr, info@obrela.gr

Editorial Board

Author Guidelines

The open-access, peer reviewed, international online Journal *Dialogues in Clinical Neuroscience & Mental Health* (ISSN 2585-2795)**, is the official Journal of the non-profit organization "*obrela*".**

The quarterly issued Journal *Dialogues in Clinical Neuroscience & Mental Health* (**DCNMH)** considers the publication of **Editorial** and **Guest Editorials**, **Review articles, *Forefront Reviews*, *Drug reviews*, *General*** *articles,* ***Special*** *articles,* **Original Research articles, as well as of Case Reports, Viewpoints and Letters to the Editor.** The editorial board of the journal also has the right to publish the *abstracts of Congresses, Seminars* etc. **The DCNMH** does not have page, table or figure restrictions, and authors are encouraged to write complete papers that contain all the data necessary to present their findings persuasively. **The DCNMH also features studies that focus on negative results, failure to reproduce, tools and methods, as well as on new theories, models or hypothesis.**

Publications of the **DCNMH** are available to every internet user. Authors remain the copyright holders and grant the community the right to copy, distribute, display, use commercially and make derivative works. The third party (the person who uses the published works) has to give credit to the original author. **The DCNMH** follows the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (ICJME). Articles submitted for publication should be written in English language. Each paper is typically evaluated by at least two Editors or ad hoc reviewers and is accepted by the Chief Editors. The copy-editor of the journal has the right to change the language structure of the manuscript without transforming its meaning by the author. Prior to submitting your manuscript, please ensure that it has been prepared according to the guidelines below.

Submission

Manuscripts may be submitted only by using the online submission system accessible via our website (**http://www.obrela-journal.gr**). Create a user account, log in and follow the onscreen directions.

Manuscripts

Title page

On the title page provide the **title of the article**, list **each author's name** and **institutional affiliation**, and indicate the **corresponding author**. Especially, the first page should include: The title of the manuscript, full names and full postal and e-mail addresses of all authors, the affiliations of the authors by number, and the name, full postal address, including street number and name, and e-mail address of the corresponding author. In addition, provide abbreviations, if relevant, the a*cknowledgement, and 5-7 k*ey words.

Abstract page

On the abstract page provide the **Abstract** with no more than **500 words** (background, methods, results, conclusions) and **5-7 key-words**.

Cover letter

The submitted manuscript must be accompanied by a *cover letter* which should specify: 1. A statement that the submission is not under consideration by any other journal or published previously (apart from abstracts); 2. A statement by the responsible author certifying that all co-authors have seen and agree with the contents of the manuscript. 3, Full disclosure of the conflict of interest is to be made in the cover letter and manuscript at the time of submission, even if the author judges that it has not influenced the work. If no conflict exists, this must also be stated clearly. All authors should confirm its accuracy.

References

References should be sent in numerical and NOT in alphabetical order. In the text, references should be cited by number in soft brackets, e.g. (1-3) (1,2) and must be numbered consecutively. The **list of references** should be arranged and numbered *in order of appearance in the text*, not alphabetically. The full titles of the quoted publications should be listed. List only the first six authors followed by "et al.". The DOI number should be included at the end of the reference. If an article without DOI is included in PubMed, then its PMID number should be reported at the end of the reference. Also, it is necessary the DOI or PMID number at the end of every reference. Examples: (1) Journal article with DOI : Bebbington EP, Freeman D. Transdiagnostic Extension of Delu-

sions: Schizophrenia and Beyond. *Schizophr Bull* 2017, 43:273–282, doi: 10.1093/schbul/sbw191, (2) Journal article with PMID: Deckersbach T, Savage CR, Phillips KA, Wilhelm S, Buhlmann U, Rauch SL et al. Characteristics of memory dysfunction in body dysmorphic disorder. *J Int Neuropsychol Soc* 2000, 6:673–681, PMID: 11011514, (3) Chapter in book: Brenner M. Influence of the Social Environment on Psychology: The Historical Perspective. In: Barrett JE (ed) *Stress and Mental Disorder.* Raven Press, New York, 1979, (4) Book: Kinden A. *Stress and emotion.* Springer, Berlin, 1990, (5) Article in journal supplement : McKee M, Balabanova D, Basu S, Ricciardi W, Stuckler D. Universal health coverage: a quest for all countries but under threat in some. *Value Health* 2013, 16(Suppl 1):S39–S45, doi: 10.1016/j.jval.2012.10.001, (6) Presentation in Congress – Abstract book : Silverstone A, Leman H, Stark J. *Attempted suicide by drug-overdose.* Paper presented at 2nd Congress on Suicide behaviour, 4–6 May 2002. Rome, Abstracts Book, pp 212–213, (7) Webpage : Henry A, Andrews B. *Critical issues for parents with mental illness.* N.Y. Centre for Mental Health Services 2001 (Cited 2 June 2005). Available from www.mentalorg/publications. Abbreviations of journals should conform to the style used in Index Medicus; journals not indexed there should not be abbreviated.

Figures and **Tables**

Figures: For reproduction in the journal you will be required, to supply high resolution .tiff images in separate files (1200 dpi for line drawings and 300 dpi for color and half tone work at intended display size – column width of 76 mm or page width of 160 mm). It is advisable to create your high resolution images first as they can easily converted into low resolution images for on line submission. Line drawings, graphs, and charts should be professionally drawn or computer generated and printed on a high resolution laser printer. Any lettering in the figures should be large enough to stand photographic reduction. Authors should prepare their figures for either one column (76 mm) or the entire page width (160 mm). The editors reserve the right to reduce the size of illustrated material. Authors may, however, specifically request a larger reproduction. The author is responsible for obtaining written permission to reproduce previously published material (illustrations, tables) from the copyright holder. The consent of the senior author must also be acquired.

Informed consent statement

For studies involving experimentation with human subjects or tissues, the manuscript should include a statement declaring that informed consent was obtained from the subjects for participation in the study or use of their tissue. Furthermore, in case reports or other studies in which case details, personal information or images are included that may enable an individual to be identified, the individual or a parent, guardian or next of kin must consent to its publication, and this consent should be declared in the manuscript. Authors should disclose to patients that personally identifiable material would be available via the Internet as well as in print after publication (http://www.icmje.org).

Human and Animal rights statement

Research that is performed on humans should follow international and national regulations in accordance with the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-ofhelsinki-ethical-principles-for-medical-research-involving-human-subjects/) or any other relevant set of ethical principles. With regard to the use of experimental animals, any research performed must follow internationally recognized guidelines on animal welfare, as well as local and national regulations, in accordance with the U.K. Animals (Scientific Procedures) Act and associated guidelines, the EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals. All animal studies should also comply with the ARRIVE guidelines (http://www.nc3rs.org.uk/arrive-guidelines) and the 2013 AVMA euthanasia guidelines. A statement must be included in the Materials and methods section of the manuscript, identifying the institutional and/or licensing committee that has approved the experiments undertaken. Signed proof of this approval from the committee must also be provided.

Proofs

A letter for articles accepted for publication accompanied by the reviewers' comments is sent to the authors for final corrections. Authors must check their manuscript carefully before submission, after responding to peer- review, and when answering queries raised at the proof stage. Any errors will be faithfully transferred into the final PDF and print versions.

Article charges

The invited articles, as well articles from the collaborative institutions and organizations, may be published free of charge. For the rest articles, the fees are €200 / £180 / $230.

Copyright Notice

Authors who publish with this journal agree to the following terms:

1. Authors retain copyright and grant the journal right of first publication with the work simultaneously licensed under a Creative Commons Attribution License that allows others to share the work with an acknowledgement of the work's authorship and initial publication in this journal.
2. Authors are able to enter into separate, additional contractual arrangements for the non-exclusive distribution of the journal's published version of the work (e.g., post it to an institutional repository or publish it in a book), with an acknowledgement of its initial publication in this journal.
3. Authors are permitted and encouraged to post their work online (e.g., in institutional repositories or on their website) prior to and during the submission process, as it can lead to productive exchanges, as well as earlier and greater citation of published work (The Effect of Open Access).

Privacy Statement

The names and email addresses entered in this journal site will be used exclusively for the stated purposes of this journal and will not be made available for any other purpose or to any other party. All rejected manuscripts will be archived on our journal management system.

CODE OF CONDUCT

For authors

i) The research being reported should have been conducted in an ethical and responsible manner and should comply with all relevant legislation.
ii) Researchers should present their results clearly, honestly, and without fabrication, falsification or inappropriate data manipulation.
iii) Researchers should strive to describe their methods clearly and unambiguously so that others can confirm their findings.
iv) Researchers should adhere to publication requirements that submitted work is original, is not plagiarized, and has not been published elsewhere.
v) Authors should take collective responsibility for submitted and published work.
vi) The authorship of research publications should accurately reflect individuals' contributions to the work and its reporting.
vii) Funding sources and relevant conflicts of interest should be disclosed.

For reviewers

i) Only agree to review manuscripts for which they have the subject expertise required to carry out a proper assessment and which they can assess in a timely manner.
ii) Respect the confidentiality of peer review and not reveal any details of a manuscript or its review, during or after the peer-review process, beyond those that are released by the journal.
iii) Not use information obtained during the peer-review process for their own or any other person's or organization's advantage, or to disadvantage or discredit others.
iv) Declare all potential conflicting interests, seeking advice from the journal if they are unsure whether something constitutes a relevant interest.
v) Not allow their reviews to be influenced by the origins of a manuscript, by the nationality, religious or political beliefs, gender or other characteristics of the authors, or by commercial considerations.
vi) Be objective and constructive in their reviews, refraining from being hostile or inflammatory and from making libelous or derogatory personal comments.

vii) Acknowledge that peer review is largely a reciprocal endeavor and undertake to carry out their fair share of reviewing and in a timely manner.
viii) Provide journals with personal and professional information that is accurate and a true representation of their expertise.
ix) Recognize that impersonation of another individual during the review process is considered serious misconduct.

For editors

i) Editors are accountable and should take responsibility for everything they publish.
ii) Editors should make fair and unbiased decisions independent from commercial consideration and ensure a fair and appropriate peer review process.
iii) Editors should adopt editorial policies that encourage maximum transparency and complete, honest reporting.
iv) Editors should guard the integrity of the published record by issuing corrections and retractions when needed and pursuing suspected or alleged research and publication misconduct.
v) Editors should pursue reviewer and editorial misconduct.
vi) Editors should critically assess the ethical conduct of studies in humans and animals.
vii) Peer reviewers and authors should be told what is expected of them.
viii) Editors should have appropriate policies in place for handling editorial conflicts of interest.

If the **Reviewers** have further queries, they may go through the "Instructions to Authors". They can also **use the questions** below, when reviewing the manuscripts:

- Please state any conflict(s) of interest that you have in relation to the review of this manuscript (state "none" if this is not applicable).
- Do you suspect any research or publication misconduct? If yes, please indicate in detail.
- Does the manuscript contain new and significant information to justify publication?
- Is the title of the article appropriate?
- Does the abstract clearly and accurately describe the content of the article?
- Is the problem significant and concisely stated?
- Are the methods described comprehensively?
- Is the results section clear and satisfactory?
- Are the interpretations and conclusions justified by the results?
- Is adequate and current reference made to other work in the field?
- Is the language acceptable?
- Please rate the priority for publishing this article (1 is the highest priority, 10 is the lowest priority).
- Is the appropriate terminology used in the text?
- Is it sufficient that figures and/or tables?
- Is it necessary to shorten the article?

Obrela JOURNAL
Dialogues in Clinical Neuroscience & Mental Health

Contact

Editorial management & manuscript submission:
editor@obrela-journal.gr

Editorial office:
Obrela, 2 Erifilis, 11634 Athens, Greece, 0030 210 7290496,
info@obrela.gr, www.obrela.gr

Legal support:
www.mtboutiquelaw.com, info@mtboutiquelaw.com

Index

Dialogues in Clinical Neuroscience & Mental Health

DOI 10.26386/obrela.v1i2.42 ISSN 2585-2795

Review

Psychobiology of feeding behaviour

George Konstantakopoulos

Abstract

Adequate nutrition is essential for survival and therefore is ensured by a complex brain system regulating the levels of various nutrients in the blood and in the body stores. This system includes two distinct mechanisms of control on food intake, i.e. the homeostatic and the hedonic control. Over the last two decades our knowledge of neural circuits and molecules involved in these mechanisms has improved substantially, in large part due to the findings of research in experimental animals and functional neuroimaging in humans. These findings also provide insight into the mechanisms underlying obesity and abnormal feeding behaviour in neuropsychiatric disorders. The hypothalamic network that regulates food intake and energy balance consists of interconnected neurons located in the arcuate (infundibular in humans) nucleus, ventromedial nucleus, paraventricular nucleus, dorsomedial nucleus, and lateral hypothalamic area. Central regulation is mediated by α- and β- melanocyte-stimulating hormone, neuropeptide Y, Agouti-related protein, γ-aminobutyric acid, brain-derived neurotrophic factor, and melanin-concentrating hormone. Peripheral signals that stimulate (orexigenic) or inhibit (anorexigenic) food intake are received by neurons in the medial zones of the hypothalamus, including signals from circulating nutrients (glucose, fatty acids), hormones (insulin, leptin, ghrelin), and gastrointestinal peptides (cholecystokinin and peptide YY3-36). The pleasure of palatable food is associated with activation of the brain reward system, including the ventral tegmental area, dopaminergic system, nucleus accumbens, ventral pallidum, and amygdala. Dopamine release in the nucleus accumbens mediates the motivational aspects of food intake, especially the drive to eat food that is hedonically desirable ("wanting"). Orexin, cocaine- and amphetamine- regulated transcript, and galanin play significant role in hedonic regulation of feeding. The hedonic reaction per se to the pleasure of food reward ("liking") is regulated by endogenous opioids and endocannabinoids. There are homeostatic – hedonic control interactions via functional connections of nucleus accumbens with the prefrontal cortex, amygdala, and lateral hypothalamus, as well as between hypothalamic, cortical, and mesolimbic circuits. There is also a "top-down" control of human feeding behavior: interactions between cognitive and emotional processes could lead to different responses to food cues and changes in food intake.

Keywords: nutrition, homeostatic control, hedonic eating, hypothalamus, reward system.

Corresponding Author: George Konstantakopoulos, MD, PhD, Section of Cognitive Neuropsychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK & 1st Department of Psychiatry, University of Athens, Greece, e-mail: gekonst@otenet.gr; george.konstantakopoulos@kcl.ac.uk

Received: February 2, 2018, Accepted: March 5, 2018

DOI 10.26386/obrela.v1i2.42 ISSN 2585-2795

INTRODUCTION

Feeding provides the energy that is essential for survival and therefore is subject to intense regulation by human brain. Adequate nutrition is ensured by a complex brain system regulating the levels of various nutrients in the blood and in the body stores. The hypothalamus is the centre of the network of control on food intake and metabolism in response to peripheral signals that reflect the feeding state and energy reserve, i.e. homeostatic control.

Hunger is associated with discomfort providing a strong drive for feeding and satiety is accompanied with satisfaction preventing further consumption of food. However, the rewarding nature of food goes beyond the feelings of hunger and satiety. Modern humans often eat in the complete absence of hunger and nowadays obesity is a serious public health problem. Hedonic eating, i.e. eating based on pleasure rather than energy needs, is controlled by complex neural mechanisms associated with reward. The insular cortex, orbitofrontal cortex, nucleus accumbens, amygdala, and ventral tegmental area have a key role in control of feeding behaviour in response to the hedonic aspects of food.

Over the last two decades our knowledge of neural circuits and molecules involved in homeostatic and hedonic control of food intake, has improved substantially, in large part due to the findings of research in experimental animals and functional neuroimaging in humans. These findings also provide insight into the mechanisms underlying obesity and abnormal feeding behaviour in neuropsychiatric disorders. Only the main aspects of the current knowledge on mechanisms controlling feeding behaviour can be emphasized here.

HOMEOSTATIC CONTROL OF FOOD INTAKE

The hypothalamic network that regulates food intake and energy balance consists of interconnected neurons located in the arcuate (infundibular in humans) nucleus (ARC), ventromedial nucleus (VMH), paraventricular nucleus (PVN), dorsomedial nucleus (DMH), and lateral hypothalamic area (LHA). Peripheral signals that stimulate (orexigenic) or inhibit (anorexigenic) food intake are received by neurons in the medial zones of the hypothalamus, including signals from circulating nutrients (glucose, fatty acids), hormones (insulin, leptin, ghrelin), and gastrointestinal peptides (cholecystokinin and peptide YY_{3-36}) **[1]**. The dorsomedial and lateral hypothalamic neurons receive circadian influences and interact with neural circuits for thermoregulation and arousal **[2]**. The integration between orexigenic and anorexigenic signals proceeds via complex interactions between the hypothalamic nuclei mediated by a variety of neurotransmitters **[3]**. The hypothalamic network exerts control on food intake and peripheral metabolism acting via projections to sympathetic and parasympathetic nuclei (nucleus of the solitary tract, area postrema, dorsal motor nucleus of the vagus, and locus coeruleus) on the endocrine glands and the gastrointestinal system **[4]**. Cognitive and emotional aspects of food intake relay on reciprocal connections of hypothalamus with cortical and mesolimbic circuits, and hippocampus **[5].**

In the following we present the main peripheral and central signals and hypothalamic pathways related to feeding behaviour, which are also briefly displayed in *Table 1*.

Table 1: Main signals and mechanisms for homeostatic control of food intake

Signal	Source	Target (receptors)	Effect	Mechanisms of action
Peripheral (hormones)				
Insulin	Pancreas	Hypothalamus (Insulin Receptors, IR)	↓Food intake	Activation of POMC neurons in ARC Activation of BDNF neurons in VMH Inhibition of LHA neurons

DOI 10.26386/obrela.v1i2.42 ISSN 2585-2795

Cholecystokinin Peptide YY_{3-36}	Gut	Hypothalamus via vagus nerve (CCK-1, Y2)	↓Food intake	Stimulation of vagus nerve – signals via NTS and PBN projections to POMC neurons in ARC
Leptin	Adipose tissue	Hypothalamus (Leptin Receptors, OB-R)	↓Food intake ↑Metabolism	Activation of POMC neurons in ARC Activation of BDNF neurons in VMH Inhibition of LHA neurons
Ghrelin	Stomach	Hypothalamus (GHR1)	↑Food intake	Activation of Neuropeptide Y, Agouti-related peptide, and GABA neurons in ARC
Central				
α- and β-MSH	ARC	Hypothalamus (MC4R)	↓Food intake	Agonists of MC4R in PVN and VMH
Agouti-related peptide	ARC	Hypothalamus (MC4R)	↑Food intake ↓Metabolism	Inverse agonist of MC4R in PVN
Neuropeptide Y	ARC	Hypothalamus (Y1, Y2, Y5)	↑Food intake ↓Metabolism	Direct activation of PVN Inhibition of POMC neurons in ARC
BDNF	VMH	Hypothalamus (Tropomyosin receptor kinase B, TrkB)	↓Food intake	Agonist of TrkB and MC4R in PVN and VMH
Melanin-concentrating hormone	LHA	Hypothalamus, VTA (MCH1 and MCH2)	↑Food intake ↓Metabolism	Agonist of MCH receptors in hypothalamus and VTA
Orexin/hypocretin	LHA	Hypothalamus (OX1 and OX2)	↑Food intake	Agonist of OX1 and OX2 in PVN (short-term regulation of energy balance)
Endocannabinoids	LHA	Hypothalamus (cannabinoid-1 receptors, CB1)	↑Food intake ↓Metabolism	Inhibition of anorexigenic signals via CB1

Abbreviations: ARC, arcuate (infundibular in humans) nucleus; BDNF, brain-derived neurotrophic factor; GABA, γ-aminobutyric acid; LHA, lateral hypothalamic area; MC4R, Melanocortin 4 receptor; MSH, melanocyte-stimulating hormone; NTS, nucleus of the solitary tract; PBN, parabrachial nucleus; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus; VMH, ventromedial nucleus; VTA, ventral tegmental area.

Central regulation of feeding and energy balance

The ARC is a key regulator of food intake and energy balance containing a group of neurons that synthesizes α- *and* β- *melanocyte-stimulating hormone (MSH)*, neuropeptides derived from *pro-opiomelanocortin (POMC)*, and another group of neurons synthesizing *neuropeptide Y (NPY), Agouti-related protein (AgRP),* and γ-*aminobutyric acid (GABA)*. A- and β- MSH decrease food intake and increase energy expenditure acting on melanocortin 4 receptors (MC4R) in the PVN and VMH **[6].** By contrast, NPY via Y1, Y2, Y5 receptors and AgRP acting as an inverse agonist of MC4R in the PVN increase food intake and reduce energy expenditure **[3].** Moreover, the same group of neurons can inhibit POMC neurons in the ARC via GABA and NPY projections **[7].** Thus, the ARC mediates both orexigenic and anorexigenic signals from periphery and regulates feeding and energy metabolism integrating these mutually opposing influences.

Neurons in the VMH that synthesize *brain-derived neurotrophic factor (BDNF)* receive signals from POMC neurons of the ARC and they also respond to glucose and leptin reducing food intake and increasing energy metabolism **[8]**. Groups of neurons in the PVN receiving signals from the ARC synthesize hormones

DOI 10.26386/obrela.v1i2.42 ISSN 2585-2795

with anorexigenic effects – corticotrophin releasing hormone (CRH), thyrotrophin releasing hormone (TRH), and oxytocin **[7].**

The LHA has also a key role in regulation of feeding and metabolism, integrating signals from the periphery (i.e., glucose, leptin, ghrelin) and interacting with other hypothalamic areas and the mesolimbic system **[4] [9] [10]**. A group of neurons in the LHA synthesizing *orexin* (or *hypocretin*) plays a significant role in the short-term regulation of energy balance. Orexin neurons are inhibited by glucose and stimulated during fasting and they promote food intake acting on specific receptors (OX1 and OX2) in the PVN **[11]** up of LHA neurons synthesizes *melanin-concentrating hormone (MCH)* and they act on specific receptors (MCH1 and MCH2) increasing food intake and decreasing energy metabolism **[12].** The function of LHA on food intake is related to sleep-wake cycle: the MCH neurons are active during slow-wave sleep while the orexin neurons are activated in wakefulness **[7].**

Peripheral factors regulating food intake and metabolism

Gut peptides (cholecystokinin, peptide YY$_{3-36}$) are released after a meal and suppress food intake and meal size activating via vagal afferents the nucleus of the solitary tract, which signals fullness to the hypothalamus and other brain regions, initiating satiety and resulting in meal termination **[13], [9].** Another gut peptide under investigation with similar effects on food intake and a significant role in the control of glucose and energy homeostasis is *glucagon-like peptide-1* **[14].** On the other hand, *ghrelin* is the hormone that is released from the stomach during fasting and provokes hunger and meal initiation. Ghrelin, acting on the growth hormone secretagogue receptor (GHSR) in the ARC, stimulates NPY, AgRP and GABA neurons **[15].** *Leptin* is a hormone synthesized in the adipose tissue that circulates at levels proportional to the amount of fat. Leptin, acting on specific receptors in the ARC, stimulates POMC neurons and inhibits the release of NPY and AgRP, thus contributing in long-term weight and glucose homeostasis **[16], [14]**. It also produces anorexigenic effect stimulating BDNF neurons in VMH while inhibiting LHA neurons **[16].** *Insulin*, the hormone released by beta-cells in pancreas and regulating glucose homeostasis, has also anorexigenic effects possibly through similar mechanisms of action as those of leptin **[17], [14].**

HEDONIC CONTROL OF FEEDING BEHAVIOUR

Many aspects of human behaviour, like seeking for pleasant food, cooking, or obesity, indicate that feeding is not controlled solely by homeostatic mechanisms but is also influenced by the rewarding nature of food.

Gustatory regulation of feeding

Food reward is associated with palatability qualities, particularly taste and smell. Animals consume sweet and salty food beyond their homeostatic needs and avoid sour or bitter food even if they are hungry. In human brain, taste information passes via the nucleus of the solitary tract and parabrachial nucleus to the thalamus, the lateral frontal cerebral cortex, the central nucleus of amygdala, and several hypothalamic areas, including LHA. Although gustatory thalamus is critical for hedonic aspects of taste, other subcortical areas also mediate the motivational qualities of palatable food cues **[2].**

Reward system for feeding

The pleasure of palatable food is associated with activation of many areas of the brain reward system, including the ventral tegmental area (VTA) dopaminergic system, nucleus accumbens (NAc), ventral pallidum, and amygdala **[10], [18].** Dopamine release in the NAc mediates the motivational aspects of food intake, especially the drive to eat food that is hedonically desirable ("wanting") **[19]**. As yet, the mechanisms by which food stimulates dopamine release are not well understood. It has been found that food can stimulate dopamine signalling independent of the processing of taste information **[20].**

Release of *orexin* during feeding directly stimulates dopamine neurons in the VTA increasing dopamine release in the NAc **[21]**. Other hypothalamic neuropeptides may also play a

DOI 10.26386/obrela.v1i2.42 ISSN 2585-2795

role in hedonic regulation of feeding influencing dopamine release. The *cocaine- and amphetamine- regulated transcript (CART)* which is found in several hypothalamic areas decreases food intake possibly inhibiting dopaminergic neurons in VTA. However, the anorexigenic effect of CART is associated with its multiple actions in hedonic and homeostatic regulating systems, which are not clear yet **[22].** By contrast, *galanin* stimulates food intake, in particular the intake of fat, possibly acting on specific receptors in the PVN. However, it still remains unknown which of the multiple central and peripheral effects of galanin might be related with this effect **[23].**

The hedonic reaction *per se* to the pleasure of food reward ("liking") is regulated by *endogenous opioids* and *endocannabinoids* acting via μ-type opioid receptors and CB1 receptors respectively, within the shell of the NAc and possibly within the ventral pallidum **[10].** Although 'liking' and 'wanting' are needed together for complete food reward, are mediated by interacting but partially independent neural substrates.

Interactions of homeostatic and hedonic regulatory mechanisms

The stability of body weight over adult life in spite of the availability of highly palatable and energy dense food, as well as the discrepancies from normal eating, e.g. overweight, obesity and eating disorders, indicate an interface between the metabolic and hedonic drives of eating. Therefore, the possible neural circuits and mechanisms that underlie interactions between homeostatic and hedonic regulation of feeding have been a focus of research during the last two decades.

The NAc plays a key role in the integration of homeostatic, hedonic, and cognitive aspects of food intake via its connections with the prefrontal cortex, amygdala, and lateral hypothalamus **[10], [24]**. There are also multiple functional connections between hypothalamic, cortical, and mesolimbic circuits mediated by POMC, orexin and MCH that may play a role in homeostatic – hedonic control interactions **[18].** Hormones involved in homeostatic regulation of feeding, such as leptin, insulin, and ghrelin, also exert effects on motivation to obtain food through their influence on mesolimbic dopamine signalling, especially on the dopaminergic neurons in the VTA **[25].** Leptin decreases the firing rate of the VTA dopaminergic neurons. Insulin increases dopamine release and the firing rate of dopaminergic neurons but reduces dopamine levels in the VTA probably by upregulation of the dopamine active transporter (DAT). Ghrelin enhances signalling from the VTA to the NAc increasing the activation of dopamine D_1 and D_2 receptors and dopamine levels.

Like ghrelin, other factors involved in meal-to-meal regulation of feeding may also affect food reward in a way that even highly palatable food may be unpleasant after satiation. There is evidence that the rewarding effects of food are potently modulated by indicators of satiety, such as peptide YY_{3-36} that was found to elicit a switch of activation from the hypothalamus to the orbitofrontal cortex and diminished orbitofrontal activation in response to the rewarding aspects of food **[26].** The main pathways related to hedonic control of feeding behaviour are briefly displayed in *Table 2*.

Table 2: Main signals and mechanisms for hedonic control of eating behaviour

Signal	Source	Target (receptors)	Effect	Mechanisms of action
Peripheral (hormones)				
Leptin	Adipose tissue	VTA (Leptin Receptors, OB-R)	↓ Food intake ↑ Metabolism	Inhibition of dopaminergic neurons in VTA
Insulin	Pancreas	VTA (Insulin Receptors, IR)	↓ Food intake	Reduction of dopamine levels in VTA probably by upregulation of DAT
Central				

DOI 10.26386/obrela.v1i2.42 ISSN 2585-2795

Ghrelin	ARC	VTA (GHR1)	↑ Food intake	Activation of dopaminergic neurons in VTA Increase of the activation of dopamine D1 and D2 receptors and dopamine levels in NAc
Orexin/hypocretin	LHA	VTA (OX1 and OX2)	↑ Food intake	Activation of dopaminergic neurons in VTA
Endocannabinoids	Local	Nucleus accumbens (cannabinoid-1 receptors, CB1)	↑ Food intake ↓ Metabolism	Enhancement of dopamine effect on nucleus accumbens
Endogenous opioids	Local	Nucleus accumbens (μ-opioid receptors)	↑ Food intake	Increase of dopamine release in nucleus accumbens
CART	ARC, LHA	Hypothalamus, Mesolimbic system	↓ Food intake	Unknown
Galanin	ARC	Hypothalamus, especially PVN (GALR)	↑ Food intake	Unknown

Abbreviations: ARC, arcuate (infundibular in humans) nucleus; CART, cocaine- and amphetamine- regulated transcript; DAT, dopamine active transporter; LHA, lateral hypothalamic area; NAc, nucleus accumbens; PVN, paraventricular nucleus; VTA, ventral tegmental area.

COGNITIVE AND EMOTIONAL CONTROL OF FEEDING BEHAVIOUR

Homeostatic and hedonic mechanisms controlling feeding behaviour described above only partially operate outside awareness. However, there is also a "top-down" control of human feeding behavior: interactions between cognitive and emotional processes could lead to different responses to food cues and changes in food intake **[27].** Thus, humans can voluntary inhibit their drive to eat or develop involuntary changes in their appetite and body weight related to emotional states.

Cognitive control of feeding behaviour involves integration of peripheral signals related to energy status of the body, food-related signals in the form of sensory and environmental cues, and memory of past feeding experiences **[7].** The insular, orbitofrontal, and anterior cingulate cortical areas have a key role in the processing of interoceptive and food-related information and participate in motivational aspects of feeding behaviour **[28], [29], [2].**

There is now evidence from preclinical studies that emotional factors influence both hedonic and homeostatic aspects of food intake, altering the activation of many mediators such as ghrelin, orexin and leptin. For example, chronic stress may influence feeding and body weight independent of palatability of food or energy status of the individual **[19].** This is more obvious in human behaviour, since changes in appetite and body weight are frequent symptoms and one of the core diagnostic features of major depressive disorder. Furthermore, the association rate between mood disorders and obesity is about 25% **[30].** Influences of mood on hedonic and homeostatic control of feeding may partially mediated by the effects of serotoninergic system, e.g. action of serotonin on POMC neurons in ARC via $5HT_{2C}$ receptors **[31].** Aside from depression, serotonin dysfunctions are also implicated in the pathophysiology of eating disorders, i.e. anorexia nervosa and bulimia nervosa **[32].**

References

1) Adan RA, Vanderschuren LJ , la Fleur SE. Anti-obesity drugs and neural circuits of feeding. *Trends Pharmacol Sci* 2008, 29:208-217, doi:10.1016/j.tips.2008.01.008

2) Saper CB, Chou TC, Elmquist JK. The need to feed: homeostatic and hedonic control of eating. *Neuron* 2002, 36:199-211, doi: 10.1016/S0896-6273(02)00969-8

3) Meister B. Neurotransmitters in key neurons of the hypothalamus that regulate feeding behavior and body weight. *Physiol Behav* 2007, 92:263-271, doi:10.1016/j.

DOI 10.26386/obrela.v1i2.42 ISSN 2585-2795

physbeh.2007.05.021

4) Williams G, Bing C, Cai XJ, Harrold JA, King PJ , Liu XH. The hypothalamus and the control of energy homeostasis: different circuits, different purposes. *Physiol Behav* 2001, 74:683-701, doi: 10.1016/S0031-9384(01)00612-6

5) Gao Q , Horvath TL. Neurobiology of feeding and energy expenditure. *Annu Rev Neurosci* 2007, 30:367-398, doi:10.1146/annurev.neuro.30.051606.094324

6) Hillebrand JJ, Kas MJ, Adan RA. To eat or not to eat; regulation by the melanocortin system. *Physiol Behav* 2006, 89:97-102, doi:10.1016/j.physbeh.2006.01.034

7) Benarroch EE. Neural control of feeding behavior: Overview and clinical correlations. *Neurology* 2010, 74:1643-1650, doi:10.1212/WNL.0b013e3181df0a3f

8) King BM. The rise, fall, and resurrection of the ventromedial hypothalamus in the regulation of feeding behavior and body weight. *Physiol Behav* 2006, 87:221-244, doi:10.1016/j.physbeh.2005.10.007

9) Dietrich MO, Horvath TL. Feeding signals and brain circuitry. *Eur J Neurosci* 2009, 30:1688-1696, doi:10.1111/j.1460-9568.2009.06963.x

10) Berridge KC. ‹Liking› and ‹wanting› food rewards: brain substrates and roles in eating disorders. *Physiol Behav* 2009, 97:537-550, doi:10.1016/j.physbeh.2009.02.044

11) Tsujino N, Sakurai T. Orexin/hypocretin: a neuropeptide at the interface of sleep, energy homeostasis, and reward system. *Pharmacol Rev* 2009, 61:162-176, doi:10.1124/pr.109.001321

12) Guyon A, Conductier G, Rovere C, Enfissi A , Nahon JL. Melanin-concentrating hormone producing neurons: Activities and modulations. *Peptides* 2009, 30:2031-2039, doi:10.1016/j.peptides.2009.05.028

13) Chaudhri O, Small C, Bloom S. Gastrointestinal hormones regulating appetite. *Philos Trans R Soc Lond B Biol Sci* 2006, 361:1187-1209, doi:10.1098/rstb.2006.1856

14) Williams KW, Elmquist JK. From neuroanatomy to behavior: central integration of peripheral signals regulating feeding behavior. *Nat Neurosci* 2012, 15:1350-1355, doi:10.1038/nn.3217

15) Kageyama H, Takenoya F, Shiba K, Shioda S. Neuronal circuits involving ghrelin in the hypothalamus-mediated regulation of feeding. *Neuropeptides* 2010, 44:133-138, doi:10.1016/j.npep.2009.11.010

16) Farooqi IS, O'Rahilly S. Mutations in ligands and receptors of the leptin-melanocortin pathway that lead to obesity. *Nat Clin Pract Endocrinol Metab* 2008, 4:569-577, doi:10.1038/ncpendmet0966

17) Konner AC, Klockener T, Bruning JC. Control of energy homeostasis by insulin and leptin: targeting the arcuate nucleus and beyond. *Physiol Behav* 2009, 97:632-638, doi:10.1016/j.physbeh.2009.03.027

18) Kampe J, Tschop MH, Hollis JH, Oldfield BJ. An anatomic basis for the communication of hypothalamic, cortical and mesolimbic circuitry in the regulation of energy balance. *Eur J Neurosci* 2009, 30:415-430, doi:10.1111/j.1460-9568.2009.06818.x

19) Lutter M, Nestler EJ. Homeostatic and hedonic signals interact in the regulation of food intake. *J Nutr* 2009, 139:629-632, doi:10.3945/jn.108.097618

20) de Araujo IE, Oliveira-Maia AJ, Sotnikova TD, Gainetdinov RR, Caron MG, Nicolelis MA , Simon SA. Food reward in the absence of taste receptor signaling. *Neuron* 2008, 57:930-941, doi:10.1016/j.neuron.2008.01.032

21) Harris GC , Aston-Jones G. Arousal and reward: a dichotomy in orexin function. *Trends Neurosci* 2006, 29:571-577, doi:10.1016/j.tins.2006.08.002

22) Rogge G, Jones D, Hubert GW, Lin Y , Kuhar MJ. CART peptides: regulators of body weight, reward and other functions. *Nat Rev Neurosci* 2008, 9:747-758, doi:10.1038/nrn2493

23) Fang PH, Yu M, Ma YP, Li J, Sui YM, Shi MY. Central nervous system regulation of food intake and energy expenditure: role of galanin-mediated feeding behavior. *Neurosci Bull* 2011, 27:407-412, doi:10.1007/s12264-011-1841-7

24) Kelley AE, Baldo BA, Pratt WE, Will MJ. Corticostriatal-hypothalamic circuitry and food motivation: integration of energy, action and reward. *Physiol Behav* 2005, 86:773-795, doi:10.1016/j.physbeh.2005.08.066

25) Murray S, Tulloch A, Gold MS, Avena NM. Hormonal and neural mechanisms of food reward, eating behaviour and obesity. Nat Rev Endocrinol 2014, 10:540-552, doi:10.1038/nrendo.2014.91

26) Batterham RL, ffytche DH, Rosenthal JM, Zelaya FO, Barker GJ, Withers DJ, Williams SC. PYY modulation of cortical and hypothalamic brain areas predicts feeding behaviour in humans. *Nature* 2007, 450(7166):106-109, doi:10.1038/nature06212

27) Berthoud HR. Metabolic and hedonic drives in the neural control of appetite: who is the boss? *Curr Opin Neurobiol* 2011, 21:888-896, doi:10.1016/j.conb.2011.09.004

28) Craig AD. How do you feel--now? The anterior insula and human awareness. *Nat Rev Neurosci* 2009, 10:59-70, doi:10.1038/nrn2555

29) Shin AC, Zheng H , Berthoud HR. An expanded view of energy homeostasis: neural integration of metabolic, cognitive, and emotional drives to eat. *Physiol Behav* 2009, 97:572-580, doi:10.1016/j.physbeh.2009.02.010

30) Simon GE, Von Korff M, Saunders K, Miglioretti DL, Crane PK, van Belle G , Kessler RC. Association between obesity and psychiatric disorders in the US adult population. *Arch Gen Psychiatry* 2006, 63:824-830, doi:10.1001/archpsyc.63.7.824

31) Heisler LK, Cowley MA, Tecott LH, Fan W, Low MJ, Smart JL, et al. Activation of central melanocortin pathways by fenfluramine. *Science* 2002, 297(5581):609-611, doi:10.1126/science.1072327

32) von Hausswolff-Juhlin Y, Brooks SJ , Larsson M. The neurobiology of eating disorders – a clinical perspective. *Acta Psychiatr Scand* 2015, 131:244-255, doi:10.1111/acps.12335

Dialogues in Clinical Neuroscience & Mental Health

DOI 10.26386/obrela.v1i2.43 ISSN 2585-2795

Drug review

Psychotropic medication and cataract: a review of case-control studies

Spyridon Siafis, Theodora Siafi, Georgios Papazisis
Department of Clinical Pharmacology, School of Medicine, Aristotle University of Thessaloniki, Greece

Abstract

Ocular side effects are possible to occur as side effect of psychotropic drug treatment. Antidepressants and typical antipsychotics have been associated with increased intraocular pressure, glaucoma, lenticular pigmentation, visual disturbances and cataract, whereas the risk of atypical antipsychotics and mood stabilizers remains unclear. The aim of our study was to review the case-control studies assessing the risk for cataract of three major classes of psychotropic medication: antidepressants, antipsychotics and mood stabilizers. Four studies assessed the risk of antidepressant drugs. A higher risk for cataract diagnosis or surgery was observed in three studies, especially on long-term use of antidepressants. One study could not identify a higher risk of antidepressant use in general, yet a higher risk was observed in patients younger than 65 years. Different types of antidepressant seem to carry different risks, with proposed harmful effects of dual mechanism and intermediate SERT affinity. Three studies suggested that the association of atypical antipsychotics and high potency typical antipsychotics with cataract is unlikely, or even that atypical antipsychotic drugs might be protective against cataract. However, there is inconsistency between the sparse preclinical and clinical evidence of their protective and harmful effects. Only one study suggested a possible association of mood stabilizers with cataract, despite the discrepant results on individual drugs. Concluding, these case-control studies cannot establish a harmful or protective causal relationship between psychotropic medication and development of cataract. Further research is needed in order to provide proper recommendations.

Keywords: antidepressants, antipsychotics, mood stabilizers, cataract.

Corresponding Author: Georgios Papazisis MD, PhD, Psychiatrist, Assistant Professor of Basic and Clinical Pharmacology, Department of Clinical Pharmacology School of Medicine, Aristotle University of Thessaloniki ,Tel and Fax: +30 2310 999323, e-mail: papazisg@auth.gr

Received: January 8, 2018, Accepted: February 15, 2018

DOI 10.26386/obrela.v1i2.43 ISSN 2585-2795

Introduction

Cataract is a common cause of visual impairment with significant health consequences. Several risk factors may be associated with cataract, such as increased age, female gender, smoking, unhealthy lifestyle, diabetes mellitus, hypertension and other physical comorbidities, as well as ophthalmic comorbidities, family history of cataract and increased exposure to ultraviolet radiation. Certain drugs seem to predispose to cataract, such as systemic steroids, beta adrenergic antagonists, statins, cholinesterase inhibitors and possibly some psychotropics [1]. Antipsychotic and antidepressant medication targets mainly neurotransmitter receptors and transporters, which along with other mechanisms could play important roles in ocular physiology and cataract development [2]. Ophthalmic events, such as increased intraocular pressure, glaucoma, cataract and visual disturbances have been associated with antidepressants [3]. Typical antipsychotics, especially phenothiazines, have been associated with lenticular pigmentation and cataract, whereas the risk of atypical antipsychotics and mood stabilizers is questioned [4, 5]. As a result, psychotropic medication, i.e. antipsychotics, antidepressants and mood stabilizers, might be modifiable factor for cataract development. Herein, the most recent case-control studies of the risk of psychotropic medication for cataract development are reviewed and discussed.

Search strategy

A literature search was conducted on PubMed (21/12/2017) using the keyword cataract combined with antidepressants (antidepressant, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, desvenlafaxine, duloxetine, levomilnacipran, milnacirpan, venlafaxine, amitriptyline, amoxapine, desipramine, dosulepin, doxepin, clomipramine, imipramine, maprotriline, nortriptyline, protriptyline, tianeptine, trimipramine, isocarboxazid, metralindole, moclobemide, phenelzine, pirlindole, selegiline, toloxatone, tranylcypromine, mianserin, mirtazapine, vilazodone, vortioxetine, agomelatine, buspirone, bupropion, reboxetine, nefazodone, trazodone), antipsychotics (antipsychotic, haloperidol, olanzapine, clozapine, ziprasidone, aripiprazole, asenapine, cariprazine, brexpiprazole, iloperidone, sertindole, risperidone, quetiapine, zotepine. lurasidone , chlorpromazine, perphenzine, amisulpride, sulpiride, butyrophene, phenothiazine, pimozide, fluphenazine, perazine, promethazine, prochlorperazine, trifluoperazine, clopenthixol, thiothixene, zuclopenthixol, loxapine, perospirone, blonanserin) and mood stabilizers (mood stabilizer, lithium, valproic, valproate, lamotrigine, carbamazepine, oxcarbamazepine). The search resulted in 176 hits. We included studies published in English with a case-control design, specified to assess the risk of psychotropic medication and using as cases patients with first cataract diagnosis and/or surgery. Four studies were identified, one of them a conference abstract [6] and three additional were added from external sources.

Antidepressant drugs

The first large case-control study, which assessed the association of antidepressants and cataract, included residents 65+ years with previously coronary revascularization in Canada [7]. The study included 18784 cases (73+/-8.1 years, 59.3% males) with first cataract diagnosis and 187840 age-matched controls. The association of cataract with antidepressant use was adjusted to gender, blood pressure and concomitant drugs. Current use of SSRI within 30 days from cataract diagnosis was associated with cataract (adjusted rate ratio: 1.15; 95% CI: 1.08-1.23). Regarding individual drugs, an association was observed with current use of fluvoxamine (adjusted rate ratio: 1.39; 95% CI: 1.07-1.8) and venlafaxine (adjusted rate ratio: 1.33; 95% CI: 1.14-1.5), but not current use of citalopram, fluoxetine, paroxetine and sertraline. Past use of antidepressants in general was not associated with cataract, but an association of past use of sertraline was observed (adjusted rate ratio: 1.19; 95% CI: 1.01-1.41). A secondary analysis assessed the risk for cataract surgery, and an association of current use of fluvoxamine and venlafaxine, as well as paroxetine (adjusted rate ratio: 1.23; 95% CI: 1.05-1.45) was observed. SSRI treatment needed 656 and 690 days on average from time of onset in order to associate with diagnosis and surgery of cataract, respectively.

DOI 10.26386/obrela.v1i2.43 ISSN 2585-2795

Another case-control study with residents 50+ years of the Rochester Epidemiology Project (Minnesota, USA) found an association of antidepressant use and first-eye cataract surgery [8]. The study included 6024 cases, i.e. patients with first-eye cataract surgery and equal number of controls. There was no difference between cases (79+/-9 years, 40% males) and controls in terms of age and gender. Continuous prescription of SSRI for 1 or more year was associated with cataract surgery (crude odds ratio: 1.36, 95% CI: 1.23-1.51). The association remained even after adjusting for gender, diabetes and use of oral glucocorticosteroids. Regarding individual SSRI, citalopram (crude odds ratio: 1.53; 95% CI: 1.33-1.77) and sertraline (crude odds ratio: 1.27; 95% CI: 1.06-1.52) were associated with cataract-surgery, in contrast to paroxetine, fluoxetine, escitalopram and fluvoxamine. Prescription of SNRI for 1 or more year was also associated with cataract-surgery (crude odds ratio: 1.37; 95% CI: 1.11-17), with venlafaxine (crude odds ratio: 1.32; 95% CI: 1.05-1.67) and duloxetine (crude odds ratio: 1.82; 95% CI: 1.08-3.07). This association remained after adjusted for diabetes and corticosteroid use, but only in women.

A case-control study on the database of the National Health Insurance of Taiwan has also detected an association of antidepressant use and first cataract diagnosis [9]. The study included 7651 patients with schizophrenia or mood disorders and first cataract diagnosis and 6637 patients without cataract as controls. Age and gender was similar between cases (55.7 +/- 10.5 years, 35.8% males) and controls. The risk was adjusted to ophthalmic and other physical comorbidities, healthcare utilization, as well as use of antipsychotics or systemic steroids. An association with cataract diagnosis was observed for continuous use of SSRI (adjusted odds ratio: 1.26; 95% CI: 1.12-1.41), SNRI (adjusted odds ratio: 1.21; 95% CI: 1.02-1.43) and other antidepressants (adjusted odds ratio: 1.18, 95% CI: 1.18-1.34), i.e. bupropion, mirtazapine, trazodone and moclobemide. This association could be mediated by antidepressants with intermediate SERT affinity, i.e. dissociation constant 1-10 nM, (adjusted odds ratio: 1.68; 95% CI: 1.10-2.56) or use of multiple drugs with different SERT affinities (adjusted odds ratio: 1.31; 95% CI: 1.21-1.42). Regarding individual drugs, continuous use of venlafaxine (adjusted odds ratio: 1.44; 95% CI: 1.19-1.74), fluoxetine (adjusted odds ratio: 1.21; 95% CI: 1.01-1.46) and fluvoxamine (adjusted odds ratio: 147; 95% CI: 1.01-2.12) were associated with cataract, but not duloxetine, milnacirpan, paroxetine, citalopram, sertraline or their combination with other antidepressants. An association with cataract was also observed for past use, i.e. >30 days from cataract diagnosis, of SSRI, TCA (adjusted odds ratio: 1.26; 95% CI: 1.16-1.36) and other antidepressants. The cumulative dosage of antidepressants required for cataract diagnosis seems to vary. Low cumulative dosage of paroxetine, citalopram, escitalopram and sertraline, as well as high cumulative dosage of venlafaxine, sertraline and fluvoxamine might be associated with cataract.

However, a recent case-control study on the UK-based Clinical Practice Research Datalink is inconsistent to previous studies [6]. The 206931 cases were patients 40+ years with first time cataract diagnosis and equal number of age and gender matched controls were included. Long term continuous prescription of SSRI was not associated with cataract diagnosis (adjusted odds ratio: 0.99; 95% CI: 0.94-1.03) in general, but it was associated in younger patients aged from 40 to 64 years (adjusted odds ratio: 1.24; 95% CI: 1.15-1.34). The risk was adjusted to body mass index, glucocorticosteroid use, hypertension, diabetes and smoking.

The recent case-control studies have examined the association of antidepressants with cataract diagnosis or surgery. The studies have adjusted the risk for several confounding factors, such as ophthalmic comorbidities, components of metabolic syndrome and concomitant cataractogenic drug use. However, only one study adjusted for body mass index and smoking [6], and it was unable to detect an association in general. In accordance to the recent studies, the Beaver Dam Study assessed the incidence of drug-associated cataract within 5 years of follow-up, and amitriptyline was associated with an odds ratio of 2.03 (95% CI 1.09-1.39) [10]. In addition preclinical evidence suggested possible roles of serotonin, catecholamines and their receptors on the development of cataract [7].

DOI 10.26386/obrela.v1i2.43 ISSN 2585-2795

Case-control studies cannot confirm a causal relationship, as well as several confounding factors could be encrypted, such as family history of cataract. Populations at risk could be younger patients on long term continuous use of antidepressants. In addition, differences among individual antidepressants could emerge and intermediate SERT affinity, along with NET inhibition could be possible mediators. Longitudinal prospective studies should further establish the association between antidepressant and cataract, but ocular examination of antidepressant users, especially younger patients with comorbidities, could be justified.

Antipsychotic drugs

The first case-control study assessed the risk of antipsychotics for cataract surgery using the British Columbia Ministry of Health Database [11]. The study included 162501 cases of cataract surgery and 650004 controls. The age and gender of cases (74.4 +/-11.8 years, 41.6% males) were similar to controls. The risk was adjusted to age, gender, concomitant SSRI, antidiabetics and steroids, as well as history of uveitis, vitrectomy and hypertension. Prescription of atypical antipsychotics within 90 days of cataract surgery was protective (adjusted rate ratio: 0.84; 95% CI: 0.8-0.89). In addition, current use of typical antipsychotics was also protective (adjusted rate ratio: 0.84; 95% CI: 0.74-0.96), though haloperidol has suggested to be the most common prescribed antipsychotic. A dose-response of protection was observed, with higher number of prescriptions (more than 7 within the previous year) were associated with lower rate ratio (adjusted rate ratio: 0.7; 95% CI: 0.65-0.75), in comparison to smaller number of prescriptions (adjusted rate ratio: 0.85; 95% CI: 0.79-0.91).

Two studies on the National Health Insurance of Taiwan examined the role of antipsychotics on cataract development. The first one included 2222 patients with schizophrenia and cataract diagnosis were defined as cases and 2144 patients with schizophrenia without cataract diagnosis as controls [12]. There was no difference in age and gender between cases (53.1+/- 11.3 years, 39% males) and controls. The risk was adjusted to ophthalmic and other physical comorbidities, antidepressant or steroid use, as well as utilization of the healthcare system. An association with cataract was not observed for continuous use of atypical (adjusted odds ratio: 1.1; 95% CI: 0.94-1.3) and typical antipsychotics (adjusted odds ratio: 1.08; 95% CI: 0.91-1.29), when compared to past use of antipsychotics, i.e. > 90 days before of the cataract diagnosis. Regarding individual atypical antipsychotics, none was associated with cataract. In contrast to the previous case-control study [11], a protective association, i.e. the higher boundary of odds ratio < 1, was not observed.

However, a protective association was observed in the second study using patients with bipolar disorder [2]. The cases were 1684 patients with bipolar disorder and cataract diagnosis (55.3+/-10.3 year, 36% females) and 1608 matched controls with bipolar disorder and without a cataract diagnosis. Similar to the previous study, the risk was adjusted to ophthalmic and other physical comorbidities, utilization of the health system, as well as use of steroids, antidepressants and mood stabilizers. Continuous or past use of atypical antipsychotics seem to be protective (adjusted odds ratio: 0.71; 95% CI: 0.59-0.85), whereas an association with typical antipsychotics was not observed (adjusted odds ratio: 0.97; 95% CI: 0.71-1.34). In addition, continuous or past use of individual atypical antipsychotic was not associated with cataract.

Several lines of evidence suggest the risk of typical antipsychotics, especially phenothiazines, for cataract, but the risk of atypical antipsychotics is still under question [13]. Earlier studies suggest that patients with schizophrenia have a lower risk for cataract in general, but a higher prevalence of anterior subcapsular cataract [14]. Phenothiazines seem to induce lenticular pigmentation and the associated anterior subcapsular cataract [13]. Case reports suggest that chlorpromazine-induced lenticular opacities could cause visual impairment, which could be reversed after switching to risperidone [15]. Regarding the newer antipsychotics, high doses of quetiapine has been accused for cataract in

DOI 10.26386/obrela.v1i2.43 ISSN 2585-2795

preclinical research, so that biannual ocular examination has been suggested. Though, clinical evidence was not able to replicate these results in humans. A recent 2-year randomized open label study suggested that quetiapine was not cataractogenic in comparison to risperidone [16]. However, bilateral cataract has been reported in a 27-year old male with bipolar disorder on treatment with risperidone and lithium [17].

The above case-control studies suggest a possible protective mechanism of atypical antipsychotics against cataract development. It is suggested that antagonism of serotonin receptors, as well as anti-oxidative and anti-inflammatory properties could play important roles [2]. Individual typical antipsychotics were not tested. However, haloperidol could be the most frequently prescribed typical antipsychotic, underestimating the risk [11]. Important confounding factors such as smoking, family history of cataract, obesity was also not included in these studied. The possible protective association should also be replicated in other ethnicities and prospective studies.

Mood stabilizers

A secondary analysis of the case-control study on the National Health Insurance Research Database of Taiwan [9], has studied the association between mood stabilizers and cataract diagnosis in patients with schizophrenia or mood disorders [5]. The study included 7651 patients with schizophrenia or mood disorders and first cataract diagnosis and 6637 patients without cataract as controls. The risk was adjusted to comorbidities, concomitant cataractogenic drugs and healthcare utilization. Use of mood stabilizers for more than 2 years was associated with cataract (adjusted odds ratio: 1.14; 95% CI: 1.01-1.29), and the risk remained only for doses higher than the half of the daily defined dose (adjusted odds ratio: 1.28; 95% CI: 1.08-1.53). Regarding individual drugs, long-term use of lithium alone (adjusted odds ratio: 1.39; 95% CI: 1.01-1.92) or combined with other mood stabilizers (adjusted odds ratio: 1.44; 95% CI: 1.13-1.85), as well as valproic acid combined with other mood stabilizers (adjusted odds ratio: 1.26; 95% CI: 1.02-1.57), but not alone, was associated with cataract. Association was not observed with long term use of carbamazepine, lamotrigine and their combinations with other mood stabilizers. However, their sample size was small and probably not sufficient.

The role of mood stabilizers on the risk of cataract is studied to a lesser degree than antidepressants and antipsychotics. Carbamazepine, lamotrigine and valproic acid are also used as anticonvulsants. A study has suggested that patients with epilepsy on carbamazepine (odds ratio: 1.4, 95% CI: 1.05–1.8) may have been in higher risk for cataract surgery, in contrast to barbiturates and valproic acid [18]. In addition, a case report of carbamazepine-induced bilateral cataract in a 14-year old boy have been reported [19]. The cataractogenic properties of mood stabilizers could lie on inhibiting anti-oxidant mechanisms or inducing other ocular side effects [5].

Conclusion

Psychotropic medication could alter ocular physiology contributing to cataract development. Use of antidepressant drugs seem to predispose to cataract, especially long-term use and probably in younger patients. However, there is discrepancy regarding the risk of individual drugs, but dual mechanism and intermediate SERT affinity has been suggested as possible risk factors. Furthermore, mood stabilizers could also associate with cataract, despite the inconsistent results on individual drugs. On the other hand, atypical antipsychotics and high potency typical antipsychotics seem not to associate with cataract. Atypical antipsychotic drugs might also be protective against cataract, despite sparse preclinical and clinical evidence of their harmful effects. Phenothiazines and low-potency typical antipsychotics could induce lenticular opacities and cataract. A harmful or protective causal relationship between psychotropic medication and development of cataract cannot be established by case-control studies, and further research is needed. However, ocular examinations should be suggested to patients on psychotropic medication, especially on antidepressant or mood stabilizers, as well as with comorbidities and concomitant use of cataractogenic drugs.

DOI 10.26386/obrela.v1i2.43 ISSN 2585-2795

References

1. Prokofyeva, E., A. Wegener, and E. Zrenner, Cataract prevalence and prevention in Europe: a literature review. *Acta Ophthalmol* 2013, 91(5): p. 395-405. PMID: 22715900 , DOI: 10.1111/j.1755-3768.2012.02444.x

2. Chu, C.S., et al., Association between antipsychotic drug use and cataracts in patients with bipolar disorder: A population-based, nested case-control study. *J Affect Disord* 2017, 209: 86-92. PMID: 27889598 , DOI: 10.1016/j.jad.2016.11.019

3. Carvalho, A.F., et al., The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. *Psychotherapy and Psychosomatics* 2016, 85(5): 270-288. PMID: 27508501, DOI: 10.1159/000447034

4. Shahzad, S., et al., Cataract occurrence with antipsychotic drugs. *Psychosomatics* 2002. 43(5): 354-9. PMID: 12297603 , DOI: 10.1176/appi.psy.43.5.354

5. Chu, C.-S., et al., Associations between use of mood stabilizers and risk of cataract: A population-based nested case-control study. *J Affective Disorders* 2017, 227 (Supplement C): p. 79-81. PMID: 27889598 , DOI: 10.1016/j.jad.2016.11.019

6. Becker, C., S.S. Jick, and C.R. Meier, Selective Serotonin Reuptake Inhibitors and Cataract Risk: A Case-Control Analysis. *Ophthalmology* 2017. 124(11): 1635-1639, doi: 10.1016/j.ophtha.2017.05.002

7. Etminan, M., F.S. Mikelberg, and J.M. Brophy, Selective serotonin reuptake inhibitors and the risk of cataracts: a nested case-control study. *Ophthalmology* 2010. 117(6): 1251-5, doi: 10.1016/j.ophtha.2009.11.042

8. Erie, J.C., et al., Selective serotonin reuptake inhibitor use and increased risk of cataract surgery: a population-based, case-control study. *Am J Ophthalmol* 2014. 158(1): 192-197.e1. MID: 24631758, PMCID: PMC4356987, DOI: 10.1016/j.ajo.2014.03.006

9. Chou, P.H., et al., Antidepressants and risk of cataract development: A population-based, nested case-control study. *J Affect Disord* 2017, 215: 237-244. PMID: 28342338 , DOI: 10.1016/j.jad.2017.03.044

10. Klein, B.E., et al., Drug use and five-year incidence of age-related cataracts: The Beaver Dam Eye Study. *Ophthalmology* 2001. 108(9): 1670-4. PMID: 11535471

11. Pakzad-Vaezi, K.L., M. Etminan, and F.S. Mikelberg, The association between cataract surgery and atypical antipsychotic use: a nested case-control study. *Am J Ophthalmol* 2013. 156(6): 1141-1146. doi: 10.1016/j.ajo.2013.07.012

12. Chou, P.H., et al., Use of atypical antipsychotics and risks of cataract development in patients with schizophrenia: A population-based, nested case-control study. *Schizophr Res* 2016. 174(1-3): 137-43. PMID: 27061658 , DOI: 10.1016/j.schres.2016.03.027

13. Souza, V.B., et al., Cataract occurrence in patients treated with antipsychotic drugs. *Rev Bras Psiquiatr* 2008. 30(3): 222-6. PMID: 18833422

14. McCarty, C.A., et al., Schizophrenia, psychotropic medication, and cataract. *Ophthalmology,* 1999. 106(4): 683-7. PMID: 10201587 , DOI: 10.1016/S0161-6420(99)90151-3

15. Gowda, G.S., et al., Kerato-lenticular ocular deposits and visual impairment with prolonged chlorpromazine use: A case series. *Asian J Psychiatr* 2017. 25: 188-190. PMID: 28262147 , DOI: 10.1016/j.ajp.2016.11.002

16. Laties, A.M., Flach AJ, Baldycheva I, Rak I, Earley W, Pathak S.., Cataractogenic potential of quetiapine versus risperidone in the long-term treatment of patients with schizophrenia or schizoaffective disorder: a randomized, open-label, ophthalmologist-masked, flexible-dose, non-inferiority trial. *J Psychopharmacol* 2015. 29(1): 69-79. PMID: 25315830 , DOI: 10.1177/0269881114553253

17. Patel, E. and J.A. Gallego, Bilateral cataracts in a young patient with bipolar disorder on treatment with risperidone. *Aust N Z J Psychiatry* 2016. 50(12): 1210, DOI: 10.1177/0004867416655604

18. Hanhart J, Vinker S, Nemet A, Levartovsky S, Kaiserman I., Prevalence of Epilepsy among Cataract Patients. *Curr Eye Res* 2010. 35(6): 487-91. PMID: 20465442 , DOI: 10.3109/02713681003664915

19. Kinoshita A, Kitaoka T, Oba K, Amemiya T., Bilateral drug-induced cataract in a patient receiving anticonvulsant therapy. *Jpn J Ophthalmol* 2004. 48(1): 81-2, DOI: 10.1007/s10384-003-0017-z

Dialogues in Clinical Neuroscience & Mental Health

DOI 10.26386/obrela.v1i2.44 ISSN 2585-2795

Research article

Nonindependent mate choice: the first study with real-life couples in a Greek sample

Georgios Tsouvelas[1], Argyroula Kalaitzaki[2] , Antonios Vakirtzis[3]

1. Department of Psychology, National & Kapodistrian University of Athens, Greece
2. Laboratory of Interdisciplinary Approaches for the Enhancement of Quality of Life, Social Work Department, Technological Educational Institute of Crete, Greece
3. 19 Rippington Drive, Oxford, OX3 ORH, UK

Abstract

In humans, as in other species, nonindependent mate choice takes place when females are influenced in their mate choice by the choices of other females. Previous studies have used almost exclusively experimental methods, with the most robust finding being that women tend to be more attracted to men who are paired with attractive women. Results, however, have often been conflicting, and the degree to which experimental methods are capturing real-life social processes has not been validated. In this study a self-report questionnaire was administered to a sample of young Greek men and women who were in monogamous romantic relationships. Participants also provided facial photographs of themselves that were rated for attractiveness. Men in these relationships tended to report more perceived opposite-sex interest than their partners, though this difference was not as clear or strong as expected. Furthermore the degree to which men - and women - reported opposite-sex interest was not related to the attractiveness of their partners. We discuss what might account for these unexpected results and suggest ways for improving the current methodology.

Keywords: Nonindependent mate choice, attractiveness, mate choice copying, romantic couples, evolutionary psychology.

Corresponding Author: Georgios Tsouvelas, Psychologist, MSc, MPH, PhD, Department of Psychology, School of Philosophy, National & Kapodistrian University of Athens, e-mail: gtsouvelas@psych.uoa.gr

Received: March 4, 2018, Accepted: April 1, 2018

DOI 10.26386/obrela.v1i2.44 ISSN 2585-2795

Introduction

Non independent mate choice refers to female mate choice that is adaptively influenced by the choices of other females [1]. Observing females (focal females) that take into consideration the mate choices of other females (model females) can, under certain circumstances, make a better than random choice of mate while paying very little or none of the mate choice costs [2]. The costs of mate choice can be extensive, ranging from the expenditure of time and energy to the risks of predation and harassment by males that get rejected along the way [3-6]. Added to this, certain females that are not very competent in their mate choice abilities should be adaptively inclined to take into consideration the choices of more competent females [7]. It has been consistently found that while younger and more inexperienced females are influenced in their choices by the choices of older females, the latter are not influenced by the choices of the former [8-10].

Mate choice copying is the most straightforward and widely studied type of nonindependent mate choice, having been demonstrated in a variety of promiscuous and polygamous species of fish, birds, insects and mammals (reviewed in Vakirtzis [11]). Copying takes place when a male is most likely to be selected by focal females after having been selected by a model female and is more likely to be rejected by focal females after having been rejected by a model female [1see also 12-13]. In other words a male's prior success with one or more females will breed more success with females who are privy to these interactions and a male's failure with breed more failure. This process is expected, given the appropriate mating system, to lead to large male mating skews [14].

The idea that women are influenced in their romantic choices by the choices of other women goes back at least to the 1970s [15], and recent years have seen a resurgence of experimental interest in this topic. Studies have shown mixed results: while some studies found that men in relationships were perceived as more attractive by the women raters [16-17], other studies failed to find this [18-20].Unlike most promiscuous and polygamous species where a copying process has been found, contemporary western societies do not exhibit a substantial male mating skew, and most men tend to have one monogamous partner at any given time [21-23]. In the absence of substantial male mating skew the absence or presence of a partner does not provide much information to other women. A more promising variable for research into human nonindependent mate choice appears to be the attractiveness of a man's partner [20, 24]. In particular the mate value of women is more heavily dependent on physical appearance than the mate value of men [25-26], meaning that, due to assortative mating in terms of mate value, the visual inspection of a man's mate will likely yield a more precise estimate of his mate value than a simple visual inspection of the male alone [27]. We should, in other words, expect women to be especially sensitive to how attractive the female partner of a man is: women should be more attracted to men with attractive mates and less attracted to men with unattractive mates [27]. Experimental studies in humans tend to confirm this, with women rating men who are paired to attractive partners as more attractive compared to men who are paired to unattractive partners [20, 28-30]. From an evolutionary perspective there should be not gender symmetry with regards to this effect, i.e. it would be expected that men should not be influenced by the attractiveness of a potential mate's partner [27], and this is what many studies have found [17, 24, 28, 29, 31, 32].

How well, if at all, results obtained in the lab generalise to real-life situations is difficult to know given the lack of non-experimental studies in the field [32]. To date only two studies have used questionnaire methodology to capture men and women's perceptions of how their own attractiveness varies as a function of being in a relationship. Using a two-item questionnaire Platek et al. [33] found that both male and female undergraduates retrospectively reported an increase in dating opportunities upon entering a new dating relationship. Vakirtzis and Roberts [32] administered a more detailed questionnaire of perceived opposite-sex attractiveness to a large sample of men and women (N=381) who were either single or in a relationship. Additionally, the subset of respondents who were in a relationship rated their

DOI 10.26386/obrela.v1i2.44 ISSN 2585-2795

own and their partner's attractiveness and reported how their self-perceived attractiveness to the opposite sex had changed before and after the relationship. Men who were in a relationship agreed more strongly with items like ‹*In general, I feel that I have become more attractive to other women (men) since I started dating my girlfriend (boyfriend)*› compared to women who were in a relationship. Furthermore, the higher the reported attractiveness of their partner, the more males tended to agree with these items, while there was no corresponding relationship between the reported attractiveness of their partner and the degree to which women agreed with these items. In the same study, males who were single agreed more strongly with items like ‹*In general, I feel that I have become less attractive to women (men) since I became single*› compared to women. Although the study by Vakirtzis and Roberts [32] was very suggestive of the reality of human nonindependent mate choice outside the laboratory, it had two weaknesses. Firstly, participants rated their own and their partner's attractiveness, a process which certainly introduced substantial error variance. Secondly, a more powerful methodology would have been to capture the responses of men and women from the same couples, allowing for a ‹within-couples› comparison.

In the present study we expand on Vakirtzis and Roberts' [32] earlier research by replicating their questionnaire methodology but with a design that overcomes the aforementioned weaknesses. In particular we recruited a sample of undergraduate Greek couples who were in a stable romantic relationship and administered to both members of each couple a modified version of the questionnaire used in the 2012 study. In addition, participating couples were also asked to provide photographs of themselves that were subsequently rated for attractiveness by an independent panel, thus providing far more accurate measures of attractiveness. We predicted that a) men in a romantic relationship would report more perceived opposite-sex interest than their female partners and that b) that this reported opposite-sex interest would be moderated by the attractiveness of their romantic partner for male but not female participants. We also predicted that c) a number of contextual factors that allow for nonindependent mate choice to take place, like the degree to which the couples frequented public places together and shared the same social networks, would similarly moderate the degree to which men reported increased opposite-sex interest.

Methods

Participants

Two hundred and thirty two romantically involved heterosexual couples (mean age 25.1 and 22.5 years for men and women, respectively) were recruited for this study from the undergraduate students at the Department of Social Work of the TEI of Crete. No outliers were excluded after using anomaly detection technique. Participants were provided an information sheet and were invited to participate in the study on the condition that a) they were in a monogamous romantic relationship of at least three months' duration and b) that their partner would also be willing to participate. It was not a requirement for participation that the partner also be a student.

Students were briefed on the purpose and requirements of the study and the voluntary nature of participation by the professor (A. K.) who was one of the researchers. Anonymity and confidentiality were guaranteed. Students who consented were given the study questionnaire and were asked to complete it onsite. They were then given another questionnaire for their partner, placed inside an envelope. The questionnaires were identical for males and females, with the obvious changes to sex-specific terms like ‹*my girlfriend/my boyfriend*› etc, as necessary. Each questionnaire was numbered uniquely for each couple, to allow us to match the male to the female responses, as well as to match both the questionnaires to the photographs of the couple. Students were instructed to invite their partner to complete the questionnaire, place it back in the envelope and seal it for privacy. An online URL was provided to the participants who would like more information about the study. The sealed envelope with the partner's questionnaire was then handed back to the professor at the following week's class or as soon as possible thereafter.

DOI 10.26386/obrela.v1i2.44 ISSN 2585-2795

As part of the study students were asked to send a) one facial photo of themselves and one of their partner or b) one photo with both partners' faces, though it was stated that the former option was preferable. Participants were advised that the photos were to be evaluated for attractiveness by a group of raters and were instructed to email them to an email address specifically created for the purpose of the study. The students were reminded to indicate their unique identifying code when emailing the photos, so that the researchers could match the anonymous questionnaires with the photos. The final response rate - i.e. submission of the partner's questionnaire and the photographs, where one partner had already consented - was over 90%.

Measures

The questionnaire, entitled ‹*Interpersonal relationship questionnaire for couples*› was based on Vakirtzis and Roberts [32] earlier study and consisted of the following parts:

a) Personal details including age, height, weight, and whether the participant was a student or not

b) Self-rated attractiveness and attractiveness of partner on a scale from 1-10

c) Factual information regarding the relationship. This included the duration of the relationship and how frequently (‹*almost never*› to ‹*almost daily*›) the couple visited the following places for socializing: clubs/bars, restaurants, cafes, cinemas, house parties. Participants were also asked ‹*to what degree do you and your partner share the same social networks, e.g. friends, acquaintances, colleagues etc?*›.

d) Subjects expressed their agreement or disagreement (on a 5-point scale) with the following four items [32], referring to how they believed they were viewed by opposite sex individuals in the context of their relationship.

1. *Women (men) seem to look at me more when I'm with my girlfriend (boyfriend) than when I'm alone.*
2. *In general, I feel that I have become less attractive to other men (women) since I started dating my boyfriend (girlfriend).*
3. *Some women (men) who previously showed little interest in me seem to flirt more with me since I started dating my girlfriend (boyfriend).*
4. *In general, women (men) flirt more with me since I started dating my girlfriend (boyfriend).*

Item 2 was reverse coded and the four items were summed to produce one composite measure of opposite-sex interest which was used as the dependent variable in the analysis.

e) The Rosenberg self-esteem scale [34] and the Social Information Processing subscale of the Tromso Social Intelligence Scale, were both translated in Greek [35]. These were administered to rule out spurious correlations with perceived opposite-sex interest due to participant variability in self-esteem or social intelligence [32].

Ten (10) pairs of questionnaires were identified which were largely incomplete and/or had other problems (like identical or nonsensical answers). Their exclusion reduced the final sample to 222 (mean age 25.1 and 22.5 years for men and women, respectively). A small number of these remaining 222 questionnaires had some missing items, which explains the slight sample size variability in different analyses. 91.7% of female respondents and 48.1% of males were students.

Results

Questionnaires

Table 1 shows the gender differences for the four items that served as dependent variables.

Table 1.: Comparison of Responses by Men and Women in romantically involved couples.

Items	Male		Female		
	M	SE	M	SE	t(df)
1.Women (men) look at me more when I am with my girlfriend (boyfriend) than when I'm alone	3.05	0.06	2.58	0.06	5.79(220)***

DOI 10.26386/obrela.v1i2.44 ISSN 2585-2795

2. In general, I feel that I have become less attractive to other women (men) since I started dating my girlfriend (boyfriend)	2.31	0.05	2.17	0.06	2.04(220)*
3. Some women (men) who previously showed very little interest in me seem to flirt more with me since I started dating my girlfriend (boyfriend)	2.69	0.07	2.55	0.07	1.55(220)
4. In general, women (men) flirt more with me since I started dating my girlfriend (boyfriend)	2.64	0.06	2.52	0.07	1.4(219)
Composite: 1+2 (reverse scored)+3+4	12.1	0.17	11.5	0.17	2.5(219)*

Note. M = Mean; SE = Standard Error; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

Items 1, 3 and 4 were in the expected direction, though the difference was only significant for item 1. Item 2 was reverse coded, so the fact that males reported higher values than females was unexpected. Overall the composite measure of opposite sex interest showed a significant difference in the expected direction, with men reporting more overall opposite-sex interest than women. We examined if the sex difference in the composite measure of reported opposite sex interest (henceforth 'dependent variable') could be attributed to differences in male and female participants' self-esteem and social intelligence. We regressed the sex difference in the dependent variable against female self-esteem, female social intelligence, male self-esteem and male social intelligence. The only significant predictor was female self-esteem ($\beta = -.22$, $p = 0.003$). While the overall model was significant ($F(4,190) = 3.234$, $p = .014$), it only accounted for 4.4% of the adjusted variance. To ensure that the sex difference was not spurious we conducted a repeated-measures analysis of covariance on the dependent variable, with female self-esteem as the covariate. Using Wilks' criterion there was a significant efffect on dependent variable after controlling for the effect of gender, $\Lambda = 0.96$, $F(2,206) = 9.58$, $p = .002$, $\eta^2 = 0.04$. The covariate females' self esteem was significantly related to the dependent variable $\Lambda = 0.96$, $F(1,206) = 7.93$, $p = .005$, $\eta^2 = 0.04$. Men had significantly higher levels in the dependent variable ($M = 12.06$, $SD = 2.57$) in comparison with their women counterparts ($M = 11.46$, $SD = 2.66$).

The significant sex differences found earlier for items 1 and 2 remained, whereas the sex difference for the composite statement was very close to significance.

The next part of the analysis examined how the composite measure of reported opposite-sex interest (henceforth ‹dependent variable›) varied as a function of several variables that were expected to influence the strength of nonindependent mate choice and the opportunities for nonindependent mate choice to take place [32]. These were a) the duration of the relationship b) the degree to which the couple's social circles overlapped and c) the extent to which the couple frequented public places like clubs or bars, eateries, house parties etc.

There was very high agreement in the duration of the relationship provided separately by male and female participants in months ($r = .98$), and an average of the two values was correlated with the dependent variable for both women ($r = -.06$, $p = .402$) and men ($r = -.17$, $p = .013$). Surprisingly, men who had been in relationships for a longer time tended to report diminished opposite sex interest, which was the opposite of what we had expected.

The extent to which a couple's social circle overlapped was captured by the one-item question ‹*to what degree do you and your partner share the same social circle, e.g. friends, acquaintances colleagues etc?*›. Answers were given on a 4-point ordinal scale ranging from ‹*completely or almost completely different social circle*› to ‹*completely or almost completely common social circle*›. Agreement amongst the male and female of each couple was very high ($rho = .77$, $p = .001$), and an average of the two responses was used, but this did not correlate with the dependent variable for either the male or female participants (both *NS*).

DOI 10.26386/obrela.v1i2.44 ISSN 2585-2795

Lastly, the frequency with which the couple frequented public places, such as clubs/bars, eateries, cafes, cinemas and house parties was examined on a 7-point ordinal scale that ranged from ‹almost never› to ‹almost daily›. Within-couple non-parametric correlations were very high and significant for every category of public place (all p <.001), and an average of the male and female response was taken for each category. For male participants only the frequency with which the couple frequented bars or clubs correlated with the dependent variable (*rho* =.18, p = .009), whereas for women the dependent variable correlated with frequency of attending bars/clubs (*rho* =.15, p =.033), as well as cinemas (*rho* =.17, p =.016). All of these significant correlations were in the expected direction, with increasing frequencies of outings resulting in higher reported opposite sex interest.

Photographs, self-rated attractiveness and physical characteristics of participants

A number of pictures provided by participants were not of sufficient quality to be evaluable for attractiveness (e.g. overlapped faces, out of focus, dark or too small photos). Photographs of acceptable quality where the man and woman were pictured together were digitally cropped, resulting in the creation of two new images, one for each partner alone. Photographs where the man and woman were pictured alone were also cropped where necessary, most often to resize the image to suitable size or to crop unnecessary background/landscape information. In the end 128 acceptable photographs of men (M_{age} = 25.3) were rated by five female judges, undergraduate students from a different university than the one the sample came from (M_{age} = 24.8 years), and 126 acceptable photographs of women (M_{age} = 22.5) were rated by six male undergraduate students, also from a different university (M_{age} = 22.5). Inter-rater reliability was high both for the female (alpha = .79) and male raters (alpha = .78). The ratings for every image were subsequently averaged to produce a single rating. Interestingly, for women the judges' ratings were correlated with self-ratings of attractiveness (r = 0.19, p = .036) but not with the attractiveness ratings given by the women's partners (r = 0.04, p = .682). The same pattern held for the male images, where the judges' ratings correlated significantly with men's self-rated attractiveness (r = 0.21, p =.019) but not with the ratings given by the men's partners (r = 0.001, p =.991). Self-rated attractiveness was approximately normally distributed for both males and females, and the means did not differ by sex (7.2 for both).

Unexpectedly, the composite measure of self-reported opposite sex interest (i.e. the dependent variable) did not correlate with the attractiveness of one's partner as rated by the judges. This held true both for female (r = 0.01, p = .925) and male participants (r = 0.06, p = .521). For both sexes there were also no correlations between the dependent variable and the attractiveness of one's partner as reported by both the participants and their partners (all correlations *NS*). Surprisingly, self-rated attractiveness measure correlated with the dependent variable, both for female (r = 0.20, p = .003) and male participants (r = 0.22, p = .001).

Furthermore, we examined if the dependent variable correlated with more objective variables of physical attractiveness like self-reported height, weight and BMI. The opposite-sex interest reported by both men and women did not correlate with their partner's height, weight or BMI (all correlations *NS*).

After conducting a principal component analysis on items of dependent variable we found that the first item accounted for 50% of the variance. We therefore decided to use it as an index instead of the composite index in a structural equation model where we examined the hypothesis that social opportunities would mediate the relationship of male attractiveness and self-rated attractiveness by female. Our choice was also supported through the elbow method in scree plot, where the second factor had eigenvalue lower than 1.

We created a latent variable for the frequency of the couple's joint attendance of public places (bars, cinemas, cafes

DOI 10.26386/obrela.v1i2.44 ISSN 2585-2795

and restaurants). The relationship between women's self-rated attractiveness and males' perception that "women look at me more when I am with my girlfriend" was mediated by the frequency of joint attendance of these public places. As Figure 1 shows, the standardized regression coefficient between women's self-rated attractiveness and males' perception that "women look at me more when I am with my girlfriend" was statistically significant. We tested the significance of this indirect effect using bootstrapping procedures. Standardized indirect effects were computed for each of 2,000 bootstrapped samples, and the 95% confidence interval was computed by determining the indirect effects at the 2.5th and 97.5th percentiles. The bootstrapped standardized direct effect was .10, $p = .252$, and the standardized indirect effect was .05, $p = .027$ validating a full mediation effect of the joint attendance of public places.

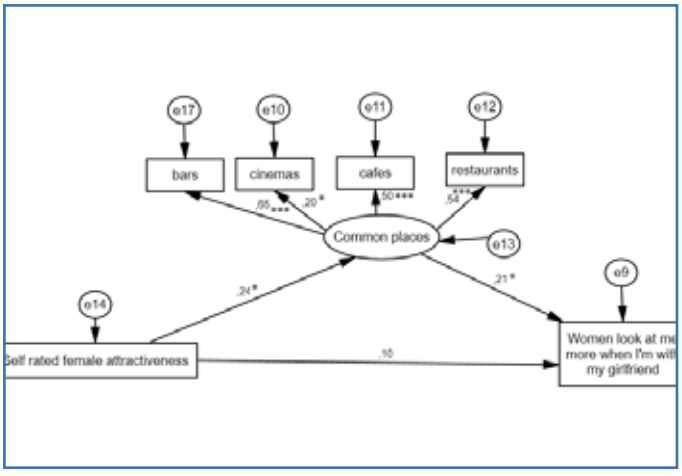


Figure 1. Structural equation model of the mediation of joint attendance of public places in the relationship between self-rated female attractiveness and self-reported increased levels of attractiveness by their male partner.

Note. * $p<.05$; ** $p<.01$; *** $p<.001$. Values are standardized regression weights. Fit indices for the model: CMIN=19.04, DF=8, $p=.015$; CMIN/DF=2.38; CFI=.88; RMSEA=.078 (LO=.03, HI=.13); SRMR=.05.

Discussion

This is the first study that investigated human nonindependent mate choice in real-life couples. In line with the results of a previous study on which the present one builds [34], we found that men who were in romantic relationships tended to report more opposite sex interest than their girlfriends, though this relationship was not as strong or as unanimous across all the questionnaire items as expected. We also found that the relationship between women's self-rated attractiveness and their partners' reported opposite-sex interest was mediated by the couples' joint attendance of public places like bars and clubs. Outside of these findings, most of the expected relationships failed to appear. Most importantly, the attractiveness of men's romantic partners, as rated by an independent set of raters, was not in any way correlated with the men's self-reported attention from the opposite sex. Setting aside the lack of statistical significance, it was very surprising that the actual correlation itself was practically zero. This unexpected finding contradicts the core finding of prior research in this area [e.g. 20, 28-30] and is very difficult to interpret. In addition, elements of couples' social life that were expected to be of relevance to nonindependent mate choice, like the degree to which couples shared a common social circle or frequented public places turned out to be marginally significant.

To date studies in this field have overwhelmingly used experimental methods, with only two prior studies using questionnaire studies [32-33]. The strengths of the current research are a) the aforementioned use of real-life couples that allows for within-couples comparisons, b) the collection of an extensive series of information relating to the couples' social life, c) the collection of photographs that allows, for the first time, a more objective evaluation of participants' attractiveness, d) the collection of physical data like height, weight and BMI and e) the cross-cultural element, as the majority of the relevant studies have been confined to English-speaking samples.

DOI 10.26386/obrela.v1i2.44 ISSN 2585-2795

The most obvious improvement for future studies relates to the photographs collected; rather than participants providing photographs themselves, researchers would be well advised to take high quality, standardised photographs themselves. While logistically more demanding, we suspect that this step will dramatically improve the quality of the results obtained, and relationships that remained obscured in the present study will stand out in sharp relief. Another obvious improvement would involve the development of a more extensive and sophisticated self-report scale for capturing opposite sex interest as a function of one's romantic relationship status; whereas Vakirtzis and Roberts [34] showed promising results using the scale, the results presented here were disappointing. An overview of the results obtained here strongly suggest that, unlike the first study [34], the questionnaire was not quite capturing what it was meant to, at least when it comes to this Greek sample of undergraduate students.

References

1. Pruett-Jones S. *Independent Versus Nonindependent Mate Choice: Do Females Copy Each Other? The American Naturalist* 1992, 140(6):1000–9. http://dx.doi.org/10.1086/285452

2. Pomiankowski A. How to find the top male. *Nature* 1990: 347(6294):616–7. http://dx.doi.org/10.1038/347616a0

3. Andersson M. *Sexual selection*. Princeton: Princeton University Press, 1994.

4. Dugatkin LA, Höglund J. Delayed breeding and the evolution of mate copying in lekking species. Journal of Theoretical Biology 1995, 174(3):261–7. http://dx.doi.org/10.1006/jtbi.1995.0097

5. Pomiankowski A. The costs of choice in sexual selection. Journal of Theoretical Biology . *Elsevier BV* 1987, 128(2):195–218. http://dx.doi.org/10.1016/s0022-5193(87)80169-8

6. Reynolds JD, Gross MR. *Costs and Benefits of Female Mate Choice: Is There a Lek Paradox? The American Naturalist* 1990, 136(2):230–43. http://dx.doi.org/10.1086/285093

7. Nordell, Valone. Mate choice copying as public information. *Ecology Letters* 1998, 1(2):74–6, http://dx.doi.org/10.1046/j.1461-0248.1998.00025.x

8. Amlacher J, Dugatkin LA. Preference for older over younger models during mate-choice copying in young guppies. *Ethology Ecology & Evolution* 2005, 17(2):161–9. http://dx.doi.org/10.1080/08927014.2005.9522605

9. Dugatkin LA, Godin J-GJ. Female mate copying in the guppy (Poecilia reticulata): age-dependent effects. *Behavioral Ecology* 1993, 4(4):289–92. http://dx.doi.org/10.1093/beheco/4.4.289

10. Vukomanovic J, Rodd FH. Size-Dependent Female Mate Copying in the Guppy (Poecilia reticulata): Large Females are Role Models but Small Ones are not. *Ethology* 2007, 113(6):579–86. http://dx.doi.org/10.1111/j.1439-0310.2007.01343.x

11. Vakirtzis A. Mate Choice Copying and Nonindependent Mate Choice: A Critical Review. *Annales Zoologici Fennici* 2011, 48(2):91–107. http://dx.doi.org/10.5735/086.048.0202

12. Dugatkin LA. Sexual Selection and Imitation: Females Copy the Mate Choice of Others. *The American Naturalist* 1992, 139(6):1384–9. http://dx.doi.org/10.1086/285392

13. Dugatkin LA. Copying and Mate Choice. Social Learning in Animals In: Heyes QCM, Galef JBG editors. *Social learning in animals: The roots of culture.* London: Academic Press; 1996;85–105. http://dx.doi.org/10.1016/b978-012273965-1/50006-6

14. Gibson RM, Bradbury JW, Vehrencamp SL. Mate choice in lekking sage grouse revisited: the roles of vocal display, female site fidelity, and copying. *Behavioral Ecology* 1991, 2(2):165–80. http://dx.doi.org/10.1093/beheco/2.2.165

15. Sigall H, Landy D. Radiating beauty: Effects of having a physically attractive partner on person perception. *Journal of Personality and Social Psychology* 1973:28(2):218–24. http://dx.doi.org/10.1037/h0035740

16. Eva KW, Wood TJ. Are all the taken men good? An indirect examination of mate-choice copying in humans. *Canadian Medical Association Journal* 2006, 5:175(12):1573–4. http://dx.doi.org/10.1503/cmaj.061367

17. Parker J, Burkley M. Who's chasing whom? The impact of gender and relationship status on mate poaching. *Journal of Experimental Social Psychology*. 2009, 45(4):1016–9. http://dx.doi.org/10.1016/j.jesp.2009.04.022

18. Uller T, Johansson LC. Human mate choice and the wedding ring effect. *Human Nature* 2003, 14(3):267–76. http://dx.doi.org/10.1007/s12110-003-1006-0

19. Milonoff M, Nummi P, Nummi O, Pienmunne E. Male friends, not female company, make a man more attractive. *Annales Zoologici Fennici* 2007, 44(5) : 348–54.

20. Waynforth D. Mate Choice Copying in Humans. Human Nature 2007, 3:18(3):264–71. http://dx.doi.org/10.1007/s12110-007-9004-2

21. Adimora AA, Schoenbach VJ, Doherty IA. Concurrent Sexual Partnerships Among Men in the United States. *American Journal of Public Health* 2007, 97(12):2230–7. http://dx.doi.org/10.2105/ajph.2006.099069

22. Greeley AM, Michael RT, Smith TW. Americans and their sexual partners. *Society* . *Springer Nature* 1990, 27(5):36–42. http://dx.doi.org/10.1007/bf02698729

DOI 10.26386/obrela.v1i2.44 ISSN 2585-2795

23. Seidman SN, Rieder, RO. A review of sexual behavior in the United States. *American Journal of Psychiatry* 1994, 151(3):330–41. http://dx.doi.org/10.1176/ajp.151.3.330

24. Vakirtzis A, Roberts SC. Mate Quality Bias: Sex Differences in Humans. *Annales Zoologici Fennici* 2010, 47(2):149–57. http://dx.doi.org/10.5735/086.047.0208

25. Townsend JM. Mate selection criteria. *Ethology and Sociobiology* 1989, 10(4):241–53. http://dx.doi.org/10.1016/0162-3095(89)90002-2

26. Townsend JM. *What women want - what men want*. New York: Oxford University Press; 1999.

27. Vakirtzis A, Roberts SC. Nonindependent mate choice in monogamy. *Behavioral Ecology* 2010, 21(5):898–901. http://dx.doi.org/10.1093/beheco/arq092

28. Little AC, Burriss RP, Jones BC, DeBruine LM, Caldwell CA. Social influence in human face preference: men and women are influenced more for long-term than short-term attractiveness decisions. *Evolution and Human Behavior* 2008, 29(2):140–6. http://dx.doi.org/10.1016/j.evolhumbehav.2007.11.007

29. Yorzinski JL, Platt ML. Same-Sex Gaze Attraction Influences Mate-Choice Copying in Humans. Reby D, editor. PLoS ONE 2010, 9:5(2):e9115. http://dx.doi.org/10.1371/journal.pone.0009115

30. Rodeheffer CD, Proffitt Leyva RP, Hill SE. Attractive Female Romantic Partners Provide a Proxy for Unobservable Male Qualities. *Evolutionary Psychology* 2016, 31:14(2):1-8. http://dx.doi.org/10.1177/1474704916652144

31. Dunn MJ, Doria MV. Simulated attraction increases opposite sex attractiveness ratings in females but not males. *Journal of Social. Evolutionary, and Cultural Psychology* 2010, 4(1):1–17. http://dx.doi.org/10.1037/h0099305

32. Place SS, Todd PM, Penke L, Asendorpf JB. Humans show mate copying after observing real mate choices?. *Evolution and Human Behavior* 2010, 31(5):320–5. http://dx.doi.org/10.1016/j.evolhumbehav.2010.02.001

32. Vakirtzis A, Roberts SC. Do women really like taken men? Results from a large questionnaire study. *Journal of Social, Evolutionary and Cultural Psychology* 2012, 6(1):50–65. http://dx.doi.org/10.1037/h0099225

33. Platek SM, Burch RL, Gallup GG. The reproductive priming effect. *Social Behavior and Personality* 2001, 29(3):245–8. http://dx.doi.org/10.2224/sbp.2001.29.3.245

34. Rosenberg M. *Society and the adolescent self-image.* Princeton: Princeton University Press; 1965.

35. Silvera D, Martinussen M, Dahl TI. The Tromso Social Intelligence Scale, a self-report measure of social intelligence. *Scandinavian Journal of Psychology* 2001, 42(4):313–9. http://dx.doi.org/10.1111/1467-9450.00242

Dialogues in Clinical Neuroscience & Mental Health

DOI 10.26386/obrela.v1i2.45 ISSN 2585-2795

Research article

The Greek Version of AD8 Informant Interview: Data from the Neurocognitive Study on Aging (NEUROAGE)

Fofi Constantinidou and Fotini Demetriou

Center for Applied Neuroscience & Department of Psychology, University of Cyprus

Abstract

Objective: The Alzheimer Disease 8 (AD8) is a simple and short informant-based tool that could assist in the screening of early stages of dementia. This study aimed to explore preliminary psychometric properties of the Greek version of the AD8 (CY-AD8) and its utility in cognitive screening in a large cohort of community dwellers over the age of 60.

Methods: Evaluation was made on 182 informant reports of community dwellers without a diagnosis of a neurological condition or dementia. The CY-AD8 scores were correlated with Mini Mental State Examination (MMSE) scores.

Results: Internal consistency of the CY-AD8 was acceptable (Cronbach α =0.827). The CY-AD8 correlated moderately with the MMSE (Pearson's r = -.524 p < .001). Median split resulted in two groups based on the CY-AD8 scores. An independent samples t-test was conducted to examine whether there was a significant difference between group 1 (AD8=0-1) and group 2 (AD8=2+) in relation to their performance in MMSE. The test revealed a statistically significant difference between group 1 and group 2 in MMSE (t= 5.53, df =176, p < .001). Those with more symptoms on the CY-AD8 were significantly older than those with fewer symptoms.

Conclusions: The CY-AD8 is a useful screening tool for early detection of individuals who may be at risk for dementia, but still further investigation is needed to explore the psychometric properties of this tool.

Corresponding Author: Fofi Constantinidou, Ph.D., CCC-S, CBIS, ASHA and ACRM Fellow, Professor of Language Disorders and Clinical Neuropsychology, Director, Center for Applied Neuroscience, Board of Governors, American Congress of Rehabilitation Medicine, Kallipoleos 75, University of Cyprus, Nicosia 1678, Cyprus
e-mail: fofic@ucy.ac.cy

Received: February 21, 2018, Accepted: March 15, 2018

DOI 10.26386/obrela.v1i2.45 ISSN 2585-2795

Introduction

Dementia is a global public health burden that causes major disability. The number of persons with dementia (PwD) is expected to increase from 35.6 million in 2010 to 66 million in 2030 and 115 million in 2050 **[1]**. Early detection of dementia is challenging as research findings show that more than half of elderly patients who meet the criteria of dementia remain undiagnosed **[2, 3]**.

Health care professionals oftentimes implement global cognitive screening tests such as the Mini Mental State Examination (MMSE**) [4]** and the Montreal Cognitive Assessment (MOCA**) [5]** to discriminate between normal cognitive decline and pathological performance. These tools are time-efficient since they can be completed within 10 minutes or less, and capture an array of cognitive abilities **[6, 7, 8]**. Despite criticism regarding lack of sensitivity to detect subtle cognitive changes **[9]**, cognitive screening tests are used by multiple disciplines including neurology, psychiatry, psychology, speech language pathology, and nursing; they serve as a common point of reference and facilitate collaboration and communication among professionals.

One limitation of global cognitive screening measures relates to their static nature. These tests were developed to measure performance at the time of testing and cannot be used to accurately capture cognitive change across time. Furthermore, despite the high prevalence and burden resulting from dementia, most health care systems have not established a standard of care for screening and periodic monitoring. Subsequently, information obtained from common cognitive screening tools reflects performance at the time of testing, without a historical context of the person's prior abilities or changes in cognitive or functional performance across time. Therefore, cognitive screening procedures should include contextual and historical information in addition to cognitive screening tests in order to make accurate clinical decisions.

Clinicians worldwide are encouraged to consider the WHO-ICF framework (World Health Organization [WHO], 2001) when selecting assessment methodologies. According to the ICF model, assessment should incorporate the individual's functioning and the context **[8]**. Structured questionnaires and informant reports that capture how the individual functions within the daily context can supplement neuropsychological test performance and improve the ecological validity of the assessment process [**10]**.

The Alzheimer Disease 8 (AD8) is a simple, sensitive and short informant-based tool that could assist in the screening of early stages of dementia **[11]**. The initial goal of the authors was to develop a sensitive and specific cognitive screening tool that is valid, easy to administer, and minimally time-consuming as formal neuropsychological assessments are time-consuming, costly, and not readily available in all clinical situations **[11]**. Galvin et al **[11]** proposed that combining the AD8 interview with brief psychometric tests boosts its ability to discern a cognitive impairment in people who do not meet formal clinical criteria for dementia, and the combined procedure is still short enough to be administered in everyday clinical practice. The AD8 includes eight questions asking the informant to assess change (Yes vs No) in memory, problem-solving abilities, orientation and daily activities. The number of Yes answers is summarized to obtain the AD8 score. It was developed using a longitudinal research sample as authors intended to test how well informants of "realworld" patients would rate the cognitive and functional abilities of patients compared to the Clinical Dementia Rating (CDR). Another goal was to investigate the ability of the AD8 to detect nonamnestic forms of dementia using informants from varied social and demographic backgrounds. AD8 can be used in primary care practice during the annual wellness visit and research **[12]**. Moreover it has been validated for use in emergency departments and other settings **[13]**.

The AD-8 was developed in English and has been validated in multiple languages, including Spanish, French, Portuguese, Norwegian, Chinese, Korean, Indonesian and Tagalog (Filipino) **[12]**. The AD-8 validation in both English

DOI 10.26386/obrela.v1i2.45 ISSN 2585-2795

and Korean, showed strong internal consistency (Cronbach's = 0.84–0.88), interrater reliability (0.82-0.89) and concurrent validity with the Clinical Dementia Rating scale and other neuropsychological tests **[11, 13]**. In another study, AD8 was used for the assessment of African-American older adults and reported good sensitivity and specificity by discriminating cognitively normal older adults from those with very mild dementia **[15]**.

The present study was part of the first nation-wide longitudinal project, the Neurocognitive Study on Aging (NEUROAGE, https://clinicaltrials.gov/ct2/show/NCT01481246) which investigates several aspects of aging, including neurocognitive and linguistic performance, psychosocial factors, biological markers, and quality of life in a large cohort of more than 800 older Greek-Cypriot adults. The aim of the present study was to provide preliminary data on the psychometric properties of the Greek-Cypriot version of the AD8 (CY-AD8) in a large cohort of community dwellers over the age of 60 who were living independently and did not have a diagnosis of dementia or MCI.

Method

Participants

Participants were recruited from the community and from social organizations for the elderly from all around Cyprus and were native Greek speakers (mainland Greek or Cypriot/Greek dialect). All participants resided independently at home at the time of participation. Informant reports were obtained for 182 study participants over the age of 60 (range = 60-99; mean = 71.24; SD = 7.34) who met the study inclusion/exclusion criteria as following: 1) native Greek speakers from Cyprus; 2) males and females over the age of 60; 3) good general health with no previous history of neurological pathology such as head trauma, epilepsy, stroke or neurodegenerative disorder; 4) No diagnosis of dementia or MCI and 5) absence of history of severe psychiatric or emotional disorder requiring hospitalization.

Measures

As part of the NEUROAGE project, participants were administered a battery of established neurocognitive and language tests, sensitive to cognitive decline **[16, 17, 18, 10]**. In the present study we analyzed data from the following screening tools:

General Cognitive Screening: Mini Mental State Examination (MMSE) **[19]**. We have used the validated Greek version of the test by Fountoukakis et al., 2000 **[4]**. A cut-off of 20 was used in the present analysis.

Depression Screening: Geriatric Depression Scale (GDS-15) **[20]**. A cut-off score of 6 is recommended in the literature and was incorporated in the present study.

Alzheimer Disease 8: The Alzheimer Disease 8 (AD8) **[11]**. For the purposes of the present project, the tool was translated and adapted from English into Greek. A blind backwards translation was conducted and the final version of the tool, the CY-AD8 was implemented in the study. The CY-AD8 instructs the informant to indicate whether there has been a change in the last years in 8 different domains due to cognitive difficulties, e.g. remembering appointments, managing finances, manipulating common objects, critical thinking and judgment, etc. Each positive response indicating a change was worth 1 point for a maximum total of 8 points.

Procedures

Study participants were tested at their social club, the Center for Applied Neuroscience at the University of Cyprus or at their home. Participants provided contact information and permission to contact the informant which was typically the spouse, the siblings, or an adult child. The AD-8 was administered either in person or over the phone at a convenient time for the informant. Time of administration was approximately 3 minutes.

Data and Analyses

The total number of points for the CY-AD8 was calculated for each participant. Internal consistency for the CY-AD8 was evaluated by calculating Cronbach's alpha. Independent samples

DOI 10.26386/obrela.v1i2.45 ISSN 2585-2795

t-test was used to investigate the presence of differences between those with high vs low scores on the CY-AD8 instrument. Additionally Pearson's correlation analyses were conducted to examine relationships between AD8 and MMSE measures.

Results

Informant reports on the CY-AD8 ranged from 0-8. The median score was 2. The internal consistency of the CY-AD8 was acceptable (Cronbach's α =0.827). The CY-AD8 total score correlated moderately and significantly with the MMSE (Pearson's r = -.524 p < .001).

Median split resulted in two groups based on the CY-AD8 symptom scores. An independent samples t-test was conducted to examine whether there was a significant difference between group 1 (CY-AD8 = 0-1) and group 2 (CY-AD8 = 2+) in relation to their performance on the MMSE. A statistically significant difference was revealed between the two groups t(176) = 5.53, p < .0001). Individuals in group 1 scored significantly higher (M=27.58, SD = 1.78) than individuals in group 2 (M= 25.71, SD= 2.59). The difference was about 2 points and greater than 1 standard deviation. Furthermore, individuals with more CY-AD8 symptoms were significantly older than those with almost no symptoms, t(176) = 5.04, p = .0001 by about 5 years (mean = 73.73, and SD = 7.85 mean = 68.52, SD = 5.62 respectively).

Conclusions

The CY-AD8 is a brief informant-based measure that can be implemented by health care professionals to obtain some preliminary information regarding functional abilities in activities of daily living. Informant reports of changes in two or more questions would warrant further neurocognitive assessment in order to determine the etiology and extend of the cognitive change. Our findings are in line with previous studies that support the classification of a score higher than 2 as a cutoff score and suggest that the use of the AD8 in conjunction with a brief cognitive assessment could improve diagnostic accuracy **[9]**.

Symptom reporting on the CY-AD8 was related to MMSE performance. Although the relationship is significant, it is a moderate relationship suggesting that the two measures can be used concurrently and that they are complimentary of each other. Specifically, individuals with high CY-AD8 symptoms still performed as a group within the normative range of the MMSE. However, their performance was in the lower end of normal. Brief cognitive tests such as the MMSE may help differentiate cognitively normal older adults from those with moderate dementia but MMSE and other brief tests lack the sensitivity and specificity to detect very mild impairment **[7, 11, 21, 22]**. Additionally, performance-based measures such as MMSE may not be able to detect or quantify change from previous levels of function, particularly in very high-functioning individuals. Therefore, information obtained by the CY-AD8 could provide information regarding subtle but significant changes in functioning that would be of clinical significance.

The present findings indicate that the Greek version (CY-AD8) has adequate internal consistency. Therefore, the CY-AD8 could be a useful screening tool for early detection of individuals who may be at risk for dementia and could be used to gain a preliminary understanding of an individual's cognitive status. Still further investigation is needed to explore the psychometric properties of this tool in Greek. Future research should also incorporate self-report data to determine congruency of the scores between the two versions (self and informant versions) in Greek. The current study used data from healthy older adults with varied educational and social-demographic backgrounds. Although some participants had low scores on the MMSE, none of them had a formal diagnosis of MCI or dementia. Future studies should incorporate adults diagnosed with MCI and early stage dementia in order to validate the CY-AD8.

DOI 10.26386/obrela.v1i2.45 ISSN 2585-2795

References

1 Wortmann, M.. Dementia: a global health priority-highlights from an ADI and World Health Organization report. Alzheimer's research & Therapy 2012, 4(5): 40. doi: 10.1186/alzrt143

2. Boustani, M., Peterson, B., Hanson, L., Harris, R., & Lohr, K. N.. Screening for dementia in primary care: a summary of the evidence for the US Preventive Services Task Force. Annals of internal medicine 2003, 138(11): 927-937. PMID: 12779304

3. Connolly, A., Gaehl, E., Martin, H., Morris, J., & Purandare, N. Underdiagnosis of dementia in primary care: variations in the observed prevalence and comparisons to the expected prevalence. Aging & mental health 2011, 15(8): 978-984. doi: 10.1080/13607863.2011.596805

4. Fountoulakis, K. N., Tsolaki, M., Chantzi, H., & Kazis, A. Mini mental state examination (MMSE): a validation study in Greece. American Journal of Alzheimer's Disease 2000, 15(6): 342-345. DOI 153331750001500604

5. Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., & Chertkow, H.. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society 2005, 53(4): 695-699. DOI: 10.1111/j.1532-5415.2005.53221.x

6. Smith, T., Gildeh, N., & Holmes, C. The Montreal Cognitive Assessment: validity and utility in a memory clinic setting. The Canadian Journal of Psychiatry 2007, 52(5:, 329-332. DOI: 10.1177/070674370705200508

7. Mitchell, A. J.. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. Journal of psychiatric research 2009, 43(4): 411-431. doi: 10.1016/j.jpsychires.2008.04.014.

8. Sanders, A., Nakase-Thomson, R., Constantinidou, F., Wertheimer, J., & Paul, D. Memory Assessment on an Interdisciplinary Rehabilitation Team: A Theoretically Based Framework. American Journal of Speech-Language Pathology 2007, 16: 316-330.

9. Galvin, J. E., Roe, C. M., Xiong, C., & Morris, J. C.. Validity and reliability of the AD8 informant interview in dementia. Neurology 2006, 67(11): 1942-1948. DOI: https://doi.org/10.1212/01.wnl.0000247042.15547.eb

10. Constantinidou, F., Christodoulou, M., & Prokopiou, J. The effects of age and education on executive functioning and oral naming performance in Greek Cypriot adults: the neurocognitive study for the aging. Folia Phoniatrica et Logopaedica 2012, 64(4): 187-198. https://doi.org/10.1159/000340015

1.1 Galvin, J. E., Roe, C. M., Coats, M. A., & Morris, J. C.. Patient's rating of cognitive ability: using the AD8, a brief informant interview, as a self-rating tool to detect dementia. Archives of Neurology 2007, 64(5): 725-730. doi:10.1001/archneur.64.5.725

12. Galvin, J. E., & Zweig, Y. The AD8: The Washington University Dementia Screening Test. Family Medicine 2013, 25(3): 367-382. doi: 10.3122/jabfm.2012.03.100181

13. Ryu, H. J., Kim, H. J., & Han, S. H.. Validity and reliability of the Korean version of the AD8 informant interview (K-AD8) in dementia. Alzheimer Disease & Associated Disorders 2009, 23(4): 371-376. DOI: 10.1097/WAD.0b013e31819e6881

14. Carpenter, C.R., DesPain, B., Keeling, T.N., Shah, M., & Rothenberger, N.. The Six-Item Screener and AD8 for the detection of cognitive impairment in geriatric emergency department patients. Annals of Emergency Medicine 2011, 57(6), 653-661. doi: 10.1016/j.annemergmed.2010.06.560.

15. Malmstrom, T. K., Miller, D. K., Coats, M. A., Jackson, P., Miller, J. P., & Morris, J. C. Informant-based dementia screening in a population-based sample of African Americans. Alzheimer disease and associated disorders 2009, 23(2): 117. PMID: 19484913

16. Greenlief, C. L., Margolis, R. B., & Erker, G. J. Application of the Trail Making Test in differentiating neuropsychological impairment of elderly persons. Perceptual and motor skills 1985, 61(3_suppl), 1283-1289.

17. Margolin, D. I., Pate, D. S., Friedrich, F. J., & Elia, E.. Dysnomia in dementia and in stroke patients: Different underlying cognitive deficits. Journal of Clinical and Experimental Neuropsychology 1990, 12(4): 597-612. http://dx.doi.org/10.1080/01688639008401004

18. Lezak, M. D. Neuropsychological assessment. Oxford University Press, USA. 2004

19. Folstein, M. F., Folstein, S. E., & McHugh, P. R.. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research 1975, 12(3): 189-198. PMID: 1202204

20. Fountoulakis, K. N., Tsolaki, M., Iacovides, A., Yesavage, J., O'Hara, R., Kazis, A., & Ierodiakonou, C. The validation of the short form of the Geriatric Depression Scale (GDS) in Greece. Aging Clinical and Experimental Research 1999, 11(6): 367-372. PMID: 10738851

21. Galvin, J. E., Roe, C. M., & Morris, J. C. Evaluation of cognitive impairment in older adults: combining brief informant and performance measures. Archives of neurology 2007, 64(5): 718-724. doi:10.1001/archneur.64.5.718

22. Galvin, J. E., Roe, C. M., Powlishta, K. K., Coats, M. A., Muich, S. J., Grant, E., & Morris, J. C. The AD8 A brief informant interview to detect dementia. Neurology 2005, 65(4): 559-564. DOI: https://doi.org/10.1212/01.wnl.0000172958.95282.2a

Dialogues in Clinical Neuroscience & Mental Health

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

Special article

Is there a connection between lithium induced hypothyroidism and lithium efficacy in bipolar disorder?

Orestis Giotakos

Abstract

Hypothyroidism, more commonly subclinical, appears a common abnormality, while the hypothalamic-pituitary-thyroid (HPT) axis abnormalities are quite common among patients with bipolar disorder. On the other hand, lithium has been used successfully in treating bipolar disorders, but lithium influence on the thyroid gland is one of the key side effects in the long-term therapy. Lithium administration leads to a decrease of production and release of thyroid hormones, which results in increased levels of thyroid stimulating factor (TSH), and excessive TSH response to stimulation with TRH. Inhibition of thyroid hormone release, a process mediated by cyclic adenosine monophosphate, appears to be the critical mechanism in the development of lithium-induced hypothyroidism. Lithium also inhibits thyroidal iodine uptake and iodotyrosine coupling, alters thyroglobulin structure, and interferes with the deiodination of T4 to T3, by inhibiting type-II deiodinase in the brain. Lithium may also demonstrate an immunostimulant effect, either by inducing, or by exacerbating a preexisting autoimmune disease. Additionally, lithium alters cellular responsiveness to thyroxine, and influences thyroid hormone receptor gene expression. Deficits in any one or more of these mechanisms may result in reduced bioavailability of thyroid hormones at cerebral target regions despite normal peripheral serum levels of thyroid hormones. Rethinking lithium mechanisms of action, and especially lithium induced hypothyroidism, may help to enhance our understanding of the thyroid-bipolar disorder connection. In the course of lithium therapy, excessive TSH response to TRH occurs in at least 50% of bipolar patients. This "disordered" thyroid-hypothalamic-pituitary axis seems to be temporary in most patients, which suggests that the axis is adjusting to the new «state» during therapy. Moreover, rapid cycling bipolar disorder is associated with a latent hypofunction of the HPT system, which becomes manifest even with short-term lithium challenge. Lithium-treatment exaggeration of TSH responses to TRH, indicate that lithium push forward these patients in a temporary "more hypo-thyroid" status". It is possible that the lithium induced 'central hypothyroidism' may enhance the HPT axis activation, resulting to the thyroid system re-activation, and to the thyroid hormones' availability and effect re-adaptation. This compensatory process may results to the correction of a possible peripheral resistance to thyroid hormones, as well as to the correction of an isolated CNS hypothyroidism. We may hypothesize that these compensatory mechanisms, which operate to prevent the development of hypothyroidism or goiter, represent a therapeutic process of lithium therapy in bipolar disorder, acting through a thyroid system resetting.

Key words: *thyroid hormones, hypothyroidism, thyroid, lithium, bipolar disorder.*

Corresponding Author: Orestis Giotakos, Psychiatrist (MD, MSc, PhD), Founder of the non-profit organization "obrela", Erifilis 2, 11634 Athens, Greece, Info@obrela.gr, www.obrela.gr

Received: January 2, 2018, Accepted: February 5, 2018

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

The thyroid hormones

Thyroid hormones are made from the amino acid tyrosine. T3 is the "active" version of the hormone. About one fifth of the hormone produced by thyroid gland comes out as T3. Cells in the brain, liver and some other organs take T4 from the bloodstream and convert it to T3 by removing one of the iodine atoms. The activity of specific thyroid hormone transporters, like monocarboxylate transporter, and the carrier transthyretin, is involved in determining intracellular concentrations of thyroid hormones via mediating their cellular influx and efflux [1]. Deiodinases control regional effectivity of T3 in concert with other mechanisms [2], that is, the local distribution of the different nuclear thyroid hormone receptors TRα and TRβ. As part of the nuclear superfamily of ligand-modulated transcription factors, thyroid hormones bind to nuclear receptors [3], where they control, and usually increase, gene expression influencing a broad array of metabolic processes [4]. Genes that are regulated by thyroid hormones are known to encode for proteins essential for important brain function such as myelin and neurotrophines. Non-genomic actions after binding to cytoplasmic thyroid hormone receptors include rapid activation of the phosphatidylinositol-3-protein kinase pathway and thereby achievement of vasodilatory and neuroprotective effects [5]. Thyroid hormone in general, regulates nuclear transcription of genes responsible for protein synthesis, increases cellular metabolism and growth rates, facilitates mental processes, increases endocrine gland activity, stimulates carbohydrate and fat metabolism, increases fatty acids, and also increases heart rate, respiration and muscle action. In parallel, thyroid hormones decreases body weight, as well as cholesterol, phospholipids, and triglycerides [4].

Thyroid hormones and affective disorders

Thyroid hormone receptors are widely distributed in the brain with high concentrations in the cerebral cortex, hippocampus and the amygdala, the latter being limbic structures that are implicated in the pathogenesis of mood disorders [6]. The regulation of thyroid hormone homeostasis in the brain underlies a complex interaction of different mechanisms, some of which overlap with mechanisms involved in affect regulation. A lack of thyroid hormones can lower the threshold for depression, while an excess can contribute to a state of tense dysphoria. Thyroid function in some persons also appears to influence the course of affective disorders. Adequate mobilization of thyroid hormones favors recovery from depression; excess mobilization increases the risk of mania in vulnerable individuals [7]. Although other mechanisms may be involved, evidence suggests that the modulation by thyroid hormones of the β-adrenergic receptor response to catecholamines may contribute to these effects. Norepinephrine stimulates such receptors and thyroid hormones increase their ability to receive stimulation. The plausibility of such interactions between catecholamines and thyroid hormones occurring in the CNS is strengthened by their common origin in the amino acid tyrosine and by their synergism in many metabolic processes [8]. Interactions of the thyroid and neurotransmitter systems, primarily norepinephrine and serotonin, which are generally believed to have a major role in the regulation of mood and behavior, contributes also to the mechanism of action in the developing and mature brain. In particular, there is robust evidence from animal research that thyroid hormones have a modulatory effect leading to an increase in serotonergic neurotransmission. Thyroid hormones also interact with other neurotransmitter systems involved in mood regulation, including dopamine postreceptor and signal-transducing processes, as well as gene regulatory mechanisms [9, 10].

Overt psychiatric disorder occurs in no more than 10% of the thyroid disordered patients [11]. The most common psychiatric symptoms related to hypothyroidism are depression and cognitive dysfunction [12], with possible underlying mechanism the dysregulation of CNS catecholamine receptor sensitivity or the disruption of circadian rhythms [13]. On the other hand, hyperthyroidism or thyrotoxicosis is usually associated with symptoms such as anxiety, depression, mood lability, and insomnia. Overt hyperthyroidism prevalence is no greater than 2% in bipolar patients [14], while much of this

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

has been attributed to lithium [15], which can induce thyrotoxicosis by autoimmune mechanisms or thyroiditis [16]. In addition, mixed affective states have been associated with reduced thyroid functioning [7] and a higher rate of positive anti-thyroid antibody titres, than other unipolar or bipolar subgroups, apparently unrelated to lithium treatment, although not all studies confirm this association [17].

The hypothesis that interactions between thyroid and neurotransmitter systems may have a causal role in the pathophysiology of mood disorders was originally proposed by Whybrow and Prange (1981) [8]. They suggested that the antidepressant properties of T3 could be explained by its augmentation of postsynaptic beta-adrenergic activity. Hypothyroidism was, thus, believed to cause depression by producing a functional decrease in noradrenergic transmission. The role of several neurotransmitter systems including norepinephrine (NE), serotonin (5-HT), dopamine (DA), and gamma aminobutyric acid (GABA) in the pathogenesis of mood disorders is now well established [18, 19, 20]. Interactions between thyroid hormones and these neurotransmitter systems may not only account for the psychiatric symptoms accompanying thyroid disease, but also for the hypothalamic-pituitary-thyroid (HPT) dysfunction in mood disorders, and the therapeutic actions of thyroid hormones in mood disorders [21]. The interactions between thyroid and neurotransmitter systems are often complex and reciprocal. NE stimulates both TRH and TSH release, while 5-HT, DA, and GABA inhibit their release [22, 23]. Evidence about the effect of thyroid hormones on neurotransmitters is mostly derived from animal studies. Such evidence principally consists of altered responsiveness of NE, 5-HT, DA, and GABA systems in the adult/mature brain, resulting from experimentally induced hypothyroid or hyperthyroid states [24].

The hypothalamic-pituitary-thyroid axis in affective disorders

The features of thyroid dysfunction in affective disorders have been indicated for many years. The activity of the thyroid gland and hypothalamic-pituitary-thyroid (HPT) axis seems to be important for the pathophysiology, clinical course and treatment of bipolar disorder. The most common abnormalities include features of subclinical or clinical hypothyroidism, with associated lower levels of thyroxine [25], and elevated levels of thyrotropin (thyreotropic stimulating hormone-TSH) [26].

The TSH is the most widely used test for detecting HPT dysfunction response to an intravenous dose of TSH. The response is usually exaggerated in hypothyroidism and blunted in hyperthyroidism. A blunted TSH response occurs in 25–30% of patients with unipolar major depression, in the form of decreased pituitary TSH secretion [27], and is far more common among patients with bipolar disorder, including those with mania, bipolar depression, and rapid cycling disorder [28, 29]. Moreover, the severity of mood symptoms and milder fluctuations in these symptoms has been found to correlate with blunted TSH responses to TRH [30]. However, many patients with bipolar disorder show an exaggerated response of TSH to TRH [31], along with elevated basal levels of TSH, especially in patients with rapid cycling, and this finding is consistent with the high prevalence of subclinical hypothyroidism often found in this condition [32]. All categories of HPT axis dysfunctions have been reported in rapid cycling bipolar patients, like overt hypothyroidism [33], elevated TSH levels [34], exaggerated TSH responses to TRH [35], elevated antibody titres [36], and antidepressant-induced rapid cycling [37], although a number of studies have been unable to document this association [38, 39]. Methodological problems such as retrospective designs, lack of controls, predominance of female subjects, and varying definitions of hypothyroidism have all hindered any consistent conclusions from these data [40]. Hypothyroidism in the course of bipolar disorder is a risk factor for the development of rapid cycling bipolar disorder and a relative thyroid hormone deficiency in bipolar disorder patients predisposes to rapid cycling course. Moreover, in many cases, thyroid abnormalities reveal shortly after the start of lithium treatment [41].

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

Lithium in affective disorders

Lithium is the lightest alkali metal and a monovalent cation. Lithium shares some properties with sodium, potassium, and calcium. Substitution or competition with other cations may contribute to its effects and many other factors may influence lithium levels. Lithium displaces magnesium ions and inhibits at least 10 cellular targets, all of which are components of intracellular signalling pathways. Lithium reduces 5-HT_2 receptor function in mouse [42] and in humans [43], and this may be linked to lithium's antidepressant action. This action seem to be mediated by the prefrontal cortex [44], which is believed to be the target of lithium in the treatment of bipolar disorder [45]. In general, lithium affects cell function via its inhibitory action on adenosine triphosphatase (ATPase) activity, cyclic adenosine monophosphate (cAMP), and intracellular enzymes. The inhibitory effect of lithium on inositol phospholipid metabolism affects signal transduction and may account for part of the action of the cation in manic depression. Lithium also alters the in vitro response of cultured cells to thyrotropin-releasing hormone (TRH) and can stimulate DNA synthesis. Based in the indications that both mania and bipolar depression are characterized by elevations of intracellular sodium concentrations, Huang et al (2007) [46] suggested that lithium can normalize abnormally elevated intracellular sodium levels and this may be an important mechanism of lithium action. Reduction of sodium influx is a proposed shared mechanism of action of effective mood stabilizers, but direct documentation of this effect for lithium has never been demonstrated [47].

Multiple interactions and overlapping systems are involved in regulating mood and the chronic administration of therapeutic doses of lithium affects the function of second messenger generating systems [48]. The initial studies of molecular targets for lithium action were based on the assumption that this simple cation can interfere with transporting systems for sodium and potassium in the plasma membranes of neurons and alter the propagation of electrical signals, while some studies indicated that the lithium inhibition of the counter-transport mechanism may be significant clinically and relevant to the lithium therapeutic action [49]. Alterations in neurotransmitter systems, such as noradrenaline, dopamine, glutamate, and serotonin have been noted in patient brains, as well as in animal models. These are closely connected with changes in corresponding signalling systems in membranes, the activities of the enzymes involved and the production of second messengers. In fact, lithium has been found to alter the brain cAMP level, cAMP-mediated processes in the CNS, and fluoride stimulated adenylyl cyclase activity [50]. In addition, the allosteric modulation of some proteins including G proteins has been suggested as the mechanism of the long-term prophylactic efficacy of lithium [48].

The theory that lithium ions might exert their therapeutically relevant effect at the site of the inositol-lipid signalling pathway has been widely discussed. The hypothesis has been postulated that the stimulated turnover of phosphatidylinositol-4,5-bisphosphate (PIP_2) reflects the increased receptor activation in pathogenic neurons. Berridge et al (1989) [51], suggested the "inositol depletion hypothesis", based on a presumption that in parts of the brain where receptors are overstimulated and PIP_2 hydrolysis thus occurs, lithium inhibits the dephosphorylation of inositol-1-phosphatase. Lithium has been shown to decrease the level of neuronal inositol through the inhibition of inositol monophosphatase (IMPase), which converts myo-inositol monophosphates to myo-inositol, to reconstitute the membrane phospholipids, PIP_2 pool. Eventually, the latter generates the Ca^{2+}-mobilizing second messenger D-myo-Inositol-1,4,5-trisphosphate ($InsP_3$) and diacylglycerol (DAG). The lithium-induced inositol depletion, and the consequent disturbance of the Ca^{2+} signaling operation, showed to affect the behavior of neurons in culture, impairing neurotransmission and altering growth cone and the cytoskeleton [51, 52].

Mood stabilizers lithium and valproic acid, used for treating bipolar disorder, cause cellular inositol depletion, which has been proposed as a therapeutic mechanism of action of both

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

drugs. As glycogen synthase kinase-3α (GSK-3α) inhibition has been proposed as a likely therapeutic mechanism of action, the finding that inhibition of inositol synthesis results in the inactivation of GSK-3α suggests a unifying hypothesis for mechanism of mood-stabilizing drugs. Inositol is an essential metabolite that serves as a precursor for inositol lipids and inositol phosphates. Ye & Greenberg (2015) [53] reported that inhibition of the rate-limiting enzyme of inositol synthesis leads to the inactivation of GSK-3α by increasing inhibitory phosphorylation of this kinase. These findings have implications for the therapeutic mechanisms of mood stabilizers and suggest that inositol synthesis and GSK 3α activity are intrinsically related. Lithium also affects some enzymes involved in energy metabolism, such as hexokinase, pyruvate kinase, cholinesterase, tryptophan hydroxylase, and glycogen synthetase [54]. Plenge (1985) [55] proposed the theory that lithium inhibits enzymes which have essential cofactor cations, such as Na+, K+, Ca2+, Mg2+, and Zn2+ by displacement of these cations from the enzyme. Lithium moves into the site vacated by the Mg2+ and the resulting enzyme-phosphate-lithium complex is very stable and in this conformation it cannot hydrolyse a further substrate molecule. Lithium competes for a magnesium binding site in inositol polyphosphate 1-phosphatase, glycogen synthase kinase-3, fructose 1,6-bisphosphatase, bisphosphate nucleotidase, and phosphoglucomutase [56].

Lithium and thyroid axis

Lithium treatment seems to contribute to the development of hypothyroidism among patients with rapid cycling [4]. Low or normal T4 levels and elevated TSH levels are reported among 5 to 35% (average of about 25%) patients on lithium [57]. The investigators hypothesized that rapid cycling bipolar disorder is associated with a latent hypofunction of the HPT system, which becomes manifest even with short-term lithium challenge. A latent hypofunction of the thyroid axis in rapid cycling bipolar disorder may also explain why high doses of T4 added to the established treatment with lithium and other psychotropic drugs can reverse the rapid cycling pattern [11]. Gyulai et al. (2003) [4] found that patients with rapid cycling did not differ from controls on any of thyroid function tests prior to treatment with lithium, but after 4 weeks of lithium-treatment, exaggerated TSH responses to TRH were significantly more common among such patients. The authors proposed that rapid cycling is associated with a latent hypofunction of the HPT system, which becomes manifest with lithium treatment. Given lithium's antithyroid actions, it is not surprising that an exaggerated TSH response to TRH stimulation is extremely common and has been reported in 50–100% of lithium-treated patients [58]. In addition, evidence of overt or subclinical hypothyroidism, including raised antibody titres, has often been found among patients with bipolar disorder, prior to treatment with lithium [59]. In summary, it appears that at least in a subgroup of patients with bipolar disorder, treatment with lithium, rather than inducing hypothyroidism, actually exacerbates a preexisting (overt) HPT dysfunction [15].

Lithium and thyroid antibodies

Disturbances of the immune system may be important for the pathogenesis of bipolar disorder. This was reflected as an increased incidence of thyroid antibodies (anti-TPO) in patients with bipolar disorder, compared with the control population [59]. Studies are similarly inconsistent as to whether thyroid antibodies are elevated in bipolar disorder, unrelated to lithium-treatment; reported rates range from 0 to 43% among patients with bipolar disorder not on lithium. Some controlled comparisons have reported a higher prevalence of thyroid antibodies in bipolar disorder, especially in depressed and mixed states [60], and rapid cycling bipolar patients [36]. Kupka et al (2002) [59] found thyroperoxidase antibodies in 64 of 226 (28%) outpatients with bipolar disorder, a rate higher than general population subjects and patients with other psychiatric disorders, while the presence of anti-thyroid antibodies among patients with bipolar disorder was associated with thyroid failure, but not with age, gender, mood state, rapid cycling, or lithium exposure.

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

However, other controlled studies have not been able to find a higher prevalence of raised antibody tires in bipolar disorder, unrelated to lithium treatment, and the authors suggested that autoimmune thyroiditis, with elevated levels of antibodies as a marker, should be considered as an endophenotype for bipolar disorder and should be associated with a genetic susceptibility to the development of the disease [60, 61, 62]. Significantly higher titers of anti-TPO has been found in daughters of parents with bipolar disorder, compared to control girls of high school age and young adults. Thus, the offspring of patients suffering from bipolar disorder was more susceptible to the development of thyroid autoimmunity, regardless of their susceptibility to the development of mental disorders [47, 63]. Finally, several studies of patients on lithium have found an elevated rate of anti-thyroid antibodies, ranging from about 8 to 49% in such patients; these rates were significantly higher than those among control patients or the general population [64]. However, an almost equal number of studies have failed to find an association between elevated antibody titres and exposure to lithium [65].

Despite some evidence suggesting that the increase in titers of thyroid antibodies could be stimulated by lithium, and that there may be a risk factor for the development of hypothyroidism during treatment with lithium, there is no particular reason for monitoring these antibodies during therapy with lithium. Many patients with positive anti-TPO antibodies remain in euthyroid state, on the other hand, the absence of these antibodies does not preclude the development of hypothyroidism or hyperthyroidism during treatment with lithium [47].

The lithium anti-thyroid effect

The influence of lithium on the thyroid gland is one of the most important side-effect of long-term therapy with this drug. The anti-thyroid effects of lithium carbonate are well documented [58, 66] and include goitre, hypothyroidism, hyperthyroidism and autoimmune thyroiditis. In a meta-analysis of the potential toxicity of long-term use of lithium, it has been found that lithium causes a five-fold increased risk of hypothyroidism [67]. Goiter, due to increased thyrotropin (TSH) after inhibition of thyroid hormone release, occurs at various reported incidence rates and is smooth and nontender. Cross-sectional studies of lithium-induced goitre reveal a prevalence of 0 to 60% [58]. Prevalence estimates are much higher (30–59%) when more sensitive ultrasonographic scans are used to detect increases in thyroid volumes [15]. As already mentioned, lithium therapy is associated with exaggerated response of both TSH and prolactin to TRH in 50%-100% of patients, although basal levels are not usually high. It is probable that the hypothalamic pituitary axis adjusts to a new setting in patients receiving lithium [58]. Subclinical and clinical hypothyroidism due to lithium is associated with circulating anti-thyroid peroxidase (TPO) antibodies but may occur in their absence. Iodine exposure, dietary goitrogens, and immunogenetic background may all contribute to the occurrence of goiter and hypothyroidism during long-term lithium therapy [64].

Rates of *overt hypothyroidism* vary from 0 to 47% (average of about 10%) among patients on long-term treatment with lithium [15, 68]. Differences in study design, definitions of hypothyroidism, age, gender, and geographical origin of patients, are often responsible for such wide variations in rates. Nevertheless, both the incidence and prevalence of overt hypothyroidism is significantly higher among patients on lithium, compared to general population figures [15]. The average duration of lithium therapy before the diagnosis of hypothyroidism is around 18 months, though there are a few reports of hypothyroidism occurring within the first few months of lithium-treatment [68, 69]. Female gender, middle age (>50 years), preexisting autoimmunity, and family history of thyroid diseases are established risk factors for lithium-induced hypothyroidism [70]. An even larger number of patients appear to develop *subclinical hypothyroidism*. Low or normal T4 levels and elevated TSH levels are reported among 5 to 35% (average of about 25%) patients on lithium [57], while exaggerated TSH responses are found among 50%, or more, of such patients. *Hyperthyroidism* in the course of lithium therapy is rare, but occurs more often than in the general popu-

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

lation. Treatment of patients with hyperthyroidism associated with lithium is dependent on the mechanism of its development. Usually, treatment with antithyroid drugs such as carbimazol alone or in combination with corticosteroids brings the best results. Toxic nodular goiter may require surgical intervention, particularly if there are symptoms of constriction in the neck [71].

Hypothyroidism and clinically and/or ultrasonographically detected goiter are the most prevalent thyroid abnormalities among patients on long term lithium therapy, while lithium induced hyperthyroidism is very infrequent. Lithium affects normal thyroid functioning through multiple mechanisms. Lithium is concentrated by the thyroid and inhibits thyroidal iodine uptake, inhibits iodotyrosine coupling, alters thyroglobulin structure, and inhibits thyroid hormone secretion. The mechanism of goiter formation has been explained by the inhibition by lithium of the synthesis and release of thyroid hormones, resulting in an increase of TSH level, leading to enlargement of the gland. At the cellular level, it decreases thyroid hormone synthesis and release. It also decreases peripheral deiodination of tetraiodothyronine (T4) or thyroxine by decreasing the activity of type I 5′ de-iodinase enzyme. Other proposed mechanisms of the proliferation of thyrocytes in patients treated with lithium is an activation of tyrosine kinase by lithium ion, and lithium effects on intracellular signaling connected with adenylate cyclase and Wnt/ beta-catenin [72]. In addition, lithium increases the propensity to thyroid autoimmunity in susceptible individuals due to its effect of augmenting the activity of B lymphocytes and reducing the ratio of circulating suppressor to cytotoxic T cells [73]. Lithium affects cell function via its inhibitory action on adenosine triphosphatase (ATPase) activity, cyclic adenosine monophosphate (cAMP), and intracellular enzymes. The inhibitory effect of lithium on inositol phospholipid metabolism affects signal transduction and may account for part of the action of the cation in manic depression. Lithium also alters the in vitro response of cultured cells to thyrotropin-releasing hormone (TRH) and can stimulate DNA synthesis [72].

Thyroid hormone replacement therapy

For many years, thyroid hormones have been used for augmentation of antidepressants in treatment-resistant depression both in the course of unipolar and bipolar illness. Debate continues as to whether to use T3, T4, or T3/T4 combination for mood purposes. Results of studies in which triiodothyronine (T3) was added in a dose of 25-50μg/d have showed a significant efficacy of such procedure. Noteworthy is also the effective use of mega-doses of thyroxine (T4), up to 400 μg/d, in refractory depression and in rapid cycling bipolar illness [74]. Among patients with bipolar disorder, supraphysiological doses of T4 have been used to supplement prophylactic efficacy of mood stabilizing treatments and to augment antidepressant treatment in patients with treatment-refractory bipolar depression [75]. The mechanisms underlying successful treatment with adjunctive T4 are as yet unclear. Earlier, it was suggested that adjunctive T4 counteracts the effects of subclinical hypothyroidism on neuronal adaptation [74].

However, contrary to this notion, most patients who responded had normal thyroid functions. This has led to several alternative hypotheses, such as correction of peripheral resistance to thyroid hormones, correction of isolated CNS hypothyroidism, and positive modulation of cathecholaminergic systems by T4, being responsible for this beneficial effect (Bauer et al, 1998, 2005). Bauer et al (2005) [76] found that treatment with supraphysiologic doses of L-T4 decreased relative activity in the subgenual cingulate cortex, thalamus, amygdala, hippocampus, dorsal and ventral striatum, and the cerebellar vermis. The decrease in relative activity in the latter brain regions was significantly correlated with reduction in depression scores. In a recent research, Bauer et al (2016) [77] assessed with PET cerebral glucose metabolism in depressive patients with bipolar disorder, before and after 6 weeks of treatment with levothyroxine (L-T4), and they found activation in the bilateral thalamus, amygdala, hippocampus, dorsal striatum and ventral striatum, and midline cerebellar vermis and subgenual cingulate cortex. The findings provided evidence that administration of supraphysiologic thyroid hormone improves depressive symptoms in

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

patients with bipolar disorder by modulating function in components of the anterior limbic network.

In depression, higher baseline concentration of thyroxine (T4) is associated with better effect of antidepressant drugs, and higher concentrations of T3 predisposed to a greater likelihood of recurrence of depression during initial few years of lithium treatment [47]. On the other hand, lower levels of free T4 were associated with a greater number of affective episodes and higher severity of depression during the first year of treatment with lithium. Patients treated with lithium who required intervention during an episode of depression had significantly higher level of TSH, compared to patients treated with lithium, who did not require intervention during depressive episode [47, 69, 78]. Current practice guidelines do not specify criteria for managing thyroid replacement therapy in patients with lithium-induced hypothyroidism. Usually the form that is used as a mood stabilizer is T4. By contrast, T3 is usually used as an "add-on" to antidepressants, because some research has shown it can boost the antidepressant's effects. In the presence of elevated TSH levels without clinical signs of hypothyroidism, some authorities advise monitoring serum TSH levels every 3 months without intervening with adjunctive thyroxine, unless TSH levels rise above 10 mU/L. Others advocate thyroid supplementation whenever TSH levels rise above normal, particularly in the presence of affective symptoms. T4 is generally preferred to T3 because the former tends to produce steadier hormone levels. Typically, thyroxine (T4) is begun at .025 mg, and increased by .025 mg every 3 to 6 weeks until TSH levels have normalized. In the presence of rapid cycling or persistent affective symptoms, thyroxine is increased until the serum T4 level is in the upper quartile of the normal reference range. Lithium-induced thyroid dysfunction has occasionally been shown to remain normalized after stopping T4 following 1-2 years of thyroid supplementation. Long-term or indefinite adjunctive treatment with thyroxine carries arrhythmogenic potential, as well as an increased risk for bone demineralization , requiring medical monitoring of patients at risk [79].

Summarizing, patients with lithium-induced goiter should be treated in a similar manner to other patients who developed goiter. Because levothyroxine may protect against the development of the goiter, and as previously mentioned, it may improve the effectiveness of treatment, it is reasonable to give it to patients with significant enlargement of the thyroid gland, especially if it is associated with symptoms of neck constriction. Bauer et al (2007) [79] argue that levothyroxine should be considered, if thyroid size exceeds the norm. Other authors recommend goiter treatment in order to prevent the development of nodules and autonomous regions, while some other authors suggest levothyroxine prophylaxis in all patients treated with lithium, if they come from iodine-deficient areas [80, 81]. The indications for supplementation of levothyroxine include: overt hypothyroidism, a significant enlargement of the gland, clear evidence suggesting subclinical hypothyroidism, rapid cycling bipolar disorder and poor efficacy of lithium [70]. It is recommended to start supplementation with low doses of levothyroxine (25-75 mg/d) if TSH>10mu/l, but it can be also performed with lower TSH values. During administration of levothyroxine, lithium therapy should not be interrupted and the dose of lithium changed unless serum concentration of lithium is beyond the therapeutic range [57]. During levothyroxine replacement therapy, the dose should be adjusted allowing not to suppress totally the secretion of TSH, and fT3 and fT4 levels (especially fT3) should be maintained within normal limits. Levothyroxine therapy is not effective in patients with goiter of long duration, where fibrotic changes have developed. If such treatment does not reduce the size of goiter, or symptoms of constriction are overwhelming, a surgery should be performed [47].

Can we hypothesize that the lithium induced hypothyroidism represents a therapeutic process of lithium therapy in bipolar disorder?

Approximately 10% of bipolar patients, with no evidence of thyroid dysfunction before lithium therapy, had elevated TSH basic values, while in the course of lithium therapy, excessive TSH response to TRH occurs in at least 50% of bipolar patients.

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

The disordered thyroid-hypothalamic-pituitary axis seems to be temporary in most patients, which suggests that the axis is adjusting to the new «state» during therapy [47]. In addition, lithium effect on the concentration of antithyroid antibodies leads to a faster autoimmunization of thyroid that can cause goiter and hypothyroidism, but hyperthyroidism is also possible. Baseline thyroid function tests should be measured prior to starting lithium therapy to ensure that undetected hypothyroidism is not contributing to mood symptoms. Pertinent thyroid function tests include TSH and free T4 levels, as well as antiperoxidase and antithyroglobulin in the presence of an elevated TSH. Subsequent monitoring of thyroid function tests is usually conducted 3 months after starting lithium and every 6-12 months thereafter. Lithium-induced hypothyroidism is usually reversible upon cessation of lithium, and the development of hypothyroidism is not a contraindication to continuing lithium, although, some experts advocate thyroid augmentation therapy [47].

The mechanisms by which lithium can cause hypothyroidism are complex. As already analyzed, inhibition of thyroid hormone release, a process mediated by cyclic adenosine monophosphate, appears to be the critical mechanism in the development of lithium-induced hypothyroidism. Also, lithium is concentrated by the thyroid gland and inhibits thyroidal iodine uptake. It also inhibits iodotyrosine coupling, alters thyroglobulin structure, and interferes with the deiodination of T4 to T3 by inhibiting type-II deiodinase in the brain [58]. Lithium may also demonstrate an immunostimulant effect, either by inducing, or by exacerbating a preexisting autoimmune disease. Additionally, lithium alters cellular responsiveness to thyroxine, and influences thyroid hormone receptor gene expression [82]. Deficits in any one, or several, of these mechanisms may result in reduced bioavailability of thyroid hormones at cerebral target regions despite normal peripheral serum levels of thyroid hormones. This condition has been conceptualized as 'central hypothyroidism' [47]. Compensation for this putative 'central hypothyroidism' might be one reason why a proportion of euthyroid depressed patients benefit from administration of supraphysiologic doses of L-T4. Mice suffering from central hypothyroidism caused by a mutation of the *TRα1* gene [83], showed reduced neuronal density, resulting in reduced cortical thickness in the hippocampal CA1 region [84]. Behaviorally, these mice show increases in surrogate animal markers for depression and anxiety, as well as an increased startle response. Both the behavioral and neural density measures normalized with thyroid hormone administration [85]. Compensatory mechanisms may operate to prevent the development of hypothyroidism or goitre in the majority of patients with lithium-induced impairments in thyroxine secretion. However, when additional risk factors such as iodine deficiency, preexisting autoimmunity, or genetic vulnerability are present, such compensatory mechanisms fail and hypothyroidism eventually ensues [15].

At the moment, the fine details of the pharmacological and toxicological mechanisms of the effects of lithium remain poorly understood [50, 86, 87]. Various studies suggest that some harmful effects of lithium could be related to oxidative stress [47, 88], whereas at therapeutic concentration lithium was found to confer protection against toxic stimuli inducing oxidative stress and apoptosis [89, 90, 90, 91]. Even in trace amounts, as occurs in drinking water, lithium has been inversely related to suicidal mortality, aggression and homicidal violence [92, 93, 94]. It has been found also that chronic administration of lithium significantly changes the expression of a number of genes in rat brains [95, 96]. Lithium responders seem to have some genes different from healthy controls and patients with bipolar disorder who respond well to lithium prophylaxis may constitute a biologically distinct subgroup [97, 98, 99].

Rethinking lithium mechanisms of action, and especially lithium positive and side-effects in thyroid gland, may help to enhance our understanding of the thyroid-bipolar disorder connection and to identify those patients with bipolar disorders who are most likely to benefit from therapeutic manipulations of the HPT axis. As mentioned above, the disordered thyroid-hypothalamic-pituitary axis seems to be temporary in most patients, which suggests that the axis is adjusting to

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

the new «state» during therapy [47]. Also, the TSH response is usually exaggerated in hypothyroidism and blunted in hyperthyroidism. A blunted TSH response occurs in 25–30% of patients with unipolar major depression, [27], but many patients with bipolar disorder show an exaggerated response of TSH to TRH, along with elevated basal levels of TSH, especially in patients with rapid cycling, a finding consistent with the high prevalence of subclinical hypothyroidism often found in this condition [32]. Hypothyroidism in the course of bipolar disorder is a risk factor for the development of rapid cycling bipolar disorder and a relative thyroid hormone deficiency in bipolar disorder patients predisposes to rapid cycling course, while in many cases, thyroid abnormalities reveal shortly after the start of lithium treatment [41]. Rapid cycling bipolar disorder is associated with a latent hypofunction of the HPT system, which becomes manifest even with short-term lithium challenge. Lithium-treatment exaggerates TSH responses to TRH, which indicate that lithium seems like to push forward these patients in a temporary "more hypo-thyroid" status". It is possible that this lithium induced 'central hypothyroidism', by the reduced bioavailability of thyroid hormones at cerebral target regions, may provoke a secondary activation of the HPT axis, in order the thyroid system to be re-activated and re-arranged.

Finally, T4 added to the established treatment with lithium and other psychotropic drugs can reverse the rapid cycling pattern [11]. Possibly T4 counteracts the effects of subclinical hypothyroidism on neuronal adaptation [74], through the correction of peripheral resistance to thyroid hormones and the correction of isolated CNS hypothyroidism [76]. The dose of T4 should be adjusted allowing not to suppress totally the secretion of TSH, and fT3 and fT4 levels, while lithium-induced thyroid dysfunction has been shown to remain normalized after stopping T4 following 1-2 years of thyroid supplementation. It may occur a hypothalamic pituitary axis "adjustment to a new setting" in patients receiving lithium [58, 100]. It is possible also that lithium effect is synergistic with that of T4, which has been also used as a mood stabilizer. In this frame, lithium induced "hypothyroidism" may help to rearrange and normalize thyroid hormone secretion. It is possible that the lithium induced 'central hypothyroidism' may enhance the HPT axis activation, resulting to the thyroid system re-activation, and to the thyroid hormones' availability and effect re-adaptation. This compensatory process may results to the correction of a possible peripheral resistance to thyroid hormones, as well as to the correction of an isolated CNS hypothyroidism. We can hypothesize that these compensatory mechanisms, which operate to prevent the development of hypothyroidism or goiter, represents a therapeutic process of lithium therapy in bipolar disorder, acting through an adaptive thyroid system resetting.

References

1 Friesema EC, Grueters A, Biebermann H, Krude H, von Moers A, Reeser M et al. Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation. *Lancet* 2004, 364: 1435–1437, , PMID: 15488219, DOI: 10.1016/S0140-6736(04)17226-7

2 Visser TJ. Thyroid hormone transporters. *Horm Res* 2007, 68: 28–30, PMID: 18174701, DOI: 10.1159/000110469

3 Lechan RM, Toni R. Thyroid hormones in neural tissue. In: Pfaff DW, Arnold AP, Etgen AM, Fahrbach SE, Rubin RT. *Hormones, Brain and Behavior*. Academic Press: San Diego, 2002, pp 157–238.

4 Gyulai L, Bauer M, Bauer MS, García-España F, Cnaan A, Whybrow PC. Thyroid hypofunction in patients with rapid-cycling bipolar disorder after lithium challenge. *Biological Psychiatry* 2003, 53(10):899–905, PMID: 12742677

5 Hiroi Y, Kim HH, Ying H, Furuya F, Huang Z, Simoncini T et al. Rapid nongenomic actions of thyroid hormone. *Proc Natl Acad Sci USA* 2006, 103: 14104–14109, PMID: 16966610 PMCID: PMC1599919, DOI: 10.1073/pnas.0601600103

6 Williams GR. Neurodevelopmental and neurophysiological actions of thyroid hormone. J Neuroendocrinol 2008; 20: 784–794, PMID: 18601701 , DOI: 10.1111/j.1365-2826.2008.01733.x

7 Chang KD, Keck PE, Stanton SP, McElroy SL, Strakowski SM, Geracioti TD. Differences in thyroid function between bipolar manic and mixed states. *Biological Psychiatry* 1998, 43(10):730–733, PMID: 9606526

8 Whybrow Peter C., Prange Jr Arthur J., A Hypothesis of Thyroid-Catecholamine-Receptor InteractionIts Relevance to Affective Illness. *Arch Gen Psychiatry* 1981, 38(1):106-113, PMID: 6257196

9 Yen PM, Brent GA. Genomic and nongenomic actions of thyroid hormones. In: Braverman LE, Cooper DS (eds) Werner & Ingbar's *The Thyroid. A Fundamental and Clinical Text*, Williams & Wilkins: Philadelphia, 2013 p 127–138.

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

10 Chakrabarti S. Thyroid Functions and Bipolar Affective Disorder, *J Thyroid Res* 2011, 2011**:** 306-367, PMID: 21808723 PMCID: PMC3144691 , DOI: 10.4061/2011/306367

11 Bauer M, Goetz T, Glenn T, Whybrow PC. The thyroid-brain interaction in thyroid disorders and mood disorders. *Journal of Neuroendocrinology* 2008, 20(10):1101–1114, PMID: 18673409 , DOI: 10.1111/j.1365-2826.2008.01774.x

12 Bunevičius R, Prange AJ. Thyroid disease and mental disorders: cause and effect or only comorbidity? *Current Opinion in Psychiatry* 2010, 23(4):363–368, doi: 10.1097/YCO.0b013e3283387b50

13 Stowell CP, Barnhill JW. Acute mania in the setting of severe hypothyroidism. *Psychosomatics* 2005, 46(3):259–261. PMID: 15883148, DOI: 10.1176/appi.psy.46.3.259

14 Ezzaher A, Neffati F, Mechri A, Douki W, Gaha L, Najjar MF. Evaluation of thyroid function in bipolar patients. *Clinical Chemistry and Laboratory Medicine* 2009, 47(S1, article S371)

15 Bocchetta A, Loviselli A. Lithium treatment and thyroid abnormalities. *Clinical Practice and Epidemiology in Mental Health* 2006, 2, article 23, PMID: 16968542 , PMCID: PMC1584230 , DOI: 10.1186/1745-0179-2-23

16 Carmaciu CD, Anderson CS, Lawton CA. Thyrotoxicosis after complete or partial lithium withdrawal in two patients with bipolar affective disorder. *Bipolar Disorders* 2003, 5(5):381–384. PMID: 14525561

17 Cassidy F, Ahearn EP, Carroll BJ. Thyroid function in mixed and pure manic episodes. *Bipolar Disorders,* 2002;4(6):393–397, PMID: 12519099

18 Rot MAH, Mathew SJ, Charney DS. Neurobiological mechanisms in major depressive disorder. *CMAJ* 2009, 180(3):305–313. PMID: 19188629, PMCID: PMC2630359, DOI: 10.1503/cmaj.080697

19 Diehl DJ, Gershon S. The role of dopamine in mood disorders. *Comprehensive Psychiatry* 1992, 33(2):115–120.

20 Brambilla P, Perez J, Barale F, Schettini G, Soares JC. GABAergic dysfunction in mood disorders. *Molecular Psychiatry* 2003, 8(8):721–737, PMID: 12888801 , DOI: 10.1038/sj.mp.4001362

21 Bauer M, Heinz A, Whybrow PC. Thyroid hormones, serotonin and mood: of synergy and significance in the adult brain. *Molecular Psychiatry* 2002, 7(2):140–156. PMID: 11840307, DOI: 10.1038/sj.mp.4000963.

22 Abrahamson MJ, Millar RP. Regulation of thyrotrophin secretion. *South African Medical Journal* 1986, 70(8):476–478.

23 Mason GA, Garbutt JC, Prange AJ., Jr. Thyrotropin-releasing hormone. Focus on basic neurobiology. In: Bloom FE, Kupfer DJ, (ed). *Psychopharmacology: The Fourth Generation of Progress*. New York, NY, USA: Raven Press; 1995. pp. 493–503.

24 Strawn JR, Ekhator NN, D'Souza BB, Geracioti TD. Pituitary-thyroid state correlates with central dopaminergic and serotonergic activity in healthy humans. *Neuropsychobiology* 2004, 49(2):84–87. doi.org/10.1159/000076415

25 Rybakowski J, Sowiński J. Free-thyroxine index and absolute free-thyroxine in affective disorders. *Lancet* 1973, 7808: 889, PMID: 4123441

26 Ezzaher A, Haj Mouhamed D, Mechri A, Neffati F, Douki W, Gaha L. i wsp. Thyroid function and lipid profile in bipolar I patients. *Asian J. Psychiatr* 2011, 4: 139–143, PMID: 23051081 DOI: 10.1016/j.ajp.2011.02.002

27 Linkowski P, Brauman H, Mendlewicz J. Thyrotrophin response to thyrotrophin-releasing hormone in unipolar and bipolar affective illness. *J. Affect. Disord* 1981; 3: 9–16.

28 Rush AJ, Giles DE, Schlesser MA, et al. Dexamethasone response, thyrotropin-releasing hormone stimulation, rapid eye movement latency, and subtypes of depression. *Biological Psychiatry* 1997, 41(9):915–928.

29 Sack DA, James SP, Rosenthal NE, Wehr TA. Deficient nocturnal surge of TSH secretion during sleep and sleep deprivation in rapid-cycling bipolar illness. *Psychiatry Research* 1988, 23(2):179–191.

30 Larsen JK, Faber J, Christensen EM, Bendsen BB, Solstad K, Gjerris A. Relationship between mood and TSH response to TRH stimulation in bipolar affective disorder. *Psychoneuroendocrinology* 2004, 29: 917–924. PMID: 15177707, DOI: 10.1016/j.psyneuen.2003.08.004

31 Kirkegaard C, Faber J. The role of thyroid hormones in depression. *European Journal of Endocrinology* 1998, 138(1):1–9.

32 Hendrick V, Altshuler L, Whybrow P. Psychoneuroendocrinology of mood disorders: the hypothalamic-pituitary- thyroid axis. *Psychiatric Clinics of North America* 1998, 21(2):277–292.

33 Khouzam HR, Bhat VG, Boyer J, Hardy W. Rapid cycling in a patient with bipolar mood disorder secondary to Graves' disease. *American Journal of Psychiatry* 1991, 148(9):1272–1273.

34 Bauer MS, Whybrow PC. Rapid cycling bipolar affective disorder. II. Treatment of refractory rapid cycling with high-dose levothyroxine: a preliminary study. *Arch. Gen. Psychiatry* 1990, 47: 435–440.

35 Kusalic M. Grade II and grade III hypothyroidism in Rapid-Cycling bipolar patients. *Neuropsychobiology* 1992, 25(4):177–181.

36 Oomen HAPC, Schipperijn AJM, Drexhage HA. The prevalence of affective disorder and in particular of a rapid cycling of bipolar disorder in patients with abnormal thyroid function tests. *Clinical Endocrinology* 1996, 45(2):215–223.

37 Kiriike N, Izumiya Y, Nishiwaki S, Maeda Y, Nagata T, Kawakita Y. TRH test and DST in schizoaffective mania, mania, and schizophrenia. *Biological Psychiatry* 1988, 24(4):415–422.

38 Maj M, Magliano L, Pirozzi R, Marasco C, Guarneri M. Validity of rapid cy-

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

cling as a course specifier for bipolar disorder. *American Journal of Psychiatry* 1994,151(7):1015–1019.

39 Post RM, Kramlinger KG, Joffe RT, et al. Rapid cycling bipolar affective disorder: lack of relation to hypothyroidism. *Psychiatry Research* 1997,72(1):1–7.

40 Bernal J. Action of thyroid hormone in brain. *J Endocrinol Invest* 2002, 25: 268–288, PMID: 11936472 , DOI: 10.1007/BF03344003

41 Cole DP, Thase ME, Mallinger AG, Soares JC, Luther JF, Kupfer DJ. Slower treatment response in bipolar depression predicted by lower pretreatment thyroid function. *Am. J. Psychiatry* 2002, 159: 116–121. PMID: 11772699, DOI: 10.1176/appi.ajp.159.1.116

42 Goodwin GM, DeSouza RJ, Wood AJ, Green AR. Lithium decreases 5-HT1A and 5-HT2 receptor and α2-adrenoreceptor mediated function in mice. *Psychopharmacology* 1986, 90:482–487.

43 Friston KJ, Sharpley AL, Solomon RA, Cowen PJ. Lithium increases slow wave sleep: possible mediation by brain 5-HT2 receptors? *Psychopharmacology (Berl.)* 1989, 98:139–140.

44 González-Maeso J, et al. Hallucinogens recruit specific cortical 5-HT(2A) receptor-mediated signaling pathways to affect behavior. *Neuron* 2007, 53:439–452, PMID: 17270739, DOI: 10.1016/j.neuron.2007.01.008

45 Schloesser RJ, Martinowich K, Manji HK. Mood-stabilizing drugs: mechanisms of action. *Trends Neurosci* 2012, 35:36–46, PMID: 22217451 , DOI: 10.1016/j.tins.2011.11.009

46 Huang X, Lei Z, El-Mallakh RS. Lithium normalizes elevated intracellular sodium. *Bipolar Disord* 2007, 9(3):298-300. PMID: 17430305, DOI: 10.1111/j.1399-5618.2007.00429.x

47 Kraszewska A, Abramowicz M, Chłopocka-Woźniak M, Sowiński J, Rybakowski J. The effect of lithium on thyroid function in patients with bipolar disorder. *Psychiatr. Pol* 2014, 48(3): 417–428, PMID: 25204089.

48 Manji H.K., Potter W.Z., Lenox R.H.: Signal transduction pathways. Molecular targets for lithium actions. *Arch. Gen. Psychiatry* 1995, 52: 531-543,

49 Gallicchio V.S.: Transport of the lithium ion. In: Bach R.O. and V.C. Gallicchio (eds.): *Lithium and cell physiology*. Springer Verlag 1990, pp. 47-57.

50 Shaldubina, A., Agam, G. & Belmaker, R. H. *The mechanism of lithium action: state of the art, ten years later. Prog. Neuropsychopharmacol. Biol. Psychiatry* 2001, 25: 855–866, PMID: 11383981

51 Berridge, M. J. *Inositol trisphosphate, calcium, lithium, and cell signalling. J. Am. Med. Asso*, 1989, 262: 1834–1841, PMID: 2674489

52 Williams, R. et al. *A molecular cell biology of lithium. Biochem. Soc. Trans* 2004, 32: 799–802, PMID: 15494019 , DOI: 10.1042/BST0320799

53 Ye C, Greenberg ML. Inositol synthesis regulates the activation of GSK-3α in neuronal cells. *J Neurochem* 2015, 33(2):273-83. doi: 10.1111/jnc.12978.

54 Geisler A. and Mork A.: The interaction of lithium with magnesium-dependent enzymes. In: In: Bach R.O. and Gallicchio V.C. (eds.): *Lithium and Cell Physiology*. Springer Verlag 1990, pp.125-136.

55 Plenge P.: Lithium effects on brain energy metabolism. In: Gabay S., J. Harris, B.T. Ho (eds.): *Metal Ions in Neurology and Psychiatry,* Alan R. Liss, Inc. New York 1985, pp. 153-164.

56 Gould T.D., Zarate C.A., Manji H.K.: Glycogen synthase kinase-3: a target for novel bipolar disorder treatments. *J. Clin. Psychiatry* 2004, 65: 10-21. PMID: 14744163.

57 Kleiner J, Altshuler L, Hendrick V, Hershman JM. Lithium-induced subclinical hypothyroidism: review of the literature and guidelines for treatment. *Journal of Clinical Psychiatry* 1999, 60(4):249–255. PMID: 10221287

58 Lazarus JH. The effects of lithium therapy on thyroid and thyrotropin-releasing hormone. *Thyroid* 1998, 8(10):909-13, PMID: 9827658 , DOI: 10.1089/thy.1998.8.909

59 Kupka RW, Nolen WA, Post RM, McElroy SL, Altshuler LL, Denicoff KD. High rate of autoimmune thyroiditis in bipolar disorder: lack of association with lithium exposure. *Biol. Psychiatry* 2002, 51: 305–311. PMID: 11958781

60 Haggerty JJ, Jr., Silva SG, Marquardt M, et al. Prevalence of antithyroid antibodies in mood disorders. *Depression and Anxiety* 1997, 5(2):91–96], PMID: 9262939

61 Hornig M, Amsterdam JD, Kamoun M, Goodman DBP. Autoantibody disturbances in affective disorders: a function of age and gender? *Journal of Affective Disorders* 1999, 55(1):29–37.

62 Vonk R, van der Schot AC, Kahn RS, Nolen WA, Drexhage HA. Is autoimmune thyroiditis part of the genetic vulnerability (or an endophenotype) for bipolar disorder? *Biol. Psychiatry* 2007, 62(2): 135–140. PMID: 17141745, DOI: 10.1016/j.biopsych.2006.08.041

63 Hillegers MH, Reichart CG, Wals M, Verhulst FC, Ormel J, Nolen WA. i wsp. Signs of a higher prevalence of autoimmune thyroiditis in female offspring of bipolar parents. *Eur. Neuropsychopharmacol* 2007, 17: 394–399.

64 Ozsoy S, Mavili E, Aydin M, Turan T, Esel E. Ultrasonically determined thyroid volume and thyroid functions in lithium-naïve and lithium-treated patients with bipolar disorder: a cross-sectional and longitudinal study. *Human Psychopharmacology* 2010, 25(2):174–178. PMID: 20196184 , DOI: 10.1002/hup.1093

65 Baethge C, Blumentritt H, Berghöfer A, et al. Long-term lithium treatment and thyroid antibodies: a controlled study. *Journal of Psychiatry and Neuroscience* 2005, 30(6):423–427, PMID: 16327876, PMCID: PMC1277025

66 Livingstone C, Rampes H. Lithium: a review of its metabolic adverse effects. J. *Psychopharmacol* 2006, 20: 347–355, PMID: 16174674 , DOI: 10.1177/0269881105057515

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

67 McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. *Lancet* 2012, 379: 721–728, PMID: 22265699 , DOI: 10.1016/S0140-6736(11)61516-X

68 Johnston AM, Eagles JM. Lithium-associated clinical hypothyroidism. Prevalence and risk factors. *British Journal of Psychiatry* 1999, 175:336–339.] , PMID: 10789300

69 Frye MA, Denicoff KD, Bryan AL, Smith-Jackson EE, Ali SO, Luckenbaugh D. i wsp. Association between lower serum free T4 and greater mood instability and depression in lithium-maintained bipolar patients. *Am. J. Psychiatry* 1999, 156: 1909–1914. PMID: 10588404, DOI: 10.1176/ajp.156.12.1909

70 Ozpoyraz N, Tamam L, Kulan E. Thyroid abnormalities in lithium-treated patients. *Advances in Therapy* 2002, 19(4):176–184, PMID: 12431043

71 Lazarus J, Richards A, Adison G, Owen G. Treatment of thyrotoxicosis with lithium carbonate. *Lancet* 1974, 2: 1160–168, PMID: 4139588

72 Lazarus JH, Kirov G, Harris B. Effect of lithium on thyroid and endocrine glands. In : Bauer M, Grof P, Müller-Oerlinghausen B. *Lithium in neuropsychiatry.* Oxfordshire: Informa Healthcare, 2006. s. 259–270.

73 Kibirige D, Luzinda K, Ssekitoleko R. Spectrum of lithium induced thyroid abnormalities: a current perspective. *Thyroid Res* 2013, 6(1):3., PMID: 23391071, PMCID: PMC3568739 , DOI: 10.1186/1756-6614-6-3

74 Bauer M, Whybrow PC. Thyroid hormone, brain, and behaviour. In: Pfaff DW, Arnold AP, Etgen AM, Fahrbach SE, Rubin RT, editors. *Hormones, Brain and Behavior*. New York, NY, USA: Academic Press; 2002. pp. 238–264.

75 Kelly T, Lieberman DZ. The use of triiodothyronine as an augmentation agent in treatment-resistant bipolar II and bipolar disorder NOS. *Journal of Affective Disorders* 2009, 116(3):222–226, PMID: 19215985 , DOI: 10.1016/j.jad.2008.12.010

76 Bauer M, London ED, Rasgon N, et al. Supraphysiological doses of levothyroxine alter regional cerebral metabolism and improve mood in bipolar depression. *Molecular Psychiatry* 2005, 10(5):456–469, PMID: 15724143 , DOI: 10.1038/sj.mp.4001647

77 Bauer M, Berman S, Stamm T, Plotkin M, Adli M, Pilhatsch M, London ED, Hellemann GS, Whybrow PC and Schlagenhauf F. Levothyroxine effects on depressive symptoms and limbic glucose metabolism in bipolar disorder: a randomized, placebo-controlled positron emission tomography study. *Molecular Psychiatry* 2016, 21: 229–236;. PMID: 25600111, PMCID: PMC4790155 , DOI: 10.1038/mp.2014.186

78 Frye MA, Yatham L, Ketter TA, Goldberg J, Suppes T, Calabrese JR. Depressive relapse during lithium treatment associated with increased serum thyroid-stimulating hormone: results from two placebo-controlled bipolar maintenance studies. *Acta Psychiatr. Scand.* 2009, 120: 10–13. PMID: 19183414, DOI: 10.1111/j.1600-0447.2008.01343.x

79 Bauer M, Blumentritt H, Finke R, Schlattmann P, Adli M, Baethge C. i wsp. Using ultrasonography to determine thyroid size and prevalence of goiter in lithium-treated patients with affective disorders. J. *Affect. Disord* 2007, 104: 45–51. DOI: 10.1016/j.jad.2007.01.033

80 Martino E, Placidi GF, Sardano G, Mariotti S, Fornaro P, Pinchera A. i wsp. High incidence of goiter in patients treated with lithium carbonate. *Ann. Endocrinol*. 1982, 43: 269–276, PMID: 6818894

81 Hegedüs L, Bonnema SJ, Bennedbaek FN. Management of simple nodular goiter: current status and future perspectives. *Endocr. Rev*. 2003, 24: 102–132, PMID: 12588812, DOI: 10.1210/er.2002-0016

82 Hahn CG, Pawlyk AC, Whybrow PC, Tejani-Butt SM. Differential expression of thyroid hormone receptor isoforms by thyroid hormone and lithium in rat GH3 and B103 cells. *Biological Psychiatry* 1999, 45(8):1004–1012, PMID: 10386183

83 Venero C, Guadano-Ferraz A, Herrero AI, Nordstrom K, Manzano J, de Escobar GM et al. Anxiety, memory impairment, and locomotor dysfunction caused by a mutant thyroid hormone receptor alpha1 can be ameliorated by T3 treatment. *Genes Dev* 2005, 19: 2152–2163.

84 Alva-Sanchez C, Ortiz-Butron R, Pacheco-Rosado J. Kainic acid does not affect CA3 hippocampal region pyramidal cells in hypothyroid rats. *Brain Res Bull* 2004, 63: 167–171. DOI: 10.1016/j.brainresbull.2004.02.002

85 Pilhatsch M, Winter C, Nordstrom K, Vennstrom B, Bauer M, Juckel G. Increased depressive behaviour in mice harboring the mutant thyroid hormone receptor alpha 1. *Behav Brain Res* 2010; 214: 187–192, PMID: 20580649 , DOI: 10.1016/j.bbr.2010.05.016

86 Hill, E. J. et al. *Effects of lithium and valproic acid on gene expression and phenotypic markers in an NT2 neurosphere model of neural development*. *PLoS One* 2013, 8, e58822 , doi: 10.1371/journal.pone.0058822.

87 Ruocco N, Costantini M, Santella L New insights into negative effects of lithium on sea urchin *Paracentrotus lividus* embryos, *Scientific Reports* 2016, 6: 32157, PMID: 27562248 , PMCID: PMC4999890 , DOI: 10.1038/srep32157

88 Efrati, S. et al. *N-Acetylcysteine ameliorates lithium-induced renal failure in rats. Nephrol. Dial. Transplant*. 2005, 20: 65–70, PMID: 15546888, DOI: 10.1093/ndt/gfh573

89 Chalecka-Franaszek, E. & Chuang, D. M. *Lithium activates the serine/threonine kinase Akt-1 and suppresses glutamate-induced inhibition of Akt-1 activity in neurons*. *Proc. Natl. Acad. Sci. USA* 1999, 96: 8745–8750. PMID: 10411946 PMCID: PMC17587

90 Lai, J. S., Zhao, C., Warsh, J. J. & Li, P. P. *Cytoprotection by lithium and valproate varies between cell types and cellular stresses*. *Eur. J. Pharmacol*. 2006, 539: 18–26. PMID: 16678157 , DOI: 10.1016/j.ejphar.2006.03.076

91 Shao, L., Young, L. T. & Wang, J. F. *Chronic treatment with mood stabilizers lithium and valproate prevents excitotoxicity by inhibiting oxidative stress in rat cerebral cortical cells*. *Biol. Psychiatry* 2005, 58: 879–884. PMID: 16005436, DOI: 10.1016/j.biopsych.2005.04.052

92 Giotakos O, Nisianakis P, Tsouvelas G, Giakalou VV. Lithium in the public

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

water supply and suicide mortality in Greece. *Biol Trace Elem Res* 2013, 56(1-3):376-9. doi: 10.1007/s12011-013-9815-4. PMID: 24072668 DOI: 10.1007/s12011-013-9815-4

93 Giotakos O, Tsouvelas G, Nisianakis P, Giakalou V, Lavdas A, Tsiamitas C, Panagiotis K, Kontaxakis V. A negative association between lithium in drinking water and the incidences of homicides, in Greece. *Biol Trace Elem Res* 2015, 164(2):165-8. doi: 10.1007/s12011-014-0210-6. PMID: 25556933, DOI: 10.1007/s12011-014-0210-6

94 Giotakos O. Lithium: Implications for Neuropsychiatry and Wellness. *Int J Ment Health Psychiatry* 2016, 2: 6, 1-10. *doi: 10.4172/2471-4372.1000136*

95 Manji H.K. and Lenox R.H.: Long-term action of lithium: a role for transcriptional and posttranscriptional factors regulated by protein kinase C. *Synapse* 1994, 16: 11-28. PMID: 8134897 , DOI: 10.1002/syn.890160103

96 Lenox R. and Wang H.L.E.: molecular basis of lithium action: Integration of lithium- responsive signaling and gene expression networks. *Molec. Psychiatry* 2003, 8: 135-144. PMID: 12610644, DOI: 10.1038/sj.mp.4001306

97 Grof P., Alda M., Grof E., Zvolsky P., Walsh M.: Lithium response and genetics od affective disorders. *J. Affect. Disord*. 1994, 32: 85-95. PMID: 7829768

98 Alda M., Grof P., Grof E. et al.: Mode of inheritance in families of patients with lithiumresponsive affective disorders. Acta Psychiatr. Scand. 1994, 90: 304-310,. PMID: 7832003

99 Passmore M.J., Garnham J., Duffy A. et al.: Phenotypic spectra of bipolar disorder in responders to lithium versus lamotrigine. *Bipolar Disord* 2003, 5: 110-114. PMID: 12680900

100 Lazarus JH. Lithium and thyroid. *Best Practice and Research: Clinical Endocrinology and Metabolism* 2009, 23(6):723–733. PMID: 19942149 , DOI: 10.1016/j.beem.2009.06.002

Dialogues in Clinical Neuroscience & Mental Health

DOI 10.26386/obrela.v1i2.47 ISSN 2585-2795

Special article

Depression and suicidality as results of workplace bullying

Niki Daliana & Alexandros-Stamatios Antoniou

Abstract:

Mobbing is a new phenomenon that has emerged within the workplace and is increasingly spreading. It seems to affect the employee both psychologically (aggression, reduced resistance to stress, irritability, nervousness) and physically (fatigue, weakness, chronic fatigue syndrome and pains in different parts of the body), while serious bullying can even result in depression and suicide cases. There is a question mark if depression is the cause of mobbing or it is the effect, because individuals who experiencing a mental disorder, or have a greater vulnerability to stressful events are more likely to be bullied.

Keywords: *bullying, mobbing, depression, suicide, workplace.*

Corresponding Author: Niki Daliana, Greek Association for Adolescent Medicine, e-mail: ndaliana@yahoo.gr

Received: March 21, 2018, Accepted: April 5, 2018

DOI 10.26386/obrela.v1i2.47 ISSN 2585-2795

Introduction

Over the last decades, a new phenomenon has emerged within the workplace which is increasingly spreading. This is the psychological violence practiced either by superiors to subordinates or by one colleague to another in order to marginalize and remove the individual from the workplace via aggressive behaviors such as intimidation, threats, gestures, removing privileges and in general actions designed to complicate as much as possible the life of the individual in the workplace **[1, 2, 3]**. Regarding the reasons of this phenomenon in recent years emerges a need for a holistic approach which means that if bullying is a multifactorial phenomenon it needs a model that takes into account the individual characteristics of workers, the working conditions and the social environment **[4,5]**. In Greece, rates of bullying do not appear to differ from other European countries **[6]**. According to Manouki (2009) **[7]** one in 10 Greeks report bullying workplace conditions, while 5% report incidents of physical violence.

According to Leymann (1990) **[8]** harassment escalates into four stages. The first stage is the beginning of the conflict characterized by verbal attacks or clashes with the victim, which in the second stage become more pronounced. At the second stage, the reputation of the victim is challenged with various slanderous comments, isolated from other colleagues, criticized, and threatened leading to the inability of the individual to conduct his/her work in a constructive manner due to lack of opportunities, or being required to engage in work tasks that are below his/her potential. During this stage, the effects on the individual start to appear, in the form of psychosomatic symptoms or reduced performance and absences from work. At the third stage, the superior taking into consideration both the comments and rumors about the person and the change in the behavior of the victim, either begins to worry about the victim's professional career, or most probably prefers to pick the side of the perpetrator or not to pay attention to the victim's words.

In some cases, because of the defensive behavior of the affected individual, the superior may believe that there is some other underlying problem such as a personality disorder **[8]**. In the final stage, the victim becomes isolated from colleagues and superiors, finally leading him/her to leave the workplace. However, leaving the workplace may not resolve the problem, as the consequences of harassment still exist, and may result in the individual having difficulties in securing a new position. The individual may also be fearful that the same incidents will occur again, leading to emotional changes and a dislike for work **[1,5]**. The phenomenon of harassment may take various forms of discrimination based on the origin of psychological violence and depending on the number of people involved. This may be viewed as a division between vertical and horizontal harassment. Vertical harassment is expressed by persons of the higher rank of the hierarchy towards a person of a lower rank. In the vertical harassment there are two other cases: the rising harassment, where harassment exists from lower rank employees to a senior employee and the case of «bossing», where the role of the aggressor is the administration of the Agency or a head **[5]**. The last one is the most difficult form of harassment, because it's difficult for a colleague of the victim to defend the victim against the boss **[1]**. The second form of harassment refers to horizontal harassment involving employees of the same rank. These forms of work harassment range from simple comments behind the person's back to serious accusations and gradual isolation. According to Leymann (1990) **[8]** harassment aims to affect the reputation of the victim, decrease the ability of the individual to perform his/her tasks and interfere with communication with colleagues and in a social context. Koonin and Green (2007) **[9]** describe the following forms of harassment:

- Discomfort of the person while talking or working
- Verbal forms of sexual harassment
- Intense and offensive eye contact
- Unresponsive to calls and the individual messages
- Yells and insults
- Comments about the person behind his/her back
- «Punishment of silence›› (silent treatment) (gradual isolation of the individual).

DOI 10.26386/obrela.v1i2.47 ISSN 2585-2795

Consequences of workplace bullying: Mobbing seems to affect the employee both psychologically and physically, while serious bullying can even result in suicide cases. A survey by Leymann (1996) **[10]** argues that victims of bullying are at increased risk of suicide because of constant anxiety, while a more recent survey reinforces that view, adding that the risk of suicide and suicidal ideation occurs mainly due to depression of the victims. In 1976, Brodsky **[11]** as reported by Einarsen (2000) **[4]**, following a survey among American employees suggested three categories of the consequences of bullying: In the first category, symptoms were mostly physical, such as fatigue, weakness, chronic fatigue syndrome and pains in different parts of the body. In the second category, workers who accepted mobbing had symptoms of depression, low self-esteem and low confidence. In the third category, victims avoided social contact, and demonstrated nervousness, irritability, memory problems and victimization. Generally, the most common symptoms that mobbing can lead to are depression, aggression, reduced resistance to stress and, in some cases, various forms of mania **[1,9]**.

Moreover, feelings of guilt, inferiority, helplessness and frustration, as well as the lack of attention and concentration are often expressed. In severe cases of harassment there is the possibility of post-traumatic stress disorder (PTSD), a disorder that occurs after exposure of the individual to a traumatic event. Beyond the psychological impact, mobbing, due to the intense stress experienced by the individual, may lead to «functional disorders». Examples of such disorders include migraine headaches, difficulties in sleeping, myalgias and musculoskeletal problems **[1]**, while other problems that can occur are gastrointestinal disorders, chest pains and tachycardia **[9]**. These symptoms may be identified in an individual who is constantly under pressure and stress, and who is unable to feel security and draw satisfaction from his working environment. If mobbing continues, the intensity of the symptoms may take such a form that it is necessary for the person to seek psychological or medical support **[1]**.

Certainly, the intensity of these symptoms depends on the characteristics of the individual and how he/she has learned to react to difficult and stressful situations, thus, for some people the symptoms may be less severe **[4,12]** suggest separate stages of mobbing according to the impact on the individual. In the first stage the victim remains in the workplace or manages to escape harassment before it escalates. In the second stage the victim is unable to withstand the pressure and may suddenly leave the workplace. At this stage temporary mental or physical difficulties and a struggle to get back to work may be experienced. In the third and final stage, where the experience of harassment has escalated, the person can no longer work and has serious difficulties for a long period of time.

Depression and suicidality as consequences of workplace bullying

According to Namie and Namie (2000) **[13]** the effects of workplace bullying not only alters the self esteem and confidence of the victim, but also causes anxiety, depression, headaches, insomnia and low concentration. Mobbing is encountered as a source of stress which activates symptoms such as anxiety and depression, which can lead to major depression and suicidal ideation. «Suicidal ideation» refers to thoughts related to a possible suicidal behavior, ranging from vague thoughts of death sometime in the future to an attempted suicide plan **[14]**. The plan can be comprehensive and include the place, time and manner of suicide. The suicidal ideation may be chronic and persistent, especially when there is severe psychopathology or may be transient, the onset of it being associated with unpleasant life events **[15]**. Suicidal ideation can sometimes result in suicide or attempted suicide.

According to the World Health Organization (WHO) a suicide attempt is defined as the «*act without fatal outcome, in which the person presents an unusual behavior without the intervention of others, which causes self-harm or is characterized by taking medication at a much greater than the therapeutic dose, in order to achieve changes that the individual wants through the*

DOI 10.26386/obrela.v1i2.47 ISSN 2585-2795

actual or expected physical effects» (Platt et al., 1992, as cited to Malogiannis, 2008) **[14]**. Suicide attempts differ according to the existence of a plan and the intention of death. The existence of the plan may be pre-planned or impulsive, while the intention of death indicator is the method used and the degree of injury caused by the attempt **[15]**. Usually the path to suicide begins with occasional suicidal ideation, which then becomes repetitive and may comprise specific patterns of suicidal behavior. The suicidal behavior is characterized by one or repeated attempts of suicide whose severity is evaluated by the method of the attempt and the severity of the induced injuries **[14]** that follows.

As mentioned above, workplace harassment seems to affect the employee psychologically and physically, while serious bullying can even result in suicide cases. In a survey by Einarsen, Raknes and Matthiesen (1994) **[16]** it was revealed that 40% of mobbing victims had suicidal thoughts, whilst Leymann (1996) **[10]** argues that bullying victims are at increased risk of suicide due to constant anxiety. A more recent survey reinforces that view, adding that the risk of suicide and suicidal ideation occurs mainly due to depression of the victims. Muller (2000) **[17]** reports that in France several documented cases of suicide were related to bullying, whilst Roland (2002) **[18]** refers to a study conducted in Sweden and Italy, which showed that harassment experiences in the workplace have sometimes been interwoven with suicidal thoughts. A survey by Soares (2002) **[19]** found that 45.5% of persons that experienced harassment were severely depressed and were in need of medical assistance, while 37% of those who had experienced mobbing in the past were depressed.

Indeed, 40% of these workers expressed suicidal thoughts. The findings of this research are similar to the findings of Davendort et al (1999) **[12]**, wherein it was identified that once the employee has left the workplace they may exhibit psychological consequences. Niedhammer et al (2006) **[20]** integrate mobbing with the important factors of depressive symptoms in men and women. Pompili et al (2008) **[21]** reported that bullying increases the suicide risk in both men and women, adding that it is not necessary to have a previous psychiatric history, while Ortega et al **[22]** identify a positive relationship between mobbing and health problems including depressive symptoms. Two epidemiological studies are identified regarding the event of major depressive episodes and their connection to working intimidation. According to Kivimaki et al (2003) **[23]** harassment was identified as a trigger for depression events in Finnish hospital workers, while a study by Rugulies et al. (2012) **[24]** also revealed an associated between the onset of major depressive episodes and workplace bullying.

Depression: Effect or cause?

Sometimes, depressive symptoms and suicidal ideation are part of the effects of mobbing. Indeed, research by Kivimaki et al (2003) **[23]**, shows that psychiatric problems may emerge as a consequence of bullying in people without previous psychiatric history and stressed the potential existence of neuroticism resulting in increased sensitivity in dealing with various events. On the other hand, Kivimaki et al (2003) **[23]** raise the question as to whether the characteristics of individuals experiencing a mental disorder, or who have a greater vulnerability to stressful events are more likely to be bullied. Thus suffering from a psychiatric illness that limits a person's functionality, may render them more likely as bullying targets, however, sometimes the suspicion may be the result of a disorder leading the sufferer to perceive the behavior of others as hostile.

Within this perspective, depression is likely to be a prognostic factor for workplace bullying. This view reinforces and supports the findings by Lewis (2006) **[25]** in that stress, depression or posttraumatic stress disorder rather than the effects of work bullying may be representative of the causes, due to the existence of stigma towards mental illness. In terms of post-traumatic stress disorder, the views of Lewis contradict those of Leymann, who argues that the psychological consequences of mobbing can not only lead to post-traumatic stress disorder, but are absolutely comparable with symp-

DOI 10.26386/obrela.v1i2.47 ISSN 2585-2795

toms of posttraumatic disorder that people suffer after war or confinement in jail.

In addition, research with the Minnesota Multiphasic Personality Inventory (MMPI-2) showed that victims presented higher scores on scales related to «neurotic triad», the hypochondriasis, depression and hysteria. The victims had higher levels of anxiety, neuroticism and were less extrovert and cheerful than other workers. However, the findings of the same survey show that in some cases the victims were more emotionally unstable and less contentedly before the harassment. Emotional instability may be associated with such stress and may lead to lack of self-confidence and reduced social skills, thus the individual is more vulnerable to such phenomena. Research by Gonzalez-de-Rivera and Rodriguez-Abuin (2006) **[26]** revealed that although bullying can contribute to the development of severe psychopathology, especially with regard to anxiety and depression, a question arises as to whether this finding is conclusive, as high grades on paranoia and hostility may indicate an existing tendency of individuals to react in an excessive manner to environmental stimuli. Apart from this, the high sensitivity of the psychometric tool on the increase of the paranoia scale may have the effect of exaggerated emotions that do not correspond entirely to reality.

Also, victims are likely to be occupied so much with what is happening to them that they find it difficult to function effectively. An interesting study of Tracy et al (2006) **[27]** showed how victims of bullying used metaphors to describe what they experienced. According to the findings they saw this as a threatening and dangerous game where the perpetrator sets all rules or a war. Others saw it as an uncontrolled nightmare where things happen, that subsequently the perpetrator refuses. For example, things disappear from the victim's room or the victim is a scapegoat and accept the anger and the insults of the victimizer. Indeed, the phenomenon starts so slowly that it is difficult to realize.

Concerning how they saw themselves in terms of bullying, they responded that they felt like slaves, animals or prisoners. These answers suggest a sense of deadlock and a disconnection not only from their work, but from life also. This makes them feel lonely and empty. Others said they saw themselves as children from an abusive family. They had feelings of depression, sadness and anger. It is impressive to research how the metaphorical word used to describe unbearable feelings, and that their responses indicate the duration, intensity and consequences that covers everyday life.

It appears from the literature that depression and, in many cases, suicide is one of the main consequences of workplace bullying. A recent survey by Galletta et al (2014) **[28]** confirms that mobbing is a source of intense anxiety that can lead a person to a psychopathological suffering. Moreover, remaining in a hostile environment may be conducive to the development of psychopathology and the occurrence of depression **[26]**. It's easy to be assumed that the effects and especially the depressive symptomatology are strengthened by the reaction of the colleagues. In workplaces suffering from bullying phenomena, colleagues tend to move away from the victim and their reactions are similar to those that would have been if the victim had died. Besides, several times the victim feels like dead or wishes to die, feeling invisible and abandoned.

The high psychological demands, decreased sense of control at work, reduced social support and the imbalance between effort and reward seem to set the ground for the emergence of depressive symptoms. The labor force and intimidation as seen above can have dire health consequences on the worker. Because of workplace harassment the victim beyond the efford to avoid giving rights to negative reviews as abusers refuse aggressive behavior on their part, it is essential to look for evidence of what is happening so as to prove that what he/she claims is not the product of his/her imagination. The next stage is to identify someone in the workplace who can confirm what is happening. This step has a double meaning in order the victim to maintain his self-esteem and not to be implicated and thus a supportive framework would help, especially if the person is someone who could intervene and

DOI 10.26386/obrela.v1i2.47 ISSN 2585-2795

change the situation, for example the Director or the Head of Human Resources.

Outside the workplace the person can possibly seek support from family and friends and sometimes from a mental health specialist. Apart from what the person can do for his/her self, treatment and prevention of the phenomenon from the part of the Organization is important, the main issue being to integrate policy on bullying to organizations and employers to ensure the prevention of bullying, assess the risk of such incidents and take appropriate action. Certainly, to do this it's important for the boss/employer not to turn their leadership to a tyranny and to be willing to listen their employees, even if this means limiting their "ego"current limiting in some time **[9]**.

In Greece, surveys and literature with regard to occupational violence and intimidation are limited. But this is not because the phenomenon doesn't exist. Instead, the image of our country is not much different from that of other countries **[29]**. Bullying exists in Greek organisations, especially nowadays where the elasticity of labor increases, the working schedules are reduced and generally there is no security and stability in the workplace, thus more than ever the conditions that may manifest harassment are in existence.

As mentioned above, the reduction of wages, and deprivation of money for further education also represent forms of indirect bullying. Employers are called to select the right worker through numerous candidates, while workers are called several times to settle on any remuneration and working conditions in order to ensure a living. Certainly, this is not always easy and feasible as exemplified by the case of France-Telecom where compulsory movements of thousands of workers to other areas and to other jobs, the retraining of workers, the introduction of a customer-oriented logic, the management by stress resulted to 60 suicides from 2008 to 2011 **[29]**. Further research regarding the phenomenon of bullying is needed to investigate the causes, but mainly to find ways to address and raise awareness among both employees and employers.

References

1. Antoniou, A.-S. Moral harassment issues in the workplace. In A.-S. Antoniou (Ed.) *Business Ethics* (Vol. **I**, pp. 1-14). Athens: Sakkoula, 2008.

2. Antoniou, A.-S., Dimou, Ch., & Athinaiou, **M**. Moral concerns for the cases of sexual harassment in the workplace. In A.-S. Antoniou (Ed.) *Business Ethics* (Vol. **I**, pp. 247-283). Athens: Sakkoula, 2008.

3. Antonopoulou, A., & Antoniou, A.-S. Current types and dimensions of harassment in the workplace (moral and sexual). Suggestions for occupational counselling. *Review of Counseling and Guidance* 2012, 100 43-54.

4.Einarsen, S. Harassment and bullying at work: A review of the Scandinavian approach. *Aggression and Violent Behavior* 2000, *5*(4): 379-401. http://dx.doi.org/10.1016/S1359-1789(98)00043-3

5.Toukas, D., Delichas, M., & Karageorgiou, **A.**. Definitions and causative factors of psychological violence in workplace. Their role in assessing the dangers of mobbing. *Archives of Hellenic Medicine* 2012, 29(2): 162-173.

6.Galanaki, E., & Papalexandris, N. (2012). Measuring workplace bullying in organisations. *The International Journal of Human Resource Management, 24*(11), 2107-2130. http://dx.doi.org/10.1080/09585192.2012.725084

7.Manoukis, A. Mobbing: Manager and moral harassment. *Manager* 2009, 53-57. Retrieved from: http://career.duth.gr/cms/files/endiaferon_arthro_6_16022009.pdf

8.Leymann, H. Mobbing and psychological terror at workplaces. *Violence and Victims* 1990, *5,* 119-126. Retrieved from: http://www.mobbingportal.com/leymannmain.html

9.Koonin, M., & Green, T. M. The emotionally abusive workplace. *Journal of Emotional Abuse* 2007, *4:* 71-79. doi: 10.1300/J135v04n03_05

10.Leymann, H.The content and development of mobbing at work. *European Journal of Work and Organizational Psychology* 1996, *5*(2):165-184. http://dx.doi.org/10.1080/13594329608414853

11. Brodsky, C. M. *The harassed worker.* Toronto: Lexington Books- DC Health and Company, 1976.

12.Davenport, N., Schwartz, R., & Elliott, G. P. *Mobbing: Emotional abuse in the workplace.* Ames, IA: Civil Society Publishing, 1999.

13.Namie, G., & Namie, R. *The bully at work , what you can do to stop the hurt and reclaim your dignity on the job.* Sourcebooks, Inc, 2000.

14. Malogiannis, I. Suicidal patient: Diagnosis, understanding, therapeutic intervention and prevention of suicide. Institute for Research and Behavioral Therapy, 2008, Retrieved from: http://www.ibrt.gr/ekpaideysi/SuicideWorkshop1.pdf

15.Katsadoros, K. B., & Bekiari, E. H. (n.d). Guide to Preventing Suicide in Chil-

DOI 10.26386/obrela.v1i2.47 ISSN 2585-2795

dren and Adolescents. A Guide for Primary and Secondary Education Teachers. Retrieved from: http://www.klimaka.org.gr/newsite/downloads/odigos_sxoleia_new_.pdf

16.Einarsen, S., Raknes, B. I., & Matthiesen, S. M. Bullying and harassment at work and their relationships to work environment quality: An exploratory study. *European Work and Organizational Psychologist* 1994, *4,* 381-401. Retrieved from: http://folk.uib.no/pspsm/documents/Bullying_and_work_environment_1994_Einarsen_Raknes_Matthiesen.pdf

17.Muller, M. Quand le management tue. *Le Nouvel Observateur* 2000*, 1842:* 9-10.

18.Roland, E. Bullying, depressive symptoms and suicidal thoughts. *Educational Research*2002*, 44* (1): 55-67. doi: 10.1080/00131880110107351. Retrieved from: http://dx.doi.org/10.1080/00131880110107351

19.Soares, A. *Bullying: When work becomes indecent*. Unpublished manuscript, UQAM, Montreal, 2002.

20.Niedhammer, I., David, S., & Degioanni, S. Economic activities and occupations at high risk for workplace bullying: results from a large-scale cross sectional survey in the general working population in France. *International Archives of Occupational and Environmental Health* 2006*, 80:* 346-53. doi:10.1007/s00420-006-0139-y

21.Pompili, M., Lester, D., Innamorati, M., De Pisa, E., Iliceto, P., Puccinno, M., Nastro, F., Tatarelli, R., & Girardi, P. Suicide risk and exposure to mobbing. *Work* 2008*, 31:* 237-243, PMID: 18957741

22. Ortega, R., Elipe, P., Mora-Merchán, J. A., Calmaestra, J. y Vega, E. The emotional impact on victims of traditional bullying and cyberbullying: A study of Spanish adolescents. *Zeitschrift für Psychologie / Journal of Psychology* 2009, 217*(4):* 197- 204.

23. Kivimaki, M., Virtanen, M., Vartia, M., Elovainio, M., Vahtera, J., & Keltikangas-Jarvinen, L. Workplace bullying and the risk of cardiovascular disease and depression. *Occupational and Environmental Medicine* 2003, 60: 779-83, PMID: 14504368

24. Rugulies, R., Madsen, I. E. H., Hjarsbech, P. U., Hogh, A., Borg, V., Carneiro, I. G., & Aust, B. Bullying at work and onset of a major depressive episode among Danish female eldercare workers. *Scandinavian Journal of Work, Environment & Health* 2012, 38(3): 218-227. doi:10.5271/sjweh.3278

25. Lewis, S.E. Recognition of workplace bullying: A qualitative study of women targets in the public sector. *Journal of Community & Applied Social Psychology* 2006*, 16:* 119-135.

26.Gonzalez-de-Rivera, J., & Manuel Rodriguez-Abuin, M. *Psychopathological effects of work place harassment,* 159th Annual Meeting, Toronto, 2006.

27.Tracy, S. J., Lutgen-Sandvik, P., & Alberts, J. K. Nightmares, demons, and slaves exploring the painful metaphors of workplace bullying. *Management Communication Quarterly* 2006, 20: 148-185. doi: 10.1177/0893318906291980

28. Galletta, D., Sica, G., Califano, A., Aurino, S., Di Lorenzo, P., & Buccelli, C. Mobbing: From a Social Phenomenon to Psychopathology: Preliminary Data, *Journal of Psychiatry* 2014, 17*(5)* http://dx.doi.org/10.4172/Psychiatry.1000137

29. Karakioulafi, C. *«Psychosocial Dangers in the Workplace: Interpretation from the scope of Labor Sociology-the example of suicide at FranceTelecom».* 2014, Received: http://www.historein.gr/2011/05/france-telecom.html

Dialogues in Clinical Neuroscience & Mental Health

DOI 10.26386/obrela.v1i2.48 ISSN 2585-2795

Special article

The intriguing role of the Gut Microbiome in the etiology and pathogenesis of Neuropsychiatric Disorders

Iraklis Lefas

Abstract

Humans live in a symbiotic, evolutionarily endorsed, relationship with the plethora of microbes residing within them, but not until very recently we came to understand that our microbes are more than simply bystanders co-existing with us. They have established a communication, an inter-kingdom connection, with the host's cells, which is responsible for many physiological aspects concerning human health. The gut microbiome, by its very definition, represents the collective genome material of all microbes inhabiting our intestines, and holds tremendous capacities, for it is able to affect the host in terms of health and disease. It's intriguing the fact that the gut microbes are engaged not only in local events, but may influence remote tissues and organs as well. Via the gut-brain axis, a multichannel system of pathways connecting the two organs, microbes can affect mood, behavior and cognition and become implicated in the pathogenesis of many neuropsychological disorders. They are able to impact brain function in a variety of ways, however, their true potential lies in their ability to regulate the neural development, a delicate process whose defects can lead to long-term mental health outcomes later in life. In this article, we will review the contribution of the gut microbes in the process of neurodevelopment and attempt to shed light on the etiology of many neuropsychological disorders from the perspective of gut dysbiotic states. Unraveling the mystery behind the true meaning of symbiosis with microbes may provide novel therapeutic strategies against neuro-psychological disorders.

Key words: gut-brain axis, gut microbiome, Gut microbiota, mental health, neuro-psychological disorders.

Corresponding Author: I
raklis Lefas, Resident Doctor, Department of Pathology, Elpis Hospital, National & Kapodistrian University of Athens, Greece, e-mail: herclefas@gmail.com, herc-3@windowslive.com

Received: January 8, 2018, Accepted: February 27, 2018,

DOI 10.26386/obrela.v1i2.48 ISSN 2585-2795

Iraklis Lefas

Introduction

For millions of years the human body was inhabited by a group of little creatures, which afterwards were named microbes. Once we learned of their existence we started to observe and study them. We found them living and thriving in every possible environment, even within us. We related them with diseases and started fighting them to extinction. In time, we discovered a connection, a prosperous symbiotic relationship between some of them and us. We came to understand that the human being isn't a solely organism, but a living ecosystem with a ratio of indigenous cells to microbes 1:1 to 1:10 [1,2]. We have yet to unravel the precise nature of this symbiotic relationship, for this is a topic of research that is still in its infancy.

The Gut Microbiome (Gut microbiota, formerly called *gut flora*), a vast ecosystem of bacteria, archaea, protozoa, parasites, fungi and viruses thrives within our intestines[1]. It carries an important role on the homeostatic regulation of the human body, on immune maturation and metabolic function [1,3]. The vast variety of its activities, the interaction and communication between the microbes and the human body cells, and the apparent importance of the microbiome on human health and development have led to its description as "a forgotten organ" [1,4].

The last years, its role has been implicated in the pathogenesis of various diseases, gastrointestinal and systemic [1,2,5,6,7]. In this article, we will study its peculiar part on development and function of the CNS, focusing on the data which correlates the microbiome with the pathogenesis of neuropsychological disorders. It's unfamiliar the fact that many forms of neuro-immune and neuro-psychiatric diseases are now being related with gut dysbiotic states (disruption of a balanced composition of the gut microbiome), the microbes' detrimental activities and gut-derived metabolites.

How microbes talk to the brain: The Gut-Brain Axis

The Gut-Brain axis is a concept of connection between the two major systems, the gut and the brain. It consists of a range of multichannel pathways that integrate and transmit the brain signals to the intestines and vice versa [8]. The brain, as the prime neural organ, controls the gastrointestinal functions (e.g. motility, muscular tension, visceral sensitivity, local immune cell activity, hormonal production, nutrient absortion) and therefore shapes the luminal microenvironment affecting bacterial establishment and growth. Although it was believed for many years that the communication between the gut and the brain was one way (top-down, from brain to intestines), nowadays this axis is found to be bidirectional [1], mediating the fundamental functions of these two peculiar systems [9,10]. There have been described several paths that convey the intestinal signals centrally. Each and every of these paths comprise what we described before as "the Gut-Brain axis".

Neural Avenue

Vagus nerve, the widest distributing nerve in the body, consisting of afferent and efferent neurons, is a vital part of the MGB axis. It collects all the information from intestinal events and creates signals to be transmitted through four consecutive neurons cephalically [1,11]. Afferent projections are spread into higher brain centers such as brainstem nuclei, the thalamus, the basal ganglia and the cortex [1,11]. In this way, gut microbiota can induce changes on brain function across the vagus nerve. Compatible with this notion are the experiments done in vagotomized mice, in which probiotic treatment didn't manage to change behavioral traits, although it has been previously reported to be effective [12,13]. Moreover, the sickness behavior followed by pharmaceutical induced colitis in mice was substantially attenuated following vagotomy [14]. Spinal sympathetic neurons are also conducting information from the gut to the brain through the spinal cord [1,9]. A well documented route is the activation of GPR41 (a receptor found in sympathetic ganglia) by microbial products, which transmits the luminal signals centrally[15].

Neuroendocrine Route

Enteroendocrine cells (EECs), specialized cells of the gastrointestinal tract, secrete neurotransmitters and other signaling peptides (i.e. serotonin, CCK, GLP-1, PYY) in response to

DOI 10.26386/obrela.v1i2.48 ISSN 2585-2795

changes on luminal contents, acting as transducers for the endocrine-CNS route [16,17]. Receptors of these peptides are found locally, on the afferent endings of the vagus nerve, but also centrally, where they are involved in behavioral responses [17]. Bacteria may produce metabolites that act as paracrine signals that influence host's cells behavior and function. C1pB protein, for example, produced by commensal microbes, can stimulate the release of PYY and GLP-1 from the EECs [18].

Microbial fermentation products may act as signaling molecules with great significance on gut-brain interaction. Short Chain Fatty Acids (SCFAs), the most studied metabolic products, originate from fibers and undigested carbohydrates [16]. It has been shown to act as modulators on intestinal hormone production and as immune regulators, with many luminal and systemic interactions [19]. They can cross the BBB, regulate microglia homoeostasis [8] and have been implicated in brain development and pathogenesis of autism [8,20]. Locally, SCFAs regulate the production of gut peptides from enteroendocrine cells [8], and the synthesis of gut-derived serotonin from enterochromaffin cells, activating afferent nerve endings to signal to the CNS [8,21]. Experiments done in animal with neurodegenerative disorders have shown a profound increase in cognitive function related to the production of SCFAs[22].

Immune Pathways

The enterocytes, the immune cells and the neurons express in their surface PRRs (Pattern Recognition Receptors) which interact with bacteria molecules or products [1,23]. TLRs, a class of PRRs, are an integral part of the local innate immune system. Activation of these receptors triggers a pro-inflammatory cytokine release (Il-1, Il-6) which spreads locally and systemically via the bloodstream, reaching the brain, to activate the Hypothalamic–Pituitary–Adrenal (HPA) axis [16]. Cytokines may also signal to the brain indirectly, via the vagus nerve [24]. Local immune activation and cytokine production against microbial antigens or products leads to a stress response that stimulates the HPA axis which, in turn, induces hormonal changes in the blood [1]. An immune-endocrine activation affect cognition and behavior, mimicking the effects of bacterial infection [4,25]. LPS production, for instance, by certain types of bacteria is responsible for activation of the immune-endocrine-nervous system and the HPA axis. On the other hand, gut colonization with helpful bacteria can reduce an exaggerated HPA response [26].

Microbial Products (Neurotransmitters, Neuromodulators)

Microorganisms' metabolism can also result in neurophysiological changes with the production of chemical substances that act locally or systemically [9]. Microbiota-derived metabolites are critical intermediaries for microbiota-gut-CNS signaling. Neuropeptides are multilateral molecules and serve as messengers in many systems (endocrine, nervous, immune) [27]. The gut microbiota can produce and emit an array of neurotransmitters, such as GABA, catecholamines, histamine, norepinephrine, 5-HT, butyric acid and dopamine [28]. These molecules are engaged in paracrine communication with the nerves, immune cells and enteroendocrine cells (influencing the hormone production of the former) and also endocrine signaling, reaching distant tissues such as the brain, and further impacting on central centers[29].The physiology of the MGB axis allows a bidirectional communication between the brain and the gut so that both gastrointestinal and psychopathological entities could be both origin and consequence of one another. Both of the systems are mutually affected and depending on the other. This hypothesis is verified indirectly from the observation of the high co-morbidity between psychiatric and gastrointestinal diseases. Many patients suffering from gastrointestinal disorders experience mood and behavioral changes, whilst a lot of patients with psychiatric diseases suffer from gastrointestinal symptoms [30,31]. Due to this entangled relationship, the gut-brain axis forms a mean for the gut microbiota to speak indirectly to the brain. In dysbiotic states, where the composition or metabolic function of the indigenous bacteria is shifted against the benefit of the host, psychiatric and neurodevelopmental illnesses may occur [8,32,33].

DOI 10.26386/obrela.v1i2.48 ISSN 2585-2795

How the Microbes Influence the Brain Development

Neural development commences early in embryonic life and extends from the prenatal period to post adolescence [34], with the brain remodeling continuing into the third decade of life [35]. It involves the contribution of genetic and a long list of environmental factors [35]. The process of neurodevelopment is dynamic and spans for years which makes it vulnerable to external perturbations and thus susceptible for alteration[8]. This crucial period of neurodevelopment progresses concurrently with the establishment and growth of the gut microbiome, a vital process which guides the maturation and training of the immune system [36], the development of the neuroendocrine system [8] and the regulation of many physiological functions, regional or distal. Studies suggest that there is a crucial link between gut microbiome and CNS maturation under physiological state [8,10]. Disturbance of the gut microbiome early in life has the potential to disrupt the delicate process of neurodevelopment and can contribute to long-term mental health outcomes later in life [8,34,36,37].

Neuronal development may be modulated by the participation of the neuro-endocrino-immunological system [34] with main representative the circulating levels of hormones and cytokines. In a review of GB Rogers et al.[8], it is mentioned that a pro-inflammatory maternal state may contribute to aberrant fetal development. During pregnancy, increased levels of circulating cytokines are known to negatively impact fetal neural development affecting the gene expression of fetal brain cells [38]. This kind of disturbance may come from the disruption of the immuno-regulatory role of the maternal gut microbiome [8]. Maternal gut dysbiosis can generate an inflammatory environment that also influences blood brain barrier (BBB) formation and function which in turn exposes the microenvironment of microglia and neurons to the blood stream components[8]. Embryos of GF mice develop a deregulated BBB with reduced expression of tight junction proteins, which is shown to be significantly compromised [8,39].

The activation of the maternal hypothalamic–pituitary–adrenal axis may change the normal neurodevelopmetal trajectories and it is linked with fetal neurological defects. As GB Rogers et al.[8] reviewed, any stress factor can activate the HPA axis and contribute to a broad spectrum of neurodevelopmental abnormalities [8,40]. How the maternal HPA hyperactivation impacts the fetal development remains poorly understood, but it is believed that the maternal blood cortisol can traverse the placenta and influence the gene expression of the brain cells [8,41]. The effects of prenatal stress on offspring can be mimicked to a limited degree by giving pregnant animals a synthetic glucocorticoid hormone [8,41].

Bacteria composition is associated with neuronal connectivity development and thus the quality of neuronal circuitries during pre- and postnatal life. In the review of Rogers et al.[8] is cited that the process of neurodevelopment in utero depends on serotonin which controls the neuronal cell mitosis, differentiation and synaptogenesis. Proper neuronal morphogenesis requires quantities of 5-HT an embryo can't afford, and thus depends more on maternal plasma serotonin than its own[42]. The maternal microbiome can regulate the 5-HT biosynthesis by enterochromaffin cells in the gut and therefore affect fetal neurodevelopment by influencing the level of circulating serotonin[43].

Gut microbiota, in the postnatal period of life, mediate the epigenetic regulation of brain molecules involved in the neural development, such as neurotrophic factors (BDNF being the most studied of them) [44]. This is a result of microbiota - host chemical communication via the gut-brain or HPA axis where bacterial bioactive metabolites (SCFAs, neurotransmitters) and signaling molecules (peptides, endotoxins) make possible this interaction[16]. Germ free (GF) mice (sterile animals which are born and raised within germ free isolators) are a helpful tool for investigating the gut-brain correlation. Studies have shown that the absence of gut microbiota from birth has an impact on neural development and behavior [8,16,34]. GF mice are described with an excessive HPA response when exposed to mild stress, with elevated plasma ACTH and cortisol

DOI 10.26386/obrela.v1i2.48 ISSN 2585-2795

hormone compared to normal mice [8,26]. They also have neuroanatomical changes in brain areas such as amygdala and hippocampus [45], with reduced levels of BDNF, NMDA receptor and c-fos in the hippocampus and cortex [9,46]. The expression of BDNF, the 2A subtype of NMDA and 5-HT1a receptors in the cortex and hippocampus are microbiota regulated[26,47]. GF mice are presented with altered gene expression of myelin structural proteins in the prefrontal cortex, a brain region which has been implicated in cognitive behavior, personality expression and social behavior[48]. Specifically, it has been noticed, an increase in myelin production leading to hypermyelination of the prefrontal cortex, a process which is expected to occur later in life. These neuroanatomical changes could be correlated with the pathogenesis of emotional disorders[49].

Commensal microbes are required for programming and displaying normal social behavior, and are essential for the development of memory, repetitive behaviors and pain signaling from the body [50,51]. A dysbiotic state, with abnormal microbiota composition early in life, can result in abnormal mental development and behavior disorders which are not corrected when later microbial exposure occurs. There seems to be a maturation time window, on which exposure to microorganisms is necessary for proper CNS development, but after that, the changes in the newly formed brain remain permanent [26,52]. The association between the gut micobiota and neurodevelopment is strong. The precise nature of this relationship has yet to be unraveled mostly due to the difficulties of determining the multiple and unclear pathways that combine these systems together.

Manipulating host's brain function and behavior: An introduction to the neuropsychological disorders

Many studies experimented on GF mice or conventionally raised mice have shed light to the pathophysiological role of the gut microbiome in human brain neuropsychological diseases. GF mice receiving gut microbiome transplant from patients with depression exhibit more depression-like behaviors, in comparison with the control group of mice which were colonized with microbes from healthy donors[53]. In another experiment, the transplantation of gut microbes from a high anxiety mouse to a germ free one with low anxiety led to increased anxiety behavior in the recipient. The same experiment done in reverse showed matching results [54]. Some behavioral features seem to be transmissible via the gut microbes, and thus, the idea of brain manipulation by the gut flora appears to confirm itself. The pathways of communication remain unclear to a certain extent. The gut-brain axis plays a significant role in mediating the intestinal events and the neurochemical alteration centrally. There have been described several paths involved in this axis (for reference see chapter 2: "How microbes talk to the brain: The Gut-Brain Axis").Since the indigenous gut bacteria have a strong communication with the brain *via* the MGB axis [9,16,34], a disruption of the physiology of gut bacteria could be linked to the pathophysiology of psychopathologies. Any stress factor that influences the microenvironment of the gut microbes could also affect indirectly the cerebral development and function [8,34].

Depressive syndrome

It is right to presume that the gut microbiome is one of the many links between early environmental stress factors and the risk of developing depression later in life [55]. A disturbance of the immuno-regulatory role of the gut microbiome has been proposed to influence the developmental cues of the brain. An immune-endocrine activation could affect the process of neuronal configuration and function[5,34] via changes at the level of genetic expression of genes associated with brain development [55]. It is now known, with the assistance of animal studies, that limbic system's neurogenesis can be modified by indigenous gut microbiota[34,56]. A chronic gastrointestinal inflammation, for example, is associated with altered hippocampal neurogenesis [57], with swifts in the expression of neurotrophic factors, such a BDNF.

Stool samples from patients with depression show alterations

DOI 10.26386/obrela.v1i2.48 ISSN 2585-2795

in the proportion of indigenous bacteria in contrast to healthy individuals. Notably, there has been recorded increased concentration of Bacteroidetes, Actinobacteria and Proteobacteria (LPS-expressing)[58] and low numbers of Lactobacillus species[59]. It's interesting the fact that increased levels of IgA and IgM against the LPS of Gram-negative bacteria are found in depressed patients[60]; markers that indicate bacteria translocation into the bloodstream. Patients with depression have increased volatile fatty acids such as isovaleric acid found in their stool. These molecules are microbe-derived and can travel with the bloodstream up to the brain, crossing the BBB, and affecting neurotransmitter release[61]. Whether these mechanisms are involved in the pathogenesis of the depressive syndrome, or are consequences of the neuro-immunological disarrangement resulted by the depression, remains unclear.

Gut microbes are required for normal brain function. Altering the microenvironment of our gut microbes with the supplementation of probiotics (helpful bacteria) can lead to changes in the bidirectional communication between the gut and the brain and thus influencing the mood, cognition and brain function. Probiotic consumption has been linked with anti-depressant effects on animal and human models. Bacterial species such as Lactobacillus and Bifidobacterium can alleviate depressive symptoms in maternal separation models of rats[62]. Chronic treatment with Lactobacillus rhamnosus in mice can reduce stress-induced corticosterone levels, anxiety and depressive behaviors[12]. These effects where attributed to altered GABA expression in the cortex, amygdlala and hippocampus. In a recent functional magnetic resonance imaging (fMRI) study with healthy individuals, after a 4-week consumption of probiotics (Bifidobacterium and Lactobacillus) the subjects displayed reduced neural activity in brain regions that process emotion and sensation in response to emotional attention tasks [63]. Clinical data of probiotic consumption provides a novel, potentially useful, therapeutic strategy for neuropsychiatric conditions. However, more clinical trials are required to truly determine their extent of efficacy in treating neuropsychological disorders.

Anxiety and Stress

Exposure to biological stressors or environmental stimuli can trigger stress and anxiety responses, which involve the activation of the HPA axis[9]. Gut microbe's metabolism may be implicated in the pathogenesis of mood and emotional disorders. Mice inoculated with *Campylobacter jejuni* show a decrease in exploratory phenotype (anxiety's sign) and activated brain sections implicated in anxious behavior [64]. Pathogens, such as *C. jejuni* [64,65], *Citrobacter rodentium*[66] and *Trichuris muris*[67] can induce anxiety-like behavior via immunological and metabolic mechanisms (reviewed in [10]). In contrast, beneficial bacteria in the form of probiotics have shown to ameliorate anxiety and reduce stress. Lactobacillus and Bifidobacterium consumption has been associated with anxiolytic effects, normalizing anxiety phenotypes in animal models[12,62,67] GF mice behave differently in comparison with normal mice. They show increase motor activity, impaired cognition and demonstrate an exaggerated HPA stress response[9]. These behavioral traits are associated with altered expression of genes[55] leading to higher levels of neurotransmitters, decreased BDNF expression and reduced synaptic long-term potentiation[55]. Colonization by Bifidobacterium species can attenuate the exaggerated HPA stress response, with only condition the early life exposure for the inhibition to occur[26].

Schizophrenia

Schizophrenia is a complex mental disorder characterized by abnormal social behavior and failure to understand reality[68]. Schizophrenia is oftenly coexisting with gastrointestinal symptoms or disorders[69], however, whether this results from a deregulated brain-to-gut communication or is microbiota-derived remains unknown[16]. Even so, the correlation between gut dysbiosis and the pathogenesis of schizophrenia is well documented[8,36,70,71,72,73].

The causes of the disease include environmental and genetic factors. The genetic risk of schizophrenia relies upon genes that are involved in immune function[70,71]. This condition corre-

DOI 10.26386/obrela.v1i2.48 ISSN 2585-2795

lates with the clinical observation of upregulated inflammatory state in schizophrenia patients[69]. Bacteria translocation markers have been found in the blood of schizophrenic patients in significant higher levels than normal people[72], while high cytokine levels are related with the exaggeration of symptoms[73]. A breach in the intestinal epithelial barrier is thought to allow bacteria and their products to enter the bloodstream and cause an immune response[36]. Through molecular imitation, this response may trigger an attack upon host tissues, a fundamental process of autoimmune pathogenesis[9,36]. Schizophrenia patients bear a higher probability of autoimmune disorders, and have autoimmune antibodies against brain regions such as as the hippocampus, amygdala, and frontal cortex[9,74]. They are also found with a higher proportion of Th17 cells, a condition resembling an immune response emerging from gut dysbiosis[75].

Commensal microbiota is required for programming and displaying normal social behavior, and is essential for the development of memory and behavior[50,51]. The expression of BDNF, the 2A subtype of NMDA and 5-HT1a receptors in the cortex and hippocampus are microbiota regulated[26,47]. These factors have a significant role in brain development and function. Impaired BDNF expression leads to cognitive dysfunction, while NMDA antagonists mimic schizophrenia symptoms[9]. A dysbiotic state early in life, could affect the normal neurodevelopmental trajectory and lead to the genesis of psychiatric disorders, therefore the importance of a healthy gut microbiome becomes apparent.

Autism Spectrum Disorder (ASD)

Autism spectrum disorder (ASD) is the name for a group of developmental disorders characterized by impaired social interaction and communication. ASD includes a wide range, "a spectrum," of symptoms, skills, and levels of disability[76]. It is believed that the gut microbiota contributes, at least in part, in the pathogenesis of ASD. Children with ASD usually have a different gut microbiota profile when compared to same age healthy control group[29]. As mentioned in the chapter of brain development, a dysbiotic state may result in activation of the HPA axis and contributes as a risk factor for a broad range of neurodevelopmental abnormalities[8,40]. Children with ADHD, for instance, display an abnormal HPA response[77]. Colonization by strains of neurotoxin-producing bacteria, such as *Clostridia*, has been for long hypothesized as an etiology agent, at least in a subgroup of patients[78,79] (reviewed by Wang et al.[10]). A great number of *Clostridium* species, such as *Clostridium tetani*, have been found in fecal samples of autistic children.[10,80,81] Microbes' metabolic products may are also engaged in the pathogenesis of ASD[10]. Oral use of vancomycin can attenuate the symptoms of the disorder, while the interruption of the treatment leads to relapse of the autistic behavior[29,82]. In the same concept, oral treatment with probiotics (*Bacteroides fragillis*) ameliorates the defects of the disorder[83]. Microbiota composition and the pathogenesis of ASD are connected through the gut brain axis. Microbes are able to influence the synaptogenesis process, the production of neurotransmitters and the gene expression in many brain structures[8,55]. The main pathways employed by the gut microbiota are neural, endocrine and immune, as were seen in the Gut-Brain Axis section.

Eating Disorders

Eating disorders for long have been accepted as mental illnesses since the primary etiology of them seems to outset from psychopathological misrepresentation of body image and self acceptance [84]. They are defined by abnormal eating habits that negatively affect a person's physical or mental health [84]. The cause of these disorders is not clear yet. Both biological and environmental factors appear to play a role. In the last decade, there has been a growing body of literature that suggests a biological background in the etiology and progression of these conditions [4,85,86,87].

Millions of years ago, we permitted bacteria to live inside us and in turn they helped with digestion, protection from pathogens and production of useful molecules. They grow in accordance with the food we eat; nevertheless different bacteria have distinct nutritional demands. From an evolutionary point of view, bacteria that evolved ways of communicating

DOI 10.26386/obrela.v1i2.48 ISSN 2585-2795

with the host and enforce a feeding behavior which cultivates this kind of bacteria would impose a significant selective pressure, and thus thrive on this microbial-controlled environment [85,87]. A positive feedback loop emerges, as the host selects a specific dietary habit which nourish this kind of bacteria [4,87]. This idea of bacteria controlling their host's appetite is revolutionary. It's distrusting the fact that bacteria acquired such a capacity. However, they have had both the time and the formidable adaptive mechanism needed to fulfill this task.

Taking into account the extent of functions of the gut-brain axis and the influence of the diet on brain function, it is logical to assume the gut bacteria as an intermediate link between eating disorders and extreme feeding patterns [4,85]. Acting on the gut–brain axis, gut bacteria could affect brain function and alter the appetite control, thus considering as part of the genesis of eating disorders [4,88]. As the illness develops, abnormal eating habits can further affect the microbiota's ecosystem which potentially feeds back to the brain function, eventually creating a positive loop which maintains the disorder [4].

Studies have not been yet conducted on humans, but animal models help investigate the influence of gut microbes on host behavior. In the review of Lam YY et al. [4], the authors cite a few plausible mechanisms. The first includes the control of gut bacteria over the production of appetite-regulating hormones. In the gut reside enteroendocrine cells which produce hormones or peptides (such as cholecystokinin) in response to various stimuli and release them into the bloodstream for systemic effect, diffuse them as local messengers, or transmit them to the enteric nervous system to activate nervous responses [89]. These cells express Toll-like Receptors which are activated by binding with bacterial products (lipopolysaccharides - LPS and flagellin) causing the modification of secretion of hormones that regulate hunger and satiety [4,90]. LPS can also enter to the bloodstream and disrupt the physiological permeability of the BBB [91], to augment the effect of circulating hormones and cytokines on central appetite systems. Other direct effect of LPS is the induction of an anorexic response by activating central pathways [91]. Lastly, in a recent experiment, prebiotic food supplementation in healthy subjects led to an increase in production of gut hormones (PYY and GLP-1) and promoted the impression of satiety, lowering hunger rates [92]. Changing the microenvironment of the gut and the microbiota composition seems to contribute to alterations in appetite sensation.

Another pivotal mechanism practiced by gut bacteria to manipulate host's food intake is by producing peptides that mimic the role of the host's appetite-regulating hormones. These peptides can regulate food intake with two major ways (mentioned in [4]). The first, and direct one, is by imitating the effect of the genuine appetite hormone on its receptor, while the second one is far more complex. The peptides produced by the gut microbiota may trigger an immune response towards themselves (since they are bacterial products) with the antibodies also cross-reacting with the host's appetite hormones since they are molecular analogues with these bacteria derived peptides [4,87]. The latter has actually been confirmed, as Fetissov et al. [93] presented a subgroup of patients with Anorexia Nervosa and Bulimia Nervosa that had autoantibodies against the α-MSH (melanocyte stimulating hormone). The circulating level of these autoantibodies was found to be related to the psychological features of these diseases [93]. Similar with the concept of interference with appetite central regulation, bacteria may also manipulate the dopaminergic rewarding system of the brain, affecting the pleasure and the desire for a specific dietary regimen [85].

Conclusion

Living in a microbe-free world is an unimaginable concept. Bacteria appeared on Earth long before the first human ever emerged. We evolved together and form a symbiotic relationship. They accompany us from our birth until the time of our departure. The microbes affect us in the most significant way, but only the last few years we became aware of such influence. The fact that they are involved in the process of neurodevelopment, on brain function and the pathogenesis of many systemic dis-

DOI 10.26386/obrela.v1i2.48 ISSN 2585-2795

eases gives them substantial authority upon us. We need to learn how to optimize this relationship and comprehend the mechanisms promoting health or disease. Novel therapeutic strategies (probiotics, microbiota transplantation, genetic engineer of indigenous microbes) may appear in the near future and replace partially effective existing treatments. The most difficult attempt is to unravel the mysteries behind this state of symbiosis. Exploring the secrets of the microworld of our microbes may finally give an answer to a significant argument that puzzles humanity for a long time: "are we really us?"

References

1. Lerner A, Neidhöfer S, Matthias T. The Gut Microbiome Feelings of the Brain: A Perspective for Non-Microbiologists. *Microorganisms* 2017, 5(4): 66. PMID: PMC5748575

2. Kelly JR, Kennedy PJ, Cryan JF, Dinan TG, Clarke G, Hyland NP. Breaking down the barriers: the gut microbiome, intestinal permeability and stress related psychiatric disorders. *Front Cell Neurosci* 2015, 9:392. doi:10.3389/ fncel.2015.00392. PMID: 26528128

3. Nicholson J.K, Holmes E, Wilson I.D. Gut microorganisms, mammalian metabolism and personalized health care. *Nat. Rev. Microbiol.* 2005, 3(5):431-8. PMID: 15821725

4. Yan Y.L, Maguire S, Palacios T, Caterson I.D. Are the Gut Bacteria Telling Us to Eat or Not to Eat? Reviewing the Role of Gut Microbiota in the Etiology, Disease Progression and Treatment of Eating Disorders. *Nutrients* 2017, 14;9(6). doi: 10.3390/ nu9060602. PMID: 28613252

5. Rea K, Dinan TG, Cryan JF. The microbiome: a key regulator of stress and neuroinflammation. *Neurobiol Stress* 2016, 4:23–33. doi:10.1016/j. ynstr.2016.03.001

6. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. *Nature* 2007, 449: 804–810. PMID: 17943116

7. Woting A, Blaut M. The Intestinal Microbiota in Metabolic Disease. *Nutrients* 2016, 8: 202. PMID: 27058556

8. Rogers GB, Keating DJ, Young RL, Wong ML, Licinio J, Wesselingh S. From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. *Mol Psychiatry* 2016 21(6):738–48. doi:10.1038/ mp.2016.50. PMID: 27090305

9. Zhu X, Han Y, Du J, Liu R, Jin K, Yi W. Microbiota-gut-brain axis and the central nervous system. *Oncotarget* 2017, 10;8(32):53829-53838. PMID: 28881854

10. Wang Y, Kasper LH. The role of microbiome in central nervous system disorders. *Brain Behav Immun* **2014**, 38:1-12. PMID: 24370461

11. Wang, H.X, Wang, Y.P. Gut Microbiota-brain Axis. *Chin. Med. J.(Engl)* 2016, 129: 2373–2380. PMID: 27647198

12. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci U S A.* 2011, 108:16050–16055. PMID: 21876150

13. Bercik P, Park AJ, Sinclair D, Khoshdel A, Lu J, Huang X, Deng Y, Blennerhassett PA, Fahnestock M, Moine D, Berger B, Huizinga JD, Kunze W, et al. The anxiolytic effect of Bifidobacterium longum NCC3001 involves vagal pathways for gut-brain communication. *Neurogastroenterol Motil*. 2011, 23:1132–1139. PMID: 21988661

14. Klarer M, Arnold M, Günther L, Winter C, Langhans W, Meyer U. Gut vagal afferents differentially modulate innate anxiety and learned fear. *J Neurosci* 2014, 21;34(21):7067-76. PMID: 24849343

15. Kimura I, Inoue D, Maeda T, Hara T, Ichimura A, Miyauchi S, Kobayashi M, Hirasawa A, Tsujimoto G. Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41*). Proc Natl Acad Sci U S A.* 2011, 10;108(19):8030-5. PMID: 21518883

16. Sherwin E, Sandhu KV, Dinan TG, Cryan JF. May the Force Be With **You: The Light and Dark Sides of the Microbiota-Gut-Brain Axis in Neuropsychiatry.** *CNS Drugs*. 2016, 30(11):1019-1041. PMID: 27417321

17. Latorre R, Sternini C, De Giorgio R, Greenwood-Van Meerveld B. Enteroendocrine cells: a review of their role in brain–gut communication. *Neurogastroenterol Motil.* 2016, 28(5):620-30. doi: 10.1111/nmo.12754. Epub 2015 Dec 21. PMID: 26691223

18. Breton J, Tennoune N, Lucas N, Francois M, Legrand R, Jacquemot J, Goichon A, Guérin C, Peltier J, Pestel-Caron M, Chan P, Vaudry D, do Rego JC, Liénard F, Pénicaud L, Fioramonti X, Ebenezer IS, Hökfelt T, Déchelotte P, Fetissov SO. Gut commensal E. coli proteins activate host satiety pathways following nutrient-induced bacterial growth. *Cell Metab*. 2016, 9;23(2):324-34. doi: 10.1016/j. cmet.2015.10.017. PMID: 266221107

19. Lerner A, Jeremias P, Matthias T, Nutrients, bugs and us: The short-chain fatty acids story in celiac disease. *Int. J. Celiac Dis.* 2016, 4: 92–94. doi: 10.12691/ijcd-4-3-12

20. de Theije CG, Wopereis H, Ramadan M, van Eijndthoven T, Lambert J, Knol J, Garssen J, Kraneveld AD, Oozeer R. Altered gut microbiota and activity in a murine model of autism spectrum disorders. *Brain Behav Immun.* 2014, 37:197-206. doi: 10.1016/j.bbi.2013.12.005. PMID: 24333160

21. Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, Nagler CR, Ismagilov RF, Mazmanian SK, Hsiao EY. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell* 2015,161(2):264-76. doi: 10.1016/j. cell.2015.02.047. PMID: 25860609

DOI 10.26386/obrela.v1i2.48 ISSN 2585-2795

22. Stilling RM, Dinan TG, Cryan JF. Microbial genes, brain & behaviour - epigenetic regulation of the gut-brain axis. *Genes Brain Behav.* 2014, 13(1):69-86. doi: 10.1111/gbb.12109. PMID: 24286462

23. Marcobal A, Kashyap PC, Nelson TA, Aronov PA, Donia MS, Spormann A, Fischbach MA, Sonnenburg JL. A metabolomic view of how the human gut microbiota impacts the host metabolome using humanized and gnotobiotic mice. *ISME J.* 2013, 7(10):1933-43. doi: 10.1038/ismej.2013.89. PMID: 23739052

24. El Aidy S, Dinan TG, Cryan JF. Immune modulation of the brain-gut-microbe axis. *Front Microbiol.* 2014, 7;5:146. doi: 10.3389/fmicb.2014.00146. eCollection 2014. PMID: 24778631

25. Redl H, Bahrami S, Schlag G, Traber D.L. Clinical detection of LPS and animal models of endotoxemia. *Immunobiology* 1993, 187: 330–45. PMID: 8330902

26. Sudo N, Chida Y, Aiba Y, Sonoda J, Oyama N, Yu XN, Kubo C, Koga Y. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *J Physiol*. 2004, 1:558(Pt 1):263-75. PMID: 15133062

27. Holzer P, Farzi A. Neuropeptides and the microbiota-gut-brain axis. *Adv Exp Med Biol*. (2014), 817:195-219 PMID: 24997035

28. Barrett E, Ross RP, O'Toole PW, Fitzgerald GF, Stanton C. Gamma-Aminobutyric acid production by culturable bacteria from the human intestine. *Journal of applied microbiology* 2012, 113:411–417. PMID: 22612585

29. Ghaisas S, Maher J, Kanthasamy A. Gut microbiome in health and disease: linking the microbiome-gut-brain axis and environmental factors in the pathogenesis of systemic and neurodegenerative diseases. *Pharmacol Ther* 2016, 158:52-62. doi: 10.1016/j.pharmthera.2015.11.012. PMID: 26627987

30. Neufeld KA, Foster JA. Effects of gut microbiota on the brain: implications for psychiatry. *J Psychiatry Neurosci* 2009, 34: 230–231. PMID: 19448854

31. Kennedy PJ, Cryan JF, Dinan TG, Clarke G. Irritable bowel syndrome: a microbiome-gut-brain axis disorder? *World J Gastroenterol* 2014, 20: 14105–14125. PMID: 25339800

32. Fond G, Boukouaci W, Chevalier G, Regnault A, Eberl G, Hamdani N et al. The «psychomicrobiotic»: targeting microbiota in major psychiatric disorders: a systematic review. *Pathol Biol* (Paris) 2015, 63: 35–42. PMID: 25468489

33. Evrensel A, Ceylan ME. The gut-brain axis: the missing link in depression. *Clin Psychopharmacol Neurosci* 2015, 13: 239–244. PMID: 26598580

34. Lima-Ojeda JM, Rupprecht R, Baghai TC. «I Am I and My Bacterial Circumstances»: Linking Gut Microbiome, Neurodevelopment, and Depression. *Front Psychiatry* 2017, 22;8:153. doi: 10.3389/fpsyt.2017.00153. eCollection 2017. PMID: 28878696

35. Spenrath MA, Clarke ME, Kutcher S (2011). The science of brain and biological development: implications for mental health research, practice, and policy. *Journal of the Canadian Academy of Child and Adolescent Psychiatry* 2011, 20(4):298-304. PMID: 22114611

36. Severance EG, Tveiten D, Lindström LH, Yolken RH, Reichelt KL. The Gut Microbiota and the Emergence of Autoimmunity: Relevance to Major Psychiatric Disorders *Curr Pharm Des*. 2016, 22(40):6076-6086. PMID: 27634185

37. Li Q, Han Y, Dy ABC, Hagerman RJ. The Gut Microbiota and Autism Spectrum Disorders. *Front Cell Neurosci* (2017) Apr 28;11:120. PMID: 28503135

38. Sullivan EL, Riper KM, Lockard R, Valleau JC. Maternal high-fat diet programming of the neuroendocrine system and behavior. *Horm Behav* 2015, 76: 153–61. PMID: 25913366

39. Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Tóth M, Korecka A, Bakocevic N, Ng LG, Kundu P, Gulyás B, Halldin C, Hultenby K, Nilsson H, Hebert H, Volpe BT, Diamond B, Pettersson S. The gut microbiota influences blood-brain barrier permeability in mice. *Sci Transl Med* 2014, 19:6(263):263ra158. PMID: 25411471

40. Weinstock M. The long-term behavioural consequences of prenatal stress. *Neurosci Biobehav Rev*. 2008, 32(6):1073-86. PMID: 18423592

41. Crudo A, Suderman M, Moisiadis VG, Petropoulos S, Kostaki A, Hallett M et al. Glucocorticoid programming of the fetal male hippocampal epigenome. *Endocrinology* 2013, 154(3):1168-80. PMID: 23389956

42. Côté F, Fligny C, Bayard E, Launay JM, Gershon MD, Mallet J,Vodjdani G. Maternal serotonin is crucial for murine embryonic development. *Proc Natl Acad Sci USA* 2007, 2;104(1):329-34. PMID: 17182745

43. Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, Nagler CR, Ismagilov RF, Mazmanian SK, Hsiao EY. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell* 2015, 9;161(2):264-76. PMID: 25860609

44. Park H, Poo MM. Neurotrophin regulation of neural circuit development and function. *Nat Rev Neurosci* 2013, 14(1):7-23. PMID: 23254191

45. Luczynski P, Whelan SO, O'Sullivan C, Clarke G, Shanahan F, Dinan TG, Cryan JF. Adult microbiota-deficient mice have distinct dendritic morphological changes: differential effects in the amygdala and hippocampus. *Eur J Neurosci* 2016, 44(9):2654–66. doi: 10.1111/ejn.13291. PMID: 27256072

46. Gareau MG, Wine E, Rodrigues DM, Cho JH, Whary MT, Philpott DJ, Macqueen G, Sherman PM. Bacterial infection causes stress-induced memory dysfunction in mice. *Gut* 2011, 60(3):307-17 PMID: 20966022

47. Clarke G, Grenham S, Scully P, Fitzgerald P, Moloney RD, Shanahan F, Dinan TG, Cryan JF. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. *Mol Psychiatry* 2013, 18(6):666-73. PMID: 22688187

48. Yang Y, Raine A. Prefrontal structural and functional brain imaging findings in antisocial, violent, and psychopathic individuals: a meta-analysis. *Psychiatry Res* 2009, 30;174(2):81-8. PMID: 19833485

DOI 10.26386/obrela.v1i2.48 ISSN 2585-2795

49. Hoban AE, Stilling RM, Ryan FJ, Shanahan F, Dinan TG, Claesson MJ, Clarke G, Cryan JF. Regulation of prefrontal cortex myelination by the microbiota. *Transl Psychiatry* 2016, 5;6:e774. PMID: 27045844

50. Desbonnet L, Clarke G, Shanahan F, Dinan TG, Cryan JF. Microbiota is essential lfor social development in the mouse. *Mol Psychiatry* 2014, 19(2):146-8 PMID: 23689536

51. Amaral FA, Sachs D, Costa VV, Fagundes CT, Cisalpino D, Cunha TM Silva TA, Nicoli JR, Vieira LQ, Souza DG, Teixeira MM. Commensal microbiota is fundamental for the development of inflammatory pain. *Proc Natl Acad Sci USA* 2008, 12:105(6):2193-7. PMID: 18268332

52. Neufeld KA, Kang N, Bienenstock J, Foster JA. Effects of intestinal microbiota on anxiety-like behavior. *Commun Integr Biol* 2011, 4(4):492-4. PMID: 21966581

53. Zheng P, Zeng B, Zhou C, Liu M, Fang Z, Xu X, Zeng L, Chen J, Fan S, Du X, Zhang X, Yang D, Yang Y, Meng H, Li W, Melgiri ND, Licinio J, Wei H, Xie P. Microbiome remodeling induces depression-like behaviors in a pathway that is mediated through the host's metabolism. *Mol Psychiatry* 2016, 21(6):786-96 .PMID: 27067014

54. Collins SM, Kassam Z, Bercik P. The adoptive transfer of behavioral phenotype via the intestinal microbiota: experimental evidence and clinical implications. *Curr Opin Microbiol* 2013, 16:240 –45. PMID: 23845749

55. Diaz Heijtz R, Wang S, Anuar F, Qian Y, Björkholm B, Samuelsson A, Hibberd ML, Forssberg H, Pettersson S. Normal gut microbiota modulates brain development and behavior. *Proc Natl Acad Sci USA* 2011, 15:108(7):3047-52. PMID: 2128263

56. Ogbonnaya ES, Clarke G, Shanahan F, Dinan TG, Cryan JF, O'Leary OF. Adult hippocampal neurogenesis is regulated by the microbiome. *Biol Psychiatry* 2015, 78(4):e7–9. PMID: 25700599

57. Zonis S, Pechnick RN, Ljubimov VA, Mahgerefteh M, Wawrowsky K, Michelsen KS, Chesnokova V. Chronic intestinal inflammation alters hippocampal neurogenesis. *J Neuroinflammation* 2015, 3;12:65. PMID: 25889852

58. Jiang H, Ling Z, Zhang Y, Mao H, Ma Z, Yin Y, Wang W, Tang W, Tan Z, Shi J, Li L, Ruan B. Altered fecal microbiota composition in patients with major depressive disorder. *Brain Behav Immun* 2015, 48:186-94. PMID: 25882912

59. Aizawa E, Tsuji H, Asahara T, Takahashi T, Teraishi T, Yoshida S, Ota M, Koga N, Hattori K, Kunugi H. Possible association of Bifidobacterium and Lactobacillus in the gut microbiota of patients with major depressive disorder. *J Affect Disord* 2016, 15:202:254-7. PMID: 27288567

60. Maes M, Kubera M, Leunis JC, Berk M. Increased IgA and IgM responses against gut commensals in chronic depression: further evidence for increased bacterial translocation or leaky gut. *J Affect Disord* 2012, 1:141(1):55-62. PMID: 22410503

61. Szczesniak O, Hestad K, Hanssen JF, Rudi K. Isovaleric acid in stool correlates with human depression. *Nutr Neurosci.* 2016, 19(7):279-83. PMID: 25710209

62. Gareau MG, Jury J, MacQueen G, Sherman PM, Perdue MH. Probiotic treatment of rat pups normalises corticosterone release and ameliorates colonic dysfunction induced by maternal separation. *Gut* 2007, 56:1522–1528. PMID: 17339238

63. Tillisch K, Labus J, Kilpatrick L, Jiang Z, Stains J, Ebrat B, Guyonnet D, Legrain-Raspaud S, Trotin B, Naliboff B, Mayer EA. Consumption of fermented milk product with probiotic modulates brain activity. *Gastroenterology* 2013, 144(7):1394-401. PMID: 23474283

64. Goehler LE, Park SM, Opitz N, Lyte M, Gaykema RP. Campylobacter jejuni infection increases anxiety-like behavior in the holeboard: possible anatomical substrates for viscerosensory modulation of exploratory behavior. *Brain Behav Immun* 2008, 22(3):354-66. Epub 2007 Oct 24. PMID: 17920243

65. Gaykema RP, Goehler LE, Lyte M. Brain response to cecal infection with Campylobacter jejuni: analysis with Fos immunohistochemistry. *Brain* Behav Immun 2004, 18(3):238-45. PMID: 15050651

66. Lyte M, Li W, Opitz N, Gaykema RP, Goehler LE. Induction of anxietylike behavior in mice during the initial stages of infection with the agent of murine colonic hyperplasia Citrobacter rodentium. *Physiology & behavior* 2006, 89:350–357. PMID: 16887154

67. Bercik P, Verdu EF, Foster JA, Macri J, Potter M, Huang X, Malinowski P, Jackson W, Blennerhassett P, Neufeld KA, Lu J, Khan WI, Corthesy-Theulaz I, Cherbut C, Bergonzelli GE, Collins SM. Chronic gastrointestinal inflammation induces anxiety-like behavior and alters central nervous system biochemistry in mice. *Gastroenterology* 2010, 139(6):2102-2112.e1. PMID: 20600016

68. «Schizophrenia Fact sheet N°397». WHO. September 2015. Archived from the original on 18 October 2016. Retrieved 3 February 2016.

69. Severance EG, Yolken RH, Eaton WW. Autoimmune diseases, gastrointestinal disorders and the microbiome in schizophrenia: more than a gut feeling. *Schizophr Res* 2016, 176(1):23-35. PMID: 25034760

70. Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D et al. Common variants conferring risk of schizophrenia. *Nature* 2009, 6:460(7256):744-7. PMID: 19571808

71. Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N et al. Schizophrenia risk from complex variation of complement component 4. *Nature* 2016, 11:530(7589):177-83. PMID: 26814963

72. Fond G, Boukouaci W, Chevalier G, Regnault A, Eberl G, Hamdani N, Dickerson F, Macgregor A, Boyer L, Dargel A, Oliveira J, Tamouza R, Leboyer M. The "psychomicrobiotic": Targeting microbiotain major psychiatric disorders: A systematic review *Pathol Biol (Paris)* 2015, 63(1):35-42. PMID: 25468489

73. Fan X, Goff DC, Henderson DC. Inflammation and schizophrenia. *Expert Rev Neurother* 2007, 7(7):789-96. PMID: 17610386

DOI 10.26386/obrela.v1i2.48 ISSN 2585-2795

74. Strous RD, Shoenfeld Y. Schizophrenia, autoimmunity and immune system dysregulation: a comprehensive model updated and revisited. *J Autoimmun* 2006, 27:71–80. PMID: 16997531

75. Ding M, Song X, Zhao J, Gao J, Li X, Yang G, Wang X, Harrington A, Fan X, Lv L. Activation of Th17 cells in drug naive, first episode schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2014, 51:78–82. PMID: 24447943

76. American Psychiatric Association. «Autism Spectrum Disorder. 299.00 (F84.0)». *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*. Arlington, VA: American Psychiatric Publishing, 2013

77. Kaneko M, Hoshino Y, Hashimoto S, Okano T, Kumashiro H. Hypothalamic-pituitary-adrenal axis function in children with attention-deficit hyperactivity disorder. *J Autism Dev Disord* 1993, 23:59–65. PMID: 8463202

78. Sandler RH, Finegold SM, Bolte ER, Buchanan CP, Maxwell AP, Vaisanen ML, Nelson MN, Wexler HM. Short-term benefit from oral vancomycin treatment of regressive-onset autism. *J Child Neurol* 2000, 15:429–435. PMID: 10921511

79. Bolte ER. Autism and Clostridium tetani. *Medical hypotheses* 1998, 51(2):133-44. PMID: 9881820

80. Finegold SM, Molitoris D, Song Y, Liu C, Vaisanen ML, Bolte E, McTeague M, Sandler R, Wexler H, Marlowe EM, Collins MD, Lawson PA, Summanen P, Baysallar M, Tomzynski TJ, Read E, Johnson E, Rolfe R, Nasir P, Shah H, Haake DA, Manning P, Kaul A. Gastrointestinal microflora studies in lateonset autism. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 2002; 35:S6–S16. PMID: 12173102

81. Parracho HM, Bingham MO, Gibson GR, McCartney AL. Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. *Journal of medical microbiology*. 2005; 54:987–991. PMID: 16157555

82. Finegold SM. Therapy and epidemiology of autism--clostridial spores as key elements. Med Hypotheses. 2008; 70:508–511. PMID: 17904761

83. Gilbert JA, Krajmalnik-Brown R, Porazinska DL, Weiss SJ, Knight R. Toward effective probiotics for autism and other neurodevelopmental disorders. *Cell* 2013, 19;155(7):1446-8. PMID: 24360269

84. *American Psychiatry Association: Diagnostic and Statistical Manual of Mental Disorders (5th ed.). Arlington: American Psychiatric Publishing.(2013). pp. 329–354.*

85. Norris V, Molina F, Gewirtz AT. Hypothesis: bacteria control host appetites. *J Bacteriol* 2013, 195(3):411-6. PMID: 23144247

86. Knvul Sheikh. How Gut Bacteria Tell Their Hosts What to Eat, Scientific American (2017) on April 25 (Internet), https://www.scientificamerican.com/article/how-gut-bacteria-tell-their-hosts-what-to-eat/

87. Alcock, J.; Maley, C.C.; Aktipis, C.A. Is eating behavior manipulated by the gastrointestinal microbiota? Evolutionary pressures and potential mechanisms. *Bioessays* 2014, 36: 940–949. PMID: 25103109

88. Cryan JF, Dinan TG. Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. *Nat. Rev. Neurosci*. 2012, 13: 701–712 PMID: 22968153

89. *Solcia, E; Capella, C; Buffa, R; Usellini, L; Fiocca, R; Frigerio, B; Tenti, P; Sessa, F. «The diffuse endocrine-paracrine system of the gut in health and disease: ultrastructural features». Scandinavian journal of gastroenterology 1981 Supplement. 70: 25–36.* PMID: 6118945.

90. Raybould HE. Gut chemosensing: Interactions between gut endocrine cells and visceral afferents. *Auton. Neurosci.* 2010, 153: 41–46. PMID: 19674941

91. Banks WA, Gray AM, Erickson MA, Salameh TS, Damodarasamy M, Sheibani N, Meabon JS, Wing EE, Morofuji Y, Cook DG, Reed MJ. Lipopolysaccharide-induced blood-brain barrier disruption: Roles of cyclooxygenase, oxidative stress, neuroinflammation, and elements of the neurovascular unit. *J. Neuroinflamm.* 2015, 12: 223. PMID: 26608623

92. Cani PD, Lecourt E, Dewulf EM, Sohet FM, Pachikian BD, Naslain D, De Backer F, Neyrinck AM, Delzenne NM. Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. *Am. J. Clin. Nutr*. 2009, 90:1236–1243. PMID: 19776140

93. Fetissov SO, Harro J, Jaanisk M, Jarv A, Podar I, Allik J, Nilsson I, Sakthivel P, Lefvert AK, Hokfelt T. Autoantibodies against neuropeptides are associated with psychological traits in eating disorders. *Proc. Natl. Acad. Sci. USA* 2005, 102: 14865–70. PMID: 16195379

Dialogues in Clinical Neuroscience & Mental Health

DOI 10.26386/obrela.v1i2.49

ISSN 2585-2795

Special article

Neuropsychology and Driving Behaviour: Analysis of a complex correlation

Sokratis G Papageorgiou[1], Ion N Beratis[1], Dimosthenis Pavlou[2], Petros Stamatelos[1], Stella Fragkiadaki[1], Dionysia Kontaxopoulou[1], Nikos Andronas[1], Alexandra Economou[3], Andrew Papanicolaou[4], George Yannis[2]

1. Cognitive Disorders/Dementia Unit, 2nd Department of Neurology, National and Kapodistrian University of Athens, «Attikon» University General Hospital, Athens, Greece.

2. Department of Transportation Planning and Engineering, School of Civil Engineering, National Technical University of Athens, Zografou, Athens, Greece.

3. Department of Psychology, National and Kapodistrian University of Athens, Panepistimiopolis, Ilissia, Athens, Greece.

4. The University of Tennessee Health Science Center, Memphis, TN, USA

Abstract

Driving is a multimodal task that requires the integrity of executive functions in order to process simultaneously multiple environmental cues, to predict the development of traffic situations, as well as to take rapid, accurate and safe decisions. Memory plays an important role, among others, on route planning and traffic signs recognition. In addition, visuospatial skills are crucial for vehicle's road positioning along with the estimation of distances between vehicles, while attention is necessary for the accurate perception of on-road changes. The role of Neuropsychology is of critical importance for evaluating driving ability in the elderly, especially in the case of drivers with cognitive disorders, such as Mild Cognitive Impairment and Alzheimer's Dementia. Regarding the driving competence of drivers with Mild Cognitive Impairment, in the majority of cases they are considered capable of driving. Although Alzheimer's Dementia has a well-recognized and –described negative effect on driving performance, there is a subgroup of mild Alzheimer's Dementia patients who retain satisfactory driving skills. Neuropsychological assessment needs to be harmonized across different teams and countries, in order to provide a common and reliable tool in the holistic approach of cognitive impaired drivers.

Corresponding Author: : Sokratis G Papageorgiou, Cognitive Disorders/Dementia Unit, 2nd Department of Neurology, National and Kapodistrian University of Athens, «Attikon» University General Hospital, Athens , Greece, sokpapa@med.uoa.gr

Received: March 21, 2018, Accepted: April 5, 2018

DOI 10.26386/obrela.v1i2.49 ISSN 2585-2795

Introduction

Driving is a very important function for the elderly, as it is closely related to their autonomy, their self-esteem and the overall quality of life, while loss of driving privileges may have a detrimental effect on their psychological health. Nowadays, more and more elderly are active drivers and tend to retain their driving privileges for longer periods of time, as compared to the past (Eurostat, 2014) **[1]** .

The effect of normal aging on driving ability has been thoroughly investigated. General health problems, vision difficulties and cognitive impairment are all age-related parameters associated with a decline in driving ability. However, the percentage of older drivers at high risk for an accident remains unclear. This arises from a lack of a systematic and unanimously accepted methodology to evaluate these people's both cognitive and physical deficits.

As far as cognitive status is concerned, driving is a multimodal task that requires the integrity of executive functions in order to process simultaneously multiple environmental cues, to predict the development of traffic situations, as well as to take rapid, accurate and safe decisions. Memory plays an important role, among others, on route planning and traffic signs recognition. In addition, visuospatial skills are crucial for vehicle's road positioning along with the estimation of distances between vehicles, while attention is necessary for the accurate perception of on-road changes **[2]**. Under this perspective, neurodegenerative diseases which cause cognitive impairment may have a detrimental effect on driving ability **[3]**.

Aim

The objective of this article is to present and discuss the current knowledge about the driving behaviour of patients with Alzheimer's Dementia (AD) and Mild Cognitive Impairment (MCI) and consequently their ability to drive. In addition, we present a personalized approach when taking decisions about the driving fitness of patients belonging in the above mentioned clinical groups, emphasizing on the neuropsychological aspects of this evaluation. This personalized approach is, by definition, inter-disciplinary, as it requires the collaboration of neurologists, neuropsychologists and transportation engineers.

Methods

AD: Patients with Alzheimer's dementia are 2.5 to 4.7 times more likely to get involved in a car accident than other non-demented elderly drivers of similar age. However, around 50% of AD patients continue to drive for at least three years after their initial diagnosis **[4]**, while a cross-sectional study of a memory clinic conducted in northern Italy reported that 87% of patients with dementia were still active drivers **[5]**. The fact that patients with AD are more vulnerable to driving errors is well-established in the literature and has been confirmed by our findings, too.

More specifically, as on-road driving tests have shown, they make significantly more incorrect turns, get lost more often and commit at-fault safety errors.

Findings from our driving simulator experiment indicate that patients with mild AD adopt a different driving pattern (lower average speed, longer average headway), have a longer reaction time and, most importantly, have a (statistically significant) higher probability of an accident, in comparison to healthy individuals of the same aging group **[6]**. We have also shown that distraction while driving (in terms of mobile phone use) has a clear detrimental effect on both reaction time and accident probability among individuals with AD **[7]**.

Nonetheless, not all patients with AD are incapable of driving, especially in the milder stages of the disease. Indicative is the study of Brown et al. (2005) **[8],** which observed that 76% of a group of mild AD patients were able to pass an on-road driving test.

Concerning the correlation of neuropsychological tests with the ability to drive, data are rather ambiguous. Previous research indicates that performance on tests measuring visuospatial and attentional abilities, executive functioning and possibly memory is associated with the ability to drive safely

DOI 10.26386/obrela.v1i2.49 ISSN 2585-2795

in patients with dementia. However, other studies have failed to reproduce these results, highlighting though the importance of self-assessment along with evaluation of driving fitness by patients' informants.

MCI: The fact that MCI affects not only memory (amnestic MCI- aMCI), but also other cognitive domains (including executive functions, attention, visuospatial skills and multiple domains- mdMCI) is well-established in the literature. However, the effect of MCI on driving fitness still lacks a consensus, as evidence is relatively sparse and equivocal. Although MCI patients are at risk for presenting increased driving difficulties and tend to modify their driving habits (reducing their driving frequency and avoiding driving under difficult weather conditions), overall their performance on on-road or on simulator driving tests is not consistently worse than that of healthy individuals of the same age **[9]**. Our findings are consistent with the above described evidence; furthermore we have described the detrimental impact of distraction (mobile phone use) on both reaction time and accident probability among MCI patients **[10]**. Very recently, Hird et al. (2017) **[11]** have clearly shown that patients with md MCI seem to perform worse in many important driving parameters, compared to healthy controls, highlighting the significance of differentiating between different subtypes of MCI when evaluating driving competence.

Regarding neuropsychological tests that can predict driving ability in the clinical group of MCI, current research is sparse. Measures of mental flexibility, inhibitory control and visual attention, appear to be associated with driving performance in patients with MCI, but these issues need further investigation **[12]**. It is worth to note that depressive symptoms -even in the absence of clinical depression- have a clear negative effect on driving skills, among individuals with MCI **[13]**. Interestingly enough, measures of insomnia and sleepiness (as expressed through Athens Insomnia Scale and Epworth Sleeping Scale, respectively) seem to have a negative impact on various parameters of driving behaviour **[14]**.

Conclusions

Aim of this article was to present the current knowledge about driving behaviour of patients with MCI and AD and to discuss the correlation of neuropsychological evaluation with driving performance.

Although AD has a well-recognized and –described negative effect on driving performance, there is a subgroup of mild AD patients who retain satisfactory driving skills. Hence, a diagnosis of AD should not be considered by itself as an adequate criterion for loss of driving privileges. Instead, what appears to be the best option is the adoption of a personalized and holistic approach based on the analytical evaluation of each driver with AD. In this direction, neurological and neuropsychological indexes could and should be combined with driving performance indexes (evaluated during actual or simulated road tests), in order to make well documented recommendations regarding these patients' fitness to drive.

Regarding the driving competence of drivers with MCI, in the majority of cases they are considered capable of driving. However, when a thorough and inter-disciplinary evaluation is performed, even small changes are detected: More specifically, MCI patients have the tendency of making more driving errors than their healthy counterparts, are vulnerable to on-road distraction and it seems that a portion of them (especially those with md MCI) has considerably increased driving difficulties, which may influence their ability to drive. Therefore, analytical and periodical re-evaluation of driving ability on this clinical group is suggested to be formally implemented, in order to detect small changes in driving behavior and make proper regulations on time. We should take into consideration that neuropsychiatric symptoms such as irritability, aggressiveness or depressive symptomatology and sleep abnormalities as well, may be present in up to 50% of the MCI patients and those features may have a detrimental effect on driving ability. Thus, their early recognition and treatment is of great significance, as it can elongate the continuation of driving privileges.

When evaluating driving competence of patients with neu-

DOI 10.26386/obrela.v1i2.49 ISSN 2585-2795

rodegenerative diseases (namely MCI and AD), it is very important for the patients and their relatives to participate in the decision process and the overall planning about the cessation of driving. The utility of this policy is double: not only keeps a balance between personal/public safety and self-determination, but also adds the extra aspect of self-evaluation on the holistic approach of driving competence.

To conclude with, the role of Neuropsychology is of critical importance for evaluating driving ability in the elderly, especially in the case of drivers with cognitive disorders, such as MCI and AD. However, despite necessary, neuropsychological evaluation is not sufficient alone to dictate decisions related to the critical question "continue to drive or not?". According to our view, restriction or total loss of driving privileges can be decided only by an inter-disciplinary team that integrates the specialties of neurology, neuropsychology and transportation engineering. Such a team is able to perform analytical evaluation and assess the whole spectrum of the information provided. Towards this direction, neuropsychological assessment needs to be harmonized across different teams and countries, in order to provide a common and reliable tool in the holistic approach of cognitive impaired drivers **[15]**. We must not forget that periodic re-evaluations of patients' fitness to drive are necessary, in terms of a follow-up of the temporal progression of the underlying disease.

The schematic representation of the proposed approach is illustrated in Figure 1. (Adapted from Papageorgiou et. al, 2016) **[2]**

References

1 Eurostat regional yearbook 2014. Luxembourg: Publications Office of the European Union, 2014.

2 Papageorgiou, S. G., Beratis, I. N., Kontaxopoulou, D., Fragkiadaki, S., Pavlou, D., & Yannis, G. Does the diagnosis of Alzheimers Disease imply immediate revocation of a driving license? *International Journal of Clinical Neurosciences and Mental Health,* 2016, 3(Suppl. 1)). doi:10.21035/ijcnmh.2016.3(suppl.1).s02

3 Iverson, D. J., Gronseth, G. S., Reger, M. A., Classen, S., Dubinsky, R. M., & Rizzo, M. (2010). Practice Parameter update: Evaluation and management of driving risk in dementia: Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2010*, 74*(16): 1316-1324. doi:10.1212/wnl.0b013e3181da3b0f

4 Seiler, S., Schmidt, H., Lechner, A., Benke, T., Sanin, G., Ransmayr, G., Schmidt, R. Driving Cessation and Dementia: Results of the Prospective Registry on Dementia in Austria (PRODEM). *PLoS ONE* 2012, 7(12):e52710, doi:10.1371/journal.pone.0052710

5 Mauri, M., Sinforiani, E., Cuzzoni, M. G., Bono, G., & Zucchella, C. Driving habits in patients with dementia: a report from Alzheimer's disease assessment units in northern Italy. *Functional neurology* 2014, 29(2): 107-112. PMID: 25306120, PMCID: PMC4198158

6 Pavlou, D., Beratis, I., Papadimitriou, E., Antoniou, C., Yannis, G., & Papageorgiou, S. (2016). Which Are the Critical Measures to Assess the Driving Performance of Drivers with Brain Pathologies? *Transportation Research Procedia, 14*, 4393-4402. doi:10.1016/j.trpro.2016.05.361

7 Pavlou, D., Theofilatos, A., Papadimitriou, E., Yannis, G., & Papageorgiou, S. G. Exploration of accident probability of drivers with brain pathologies. *Injury Prevention* 2016*, 22*(Suppl 2). doi:10.1136/injuryprev-2016-042156.670

8 Brown, L. B., Ott, B. R., Papandonatos, G. D., Sui, Y., Ready, R. E., & Morris, J. C. Prediction of On-Road Driving Performance in Patients with Early Alzheimers Disease. *Journal of the American Geriatrics Society* 2005*, 53*(1): 94-98. doi:10.1111/j.1532-5415.2005.53017.x

9 Kawano, N., Iwamoto, K., Ebe, K., Suzuki, Y., Hasegawa, J., Ukai, K., Ozaki, N. Effects of Mild Cognitive Impairment on Driving Performance in Older Drivers. *Journal of the American Geriatric Society* 2012, 60 (7): 1379-1381. doi: 10.1111/j.1532-5415.2012.04021.x

10 Beratis, I. N., Pavlou, D., Papadimitriou, E., Andronas, N., Kontaxopoulou, D., Fragkiadaki, S., Papageorgiou, S. G. Mild Cognitive Impairment and driving: Does in-vehicle distraction affect driving performance? *Accident Analysis & Prevention* 2017*, 103*: 148-155. doi:10.1016/j.aap.2017.03.014

11 Hird, M. A., Vesely, K. A., Fischer, C. E., Graham, S. J., Naglie, G., & Schweizer, T. A. (2017). Investigating Simulated Driving Errors in Amnestic Single- and Multiple-Domain Mild Cognitive Impairment. *Journal of Alzheimers Disease* 2017,

DOI 10.26386/obrela.v1i2.49 ISSN 2585-2795

56(2): 447-452. doi:10.3233/jad-160995

12 Vardaki, S., Dickerson, A. E., Beratis, I., Yannis, G., & Papageorgiou, S. G. Simulator Measures and Identification of Older Drivers With Mild Cognitive Impairment. *American Journal of Occupational Therapy* 2016, *70*(2): 7002270030p1-10, doi:10.5014/ajot.2016.017673

13 Beratis IN, Andronas N, Kontaxopoulou D, Fragkiadaki S, Pavlou D, Papatriantafyllou J, Economou A, Yannis G, Papageorgiou SG. Driving in mild cognitive impairment: The role of depressive symptoms. *Traffic Injury Prevention* 2017, 18(5):470-476. doi: 10.1080/15389588.2016.1265648.

14 Beratis I., Andronas N., Papadimitriou E., Kontaxopoulou D., Fragkiadaki S., Koros C., Bonakis A., Economou A., Papageorgiou S. G. The role of sleeping abnormalities on the driving performance of individuals with Mild Cognitive Impairment (MCI). *1st Congress of EAN (European Academy of Neurology*, 20-23/06/2015, Berlin, 2015.

15 Costa, A., Bak, T., Caffarra, P., Caltagirone, C., Ceccaldi, M., Collette, F., Cappa, S. F. (2017). The need for harmonisation and innovation of neuropsychological assessment in neurodegenerative dementias in Europe: consensus document of the Joint Program for Neurodegenerative Diseases Working Group. *Alzheimers Research & Therapy* 2017, 17;9(1):27doi:10.1186/s13195-017-0254-x

Dialogues in Clinical Neuroscience & Mental Health

DOI 10.26386/obrela.v1i2.50 ISSN 2585-2795

General article

Neurosurgical Neuropsychology: an emerging sub-specialty

George Stranjalis & Evangelia Liouta

Department of Neurosurgery, National and Kapodestrian University of Athens, Evangelismos Hospital & Hellenic Center of Neurosurgical Research "Prof. Petros Kokkalis", Athens, Greece

ABSTRACT

In this review the role of neuropsychology in the management of neurosurgical pathologies is highlighted. The main neurosurgical disorders that a neuropsychologist can work with are head injuries, brain tumors, epilepsy, movement disorders, hemorrhagic strokes, and idiopathic normal pressure hydrocephalus (iNPH). Neuropsychology plays a significant role during the two main phases of the neurosurgical management: (a) the pre-operative assessment, i.e. the diagnosis of the impact of a lesion on cognitive functions and (b) the post-operative or post-traumatic one, which will evaluate the cognitive result of the injury or of the surgical treatment. In the challenging field of neuro-oncological surgery, a third phase is added, namely the intraoperative one, where the neuropsychologist monitors patient's brain function during electrostimulation in order to avoid damage to the eloquent areas. All the above stress the role of neuropsychology in neurosurgery and designate the need for neuropsychologists to be incorporated in the neurosurgical teams.

Corresponding Author:
George Stranjalis, Department of Neurosurgery, National and Kapodestrian University of Athens, Evangelismos Hospital, e-mail: stranjal@otenet.gr

Received: March 21, 2018, Accepted: April 5, 2018

DOI 10.26386/obrela.v1i2.50 ISSN 2585-2795

INTRODUCTION

Although the role of neuropsychology is well established in the diagnosis of neurological diseases, the contribution of neuropsychologists in the management of the neurosurgical diseases has been only recently recognised. In this review we focus on the main neurosurgical disorders that a neuropsychologist can face in a daily clinical basis and its role in their management. Traumatic Brain Injury (TBI) is not included in our review, since the role of neuropsychology in its diagnosis and cognitive rehabilitation is well established.

NEUROPSYCHOLOGY AND EPILEPSY

In patients with epilepsy, neuropsychological assessments are most frequently used to aid diagnosis, evaluate the cognitive side effects of antiepileptic medications and monitor the cognitive decline associated with some epileptic disorders.

In conjunction with Magnetic Resonance Imaging (MRI) and other presurgical investigations, neuropsychological scores are also used to assess the suitability of patients for epilepsy surgery and can be used to predict post-operative outcome, both in terms of cognitive change and seizure control.

In 2015, the International League Against Epilepsy (ILAE) Diagnostic Commission Neuropsychology Task Force published guidelines concerning the minimum standards in the neuropsychological assessment of patients with epilepsy.

Pre- and post-operative neuropsychological evaluation in epilepsy

Neuropsychological assessment plays an important role in the evaluation of the candidates for temporal lobe surgery. Bilateral hippocampal excision is associated with profound anterograde amnesia. Unilateral resections are traditionally associated with material-specific memory dysfunction.

Post-operative deficits are dependent upon both the functional adequacy of the tissue removed and the functional reserve of the remaining structures. Some plasticity and the development of compensatory strategies post-operatively may also influence the nature and extent of post-operative neuropsychological deficits. Pre-operative neuropsychological scores, in conjunction with MRI and other clinical data, can be utilized to predict post- operative neuropsychological change.

The Intracarotid Amobarbital Procedure (Wada Test)

Traditionally the Intracarotid Amobarbital Procedure (IAP) or Wada test has been used to ensure that the memory capacity of the contralateral temporal lobe is adequate to maintain useful memory functions unilaterally prior to surgery and it is an effective test for language lateralization.

The role of neuropsychologist during this procedure is (a) the choice and the administration of behavioral stimuli whilst the cerebral hemisphere is anesthetized, as well as (b) the interpretation of patient's performance.

Functional Magnetic Resonance Imaging (fMRI)

A number of fMRI paradigms have been developed to localize language function in adults and children. fMRI paradigms have been also recently used in order to examine memory function in prospective temporal lobectomy patients. These techniques have superseded the complex and invasive IAP procedure in language lateralization. They are also combined with the traditional memory tests in order to provide lateralizing and prognostic information for medial temporal epilepsy patients.

NEUROPSYCHOLOGY AND MOVEMENT DISORDERS

The most common movement disorders treated by Neurosurgery are Parkinson's disease (PD) and dystonia. The current neurosurgical treatment of PD and dystonia is based on the results of studies indicating that the reduction of excessive neuronal activity in the internal segment of globus pallidus (GPi) and subthalamic nucleus (STN) can result in a dramatic

DOI 10.26386/obrela.v1i2.50 ISSN 2585-2795

improvement in motor control.

The neuropsychologist plays an important role in the two phases of the neurosurgical management: (a) the preoperative screening and (b) the outcome evaluation. During the screening, the differential diagnosis of dementia, the impact of depression or other psychiatric conditions, and the influence of disease and medication-induced symptoms on cognitive performance must be evaluated. It is thought that this impact is proportional to the risk of postoperative cognitive compromise.

Postoperatively, systematic evaluations elucidate the cognitive costs or benefits of the neurosurgical procedure. The neuropsychologist is then able to provide feedback and counselling to the professional staff, the patient and the family. Neuropsychologists also study alteration of cognitive processing due to lesions or stimulation, which, in tandem with functional imaging, shed light on plasticity in cortical and subcortical processing.

NEUROPSYCHOLOGY AND HEMORRHAGIC STROKE

Subarachnoid hemorrhage (SAH) involves bleeding into the space between the pia and the arachnoid matter. Ninety-percent of the cases with spontaneous SAH are due to ruptured brain aneurysms. Other causes of SAH include arteriovenous malformation (AVM), vascular inflammation and carotid artery dissection. Ruptures aneurysms are treated with either surgical clipping or endovascular coiling, though the latter is the preferred treatment due to its more favorable functional outcomes.

The neuropsychologist can be valuable in regard to the effectiveness of the two main types of treatments mentioned above. In a recent meta-analysis, neuropsychological functioning in patients after coiling and clipping of the cerebral aneurysms were compared. The coil-treated patients outperformed the clip-treated patients on executive function. In addition, all patients showed impairments when compared with healthy controls. Conclusively, coiling of ruptured aneurysms may promote superior neuropsychological functioning under certain circumstances. However, future studies needed to explore thoroughly the effect of different types of SAH interventional treatment on neurocognition.

NEUROPSYCHOLOGY AND INPH

Idiopathic Normal Pressure Hydrocephalus (INPH) is a progressive neurologic disorder which typically presents after the sixth decade of life. It is clinically characterized by disturbances in gait and balance, cognition and control of urination. The main radiological feature is ventriculomegaly in the absence of extensive atrophy.

The predominant therapy for INPH is currently the surgical placement of a cerebrospinal fluid (CSF) shunt device. While the benefits of this interventional treatment have been shown to outweigh its risks, complications can arise.

Keeping with this, diagnosis of INPH should be as accurate as possible. However, INPH diagnosis can be challenging. Alzheimer's dementia is not an uncommon comorbidity in INPH patients; in parallel, a wide range of additional neurological conditions (e.g. Binswanger disease, frontotemporal dementia, Lewy body dementia, PD and corticobasal syndrome) can resemble INPH symptomatology thus making its diagnosis challenging. In this context neuropsychological evaluation can significantly contribute to differential diagnosis and should be conducted on all patients referred with suspected INPH.

The second phase where a neuropsychologist can play a crucial role is the post-supplemental testing. At present several supplemental interventional tests are used for the diagnostic workup of INPH patients and the prediction of a favourable outcome following shunt placement. Thus, clinical improvement, mainly in gait, following lumbar puncture (LP) tap test, Lumbar Infusion Test (LIT) or External Lumbar Drainage test (ELD) is associated with an increased likelihood of improvement after shunt placement.

DOI 10.26386/obrela.v1i2.50 ISSN 2585-2795

An increasing number of studies indicate that neuropsychological investigations can provide valuable information on specific cognitive functions and their deficits in relation to INPH during the diagnostic workup and/or following supplemental tests. The cognitive impairment of INPH is typically characterized by frontal lobe dysfunctions such as psychomotor slowing (increased response latency), deficits in attention and short-term memory and decreased fine motor speed and accuracy. Improvement in frontal executive functions following the LP test is indicated by some studies and this can support patients' candidacy for shunt placement, when gait assessment is difficult to be conducted.

The third phase where neuropsychological assessment is considered important is the post-shunt period. As mentioned above, cognition is one of the three core elements affected in INPH; thus, changes in cognitive status should be reported in order to investigate treatment's efficacy. Lastly, INPH patients should followed-up in order to assess proper long-term shunt function.

NEUROPSYCHOLOGY AND BRAIN TUMORS

Brain tumor is one of the most challenging disorders for the neurosurgeons as well as for the neuropsychologists. The role of a neuropsychologist is mainly related to the effect that a tumor and/or its treatment may have on neurocognition.

Although brain tumor localization and classification is primarily performed by neuroimaging and biopsy of brain tissue, these techniques do not provide information regarding the functional impact of the tumor on cognition and behavior.

Both primary (benign or malignant) and metastatic brain tumors can produce a range of global and/or domain specific impairments in cognitive functions, with reports varying from 15 % to 90%, depending on the characteristics of the tumors studied, the patient demographics, and the treatments received.

The neuropsychological assessment should be part of the standard assessment and management of individuals with brain tumors in the following three stages:

Evaluation prior to surgery

Assessment prior to surgical resection provides insight into the functional impact of tumors and establishes a baseline against which later functioning can be compared. Neuropsychological testing can also identify functional disability that is not diagnosed by imaging and/or neurologic exams, and could not be predicted by tumor type or volume.

While rapidly progressing tumors may cause significant physical and cognitive impairment due to increased intracranial pressure and lesion momentum that outpaces brain plasticity, slowly growing tumors may allow the brain to adapt to the physical presence of the tumor, although may affect the cognitive functions.

Evaluation during surgery - Awake craniotomy

Another role of neuropsychology in the assessment and management of brain tumors, mainly gliomas, is the evaluation of cognitive and sensorimotor functions during awake craniotomy. There is a growing body of evidence that suggests better outcomes, including longer progression-free survival and superior seizure control, with greater extent of resection (EOR) and decreased contrast-enhancing residual tumor volume. However, in patients with tumors infiltrating regions of 'functional' brain, the extent of resection may be limited by the desire to preserve cognitive and motor functions, and in the absence of clear parameters regarding the location of these eloquent regions, the surgeon may be less prone to perform an extensive resection.

Functional imaging techniques can identify the areas that participate in language, motor, and sensory functions, whereas electrocortical stimulation mapping of the neurocognitive functions during awake craniotomy allows the specification of sites that are essential for the preservation of these functions.

During the awake craniotomy, the neuropsychologist administers language and cognitive tasks, monitors for involuntary movements or motor arrest in the mouth, face, and hands, and directs the patient to notice any sensory symptoms as the sur-

DOI 10.26386/obrela.v1i2.50 ISSN 2585-2795

geon stimulates selected sites. Patient's responses are reported back to surgeon in 'real time', and this allows the demarcation of brain areas with an essential role in language, motor, and/or sensory functions that should be preserved, from areas that can be safely resected during tumor removal.

Assessment during and after adjuvant therapies

The treatments used to combat brains tumor can cause damage to the healthy tissue. Screening of neurocognitive functions with neuropsychological measures during and after treatment with chemotherapy and radiation can provide information that may be missed with a brief mental status exam.

Finally, serial neuropsychological testing can also reveal regrowth of tumor weeks to months before there is radiographic evidence of tumor progression.

NEUROPSYCHOLOGY IN THE DEPARTMENT OF NEUROSURGERY AT EVANGELISMOS HOSPITAL

The University Department of Neurosurgery at Evangelismos Hospital in Athens is the first and the only one that provides advanced neuropsychological service.

The Neuropsychology Service was established in 2007 and since then it has been providing clinical and research work mainly in the fields of brain tumors, INPH, TBI, movement disorders and epilepsy.

CONCLUSION

In this review we examine the role of neuropsychology in neurosurgery. According to the literature, neuropsychologists can significantly contribute to the management of neurosurgical disorders. By combining the advanced knowledge of brain anatomy and functions, provided by neurosurgeons and neuropsychologists respectively, we can have a better understanding of the human brain and aim in a more effective treatment of patients suffering from neurosurgical disease.

References

1. Wilson S, Baxendale S, Barr W.Indications and expectations for neuropsychological assessment in routine epilepsy care: Report of the ILAE Neuropsychology Task Force. *Epilepsia* 56: 674-81, 2015, PMID: 25779625 , DOI: 10.1111/epi.12962

2. Jean A. Saint-Cyr. Neuropsychology for Movement Disorders Neurosurgery. *Can J Neurol Sci* 30: 1 – 93, 2003, PMID: 12691481

3. Egeto P, Loch Macdonald R, Ornstein TJ, Schweizer TA. Neuropsychological function after endovascular and neurosurgical treatment of subarachnoid hemorrhage: a systematic review and meta-analysis. *J Neurosurg* 14: 1-9, 2017, PMID: 28409729 , DOI: 10.3171/2016.11.JNS162055

4. Peterson KA, Savulich G, Jackson D, Killikelly C, Pickard JD, Sahakian BJ. The effect of shunt surgery on neuropsychological performance in normal pressure hydrocephalus: a systematic review and metaanalysis. *J Neurol* 263: 1669–77, 2016, PMID: 27017344 , PMCID: PMC4971036 , DOI: 10.1007/s00415-016-8097-0

5. Liouta E, Koutsarnakis C, Stranjalis G. Finger tapping and verbal fluency post-tap test improvement in INPH: its value in differential diagnosis and shunt-treatment outcomes prognosis. *Acta Neurochirurgica*, 2017 , PMID: 28828534, DOI: 10.1007/s00701-017-3301-2

6. Liouta E, Koutsarnakis C,Liakos F, Stranjalis G. Effects of intracranial meningioma location, size, and surgery on neurocognitive functions: a 3-year prospective study. *Journal of Neurosurgery*; 124: 1578-84, 2016 , PMID: 26636380 , DOI: 10.3171/2015.6.JNS1549

7. Hoffnung DS. The Role of Neuropsychology in the Assessment and Management of CNS Tumors. *Clin Oncol* 1: 1065, 2016