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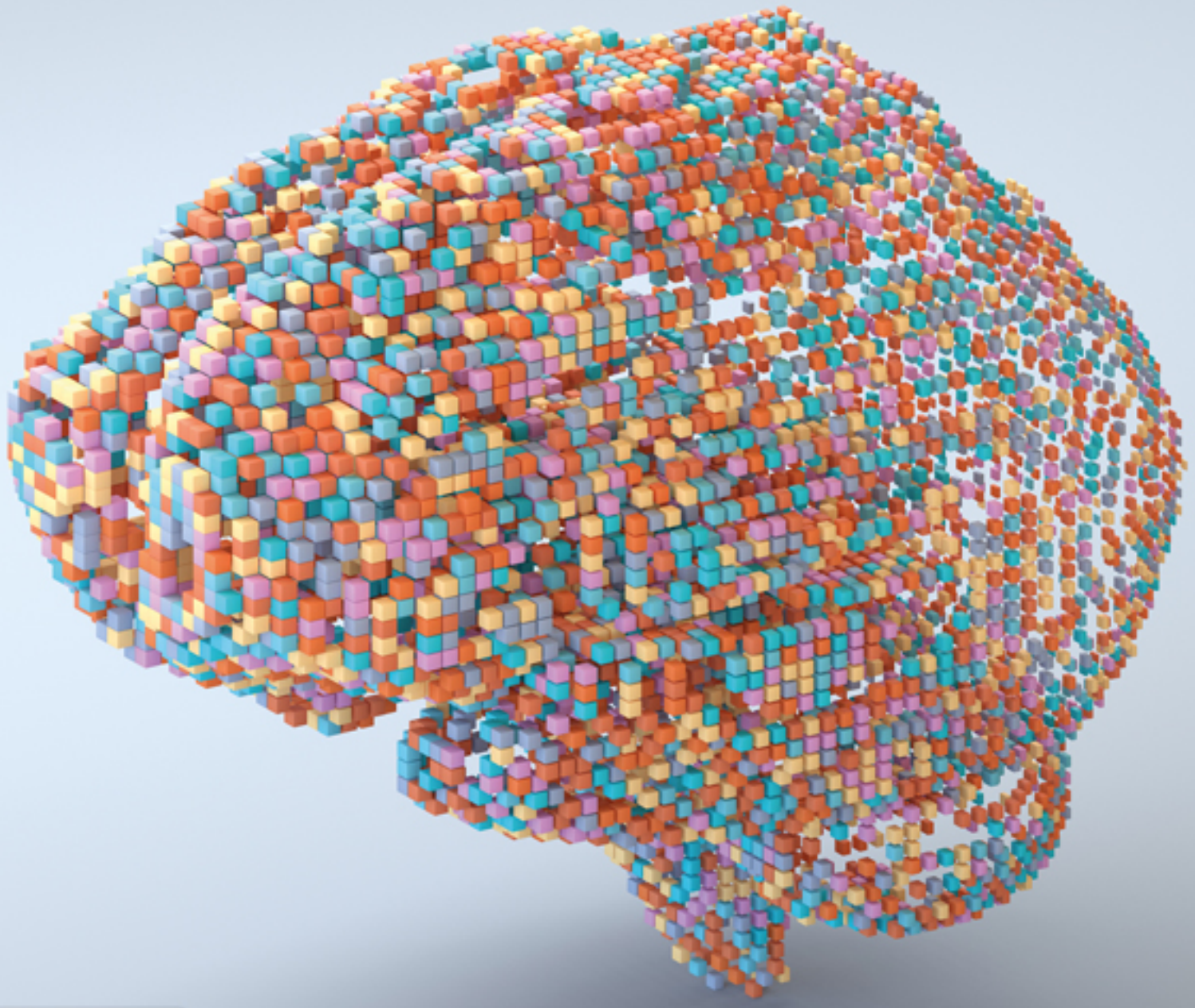

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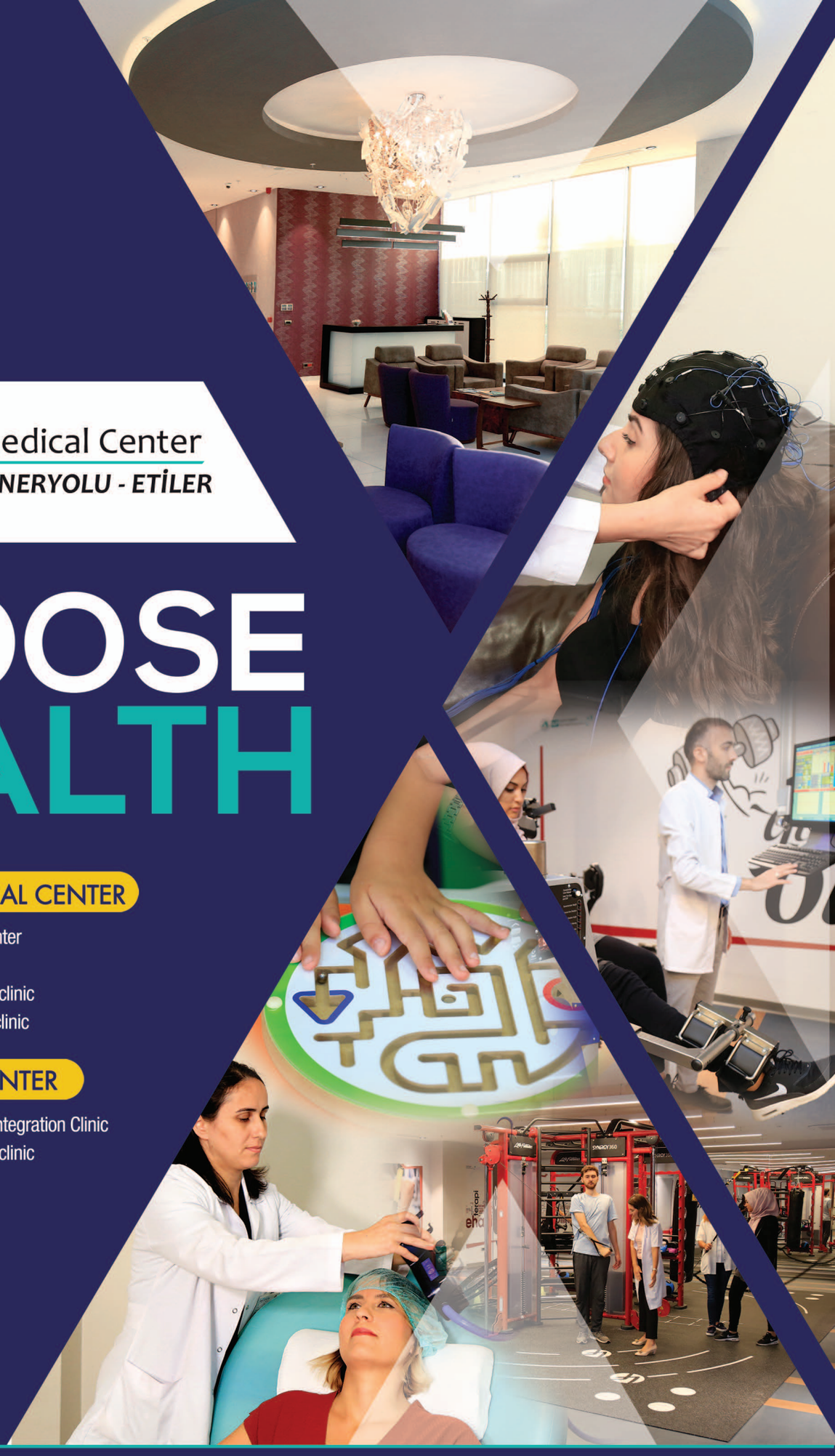

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**JNBS accepts articles written in English language.

ABOUT THIS JOURNAL

Publication Policy

The Journal of Neurobehavioral Sciences (J Neuro Behav Sci) is a peer-reviewed open-access neuroscience journal without any publication fees. All editorial costs are sponsored by the Üsküdar University Publications and the Foundation of Human Values and Mental Health. Each issue of the Journal of Neurobehavioral Sciences is specially commissioned, and provides an overview of important areas of neuroscience from the molecular to the behavioral levels, delivering original articles, editorials, reviews and communications from leading researchers in that field. JNBS is published electronically and in the printed form 3 times a year by Uskudar University. The official language of JNBS is English. The average time from delivery to first decision is less than 30 days. Accepted articles are published online on average on 40 working days prior to printing, and articles are published in print at 3-6 months after acceptance. Please see our Guide for Authors for information on article submission. If you require any further information or help, please email us (jnbs@uskudar.edu.tr)

Aims & Scope

JNBS (J. Neuro. Behav. Sci) is a comprehensive scientific journal in the field of behavioral sciences. It covers many disciplines and systems (eg neurophysiological, neuroscience systems) with behavioral (eg cognitive neuroscience) and clinical aspects of molecules (eg molecular neuroscience, biochemistry), and computational methods in health.

The journal covers all areas of neuroscience with an emphasis on psychiatry and psychology as long as the target is to describe the neural mechanisms underlying normal or pathological behavior. Pre-clinical and clinical studies are equally acceptable for publication. In this context; the articles and treatment results of computational modeling methods of psychiatric and neurological disorders are also covered by the journal.

JNBS emphasis on psychiatric and neurological disorders. However, studies on normal human behavior are also considered. Animal studies and technical notes must have a clear relevance and applicability to human diseases. Case Reports including current neurological therapies or diagnostic methods are generally covered by JNBS.

Besides; The scope of JNBS is not limited to the abovementioned cases, and publications produced from the interdisciplinary studies established in the following fields and with the behavioral sciences are included in the studies that can be published in JNBS.

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

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Submit manuscripts electronically (.doc format with including all figures inside) via the online submission system of our website (https://review.jow.medknow.com/jnbs).

Assoc. Prof. Dr. Huseyin Ozan Tekin, Ph.D Co-Editor, Journal of Neurobehavioral Sciences Department of Psychology

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

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

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

Masked Reviews

Masked reviews are optional and must be specifically requested in the cover letter accompanying the submission. For masked reviews, the manuscript must include a separate title page with the authors' names and affiliations, and these ought not to appear anywhere else in the manuscript. Footnotes that identify the authors must be typed on a separate page. Make every effort to see that the manuscript itself contains no clues to authors' identities. If your manuscript was mask reviewed, please ensure that the final version for production includes a byline and full author note for typesetting.

Similarity Rate: The similarity of the submitted articles with the Ithenticate program is determined. The similarity rate should be below 20%.

Types of Articles: Brief Reports, commentaries, case reports and minireviews must not exceed 4000 words in overall length. This limit includes all aspects of the manuscript (title page, abstract, text, references, tables, author notes and footnotes, appendices, figure captions) except figures.

Brief Reports also may include a maximum of two figures.

For Brief Reports, the length limits are exact and must be strictly followed. Regular Articles typically should not exceed 6000 words in overall length (excluding figures).

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All cover letters must contain the following: A statement that

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

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

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

Display Equations

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

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Abstract and Keywords

All manuscripts must include an English abstract containing a maximum of 250 words typed on a separate page. (It should contain headings such as Background, Aims and Objectives, Materials and Methods, Results, Conclusion etc.) After the abstract, please supply up to five keywords or brief phrases.

References:

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Citations to someone else's work in the text, indicated by the use of a number. A sequentially numbered reference list at the end of the document providing full details of the corresponding in-text reference.

General rules of in-text citation:

- A number is allocated to a source in the order in which it is cited in the text. If the source is referred to again, the same number is used.
- Use Arabic numerals (1,2,3,4,5,6,7,8,9).
- Either square [ ] or curved brackets ( ) can be used as long as it is consistent.
- In the publication, source numbers are indicated in parentheses or as superscripts at the end of the sentence - name - in which the source is used.
- If the sources with consecutive numbers are to be displayed at the same time, the first and last numbers are separated with "-"

According to some estimates, the prevalence of ADHD has increased up to 30% in the last 20 years.[1]
S variant is associated with the lower transcriptional activity of the promoter when compared to the L variant.[4,7-9,11]

The Reference Section:

• Journal Article:

Russell FD, Coppell AL, Davenport AP. In vitro enzymatic processing of radiolabelled big ET-1 in human kidney as a food ingredient. Biochem Pharmacol 1998;55(5):697-701. doi: 10.1016/s0006-2952(97)00515-7.

Gonen, M. Planning for subgroup analysis: a case study of treatmentmarker interaction in metastatic colorectal cancer. Controlled Clinical Trials 2003;24 : 355-363. doi: 10.1016/s0197-2456(03)00006-0.

• Authored Book:

Lodish H, Baltimore D, Berk A, Zipursky SL, Matsudaira P, Darnell J. Molecular cell biology. 3rd ed. New York: Scientific American; 1995.

Millares M, editor. Applied drug information: strategies for information management. Vancouver: Applied Therapeutics, Inc.; 1998.

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

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The Journal of Neurobehavioral Sciences

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Contents

Original Article

In silico Characterization of Predominant Genes Involved in Early Onset of Alzheimer's Disease

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Abstract

Objective: Alzheimer's disease (AD) is a predominant neurodegenerative disorder and one of the most prevalent forms of dementia, affecting 35 million people worldwide. The neuropathologic characteristics of this disorder show extracellular aggregation of amyloid plaques composed of amyloid-beta (Aβ) peptides and the presence of hyperphosphorylated tau protein leading to the formation of neurofibrillary tangle inside the neurons. Some of the significant clinical presentations of AD patients include memory decline, trouble in speech, personality alterations, gait imbalance, and mood changes. A tremendous core of genetics is involved in the prevalence of AD. The three vital genes such as amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2) have a definite association with AD. The objective of this study was to characterize these genes, which are immensely relevant in health-care practices and the formation of personalized medications. **Materials and Methods:** The characterization of genes has been done using several databases such as the National Center for Biotechnology Information, GeneCards, Human Protein Atlas, tissue expression database, and protein modeling server – Swiss-model. **Results:** As a result, we got the genomic and subcellular location of genes. Furthermore, we got the expression concentration of proteins in tissues, three-dimensional protein structures using amino acid sequences, string connection with various proteins, features of genes, and the protein encoded by it. **Conclusion:** We reach the conclusion that protein expression of APP is high in the brain, spinal canal, liver, lungs, and small and large intestine. PSEN1 concentration of expression is high in the brain and spinal, whereas PSEN2 concentration of expression is high in the liver, lungs, brain, and intestine.

Keywords: *Alzheimer's disease, amyloid precursor protein, PSEN1, PSEN2*

Introduction

Alzheimer's disease (AD) is the most prominent form of dementia, affecting 30 million people worldwide.[1] If symptoms come into sight to the people within the age group of 30–65 years, then it is termed early-onset AD (EOAD) or late-onset AD (LOAD when symptoms appear after 65 years of age.[2,3] Characteristic clinical presentation of AD is memory impairment, language difficulty, personality, and behavioral variations. About 25% of EOAD subjects show the nonmemory phenotype. Neuropathologic signs of an AD brain consist of amyloid plaque deposits formed extracellularly by amyloid-beta (Aβ) peptide from amyloid-beta precursor protein and accumulation of hyperphosphorylated tau protein leading to the formation of neurofibrillary tangles (NFTs) inside the nerve cells, intruding the neuronal network.[4-6] There are several risk factors associated with AD, such as familial inheritance, aluminum toxicity due to high aluminum exposure, infection, vascular diseases, traumatic brain injury, and diet.[7] Although high amyloid has been linked with strong episodic memory deterioration over 18 and 36 months in fit older adults and people with medium cognitive impairment. However, the kind and quantity of memory related to amyloid and nonmemory switch from the preclinical to the clinical degrees of AD has not been assessed over the time interval.[8] Despite the important public health concern that it postures, only five medical approaches have been licensed for AD, and these documents to manage symptoms rather than change

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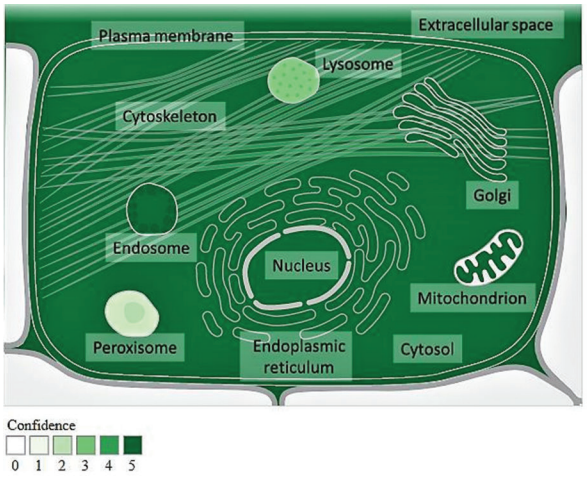
the development of the disease. Studies of potential disease-modifying treatment have usually been tried in patients with the clinically detectable disease, yet data imply that the pathological alterations connected with AD start numerous years before this. Pharmacological treatment may be helpful in this preclinical step before the neurodegenerative process is placed.[9-11] In 1907, Alois Alzheimer, a pronounced German neuropathologist and psychiatrist, performed an autopsy on a 55-year-old lady named Auguste Deter, who died of a critical cognitive disorder.[12-15] Alois Alzheimer saw abnormal intracellular accumulation during the process of necropsy, which was later defined as NFT's and the presence of "Miliary Foci" extracellularly now reported as neuritic plaques. In 1984, Wong and his colleague named Glenner isolated the neuritic plaque and described it as a fragment of 40–42 amino acids and 4.2 kDa peptide that is cleaved from a precursor protein. To extend their research, they cloned the neuritic plaque and named it an Amyloid-beta peptide. Further, Roth and Tomlinson (Father of AD Neuropathology) concluded that Aβ peptide upraises the risk of dementia in elderly people.[16-19] In Youn 2014 *et al*.'s study, γ-linolenic acid was discovered as a novel BACE1 specific inhibitor.[20] In Dhananjayan 2014 *et al*.'s study, *in silico* docking studies, it revealed that targeting BACE1 inhibition through Polyphenolic compounds can create a number of lead molecules for better therapeutic concern in future.[21] Khan 2012 *et al*. revealed that PDB ID: 3MOQ shares query coverage 78% and maximum identity 96% to a hypothetical protein of AD. Validation of structure was done by using PROCHECK available at SAVES server. The validated model is submitted in PMDB (i.e., ID: PM0078182). The predicted model of amyloid precursor protein (APP) can be further used for drug target identification.[22]

Genetic etiology of Alzheimer's disease

There is the involvement of multiple genes associated with AD, such as phospholipase D family member 3, triggering receptor expressed on myeloid cells 2, apolipoprotein E (APOE4), ATP binding cassette subfamily A member 7 (ABCA7) and A disintegrin and metalloproteinase domain-containing protein 10 (ADAM10), bridging integrator 1 (BIN1), cas scaffold protein family member 4 (CASS4), and cas scaffold protein family member 4 (CASS4) genes.[23-26] Heritability is high varying from 92% to 100% in EOAD patients as compared to LOAD patients which stretch from 70% to 80% only.[27] Based on monogenic pedigree analysis, it was identified that three major genes coding for APP, presenilin-1 (PSEN1), and presenilin-2 (PSEN2) can be involved in patients with AD.[28-31] Besides, another trial was continued to recognize genes for inherited AD by isolating Aβ peptide from vessels of people with Down syndrome (DS), caused by trisomy 21, and form plaques of AD patient's brain revealed nearly strong homology between the two diseases. Indicating there is a standard genetic framework associated with chromosome 21q, from autosomal dominant families[.32,33] 119 probands were taken in which 52 mutations were detected in the APP gene. In general, the mutations were nonsynonymous, but missense mutation was also inscribed. The most often mutated gene in AD was PSEN1,[20] it showed 215 mutations in 475 probands and 31 mutations were detected in the PSEN2 gene in 24

Figure 1: The genomic location of amyloid precursor protein gene which is on long arm (q), chromosome number 21, at position 21.1-21.3 in red-colored mark



Compartment	Confidence
plasma membrane	5
extracellular	5
mitochondrion	5
nucleus	5
endoplasmic reticulum	5
endosome	5
cytosol	5
golgi apparatus	5
cytoskeleton	4
lysosome	3
peroxisome	2

Figure 2: The subcellular localization of amyloid precursor protein gene from the compartments. The concentration is high in plasma membrane, extracellular, mitochondrion, nucleus, endoplasmic reticulum, endosome, cytosol, and Golgi apparatus. Combined confidence scores of the localization confirmation are selected based on evidence type and source and envisioned both in a table and in the schematic cell representation. The confidence scale is color coded, extending from light green color (1) for low confidence to dark green color (5) for high confidence. White color (0) indicates a lack of localization evidence

probands.[34,36] Table 1 Shows the characteristics of APP, PSEN1 and PSEN2 has been shown in Figure 1

Materials and Methods

There is no need for ethics committee approval. The databases for the completion of this study were National Center for Biotechnology (NCBI), PubMed, Swiss-model, Ensembl, GeneCards, OMIM, UniPort, HUGO Gene Nomenclature Committee, Protein Data Bank, etc., Moreover, to keep all referred articles, images, and data in an organized manner, we made use of Benchling which is an electronic digital notebook. This notebook helped me to stay on track during this study. The detailed information of some databases and the procedure has been discussed below:

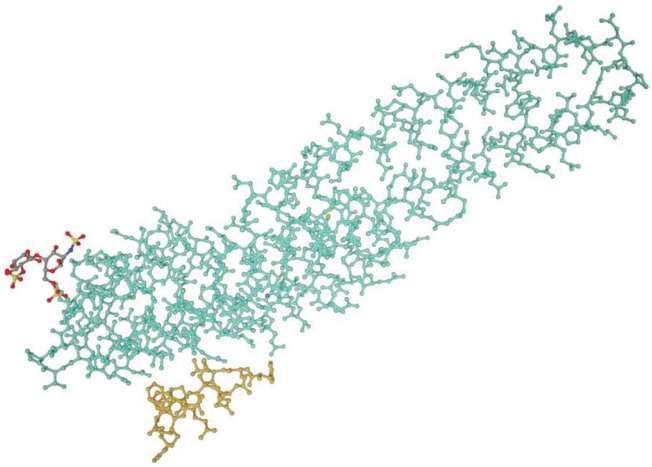


Figure 3: The three-dimensional structure of amyloid precursor protein in "Ball and Stick" molecular model. The "spheres" show the atoms of various amino acids and their bonds with other atoms are shown by "sticks." The presence of chemical elements of every atom is presented by different colors in the structure. The spheres of color turquoise blue indicate various amino acids such as leucine (Leu), phenylalanine (Phe), glutamic acid (Glu), lysine (Lys), Histidine (His), Serine (Ser), Tyrosine (Tyr), Proline (Pro), Glutamine (Gln), aspartic acid (Asp), alanine (Ala), and methionine (Met). The red-colored spheres indicate a ligand 2-deoxy-6-O-sulfo-2-(sulfoamino)-alpha-D-glucopyranose (SGN), whereas yellow colored sphere indicates a ligand 2-O-sulfo-alpha-L-idopyranuronic acid (IDS)

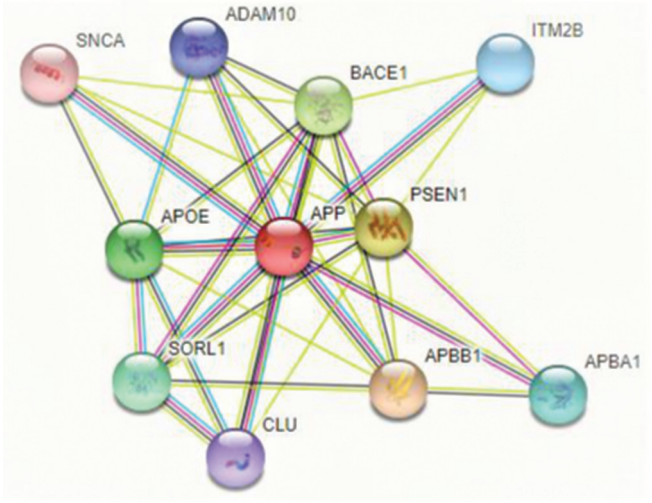


Figure 5: The protein interactions string of amyloid precursor protein (APP). The proteins which are involved in interaction are presenilin-1 (PSEN1), amyloid-betta A4 precursor protein-binding family A member 1 (APBA1), alpha-synuclein (SNCA), amyloid-beta A4 precursor protein-binding family B member 1 (APBB1), apolipoprotein-E (APOE), A disintegrin and metalloproteinase domain-containing protein 10 (ADAM10), beta-site APP cleaving enzyme-1 (BACE1), sortilin-related receptor (SORL1), clusterin (CLU), and integral membrane protein 2B (ITM2B)

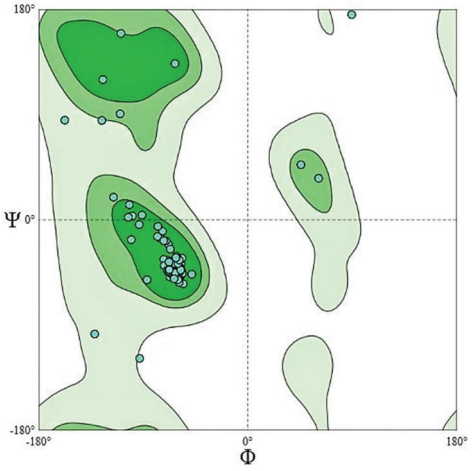


Figure 4: The Ramachandran plot for amyloid precursor protein amino acid residues. The cluster of dots in the plot suggests that the protein is making right-handed alpha-helix structure

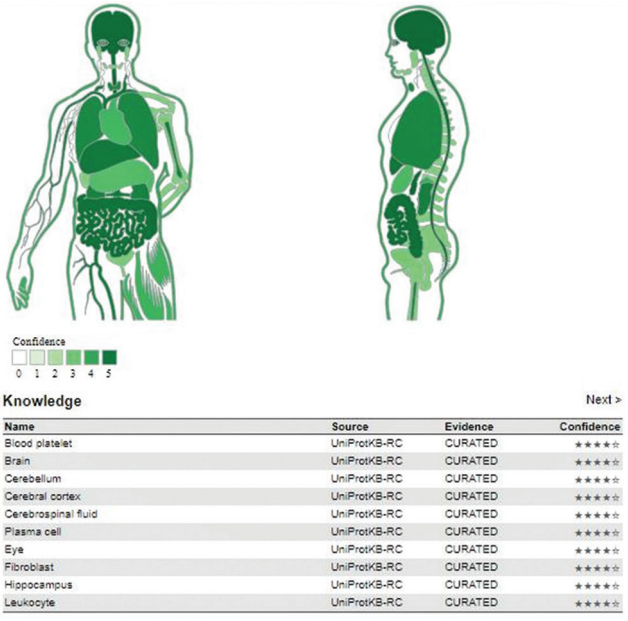
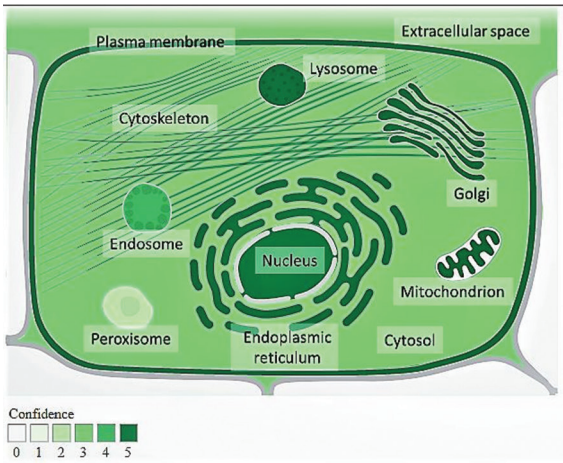


Figure 6: The concentration of expression of amyloid precursor protein (APP) in human body organs. The confidence scale extends from 0 (low concentration) to 5 (high concentration). The higher the concentration of APP in a specific tissue, the more will the number (0–5) in the confidence scale, and the darker will be green color of that organ in the figure, like brain, spinal canal, liver, lungs, and small and large intestine shows a high concentration of APP. The tissue associations are acquired from curated (Professional) information in UniProtKB manually. The confidence of individual association is implied by stars, where ★★★★★ is the most extraordinary confidence and ★☆☆☆☆ is the weakest

Figure 7: The location of gene physically on a chromosome (Genomic Location) of PSEN1 gene on long arm (q) of chromosome number 14 at position 24.2 in red coloured mark



Compartment	Confidence
plasma membrane	5
cytoskeleton	5
mitochondrion	5
nucleus	5
endoplasmic reticulum	5
lysosome	5
golgi apparatus	5
endosome	4
extracellular	3
cytosol	3
peroxisome	2

Figure 8: The localization od PSEN1 gene in the subcellular compartments. It has been detected that localization of PSEN1 gene is high in Golgi apparatus (Main Location), nucleoplasm and cell junction (additional location). Confidence scale is colour extending from light green showing low confidence to dark green showing high confidence

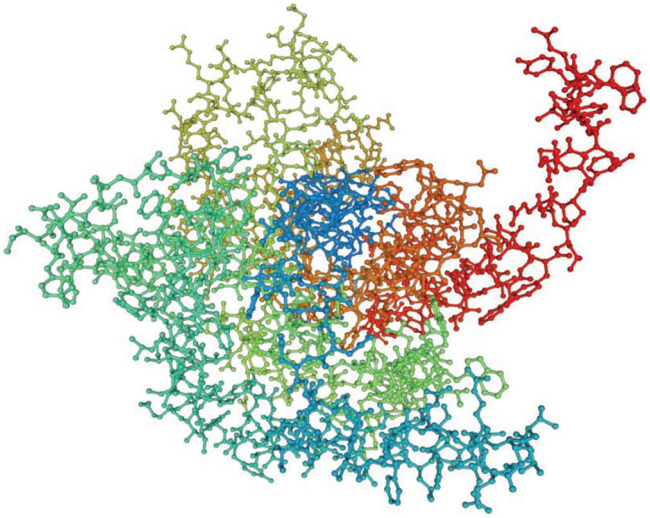


Figure 9: This is the three-dimensional structure of Presenilin-1. It is in "Ball and Stick" molecular model, where the ball represents atoms connected with other atoms by covalent bond which is shown by sticks. The different colors in the structure represent presence of multiple types of amino acids such as proline (Pro), methionine (Met), cysteine (Cys), histidine (His), alanine (Ala), threonine (Thr), tyrosine (Tyr), valine (Val), isoleucine (Ile), phenylalanine (Phe), lysine (Lys), glycine (Gly), serine (Ser), glutamic acid (Glu), aspartic acid (Asp), leucine (Leu), and asparagine (Asn)

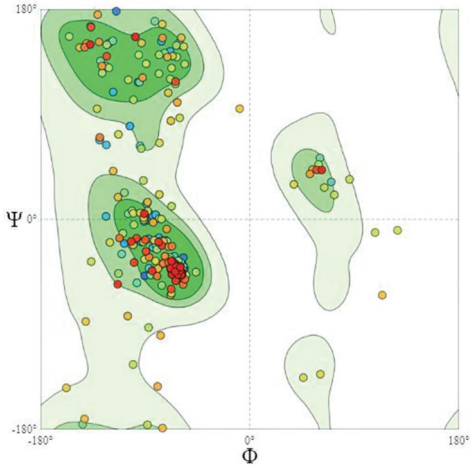


Figure 10: The Ramachandran plot for presenilin-1 amino acid residues. The cluster of dots in the plot suggests that the protein has right-handed alpha-helix or anti-parallel beta-sheet structure

PubMed

It is the main search engine which we used to collect the required information. We looked for APP, AD, PSEN1, and PSEN2.

National Center for Biotechnology Information

From NCBI, we collected genomic, mRNA, and amino acid sequences of APP, PSEN1, and PSEN2 genes. This tool is very important to analyze genomic data or molecular data. The amino acid length I chose for APP is 770, for PSEN1 is 562, and for PSEN2, it was 566 and took a sequence of 1000 base pairs only, and then, "FASTA" was used to save the nucleotide sequence.

GeneCards

This is a database used to search for human genes. It provides information regarding any gene. This database has sections to understand a gene alias, disorders, expression, localization, orthologs, functions, drugs, proteins, transcripts, variants, etc., In our study, we gathered information such as symbol, protein, synonym, and organism using GeneCards.

Table 1: The classification of Amyloid precursor protein, Presenilin- and Presenilin-2 genes

Gene Name	APP	PSEN1	PSEN2
Description	Amyloid-beta precursor protein	Presenilin-1	Presenilin-2
Gene Synonyms	AD1, A4	AD3, FAD, PS1	AD4, PS2, STM2, PSNL
Location	21q21.1-21q21.3	14q24.2	1q42.13
Organism	Homo sapiens	Homo sapiens	Homo sapiens
Gene type	Protein coding	Protein coding	Protein coding
About gene	This gene has	This gene has	This gene has
	17 transcripts	25 transcripts	37 transcripts
	279 orthologues	198 orthologues	204 orthologues
	2 paralogues	2 paralogues	2 paralogues
	9 phenotypes	11 phenotypes	4 phenotypes
Encodes	Amyloid-beta precursor protein	PSEN1 (PS-1) protein	PSEN2 (PS-2) protein
Associated conditions	Alzheimer's disease and cerebral amyloid angiopathy	Alzheimer's disease and cardiomyopathy	Alzheimer's disease and cardiomyopathy

APP: Amyloid precursor protein, PSEN1: Presenilin-1, PSEN2: Presenilin-2

Table 2: The details of amyloid precursor protein 3-D protein structure

Protein	APP
Oligo state	Homodimer
GMQE	0.16
QMEAN	−2.93
Method	X-ray diffraction
Classification	Metal transport
Peptide	Amyloid-beta A4 protein
Expression system	Homo sapiens
Included ligand	1 x MG: MAGNESIUM ION; 1 x SGN-IDS: 2-O-sulfo-alpha-L-idopyranuronic acid-(1-4)-2-deoxy-6-O-sulfo-2-(sulfoamino)-alpha-D-glucopyranose; 3 x ZN: ZINC ION

SGN-IDS: 2-O-sulfo-alpha-L-idopyranuronic acid-(1-4)-2-deoxy-6-O-sulfo-2-(sulfoamino)-alpha-D-glucopyranose, APP: Amyloid precursor protein

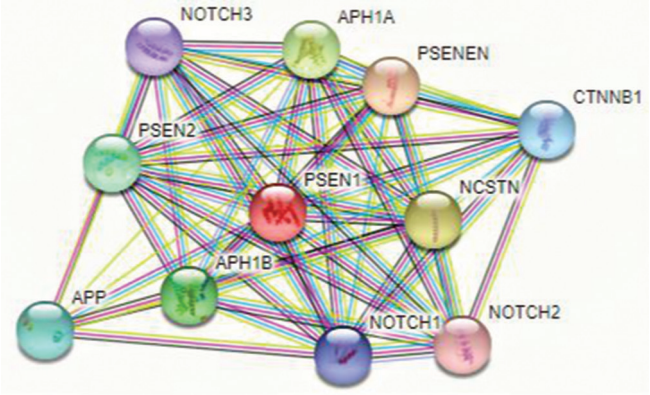


Figure 11: The protein interaction of presenilin-1. The proteins which are involved in interactions are amyloid precursor protein (APP), presenilin enhancer, gamma-secretase subunit (PSENEN), neurogenic locus notch homolog protein 3 (NOTCH3), neurogenic locus notch homolog protein 2 (NOTCH2), neurogenic locus notch homolog protein 1 (NOTCH1), nicastrin (NCSTN), aph-1 homolog B, gamma-secretase subunit (APH 1B), aph-1 homolog A, gamma-secretase subunit (APH 1A), presenilin-2 (PSEN2) and catenin beta-1 (CTNNB1)

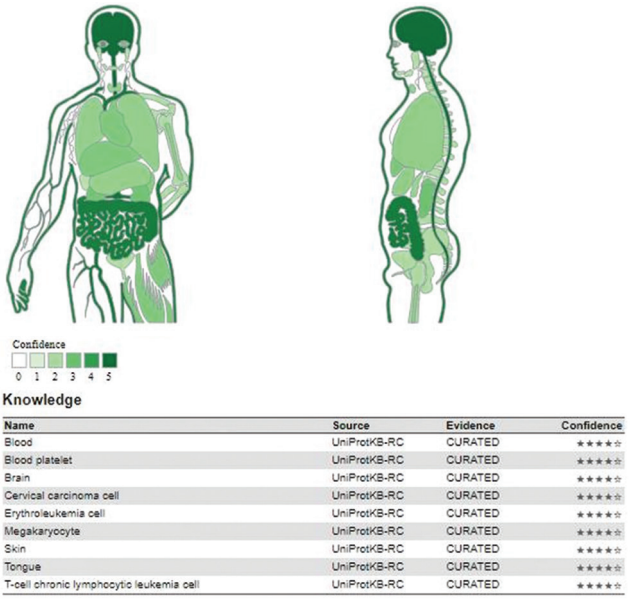
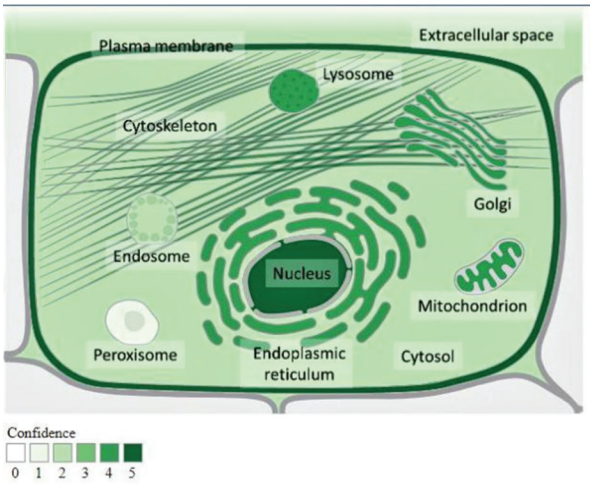


Figure 12: The concentration of expression of PSEN1 in human body organs. The confidence scale extends from 0 (low concentration) to 5 (high concentration). The higher the concentration of PSEN1 in a specific tissue, the more will the number (0-5) in the confidence scale, and the darker will be green color of that organ in the figure, such as brain and spinal canal show the highest concentration of PSEN1. The tissue associations are acquired from curated information in UniProtKB manually. The confidence of individual association is implied by stars, where ★★★★★ is the most extraordinary confidence and ★☆☆☆☆ is the weakest

Swiss-model

This is a protein modeling server, which provides us with 3D structures of proteins for analysis. It has different templates and summaries for the structure of our protein. We gathered three protein structures for APP, PSEN1,

Figure 13: The Location of gene physically on a chromosome (Genomic Location) of PSEN2 gene on long arm (q) of chromosome number 14 at position 42.13 in red coloured mark



Compartment	Confidence
plasma membrane	5
cytoskeleton	5
nucleus	5
mitochondrion	4
endoplasmic reticulum	4
lysosome	4
golgi apparatus	4
extracellular	2
endosome	2
cytosol	2
peroxisome	1

Figure 14: The subcellular localization of gene from compartments. The PSEN2 gene is mainly localized in the nucleoplasm, plasma membrane, cytoskeleton and nucleus All the rest compartments are non-detected. Collected confidence grade of the localization confirmation are selected based on evidence type and source and envisioned both in a table and in the schematic cell representation. The confidence scale is colour coded, extending from low confidence (1) shown in light green to high confidence (5) shown in dark green

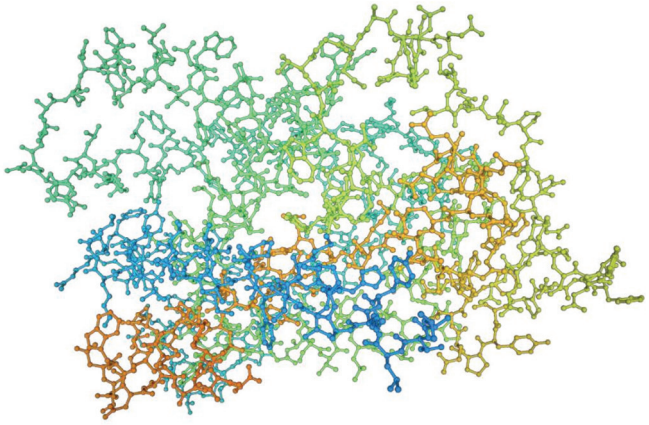


Figure 15: This is the 3-dimensional structure of Presenilin-2. It is in 'Ball and Stick' molecular model, where the ball represents Atoms connected with other atoms by covalent bond which is shown by sticks. The different colors in the structure represent presence of multiple types of amino acids such as proline (Pro), methionine (Met), cysteine (Cys), alanine (Ala), threonine (Thr), tyrosine (Tyr), valine (Val), phenylalanine (Phe), lysine (Lys), glycine (Gly), serine (Ser), glutamic acid (Glu), aspartic acid (Asp), leucine (Leu), asparagine (Asn), arginine (Arg), etc

Table 3: The chemical properties of amyloid precursor protein of 770 amino acid residues

Length	1-770
Summary	MLPG…EQMQ
Molecular weight	86828.61 Da
Isoelectric point (pI)	4.73
Instability Index	40.73 (Unstable)
Cys fully reduced	79300.00/M/cm
Cys fully oxidized	80425.00/M/cm

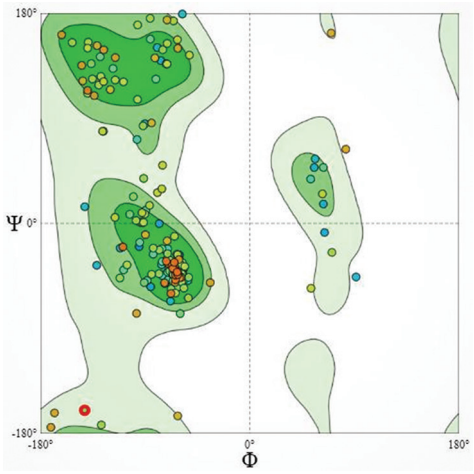


Figure 16: The Ramachandran plot for presenilin-2 amino acid residues. The cluster of dots in the plot suggests that the protein has right-handed alpha-helix or anti-parallel beta-sheet structure

and PSEN2 genes. It helps us to change the theme of the protein and allows us to download it for further reference. I also downloaded the Ramachandran plot for all three proteins. The detailed information can also be accessed using this database such as QMEAN, protein classification, GMQE, oligo state, and peptide. The Ramachandran Plot for PSEN2 has been shown in Figure 16.

Ensembl gene browser

This is a database notably beneficial to collect data on genomic sequences, transcriptional sequences, sequence variation, etc., In our study, we collected data of description, gene synonyms,

Table 4: The details of PS-1, the protein up of is made four similar subunits (Hetero tetramer)

Protein	PSEN1
Oligo state	Hetero tetramer
GMQE	0.54
QMEAN	−5.48
Method	Electron microscopy
Classification	Membrane protein/hydrolase
Peptide	Nicastrin: A, presenilin 1:B, gamma-secretase subunitAPH-1A: C, gamma-secretase subunit PEN-2:D
Expression system	Homo sapiens
Included ligand	2-[(4-chlorophenyl) sulfonyl-[[2-fluoranyl-4-(1,2,4-oxadiazol-3-yl) phenyl] methyl] amino]-5,5,5-tris (fluoranyl) pentanamide

GMQE: The global model quality estimate, QMEAN: The qualitative model energy analysis, PSEN1: Presenilin-1

Table 5: The chemical properties of Presenilin-1 of 467 amino acid residues

Length	467
Summary	MTEL…QFYI
Molecular weight	52667.34 Da
Isoelectric point pI	5.18
Instability index	45.37 (unstable)
Cys fully reduced	723100.00/M/cm
Cys fully oxidized	72560.00/M/cm

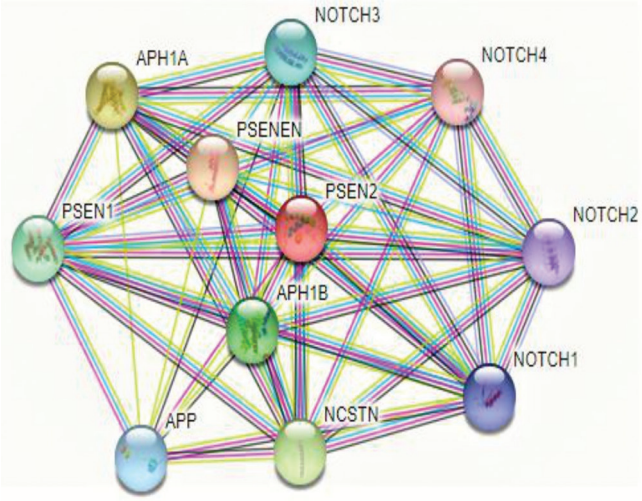


Figure 17: The protein interaction of Presenilin-2. The protein which are involved in interactions are Amyloid Precursor Protein (APP), Presenilin Enhancer, Gamma-Secretase Subunit (PSENEN), Neurogenic locus notch homolog protein 3 (NOTCH3), Neurogenic locus notch homolog protein 4 (NOTCH4) Neurogenic locus notch homolog protein 2 (NOTCH2), Neurogenic locus notch homolog protein 1 (NOTCH1), Nicastrin (NCSTN), Aph-1 Homolog B, Gamma-Secretase Subunit (APH 1B), Aph-1 Homolog A, Gamma-Secretase Subunit (APH 1A) and Presenilin-1 (PSEN1)

transcripts, chromosome location, orthologues, paralogues, and the phenotype associated with APP, PSEN1, and PSEN2 genes. More specifically, we used Ensembl Version ENSG00000142192.21 to collect information.

Benchling

This is a digital electronic notebook. This platform makes it remarkably clear to share collected data, experiment report, or information with other scientists. This digital notebook is very essential for sequence designing, documenting information regarding projects, data acquisition, reporting, etc., To proceed with any task, we must have proper formatting and theoretical plans for that, Benchling provides a very well-defined space to carry our research work.

Results

Features of amyloid precursor protein, PSEN1, and PSEN2 Gene

These three genes play a crucial role in onset of AD, the information regarding these genes has been collected from databases such as, Ensembl, UniPort, and GeneCards.

Discussion

Characterization of amyloid precursor protein gene

APP gene encodes for amyloid-beta precursor protein. This protein is a surface receptor and transmembrane protein that can be cleaved into various peptides by secretases. The two peptides for this protein show bactericidal and antifungal activities.[35,36]

Subcellular localization of amyloid precursor protein gene

In the maturation phase, the immature APP moves to the Golgi apparatus, where the maturation takes place. The soluble APP released after the action of alpha-secretase in the extracellular space. Some portion of APP also gets accumulated in the secretory transport vesicles and returns to the cell surface. APP is mainly in the Golgi apparatus.

Characterization of amyloid precursor protein

Human APP is a transmembrane protein that performs a significant function in the central nervous system. The cleavage of this protein by the γ-secretase enzyme releases a large extracellular domain known as secreted APP alpha. APP can also be cleaved to Aβ peptide in a proteolytic process; if there is the involvement of the β-secretase enzyme, it will cleave the APP in such a way that a nonsoluble peptide is formed known as amyloid β (Aβ) peptide. This peptide accumulates in the brain extracellularly

and intrudes the neuronal network, which is one of the primary characteristic features in the Onset of AD.[36,37]

Analysis of amyloid precursor protein structure

Amyloid precursor protein genomic location has been shown in Figure 1, the subcellular localization has been shown in Figure 2. Further the Ramachandran plot has been explained in Figure 4 and protein-protein interaction mesh like structure takne from database string has been shown in Figure 5.

Ramachandran plot of amyloid precursor protein

Ramachandran plot predicts the secondary structures of protein by the amino acid residues. Each amino acid has two backbone bonds that can rotate which sets the dihedral angles (ϕ and ψ). The peptide is not able to rotate because of the presence of a partial double bond. This plot is of torsional angles, where on x-axis, the values of ϕ are taken and on y-axis, values of ψ are taken.

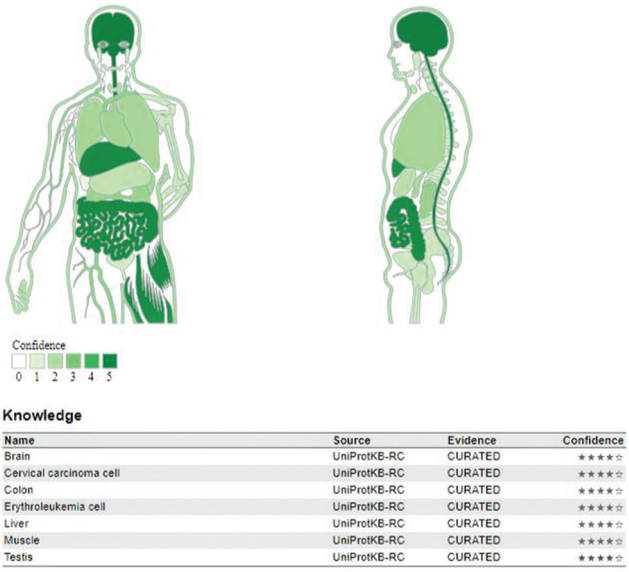


Figure 18: The concentration of expression of PSEN2 in human body organs. The confidence scale extends from 0 (low concentration) to 5 (high concentration). The higher the concentration of PSEN2 in a specific tissue, the more will the number (0-5) in the confidence scale, and the darker will be green color of that organ in the figure, such as brain, liver, and spinal canal, small and large intestine shows high concentration of PSEN2. The tissue associations are acquired from curated information in UniProtKB manually. The confidence of individual association is implied by stars, where ★★★★★ is the most extraordinary confidence and ★☆☆☆☆ is the weakest

Details of amyloid precursor protein structure

The details of the APP have been extracted from a protein modeling server – Swiss-model.

Amino acid sequence of amyloid precursor protein

The functionality and structure of a protein is determined by its amino acid residues. The amino acid sequence for APP was extracted from database Ensembl, which has been type-written below.

MLPGLALLLLAAWTARALEVPTDGNAGLL
AEPQIAMFCGRLNMHMNVQNGKWDSDPS
GTKTCIDTKEGILQYCQEVYPELQITNVVE
ANQPVTIQNWCKRGRKQCKTHPHFVIPYR
CLVGEFVSDALLVPDKCKFLHQERMDVCE
THLHWHTVAKETCSEKSTNLHDYGMLLPC
GIDKFRGVEFVCCPLAEESDNVDSADAEED
DSDVWWGGADTDYADGSEDKVVEVAEEEE
VAEVEEEEADDDEDDEDGDEVEEEAEEPYEE
ATERTTSIATTTTTTTESVEEVVREVCSEQAET
GPCRAMISRWYFDVTEGKCAPFFYGGCGGNRN
NFDTEEYCMAVCGSAMSQSLLKTTQEPLARDP
VKLPTTAASTPDAVDKYLETPGDENEHAHFQK
AKERLEAKHRERMSQVMREWEEAERQAKNLP
KADKKAVIQHFQEKVESLEQEAANERQQLVET
HMARVEAMLNDRRRLALENYITALQAVPPRPRH
VFNMLKKYVRAEQKDRQHTLKHFEHVRMVDP
KKAAQIRSQVMTHLRVIYERMNQSLSLLYNVPA
VAEEIQDEVDELLQKEQNYSDDVLANMISEPRIS
YGNDALMPSLTETKTTVELLPVNGEFSLDDLQP
WHSFGADSVPANTENEVEPVDARPAADRGLTT
RPGSGLTNIKTEEISEVKMDAEFRHDSGYEVHHQ
KLVFFAEDVGSNKGAIIGLMVGGVVIATVIVITLV
MLKKKQYTSIHHGVVEVDAAVTPEERHLSKMQ
QNGYENPTYKFFEQMQ

Chemical properties of amyloid precursor protein

The details of amyloid precursor protein 3-Expression of amyloid precursor protein in tissues D protein structure

Table 6: The details of PS-2, the protein up of is made four similar subunits (Monomer)

Protein	PSEN2
Oligo state	Monomer
GMQE	0.36
QMEAN	−6.11
Method	Electron microscopy
Classification	Membrane protein
Peptide	Nicastrin; A, presenilin 1: B, gamma-secretase subunit APH-1A: C, gamma-secretase subunit PEN-2D, Amyloid-beta A4 peptide
Expression system	Homo sapiens
Included ligand	2-acetamido-2-deoxy-beta-D-glucopyranose-(1-4)-2 acetomido-2-deoxy-beta-D-glucopyranose

GMQE: The global model quality estimate, QMEAN: The qualitative model energy analysis, PSEN2: Presenilin-1

Table 7: The chemical properties of Presenilin-2 of 471 amino acid residues

Length	471
Summary	MLTF….RGQK
Molecular weight	52623.51 Da
Isoelectric point	4.78
Instability index	51.98 (Unstable)
Cys fully reduced	87780.00/M/cm
Cys fully oxidized	88530.00 M/cm

has been shown in Table 2 and The chemical properties of amyloid precursor protein of 770 amino acid residues has been shown in Table 3.

String interactants of amyloid precursor protein

The string interacts of APP has been collected from String interaction database. It shows the possible protein–-protein interaction.

Expression of amyloid precursor protein in tissues

The expression concentration of APP in tissues and organs has been shown in Figure 6.

Characterization of PSEN1 gene

This is a protein-coding gene which encodes for presenilin-1 (PS-1) protein. This gene has 25 transcripts, 198 orthologues, 2 paralogues, and 11 phenotypes associated with it. It is involved in presenilin-mediated signaling pathway and neurogenerative pathway. This molecular function of PS-1 is of hydrolase and protease.[37,38,39]

Subcellular Location of PSEN1 gene

The genomic location of PSEN1 has been shown in Figure 7 and the detailed view of Subcellular Location of the gene is shown in Figure 8.

Characterization of presenili-1 (PS-1)

The presenilin-1 (PS-1) is an integral transmembrane protein encoded by PSEN-1 gene present on chromosome 14 (14q24.3). It is a protein of 467 amino acids and the molecular weight is 57 kDa. This protein is present in the gamma-secretase complex and helps in the processing of APP. This also helps in formation of amyloid-beta peptide, responsible for pathogenesis in AD. It facilitates multiple biological functions, but more specifically, if we talk about the brain, it helps in cerebral cortex cell migration, astrocyte activation, cerebellum development, brain morphogenesis, memory and learning, and dorsal and ventral neural tube formation.[40]

Analysis of presenilin-1 structure

The detailed view of Analysis of amyloid precursor protein structure is shown in Figure 3.

Ramachandran plot for presenili-1

Ramachandran plot predicts the secondary structures of protein by the amino acid residues. Each amino acid has two backbone bonds that can rotate which sets the dihedral angles (ϕ and ψ). The peptide is not able to rotate because of the presence of a partial double bond. This plot is of torsional angles, where on x-axis, the values of ϕ are taken and on y-Axis, values of ψ are taken.

Details of PSEN1 protein structure

Details of PSEN1 protein structure is shown in Figure 9 and Ramachandran plot for presenilin 1 has been shown in Figure 10, the string connection has been shown in Figure 11.

Amino acid sequence for presenili-1

The functionality and structure of a protein is determined by its amino acid residues. The amino acid sequence for presenilin-1 (PSEN1) was extracted from database Ensembl, which has been type-written below:

MTELPAPLSYFQNAQMSEDNHLSNTVRSQND
NRERQEHNDRRSLGHPEPLSNGRPQGNSRQV
VEQDEEEDEELTLKYGAKHVIMLFVPVTLCM
VVVVATIKSVSFYTRKDGQLIYTPFTEDTETV
GQRALHSILNAAIMISVIVVMTILLVVLYKYR
CYKVIHAWLIISSLLLLFFFSFIYLGEVFKTYN
VAVDYITVALLIWNFGVVGMISIHWKGPLRL
QQAYLIMISALMALVFIKYLPEWTAWLILAV
ISVYDLVAVLCPKGPLRMLVETAQERNETLF
PALIYSSTMVWLVNMAEGDPEAQRRVSKNSK
YNAESTERESQDTVAENDDGGFSEEWEAQRD
SHLGPHRSTPESRAAVQELSSSILAGEDPEERGV
KLGLGDFIFYSVLVGKASATASGDWNTTIACFV
AILIGLCLTLLLLAIFKKALPALPISITFGLVFYFA
TDYLVQPFMDQLAFHQFYI.

Chemical properties of Presenili-1

The details pf PSEN1 has been shown in Table 4 and The chemical properties of of PSEN1 has been shown in Table 5.

Protein interacts of PSEN1

The string interacts of PSEN1 has been collected from String interaction database. It shows the possible protein–protein interaction.

Expression of PSEN1 in tissues

The genomic location of PSEN2 has been given on Figure 13. The in Table 7 expression concentration of PSEN1 has been shown in Figure 12.

Characterization of PSEN2 gene

The gene encoding for a presenilin-2 protein is located on chromosome 1. It is a transmembrane protein located intracellularly. The molecular weight of PSEN-2 is 55 kDa. This protein has 448 amino acids. The function involves transferring the chemical signals

from the membrane of the cell to the nucleus, inside the nucleus this protein will serve to stimulate certain genes which are responsible for cellular maturation and growth.[41]

Subcellular localization of PSEN2 gene

The subcellular localization of PSEN2 gene has been shown in Figure 14.

Characterization of presenilin-2

The gene encoding for a presenilin-2 Protein is positioned on chromosome 1. It is a transmembrane protein located intracellularly. The molecular weight of PSEN-2 is 55 kDa. The presenilin-2 is a stretch of 448 amino acids. The function involves transferring the chemical signals from the membrane of the cell to the nucleus; inside the nucleus, this protein will serve to stimulate certain genes which are responsible for cellular maturation and growth. Presenilin-2 is a subunit that participates in the cleavage of APP; during this process, it can produce Aβ peptides of multiple lengths. The aggregation of Aβ peptide (Aβ42) is the main hallmark in the brains of AD patients**.** Numerous studies have shown that AD-related presenilin mutations can change intracellular calcium signaling, which directs to Aβ accumulation to form neuritic plaques and cause the loss of neurons.[42]

Analysis of presenili-2 structure

The analysis of 3D model of PSEN2 protein structure modelled from swiss model has been shown in Figure 15 and the The Ramachandran plot for presenilin-2 is shown in Figure 17.

Ramachandran plot for PSEN2

Ramachandran plot predicts the secondary structures of protein by the amino acid residues. Each amino acid has two backbone bonds that can rotate which sets the dihedral angles (φ and ψ). The peptide is not able to rotate because of the partial double bond. This plot is of torsional angles, where on x-axis, the values of Phi φ are taken, and on y-axis, values of Psi ψ are taken.

Details of presenilin-2

The details of PSEN2 has been shown in Table 6 and the chemical properties of Presenilin-2 of 471 amino acid residueshas been shown in Figure 7.

Amino acid sequence of Presenilin-2

M L T F M A S D S E E E V C D E R T S L M S A E S P
T P R S C Q E G R Q G P E D G E N T A Q W R S Q E N
E E D G E E D P D R Y V C S G V P G R P P G L E E E L
T L K Y G A K H V I M L F V P V T L C M I V V V A T I K
S V R F Y T E K N G Q L I Y T P F T E D T P S V G Q R L L
N S V L N T L I M I S V I V V M T I F L V V L Y K Y R C Y
K F I H G W L I M S S L M L L F L F T Y I Y L G E V L K T
Y N V A M D Y P T L L L T V W N F G A V G M V C I H W
K G P L V L Q Q A Y L I M I S A L M A L V F I K Y L P E W S
A W V I L G A I S V Y D L V A V L C P K G P L R M L V E T A
Q E R N E P I F P A L I Y S S A M V W T V G M A K L D P S S
Q G A L Q L P Y D P E M E E D S Y D S F G E P S Y P E V F E P
P L T G Y P G E E L E E E E E R G V K L G L G D F I F Y S V L V
G K A A A T G S G D W N T T L A C F V A I L I M A S H S C C P
G W S A M V R F G S L W P L P P G F K R F S C L S L P Y Q F N F
F R F H V H T A G G H L P D S P A A S C G Y V I E G Q P V K R
G Q K

Chemical properties of presenilin-2

The chemical properties of PSEN2 has been shown.

Protein string interactants of PSEN2

The string interacts of PSEN2 have been collected from String interaction database. It shows the possible protein–protein interaction.

Expression of PSEN2 in tissues

The tissue expression of PSEN2 has been shown in Figure 18.

Conclusion

The genes such as APP, PSEN1, and PSEN2 play an immensely crucial role in the onset of AD before 60 years of age. AD is a prominent neurodegenerative disorder. A lot of therapeutic interventions have come into sight to treat this disorder, but still, there is no cure for it; procedures implementing earlier analysis, such as cerebrospinal fluid biomarkers and amyloid positron-emission tomography neuroimaging are important to test this theory in clinical cases. We have characterized these three genes by using numerous databases such as GeneCards, Ensembl, UniPort, Swiss-model, human expression tissue, Human Protein Atlas, and Human Gene Nomenclature Committee. We have merged the information regarding genomic location, subcellular localization, protein structures, details of protein structure, chemical properties, string interactants of a protein, amino acid sequence, and features of APP, PSEN1, and PSEN2 gene in my report. The purpose of genetic studies is important to know the cause of a particular disease and to check how an individual will react to a specific therapy, also the metabolism of the drug depends on the genetic framework in an individual, which is studied in detail in pharmacogenomics. Furthermore, studies of genes are important to provide gene therapy; according to a new research, gene therapy is provided to patients of AD to activate some of the genes that play a crucial role to protect neurons from getting degenerated.

Finally, we reach the conclusion that protein expression of APP is high in the brain, spinal canal, liver, lungs, and small and large intestine. PSEN1 concentration of expression is high in the brain and spinal, whereas PSEN2 concentration of expression is high in the liver, lungs, brain, and intestine. We also got to know the secondary structures of proteins such as APP, PSEN1, and PSEN2 are generally make right-handed alpha-helix and anti-parallel beta-sheets structure in the Ramachandran plot.

Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

There is no need for ethics committee approval.

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Conflicts of interest

There are no conflicts of interest to declare.

Author contribution subject and rate

- PunyaSachdeva (70%): Conducting analysis and literature review
- Faizan Ahmad (30%): Conducting literature review.

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Original Article

Effects of Bilateral STN-DBS on Psychiatric profile, Cognitive aspects, and Quality of life in patients with Parkinson's disease

Abstract

Background: Apart from motor manifestations, Parkinson's disease (PD) and associated treatment modalities including DBS are associated with less studied psychiatric and cognitive symptoms. **Aim:** This study aims to evaluate psychiatric profile, cognition, and quality of life in patients with advanced PD and the effects on STN-DBS on them. **Study Design:** A prospective, single center, observational study using a direct, structured interview of PD patients. **Materials and Methods:** All consecutive patients undergoing bilateral STN-DBS between the period June 2017 and December 2019 were evaluated with mini international neuropsychiatric interview (MINI), Addenbrooke's Cognitive Examination (ACE), and PD questionnaire-39 (PDQ-39) before surgery. All these patients were evaluated at 6 weeks postsurgery with MINI and with MINI, ACE and PDQ-39 at 6 months postsurgery. Lead position in magnetic resonance imaging was correlated with psychiatric manifestations. Paired *t*-test and Wilcoxon sign-rank test were used to study the difference between means. **Results:** There were a total of 40 cases operated in the study period. There were two patients who had cerebral hemorrhage and two had leads removed due to infection and these patients were excluded from the final analysis. Out of 36 patients, depression was noted in 7 (19.4%), psychosis in 5 (13.8%), anxiety in 10 (27.7%), and suicidal ideation in 2 (5.5%) cases. Postoperatively, 85% of patients with depression, 80% with psychosis, and 80% of patients with anxiety disorders improved. One patient developed new-onset depression and one patient developed visual hallucination. Two patients had acute deterioration in the immediate postoperative period. The patient who developed depression and hallucination had their leads medially located. Mild cognitive decline was noted in verbal fluency which was significant ($P = 0.003$), and however, there was a significant improvement in quality of life ($P = 0.001$). **Conclusions:** Bilateral STN-DBS is a safe and effective therapeutic option and improves psychiatric disorders if the leads are appropriately placed. Although mild cognitive decline occurs, there is overall significant improvement in quality of life.

Keywords: *Addenbrooke's cognitive examination, MINI, Parkinson's disease, Parkinson's disease questionnaire-39, psychiatric disorder, STN-DBS*

Introduction

Parkinson's disease (PD) is considered one of the most common neurodegenerative motor disorders. It affects 1% of the population over the age of 50 years. It predominantly affects motor functioning which results in bradykinesia, rigidity, and resting tremor. However, it is also known to cause problems with cognition, mood, and behavior which are known as nonmotor manifestations.[1,2]

Bilateral deep brain stimulation of the subthalamic nucleus (STN-DBS) is known to be valid and relatively safe therapeutic option for the treatment of motor symptoms with low cognitive and behavioral morbidity.[3] Neuropsychological evidence seems to be consistent, which indicates substantial safety of the surgical procedure, and postsurgical cognitive deterioration is comparatively rare. Nevertheless, psychiatric and behavioral effects of this surgical procedure are still inconclusive.[4]

A wide and heterogeneous range of complications ranging from mild to severe depressive episodes, apathy, hypomania/mania, aggressive, and psychotic episodes in the postoperative period have been reported.[4]

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Ethics committee approval: The study was approved by the institutional Ethics Committee of NIMS institutional Ethics committee and Approval No EC/NIMS/1965/2017, dated 25.05.2017.

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We undertook this study to evaluate the effects of bilateral subthalamic nucleus deep brain stimulation on psychiatric profile, cognition, and quality of life, in a prospective cross-sectional study, in patients undergoing STN-DBS in PD and to evaluate the lead position and its correlation with the psychiatric symptomatology.

Materials and Methods

This study was performed in line with the principles of the Declaration of Helsinki, as revised in 2013. The study was approved by the institutional Ethics Committee of NIMS institutional Ethics committee and Approval No EC/NIMS/1965/2017, dated 25.05.2017. This was a prospective, single-center, observational study which employed a direct, structured interview of PD patients. The study was approved by the Institutional Ethics Committee. An informed written consent by the subjects was obtained for thesis study as well as for the surgical intervention.

Participants

A total of 40 patients were prospectively enrolled in the study. Two patients expired of intracerebral bleed and two patients required lead removal due to infection. Remaining 36 patients were followed up for 6 months. Of the 36 patients, 23 patients were male and 13 were female.

Inclusion criteria

All idiopathic PD patients who were found eligible as per CAPSIT-PD[5] protocol and were willing to undergo STN-DBS surgery from June 2017 to December 2019 were included in the study.

Exclusion criteria

- Patients who were not stable at the end of 6 months were excluded from the study
- Leads removed due to infection, malfunction, etc.,
- Medical comorbidities with poor medical health
- Death.

Preoperative assessment

- Psychiatric profiling of patient was done with MINI international neuropsychiatric interview version 7.0.1 which is based on DSM V criteria. (Permission obtained from Dr. Sheehan, Emeritus Professor, University of South Florida, USA, for academic purpose)
- Cognitive assessment using Addenbrooke's Cognitive Examination-III (ACE-III) was performed when the patient was in "ON" state.
- Quality of life assessment using PD questionnaire-39 (PDQ-39) questionnaire in the "ON" state.

Postoperative assessment

Six weeks: Psychiatric profile with MINI.

Six months: Psychiatric profile with MINI, cognition with ACE-III, and quality of life-PDQ-39.

All patients were operated by a single neurosurgeon. Stereotactic surgery was performed using CRW™-Illuminant frame Integra®, USA, using five channel intraoperative microelectrode recording and macroelectrode stimulation. Final lead placement (Medtronic, United Kingdom) in bilateral subthalamic nuclei was based on intraoperative recording and stimulation effects. Postoperative magnetic resonance imaging (MRI) was performed in all cases before implantable pulse generator (Medtronic Activa® P C, United Kingdom) implantation and stimulation to check the position of the leads.

Patients were maintained on monopolar stimulation with frequency of 130–180 Hz, pulse width of 60–90 μs, and amplitude ranging from 2.5 to 4.0V based on response.

Postoperative MRI was obtained and lead positions were checked in relation to the red nucleus. As size and shape of STN varies, we modified the division of STN. A horizontal line (A), tangential line to the anterior tip of red nucleus was drawn. Another tangential line was drawn on the lateral surface of the red nucleus (B). A point 3 mm lateral to the junction of A and B was the target. Line A was extended laterally to divide STN into anterior (ventral) and posterior (dorsal) segments. Another perpendicular line to line A at the target point divided it into medial and lateral compartments. Lead positions in postoperative MRI were correlated with the psychiatric manifestations.

Postoperative lead position was checked on T2-weighted axial imaging and lead position was designated as anterior, medial, posterior, lateral, and central (if at target) based on the quadrants divided [Figure 1].

Statistical analysis was done using SPSS software version 21.0.(IBM SPSS Statistics, English version 21.). Continuous variables were presented as mean ± standard deviation paired *t*-test and Wilcoxon sign-rank test were used to study the difference between means. All tests were two sided and $P < 0.05$ was considered statistically significant.

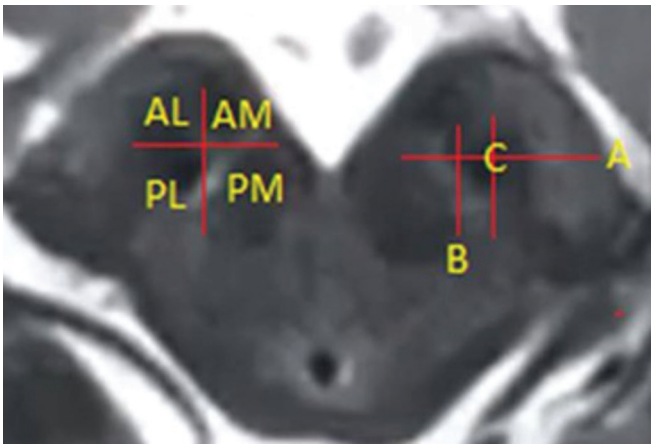

Figure 1: Postoperative T2 axial magnetic resonance imaging with subdivision of STN, A – horizontal line, B – vertical line; AL: Anterolateral, AM: Anteromedial, PL: Posterolateral, PM: Posteromedial, C: Central

Results

Mean duration of disease was 8.5 years (range 4–12 years). No significant relation could be noted between age, duration of illness, sex, and psychiatric illness. Patients were evaluated individually for psychiatric illness [Table 1]. Paired *t*-test and Wilcoxon sign-rank test were used to study the difference between means of following disease preoperatively and postoperatively.

Depression

Out of 36 patients, 7 (19.4%) had depression preoperatively. Among them, 5 (13.8%) had mild depression and 2 (5.5%) had moderate form of depression. None of the patients had any severe form of depression. Postoperatively, six patients had improvement and one patient developed new-onset depression at the end of 6 months follow-up.

Psychosis and hallucinations

Psychosis was present in 5 (13.8%) patients, of whom two patients had acute deterioration of their symptoms in the immediate postoperative period. Both patients returned to their preoperative status within 72 h. One patient had new-onset visual hallucinations at the end of 6 months follow-up [Figure 2].

Suicidal ideation and panic disorder

Mild suicidal ideation was seen in two patients. One patient improved after surgery within 6 weeks while other patient still remained the same. Panic disorder was noted in two patients out of which one patient improved after the surgery at the end of 6 weeks. Agoraphobia and obsessive compulsive disorder were noted in the same patient which improved by 6 weeks.

Social phobia and anxiety

Social phobia was noted in three patients and two patients improved at 6 weeks follow-up and one patient remained the same. Generalized anxiety disorder was noted in two patients before surgery and both patients improved postoperatively [Figure 2].

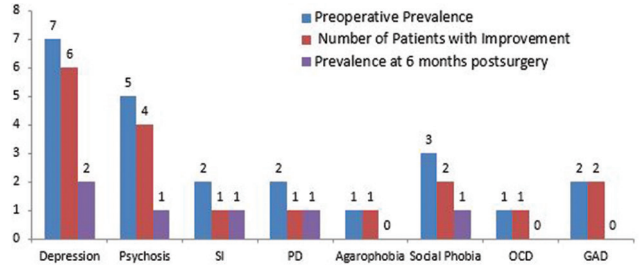

Figure 2: Psychiatric manifestations in preoperative and postoperative period. SI: Suicidal ideation, PD: Panic disorder, OCD: Obsessive compulsive disorder, GAD: Generalized anxiety disorder

Cognition

Cognition was assessed by ACE-III preoperatively and at 6 months after the surgery. Of the various subscales tested, verbal fluency was decreased which was significant (P = 0.003). Rest of all subscales, there was no significant difference noted. When all the subscales were combined, there was a significant decrease in cognition (P = 0.001) noted [Table 2].

Quality of life

Quality of life assessment was done with PDQ-39 preoperatively and at 6 months following the surgery. Except for social support, all other subscales improved significantly [Table 3].

Table 1: Prevalence of psychiatric manifestations

Psychiatric disorders	*n* (%)
Preoperative psychiatric manifestations	11 (30.5)
Depression	7 (19.4)
Psychosis	5 (13.8)
Suicidal ideation	2 (5.5)
Panic disorder	2 (5.5)
Auditory hallucinations	1 (2.7)
Visual hallucinations	3 (8.3)
Both auditory and visual	2 (5.5)
Delusions	1 (2.7)
Anxiety disorders	10 (27.7)
Depression with psychosis and anxiety	2 (5.5)

Table 2: Cognition in preoperative and postoperative period

	Preoperative mean	Postoperative mean	*P*
Attention	16.97±1.29	16.58±1.62	0.085
Memory	21.25±4.83	21.00±4.81	0.130
Fluency	9.91±2.25	8.97±2.44	0.003
Language	24.41±2.16	24.22±2.11	0.128
Visuospatial	13.13±2.94	12.91±2.97	0.118
ACE_Total	85.69±10.25	83.69±10.92	0.001

ACE: Addenbrooke's cognitive examination

Table 3: Pre- and post-operative quality of life assessment

	Preoperative mean	Postoperative mean	*P*
Mobility	44.54±28.14	25.59±31.77	0.001
ADL	39.62±27.32	22.74±30.03	0.001
Emotional well-being	15.60±16.82	7.76±16.53	0.011
Stigma	19.10±22.05	7.46±16.48	0.003
Social support	2.77±9.54	3.46±12.48	0.933
Cognitive impairment	13.88±13.62	6.77±14.04	0.002
Communication	18.73±19.95	9.70±18.19	0.006
Bodily discomfort	30.82±26.45	12.94±17.52	0.001

ADL: Activities of daily living

Lead position

Lead positions were checked based on the quadrant division system described previously [Figure 1]. Postoperatively, two patients had developed new-onset symptoms. Both the patients had leads in anteromedial quadrant. Lead positions of all patients with psychiatric manifestations are presented in Table 4.

Discussion

PD has been associated with significant nonmotor and cognitive symptoms along with motor manifestations. This, in turn, affects the overall quality of life of the individual. Variable results have been noted in literature pertaining to changes in these manifestations after deep brain stimulation [Table 5]. The present study aimed and evaluated the prevalence of psychiatric manifestations in a group of PD patients presenting for deep brain stimulation and evaluated them in terms of cognition as well as quality of life, both preoperatively and after 6 months of surgery.

Depression

Improvement in depression has been studied and reported extensively in cases of advanced PD after undergoing DBS. However, reports of new onset of depression and deterioration have also been noted. Houeto *et al*. reported 30% improvement in depression and new-onset depression in 4% of patients postsurgery.[5] Smeding

Table 4: Lead positions with pre- and post-operative psychiatric manifestations

Preoperative	Postoperative	Right lead	Left lead
SP	Nil	Anterolateral	Anterolateral
Nil	Hallucinations (6 months)	Anteromedial	Anteromedial
D + Pd + OCD + P + Ag	Pd	Posterolateral	Anterolateral
Nil	Depression (6 months)	Anteromedial	Anteromedial
D + P	Nil	Anterolateral	Anterolateral
Depression	Nil	Central	Posterolateral
D + SI + SP + P	D + P + SI	Posterolateral	Posterolateral
P	Nil	Anterolateral	Anterolateral
D	Nil	Central	Posterolateral
D	Nil	Posterolateral	Posterolateral
SP + GAD	Nil	Posterolateral	Anterolateral
D + GAD + Pd	Nil	Anterolateral	Posterolateral
D + SI + P + OCD	Nil	Central	Posterolateral

SP: Social phobia, D: Depression, Pd: Panic disorder, OCD: Obsessive compulsive disorder, P: Psychosis, Ag: Agoraphobia, SI: Suicidal ideation, GAD: Generalized anxiety disorder

Table 5: Postoperative changes in depression, psychosis, anxiety, and suicide in various studies

	Heuto *et al*.	Smeding *et al*.	Castelli *et al*.	Daniel *et al*.	Present study
Depression (%)					
Postoperative improvement	29	-	20	76	16
Postoperative deterioration	-	-	10	12	-
Postoperative same status	16	-	70	12	2.7
New onset	4	3	-	-	2.7
Psychosis (%)					
Postoperative improvement	-	-	-	-	11
Postoperative deterioration	4	-	-	-	5.5
Postoperative same status	-	-	-	-	2.7
New onset	-	2	1.5	-	2.7
Anxiety (%)					
Postoperative improvement	-	-	20	50	13.8
Postoperative deterioration	41	-	12	12	-
Postoperative same status	29	-	-	37	8.3
New onset	4	-	-	-	-
Suicide					
Postoperative improvement	-	-	-	-	2.7
Postoperative deterioration	-	-	10	-	-
Postoperative same status	12.5	-	-	-	2.7
New onset	4	1	-	-	-

et al. observed new-onset depression in 3% of patients in postsurgery cases.[6] Castelli *et al*. reported improvement in 20% of cases and stable course of their depression in the post-operative period (70%) and deterioration in 10% cases.[7] STN-DBS also may improve both mood and anxiety. This is by affecting probably the signaling features of the motor, associative, and limbic circuitry that project to and/or receive input from the STN or by neurotransmission. The exact mechanism remains unknown, but it is hypothesized to reduce disturbances in basal ganglia thalamocortical network (acts as a traffic controller) activity by increasing both excitatory and inhibitory signaling in the STN and adjacent fiber tracts.[8] Although, STN-DBS improves motor manifestations, changes in motor function are not found to correlate with changes in nonmotor symptoms. This suggests that these effects occur independently at an individual level.[9] On evaluation of lead position in case with new-onset depression, it was noted that leads were located in anteromedial quadrant bilaterally and the subsequent activation of limbic circuits could have caused new-onset depression [Table 5].

Psychosis

Postoperative psychosis following STN-DBS has been reported to vary from 1.5% to 4%.[5,7] Psychosis before stimulation can be attributed to lesionectomy effect of the lead.[10] We noted psychosis in 13.8% of patients and 11% of patients improved at 6 weeks follow-up. One patient had medication induced psychosis due to pramipexole, and following surgery, the medication was switched to levodopa leading to an improvement in symptoms. Improvement in this situation could be attributed to modification of medication postsurgery. Acute deterioration of psychosis noted in 5.5% of patients, returned to base line within 72 h. Bilateral frontal edema due to lead passage, pneumocephalus, and lesion can also cause worsening of the symptoms. New-onset psychosis was seen in about 2.7% of patients, however, after 6 months of surgery in the form of visual hallucinations. Unfortunately, we were unable to determine the cause of these hallucinations.

Anxiety

At 1 year follow-up, anxiety improves along with other mood disorders and the result is more favorable if there is early improvement within 3 months.[11] We noted improvement in anxiety in 80% of patients with no new-onset anxiety symptoms. Houeto *et al*., however, reported new-onset anxiety in 4% of the patients. Randomized controlled study of 156 patients by Witt *et al*. comparing STN-DBS with best medical treatment (BMT) available demonstrated Class I data of improvement in anxiety scales at 6-month follow-up after performing DBS. The cause of improvement is not understood completely, but reduced disturbances in basal ganglia thalamocortical network activity could be an important factor.[12] New-onset anxiety has been commonly attributed to fear pertaining to the failure of the device.[5]

Suicide

Suicide risk has been a matter of considerable debate with varied reports of prevalence, ranging from 4% to 10%.[5,7] Meta-analysis by Appleby *et al*. showed that most of the PD patients who underwent thalamic or GPi stimulation reported a suicidal ideation/attempt at 0.3%–0.7% and a completed suicide rate 0.16%–0.32%. They reported dissociation of depression and suicidal risk with improvement of depression, however, the risk of suicide remains same and improved motor outcomes actually led to less monitoring of patients by caregivers.[13] In a randomized controlled study by Weintraub *et al.*, they reported no increased rates of suicidal ideation post-DBS at 6 months.[14] Suicidal ideation in our study was noted in 5.5%, of which 2.7% of patients improved after surgery while 2.7% of patients remained the same. There were no suicidal attempts in our study [Table 5]. Major decrease in dopaminergic medications following the surgery can result in apathy, increased rates of depression. The above factors can contribute toward increased suicidal ideation. Neurological or medical complications are also listed as potential factors for increase in suicidal risk.[14]

Cognition

PD, is a neurodegenerative disorder, will have a progressive decline in cognition, but following a surgical procedure, the decline is rare. Funkiewiez *et al.* reported in follow-up of patients for 1 year and 3 years after surgery, there was no significant change noted in the overall cognition. Although, the verbal fluency decreased significantly at 1-year follow-up and remained the same at 3 years.[15] In our study, we found mild decrease in attention, memory, visuospatial, and language functions but these were not demonstrated to be statistically significant. Verbal fluency

Table 6: Comparison of cognition in various studies

	Funkiewiez et al., 2004 (*n*=77)	Witt *et al*., 2008 (*n*=123)	Castelli *et al*., 2008 (*n*=50)	Okun *et al*., 2009	Present study
Duration	3 years	6 months	3 years	7 months	6 months
Scale	Mattis Dementia Rating Scale	Mattis Dementia Rating Scale	Standardized neuropsychological test battery	Dementia rating scale and verbal fluency tasks	ACE-III
Overall cognition	No change	No change	No change	No change	Decreased
Fluency	Decreased	Decreased	Decreased	Decreased	Decreased

ACE-III: Addenbrooke's cognitive examination

and overall cognition were significantly decreased after surgery [Table 6]. In a recent meta-analysis by Kurtis *et al*. concluded after STN-DBS, there is Level I and II type evidence consistently reporting moderate decrease in verbal fluency, as well as a mild reduction in abstract reasoning, working memory and executive functions. However, this mild cognitive deterioration is not known to be clinically relevant.[16] In RCT study by Witt et al., compared with best medical treatment with a follow up of 6 months after STN DBS, concluded no significant decline in overall cognition but a significant decrease was noted in verbal fluency. This decrease albeit had no effect on quality of life. In comparison, medical treatment group had no decline in cognition or verbal fluency. This indicates that the decline was not because of disease progression, but rather the effect of surgery itself.[12] Castelli *et al*. compared STN-DBS with medical treatment with a follow-up of 3 years and observed no significant overall decline in the cognition in both groups. However, there was significant decline in the DBS group in fluency task.[4] Okun *et al.* compared with STN-DBS and GPi DBS with a follow-up of 7 months and did not find any difference in overall cognition between the groups as well as pre- and post-operative states. However, the mean letter fluency scores decreased in STN-DBS group when compared to GPi DBS group and the difference was significant.[17]

Quality of life

The main objective of DBS hinges on improving quality of life and minimizing motor symptoms of PD. Erola *et al.* reported improvement across all subscales at 1 month follow-up and significant improvement is seen in ADL, emotional well-being, stigma, and bodily discomfort. At 12 months follow-up, communication was in fact worse than preoperative status, but had not reached statistical significance.[18] In the present study, patients were evaluated at baseline and 6 months postsurgery. All subscales improved and were statistically significant except for social support which decreased from baseline, but the difference was not significant [Table 7]. Similar findings were noted previously.[19,20]

Lead position

Lead position has been correlated with psychiatric manifestations. Furthermore, ventral or medially located leads having more propensity of causing mood-related symptoms. Okun *et al.* in COMPARE trial obtained precise locations of these implanted leads with a high-resolution computed tomography (CT) scan which was fused to the preoperative MRI and used an orthogonal Cartesian coordinate system. Based on these tools, they noticed that patients who were less happy and less energetic had leads in ventral location when compared to those patients who had optimal lead location. However, no measurement was done for medial and lateral variation in the above study.[17] In our study, we used postoperative T2-weighted axial image at the red nucleus level to map quadrants of the STN [Figure 1]. Based on the lead locations, patient who had new onset depression had anteromedially placed leads according to the quadrant system. Sudhyadhom *et al.* used postoperative MRI with overlaid Schaltenbrand and Bailey atlas to accurately locate the lead after surgery and noticed similar findings. They hypothesized, there could be a spread of current to the limbic circuits which could cause mood disorders and these were seen in patients in medially placed leads.[21] Abulseoud *et al*. used COMPASS surgical planning software and evaluated the effects of different position of the lead and stimulation effects. They reported abrupt pleasant sensations transient difficulty in emotional recognition, hypomania, and mania which were reproducible with bilateral stimulation of the medial STN. However, their evaluation was only for transient stimulation and long-term effects cannot be concluded from their study.[22] We noticed new-onset visual hallucinations in a patient after the surgery who had his leads located in the medial region. Beside the known activation of limbic areas, it is also possible that STN stimulation induces the activation of extrastriate visual or the lateral temporal cortex. This has been observed by functional MRI and single-photon emission CT in patients with the Charles Bonnet syndrome.[23]

Conclusions

Bilateral subthalamic nucleus deep brain stimulation improves the psychiatric profile and quality of life significantly with a negative impact on cognition in some of the patients. Medially placed leads are more likely to cause psychiatric disturbances.

Table 7: Comparison of quality of life in various studies

	Erola *et al*., 2005 (*n*=27)	Nazzaro *et al*., 2011 (*n*=24)	Weaver *et al*., 2012 (*n*=159)	Present study
Mobility	Improved	Improved	Improved	Improved
ADL	Improved	Improved	Improved	Improved
Emotional well being	Improved	Improved	Improved	Improved
Stigma	Improved	Improved	Improved	Improved
Social support	Not improved	Improved	Improved	Not improved
Cognition	Improved	Improved	Improved	Improved
Communication	Not improved	Improved	Improved	Improved
Bodily discomfort	Improved	Improved	Improved	Improved
PDQ 39 SI	Improved	Improved	Improved	Improved

PDQ 39 SI: Parkinson's disease questionnaire 39 summary index, ADL: Activities of daily living

Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

The study was approved by the institutional Ethics Committee of NIMS institutional Ethics committee and Approval No EC/NIMS/1965/2017, dated 25.05.2017.

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Conflicts of interest

There are no conflicts of interest to declare.

Author contribution subject and rate

- Alugolu Rajesh (25%): Design the research
- Pavan S (15%): Data collection and analyses
- Padmaja Gaddamanugu (15%): Design the research
- Swapnil Kolpakwar (15%): Wrote the manuscript
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Original Article

Neuroprotective Effect of *Phoenix dactylifera* (Date Palm) on Paraquat Triggered Cortico-Nigral Neurotoxicity

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Abstract

Background: Herbicides including paraquat (PQ) have been reported to have deleterious effects on biological systems and normal functioning of the brain, especially regions related to motor functionality and coordination like the cerebrum and substantia nigra resulting in neurodegenerative conditions such as Parkinson's disease. *Phoenix dactylifera* has high nutritional value and is beneficial in the management and treatment of diverse ailments. **Aim:** This study assessed the protective properties of Aqueous fruit extract of *P. dactylifera* (AFPD) on PQ-triggered cortico-nigral neurotoxicity in rats. Neuroprotective properties of AFPD were assessed using beam walking performance (BWP) for motor coordination, oxidative stress biomarkers (Malondialdehyde [MDA], superoxide dismutase [SOD], and glutathione [GSH]) and histological examination (H and E stained) for cytoarchitectural changes. BWP across the study period revealed no motor coordination deficit with PQ exposure. **Materials and Methods:** Twenty-five rats were categorized into five groups (n = 5); the control was administered 2 ml/kg distilled H_2O, another group received 11.35 mg/kg PQ, another received 11.35 mg/kg PQ + 10 mg/kg L-dopa as reference drug, while two other groups received 11.35 mg/kg PQ + 500 mg/kg AFPD and 11.35 mg/kg PQ + 1,000 mg/kg AFPD, respectively, for 28 days. **Results:** PQ-treated group revealed oxidative stress by significant elevation of MDA levels and decrease in antioxidant enzymes (SOD and GSH). Remarkable cytoarchitectural distortions were observed with PQ treatment. However, AFPD treatment showed ameliorative properties by a significant decrease in MDA levels and increased SOD and GSH activities. Mild distortion-to-relatively normal neuronal cytoarchitecture relative to the control was also observed with AFPD treatment. **Conclusion:** AFPD possesses potential neuroprotective properties against PQ-triggered pathological changes in cortico-nigral structures of Wistar rats.

Keywords: *Beam walking performance, cytoarchitecture, motor coordination, neurodegeneration, oxidative stress*

Introduction

Exposure to environmentally based substances including chemicals, heavy metals and herbicides have been documented to have lethal effects on the health status and normal brain functioning of humans and animals.[1-4] Agrochemicals, especially those used as weed control are a major hazard challenge in some nations of the world. Paraquat (PQ) is considered to be among the main herbicide involved in intentional and accidental poisoning and is responsible for a high rate of illnesses including alteration of normal biological functions and neurological disease conditions.[5-7] PQ causes toxicity in vital regions of the brain including cerebrum and substantial nigra that play a critical role in motor coordination, supporting the idea that exposure to this herbicide may contribute to the pathophysiology of neurodegenerative diseases like Parkinson's disease (PD).[8-10] Protein aggregation, mitochondrial dysfunction, altered dopamine levels, and

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increased oxidative stress are majorly reported mechanisms by which PQ causes neurological disease conditions.[11-13]

Cerebral cortex (CC) is an imperative part of the brain responsible for the execution of higher-order cerebral functions, including cognition, sensory perception, and motor control,[14] with multiple functions connected to different brain parts.[15,16] Substantia nigra (SN), a neuronal structure located in the ventral midbrain, with vital connections with CC (cortico-nigral pathway) exerts regulatory function within the basal ganglia circuitry.[17] SN is involved in several neurological and neuropsychiatric disorders.[17-19] Secondary damage to SN has been associated with cerebral infarction with the development of sustained dementia, PD, and poor neurofunctional outcomes.[19-21]

Date palm (*Phoenix dactylifera*) is one of the members of the palm family Arecaceae.[22] There have been several reports of the high nutritional value of *P. dactylifera* and, properties that acknowledged it as potential nutraceutical agents.[23,24] Dates and their constituents are useful in the prevention and treatment of diverse ailments through antioxidant, anti-inflammatory, and antimicrobial activities.[25] The deleterious effects and health implication of PQ exposure is moderately established, especially the corticonigral structures of the brain in animal models. There is a need to assess the phytotherapeutic potentials of this plant in PQ-induced neurotoxicity. This study assessed the neuroprotective properties of *P. dactylifera* on PQ-induced corticonigral neurotoxicity in rats.

Materials and Methods

This study was performed in line with the principles of the Declaration of Helsinki, as revised in 2013. Ethical clearance for this study was provided by the Ethics Committee on Animal Use and Care, Ahmadu Bello University (ABU), Zaria: ABUCAUC/2018/097.

Plant material collection and identi ication

P. dactylifera L.(date palm) dried fruits were collected in Zaria, Kaduna State, Nigeria. Collected plant material was identified (Voucher Specimen Number: 21104) in the Department of Botany, Faculty of Life Sciences, ABU, Zaria.

Plant material extraction

Date palm fruit pulp was separated from the seed (pit) for preparation of aqueous fruit pulp extract of *P. dactylifera* (AFPD). Maceration method of extraction as described by Agbon *et al.*[26] was adopted. Extraction of the fruit pulp was carried out in the Department of Pharmacognosy and Drug Development, Faculty of Pharmaceutical Sciences, ABU, Zaria.

Experimental animals

Apparently healthy adult male Wistar rats (100–150 g) were obtained from the Animal House facility of the Faculty of Pharmaceutical Sciences, ABU, Zaria. The rats were transported to the Animal House, Human Anatomy Department, Faculty of Basic Medical Sciences, ABU, Zaria, housed under standard laboratory conditions, light and dark cycles of 12 h provided and fed with rat chow and water *ad libitum* and allowed to acclimatize for a period of fourteen (14) days before the commencement of experimentation.

Drugs

Paraquat

PQ (Paracot® PQ Dichloride) was obtained and used as neurotoxin in this study. The product is manufactured by Hubei Xianlong Chemical Industry Co, China.

Levodopa (L-dopa)

Levodopa (Sinemet) tablet was obtained and used as a reference drug to evaluate the therapeutic property of AFPD. The product is manufactured by Mylan Pharmaceuticals, Inc., Morgantown, USA.

Ketamine

Ketamine (Ketamine Hydrochloride injection USP, 50 mg/ml) was obtained and used for anesthesia. The product is manufactured by Swiss Parenterals PVT Ltd, Gujarat, India.

Experimental protocol

Twenty-five (25) rats were categorized into five (5) groups (groups A to E) of five rats each for a twenty-eight (28) day period of treatments via oral route; group A served as the control group, treated with distilled H_2O (2 ml/kg), group B was treated with PQ (11.35 mg/kg; 28.4% LD_{50} oral, Haley, 1979[27]), group C was treated with PQ (11.35 mg/kg) + *L*-dopa (10 mg/kg), groups D and E were treated with PQ + AFPD (500 mg/kg) and PQ + AFPD (1,000 mg/kg), respectively [Figure 1]. Following experimentation, rats were euthanized using Ketamine (75 kg/mg i. p)[28] anesthesia, the rats were decapitated and skull dissected to remove the brain. Harvested whole brains were dissected sagittally at the midline into two equal halves, one part homogenized for biochemical analysis and the other part fixed in Bouin's fluid for histological processing.

Neurobehavioural study

Neurobehavioral assessment was conducted using beam walking apparatus (BWA). Beam walking test in this study assessed motor coordination and balance by measuring the beam walking performance (BWP) as the rats' ability to traverse a narrow beam to reach a safety platform according to the method described by Perry *et al.*[29] A modification of BWA described by Carter *et al*.[30] was adopted.

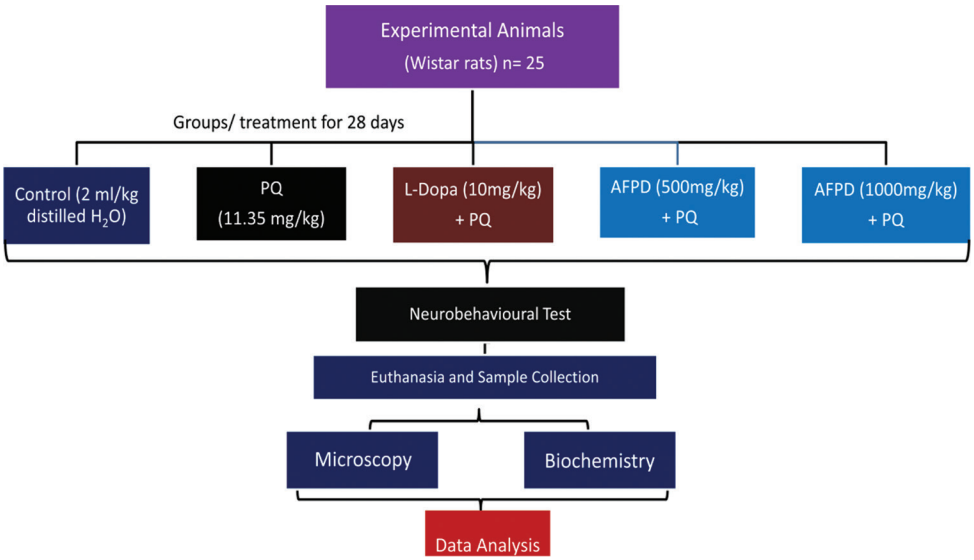

Figure 1: Experimental protocol. *N* = 5; AFPD = Aqueous fruit pulp extract of *Phoenix dactylifera*; PQ = Paraquat

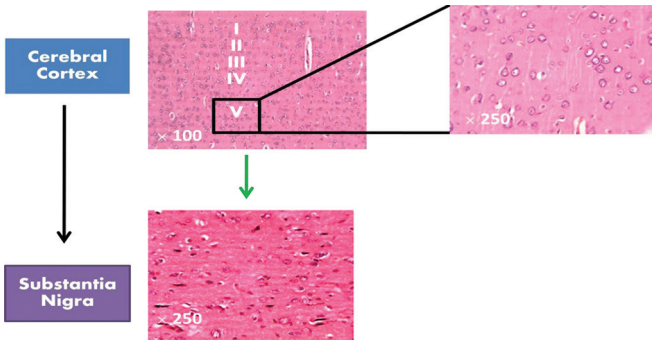

Figure 2: Structures of the cortico-nigral pathway

The BWA consisted of an elevated platform connected by a 100 cm long wood beam with a width of 3 cm. The beam was placed horizontally, 50 cm above the floor surface, with one end mounted on narrow support (connected to start platform 10 cm × 10 cm) and the other end attached to a goal box (20 cm × 20 cm × 20 cm). The start point was placed by a bright light source to motivate the rats to traverse the beam. Protection for falling rats was provided by a sawdust-filled box placed at the base of the platform.

The latency until the rat's nose entered the enclosed safety box (within 60 s) was recorded. Rats that slipped off the beam or could not make their way into the goal box were assigned latencies of 60 s. Beam-walking scores were based on an average of three (3) trials, cleaned with methylated spirit at inter-trial intervals. The rats were habituated to the apparatus for 3 days before treatment. BWP was assessed across the study period (from pretreatment through week four (4) of treatment) and data analyzed statistically.

Biochemical studies

Brains were weighed using digital weighing scale (Acculab Vicon VIC-511 Precision Balance/Scale, USA, 0.001 g) and mechanically homogenized in 0.1 M phosphate buffer (pH 7.4) (1 g tissue/4 ml) according to the method described by Ige *et al*.[31] Homogenate was analyzed for oxidative stress biomarkers (Malondialdehyde, [MDA]; superoxide dismutase, [SOD] and reduced glutathione, [GSH]). Biochemical analysis was conducted at the Department of Human Anatomy, ABU, Zaria. MDA (thiobarbituric-acid reactive substance) assay estimated lipid peroxidation levels according to the method of Ohkawa *et al*.[32] Enzymatic antioxidant activity was estimated by assaying SOD activity according to the methods of Fridovich,[33] and GSH activity according to the methods Ellman[34] as described by Rajagopalan *et al*.[35] Data obtained were subjected to statistical analysis.

Histological studies

Fixed brain samples were processed using histological techniques by making sections to target the cerebrum (layer V: internal pyramidal layer of the CC) and SN using Rats Brain Atlas as a guide.[36] The tissue sections were examined for histopathological changes using light microscopy (Optical Microscope; HM-LUX, Leitz Wetzlar, Germany) [Figure 2]. Histological paraffin sections were processed and stained with Hematoxylin and Eosin (H and E) stains for demonstration of cytoarchitecture of brain regions of interest in the Histology Unit of the Department of Human Anatomy, ABU, Zaria. Microscopy and micrography (using Digital Microscopic Camera, MA 500 AmScope®, USA) were conducted in the Microscopy and Stereology Research Laboratory of the same facility.

Data analysis

Data obtained from this study were expressed as mean ± SEM. One-way analysis of variance was used to compare mean difference between groups followed by *Tukey post hoc test*. Paired *t*-test was employed for the comparisons of means as appropriate. Values were

considered significant when $P < 0.05$. Analyses were done using the statistical software, Statistical Package for the Social Sciences (IBM SPSS *v*21.0, Armonk, NY, USA: IBM Corp).

Results

Neurobehavioural study

Beam walking, oxidative stress, cerebrum, substantia nigra

In this study, BWP was assessed as a pointer to motor coordination and balance. Increased BW*P* values (latency time to cross the beam) indicate deficit in motor coordination and balance, while decreased BW*P* values indicate improved functionality.

Results revealed significant ($P < 0.05$) improvement in BWP in the PQ-treated, control, and PQ + L-dopa-treated groups when latency time to traverse the beam were compared between pre-treatment and week 1 of the experiment [Figure 3a].

Results revealed significant ($P < 0.05$) improvement in BWP in the PQ-treated and PQ + L-dopa-treated, PQ + AFPD (1000 mg/kg) groups when latency time to traverse the beam were compared between pre-treatment and week 2 of the experiment [Figure 3b].

Results revealed significant ($P < 0.05$) improvement in BWP in the PQ-treated, control and PQ + AFPD (500 mg/kg)-treated groups when latency time to traverse the beam were compared between pretreatment and week 3 of the experiment [Figure 3c].

Results revealed significant ($P < 0.05$) improvement in BWP in all the groups when latency time to traverse the beam were compared between pretreatment and week 4 of the experiment [Figure 3d].

Results revealed difference in BWP especially ($P < 0.05$) in PQ-treated group when latency time to traverse the beam were compared between week 1 and week 2 of the experiment [Figure 4a].

Results revealed significant ($P < 0.05$) improvement in BWP in the PQ-treated and PQ + AFPD (1000 mg/kg)-treated groups when latency time to traverse the beam were compared between week 2 and week 3 of the experiment [Figure 4b].

Results revealed significant ($P < 0.05$) improvement

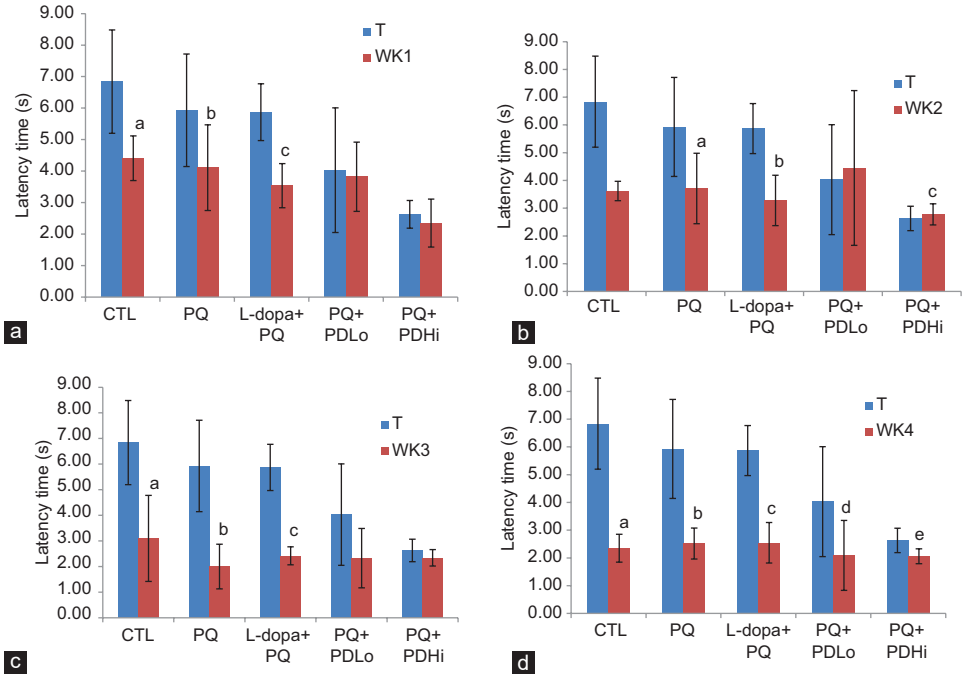

Figure 3: (a) Comparison of beam walking performance (pretreatment and Week 1) in Wistar rats. N = 5; mean ± SEM, Paired *t*-test; [a]p = 0.046, [b]p = 0.018, [c]p = 0.002 were the significant difference when pre-treatment (t) was compared with week 1 (WK1). CTL = Control (distilled water 2 ml/kg); PQ = Paraquat (11.35 mg/kg); L-dopa = *L*- dopa (10 mg/kg); PDLo = AFPD (500 mg/kg); PDHi = AFPD (1,000 mg/kg); AFPD = Aqueous fruit extract of *Phoenix dactylifera*. (b) Comparison of beam walking performance (Pre-treatment and Week 2) in Wistar rats. N = 5; mean ± SEM, Paired *t*-test; [a]p = 0.017, [b]p = <0.001, [c]p = 0.049 were the significant difference when pretreatment (t) was compared with week 2 (WK2). CTL = Control (2 ml/kg distilled water); PQ = Paraquat (11.35 mg/kg); L-dopa = *L*- dopa (10 mg/kg); PDLo = AFPD (500 mg/kg); PDHi = AFPD (1000 mg/kg); AFPD = Aqueous fruit extract of *Phoenix dactylifera*. (c) Comparison of beam walking performance (pretreatment and Week 3) in Wistar rats. N = 5; mean ± SEM, Paired *t*-test; [a]p = <0.001, [b]p = 0.018, [c]p = 0.008 were the significant difference when pre-treatment (t) was compared with week 3 (WK3). CTL = Control (distilled water 2ml/kg); PQ = Paraquat (11.35 mg/kg); L-dopa = *L*- dopa (10 mg/kg); PDLo = AFPD (500 mg/kg); PDHi = AFPD (1000 mg/kg); AFPD = Aqueous fruit extract of *Phoenix dactylifera*. (d) Comparison of beam walking performance (Pre-treatment and Week 4) in Wistar rats. N = 5; mean ± SEM, Paired *t*-test; [a]p = 0.021, [b]p = 0.040, [c]p = 0.001, [d]p = 0.043, [e]p = 0.028 were the significant difference when pre-treatment (t) was compared with week 4 (WK4). CTL = Control (2 ml/kg distilled water); PQ = Paraquat (11.35 mg/kg); L-dopa = *L*- dopa (10 mg/kg); PDLo = AFPD (500 mg/kg); PDHi = AFPD (1000 mg/kg); AFPD = Aqueous fruit extract of *Phoenix dactylifera*

in BWP in the PQ + AFPD (1,000 mg/kg)-treated group when latency time to traverse the beam was compared between week 3 and week 4 of the experiment [Figure 4c].

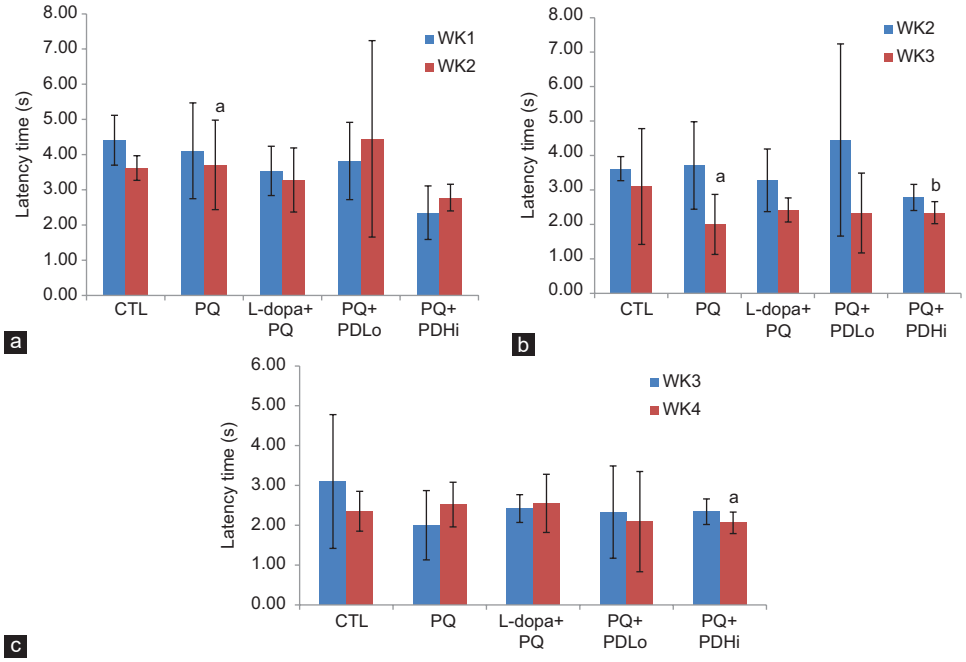

Figure 4: (a) Comparison of beam walking performance (Week 1and Week 2) in Wistar rats. N = 5; mean ± SEM, Paired *t*-test; [a]p = 0.16 was the significant difference when week 1 (WK1) was compared with week 2 (WK2). CTL = Control (2 ml/kg distilled water); PQ = Paraquat (11.35 mg/kg); L-dopa = *L*- dopa (10 mg/kg); PDLo = AFPD (500 mg/kg); PDHi = AFPD (1,000 mg/kg); AFPD = Aqueous fruit extract of *Phoenix dactylifera*. (b) Comparison of beam walking performance (Week 2 and Week 3) in Wistar rats. N = 5; mean ± SEM, Paired *t*-test; [a]p = 0.018, [b]p = 0.006 were the significant difference when week 2 (WK2) was compared with week 3 (WK3). CTL = Control (2 ml/kg distilled water); PQ = Paraquat (11.35 mg/kg); L-dopa = *L*- dopa (10 mg/kg); PDLo = AFPD (500 mg/kg); PDHi = AFPD (1000 mg/kg); AFPD = Aqueous fruit extract of *Phoenix dactylifera*. (c) Comparison of beam walking performance (Week 3 and Week 4) in Wistar rats. N = 5; mean ± SEM, Paired *t*-test; [a]p = 0.010 was the significant difference when week 3 (WK3) was compared with week 4 (WK4). CTL = Control (2 ml/kg distilled water); PQ = Paraquat (11.35 mg/kg); L-dopa = *L*- dopa (10 mg/kg); PDLo = AFPD (500 mg/kg); PDHi = AFPD (1,000 mg/kg); AFPD = Aqueous fruit extract of *Phoenix dactylifera*

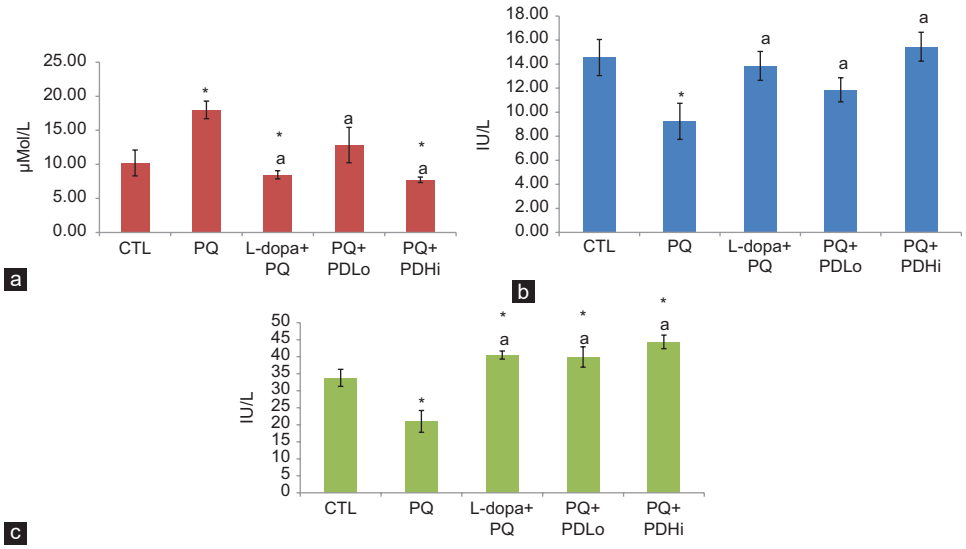

Figure 5: (a) Effect of *P. dactylifera* on Malondialdehyde levels exposed to Paraquat. N = 5; mean ± SEM; One way analysis of variance, LSD *post hoc* test; * = *P* < 0.05 when compared with control. A = p<0.05 when compared to Paraquat. CTL = Control (distilled water 2ml/kg); PQ = Paraquat (11.35 mg/kg); L-dopa = *L*- dopa (10 mg/kg); PDLo = AFPD (500 mg/kg); PDHi = AFPD (1,000 mg/kg); AFPD = Aqueous fruit extract of *Phoenix dactylifera*. (b) Effect of *P. dactylifera* on SOD activity following PQ treatment. N = 5; mean ± SEM; One way analysis of variance, LSD *post hoc* test; * = *P* < 0.05 when compared with control. A = *P* < 0.05 when compared to PQ. CTL = Control (distilled water 2ml/kg); PQ = Paraquat (11.35 mg/kg); L-dopa = *L*- dopa (10 mg/kg); PDLo = AFPD (500 mg/kg); PDHi = AFPD (1000 mg/kg); AFPD = Aqueous fruit extract of *Phoenix dactylifera*. (c) Effect of *P. dactylifera* on GSH activity following PQ treatment. N = 5; mean ± SEM; One way ANOVA, LSD *post hoc* test; *= *P* < 0.05 when compared with control. A = *P* < 0.05 when compared to PQ. CTL = Control (distilled water 2ml/kg); PQ = Paraquat (11.35 mg/kg); L-dopa = *L*- dopa (10 mg/kg); PDLo = AFPD (500 mg/kg); PDHi = AFPD (1000 mg/kg); AFPD = Aqueous fruit extract of *Phoenix dactylifera*

Biochemical studies

Results for the estimation of lipid peroxidation (MDA level) showed a significant ($P < 0.05$) increase in MDA levels in PQ-treated group, but a decrease ($P < 0.05$) in PQ + *L*-dopa-and PQ + AFPD (1000 mg/kg)-treated groups when compared to the control group. Besides, a significant decrease in MDA levels was observed in PQ + *L*-dopa-and PQ + AFPD (500 mg/kg and 1000 mg/kg)-treated groups when compared to the PQ-treated group [Figure 5a].

The SOD activity showed a significant decrease in PQ-treated group when compared to control group. However, an increase ($P < 0.05$) in SOD activity was observed in PQ + *L*-dopa-treated and PQ + AFPD-treated (1000 mg/kg) groups when compared to the PQ-treated group [Figure 5b].

GSH activity showed differences ($P < 0.05$) in all the groups when compared to the control group. Moreover, significant increase in GSH activity was observed in PQ + *L*-dopa-and PQ + AFPD (500 mg/kg and 1000 mg/kg)-treated groups when compared to the PQ-treated group [Figure 5c].

Histological studies

Histological examination of cortical cerebral region (LV) and the SN of rats revealed:

In the control, cortical cerebral region presented with normal histoarchitectural features with characteristic six layers of the CC. In particular, layer V revealed pyramidal neuron with normal cytoarchitectural features, well preserved cytoplasm, prominent nuclei and moderately dispersed neuroglia cells [Figure 2]. Relative to the control, section of the PQ-treated group showed neurodegenerative changes as cytoarchitectural distortion: pyknotic nucleus/necrosis, chromatolysis, perineuronal vacuolation and satelliotosis. The *L*-dopa and AFPD (500 mg/kg)-treated groups revealed mild distortion of the cytoarchitecture as perineuronal vacuolation and satelliotosis. AFPD (1000 mg/kg) showed relatively normal cytoarchitecture when compared to the control [Figure 6].

SN region of the control showed normal histoarchitecture with variety of cells types and neurons with normal cytoarchitectural features [Figure 2]. Relative to the control, section of the PQ-treated group showed neurodegenerative changes as cytoarchitectural distortion: pyknotic nucleus/necrosis, and perineuronal vacuolation. The *L*-dopa and AFPD (500 mg/kg)-treated groups revealed mild distortion of the cytoarchitecture as karyorrhexis. AFPD (1000 mg/kg) showed relatively normal cytoarchitecture when compared to the control [Figure 7].

Discussion

In this study, the neuroprotective property of aqueous fruit extract of *P. dactylifera* on cortico-nigral structures of Wistar rats exposed to PQ neurotoxicity was studied using neurobehavioral, biochemical and histological assessments.

BWP is an established tool for the measurement of motor coordination and balance, and is useful to detect motor deficits associated with neurologic conditions including aging, central nervous system (CNS) lesions, genetic and pharmacologic manipulation in rodents.[37] In this study, BWP was assessed for deficit or improved motor coordination and balance functionality. Comparison of BWP across the study period revealed no motor coordination deficit with PQ treatment. This finding is at variance with reports on PQ-induced motor deficit. Following PQ exposure, Mollace *et al*.,[38] Thiruchelvam *et al*.[39] and Fahim *et al*.[40] reported significant difficulties and reduced motor activities, and modified motor coordination which attributed these adverse observations to PQ neurotoxicity. Variance in findings with other reports could be attributed to differences in PQ dosage administered, duration and routes of administration and possibly the age (young adults) of the animal model adopted

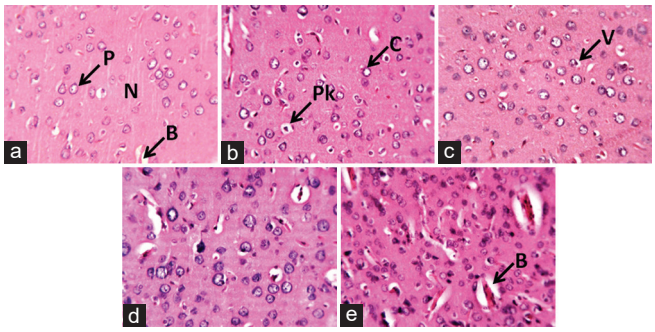

Figure 6: Micrograph of cerebral cortex (layer V) of Wistar rats (H and E ×250). (a) = Control (distilled water 2 ml/kg) group with normal histoarchitecture. B: Blood Vessel; P: Pyramidal cell; N: Neuropil. (b) = Paraquat (11.35 mg/kg) treated group with histoarchitectural distortions. Pk: Pyknotic nucleus/necrosis; C: Chromatolysis. (c) = Paraquat (11.35 mg/kg) and *L*- dopa (10 mg/kg) treated group with mild histoarchitectural distortions. V: Perineuronal vacuolation. (d) = Paraquat (11.35 mg/kg) and AFPD (500 mg/kg) treated group with relatively normal histoarchitecture. (e) = Paraquat (11.35 mg/kg) and AFPD (1000 mg/kg) group with relatively normal histoarchitecture. B: Blood Vessel

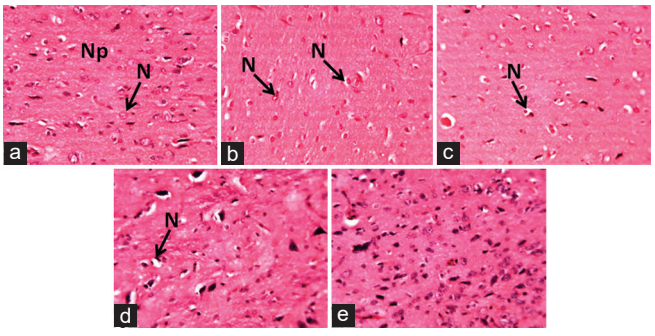

Figure 7: Micrograph of substantia nigra of Wistar rats (H and E, ×250). (a) Control (distilled water 2ml/kg) group with normal histoarchitecture. N: Neuron; Np: Neuropil. (b) Paraquat (11.35 mg/kg) treated group with histoarchitectural distortions. N: Pyknotic nucleus/necrosis/perineuronal vacuolation. (c) Paraquat (11.35 mg/kg) and *L*- dopa (10 mg/kg) treated group with mild histoarchitectural distortions. N: karyorrhexis. (d) Paraquat (11.35 mg/kg) and AFPD (500 mg/kg) treated group with mild histoarchitectural distortions. N: karyorrhexis. (e) Paraquat (11.35 mg/kg) and AFPD (1000 mg/kg) group with relatively normal histoarchitecture

in this study. Besides, Tinakoua *et al*.[41] reported slight motor deficits after several weeks of PQ administration in rats which could be similar to the findings of this study.

However, *L*-dopa and AFPD-treated groups, especially AFPD (1000 mg/kg) showed improvement in motor coordination across the period of study. This is suggestive of potential ameliorative properties of these treatments against PQ-induced motor deficit. Antioxidant agents have been reported to improve motor coordination functions in PQ-induced motor deficit in rodents.[42,43] An established mechanism of action of *L*-dopa is the downregulation of reactive oxygen species (ROS) in biological system.[44] *P. dactylifera* contains beneficial compounds with strong antioxidant activities such as polyphenolics.[24,45]

MDA is an important biomarker of cellular lipid peroxidation process strongly associated with oxidative stress levels and, the levels of endogenous enzymatic antioxidants including SOD and GSH are critical in the biochemical process of detoxifying ROS production in a pathological state.[42] In this study, remarkable elevation of MDA levels and decline in SOD and GSH activity is suggestive of PQ-triggered oxidative stress. Findings are in line with Mollace *et al*.,[38] Tinakoua *et al*.[31] and Ateş *et al*.[42] who reported significant elevation of MDA levels following PQ administration in animal models.

In this study, observed remarkable decline in lipid peroxidation levels and elevation of endogenous enzymatic antioxidant with *L*-dopa and AFPD treated groups is indicative of ameliorative activities of the treatments against PQ-triggered oxidative stress conditions. Olanow[44] reported *L*-dopa protection against ROS-induced neuronal toxicity by eliciting upregulation of endogenous antioxidant molecules such as GSH. In this study AFPD treatment relative to the control, normalized and modulated endogenous antioxidant enzymatic activities which are suggestive of antioxidant activity against PQ generated oxidative stress. Extracts of *P. dactylifera* has been reported to ameliorate oxidative stress in *in vivo* and *in vitro* models by downregulation of MDA levels and upregulation of endogenous antioxidant enzymes.[24,46] *Pheonix dactylifera* fruits contain phytonutrients that are high in antioxidants and scavenge free radicals, which is beneficial in relieving oxidative stress associated with several neurological diseases conditions including neurodegeneration and movement disorders.[24,47]

Neuropathological changes are associated with neurodegeneration triggered by neurotoxins in different regions of the brain.[48] Neurodegenerative changes observed as cytoarchitectural distortions including pyknotic nuclei and necrosis, central chromatolysis, perineuronal vacuolation, and satelliotosis in the brain regions of focus (CC-layer V and SN) following PQ exposure is suggestive of PQ-triggered neurotoxicity. Findings agree with reported toxic properties of PQ on the brain. CNS is vulnerable to PQ-related toxicity which results in cytoarchitectural distortions, neuronal damage, cell death, and glial cells reactivity in different regions of the brain.[12,49]

Fahim *et al*.[40] reported remarkably decreased number of dopaminergic neurons in SN exposed to PQ and attributed the loss of neurons to PQ-triggered oxidative stress. PQ exposure triggers mitochondrial dysfunction and glial reactivity, which results in the generation of ROS and neurodegenerative changes.[13] Neuronal damage has been associated with neurological disease conditions including PD with motor impairments as a major clinical hallmark.[50,51]

Observed mild distortion-to-relatively normal neuronal cytoarchitecture relative to the control with *L*-dopa and AFPD treated groups is suggestive of ameliorative properties of the treatments against PQ triggered neurodegenerative changes. This finding is in agreement with reports related to therapeutic properties of *L*-dopa as a established drug in the treatment and management of oxidative stress-associated neurodegenerative disease conditions like PD.[52,54] Olanow[44] reported *L*-dopa neuroprotective activity against oxidative stress triggered neurotoxicity. Additionally, findings agreed with the reported neuroprotective properties of *P. dactylifera* following neuronal pathological changes related to oxidative stress generated as a result of exposure to environmental toxins. Several studies have demonstrated extracts of *P. dactylifera* fruit to possess neuroprotective activities against neuronal cytoarchitectural changes triggered by exposure to environmental neurotoxins in different regions of the brain.[54-56]

P. dactylifera contains a variety of phytonutrients such as carotenoids, sterols, tannins, and polyphenols including flavonoids.[57,58] Abundant in dates are phenolic compounds reported to have strong antioxidant and free radical scavenging activities. These activities have been associated with neuroprotective properties of *P. dactylifera*.[45,59-62] Thus, AFPD, especially at dose 1000 mg/kg, possesses neuroprotective properties comparable to the reference drug, *L*-dopa.

Conclusion

In conclusion, aqueous fruit pulp extract of *P. dactylifera* possesses potential neuroprotective properties against PQ-triggered pathological changes in cortico-nigral structures of Wistar rats. Neuroprotective properties could be attributed to bioactive compounds present in AFPD with potent antioxidant activities against ROS-associated PQ-triggered pathologies. Further investigation is recommended to ascertain the efficacy and potentiality of AFPD and other solvent extract forms as a medicament for oxidative stress-associated biochemical and physiological alterations and neuropathologies to enable formulation for therapy.

Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

Ethical clearance for this study was provided by the Ethics Committee on Animal Use and Care, Ahmadu Bello University (ABU), Zaria: ABUCAUC/2018/097.

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Conflicts of interest

There are no conflicts of interest to declare.

Author contribution subject and rate

- Hope Dike Edobor (30%): Design the research, data collection and analyses.
- Sunday Abraham Musa (20%): Organized the research and supervised the article write up.
- Uduak Emmanuel Umana (20%): Contributed with comments on research design and slides interpretation.
- Gbenga Peter Oderinde (15%): Contributed with comments on manuscript organization and write up.
- Abel Nosereme Agbon (15%): organized the research and supervised the article write-up

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Original Article

Validity and Reliability Studies of the Psycho-Political Safety Scale

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Abstract

Aim: The psychological effects of political approaches in our country together with political developments in the world, affect the mental health of society and the individuals who hold it together. When the literature was examined, it became clear that a Psycho-political Safety Scale (PSS) was needed to address the mental health and sense of safety of the individual from a psycho-political perspective. **Materials and Methods:** This research aims to conduct a validity and reliability study in a wide sample of the PSS. The sample consists of 6420 people from all over Turkey. **Results:** Analysis revealed that the scale consists of four factors. The first factor "Economy" alone explains 43.7% of the variance, the second factor "Homeland Security" 7.9% of the variance, the third factor "Education" 6.5% of the variance, the fourth factor "Domestic Policy" 6.3% of the variance. These four factors, consisting of a total of 16 items, together explained 64.5% of the total variance. In addition, four factors confirmed PSS in the validating factor analysis. (Chi-square/degree of freedom value: 3.15; Root mean square error of approximation: 0.069; Normed fit index: 0.93; Nonnormed fit index: 0.93; Comparative fix index: 0.96; Goodness of Fit Index: 0.93; Adjusted goodness of fit index: 0.91). The internal consistency coefficient of the scale Cronbach Alpha (α) was found to be, 91. As a result of the studies, it is understood that the scale is valid and reliable. **Conclusion:** A valid and reliable scale called PSS, which measures the psycho-political safety of individuals psychometrically has emerged.

Keywords: *Politic psychology, psycho-political safety, psycho-politics, scale development*

Introduction

As in the field of psychology, it is extremely important to study "human" oriented behaviors in politics. Verbal or behavioral political content, together with people's reactions to events, facts, has the power to direct individuals and audiences unswervingly. Therefore, the field of political psychology, where political science and psychology meet in common, is becoming increasingly important.

For individuals who have a direct or indirect relationship with politics, political psychology; is defined as a discipline that addresses their behavior in a personal, social, emotional, and mass sense on many developmental grounds, especially lifestyles.[1] So much so that it is clear that the lifestyles and behavioral effects of individuals in a mass sense will differ from culture to culture. In this context, different cultural values and political understandings will vary from country to country, so psycho-political effects will diversify in the mosaic range, affecting individuals at the micro-level and societies at the macro level. Given this situation, there is a need for domestic studies that will contribute "culturally."

The concept in our country of politics is mentioned together with the concept of policy. In this context, whether the concept of political psychology can be called political psychology is debating, and every day this discipline continues to develop by covering unique concepts such as Psycho-politics and political self-sufficiency, as in other fields. Nowadays, the concept of "Psycho-politics" meets these two disciplines, as in this study.

Hence, political self-sufficiency has become one of the concepts that political psychology has frequently discussed in recent years, expressing people's

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self-sufficiency perception levels, political competence, and safety levels. In other words, it is about investigating how individuals, situations, and events are perceived and interpreted and the relationships between this perception and the interpretation.[2]

Hence, psycho-political safety concept is another concept where people's perceptions of feeling safe find themselves in the field of politics. Accordingly, the country's domestic policy, foreign policy, economy, education, and homeland security policies are vital as parameters that will affect citizens' perceptions of security. The attitude of the country's leadership, the characteristics of the political leader, and some of his administrative skills directly affect the public's perception of safety. According to Tarhan, the sociopsychological code of social conflicts in Turkey is not a right-left or a lifestyle fight but is a resounding feature of the class struggle. Managing class struggle and achieving fair balance are essential skills for strong management. If it cannot be managed, it can become a crisis and have a trauma effect on society.[3]

According to Arıboğan, some walls in people's minds are collapse much harder than been thought. It is clear from many examples that collective traumas in the past can shape today's psychology and social behaviors, even though centuries have been passed. Accordingly, the criticism and emphasis on the preconceived notion that human behavior is rational in the political psychology discipline, which focuses on solving the connection between the psychology of societies and individuals and political processes, has been an important element that differentiates it from other disciplines.[4]

On the other hand, when the literature is examined, it is seen that the relationships between leadership characteristics and social context are frequently curious by researchers. In researches, three models of the leader's personality are widely deliberated. These are the ones that are going to be the "Leader characteristics model," "Leader-State mapping model" and "Leader-Monitor match model." Accordingly, the leading characteristics model set forth that successful leaders have certain personality traits. In the leader-state matchmaking model, it is suggested that successful leaders have personality traits, that are most suitable for the political situation. In the leader-monitor matchmaking model, it is stated that successful leaders have similar characteristics to society.[5]

Although political psychology has become a voice in the world since the 1970s, it was possible to talk about it in Turkey in the early 1980s with a limited environment. However, the definition of political self-sufficiency, which paved the way for the emergence of the field of political psychology, is associated with the concept of safety, with Campbell *et al*., feeling that the political actions or political stance of the individual have an impact on processes.[6]

According to Bingol (2015), Political competence is a sense of one's confidence in one's ability to participate effectively in democratic processes.[7] Accordingly, individuals with high political competence do not hesitate to participate in activities such as voting, participating in social protests, writing in newspapers, collecting signatures, while individuals may be more prone to alienation, and political inaction when their political competence is low.[8]

As well as the political context, political behaviors and leadership properties have been carried out with a focus on business life,[9] organizational structures,[10,11] and managers[12] with many studies since previous years.[13,14]

It is stated that the influencing tactics put forward by Kipnis *et al*. shed light on many of the research and these tactics developed in the following years.[15] These tactics took place in studies as; applied pressure, putting the senior management behind it, mutual interest, coalition, trying to stand out, trying to convince by sense, sanctions, and obstruction.[16,17] Accordingly, measurement and sizing studies in previous years show that political behavior within the scope of institutions is measured by taking the subordinate-upper context into account.

When the literature is examined, it is found that a study has improved the scale of political behavior, which includes the dimensions of political behavior aimed at revealing what political behaviors are encountered in the institution.[18] The scale obtained by the dimensions of "Being Compromising," "Being Hypocritical," "Trying to Stand Out," "Forming a Coalition," "Mutual Interest," "Trying to Benefit Senior Management" and these dimensions as "Horizontal Political Behaviors" and "Vertical Political Behaviors" under two basic groups was consistent with previous political behavior dimensions.

More recently, it was developed a "Perceived Political Self-Sufficiency Scale."[8] The scale of type 5 rated Likert consists of 10 items and one dimension, and the high score from the scale shows a high level of political self-sufficiency. The internal consistency reliability of the scale was found to be, 92 in the Cronbach Alpha value. It is also aimed to determine the political effectiveness levels of health workers on another scale developed by Kuşçu-Karatepe and Atik.[19] The 26-point scale called the "General Political Activity Scale," is seen to consist of two-dimensional structures as "internal" and "external." As a result of validity and reliability studies, the Cronbach Alpha value was found to be, 96.

On an up-to-date scale on political leadership characteristics, participants' perceptions of leadership can be determined. Developed by Tarhan and Tutgun-Ünal, the "Üsküdar Democratic Leadership Scale (USDELID)" is a five-type Likert psychometric scale consisting of 25 items and four factors. People's perceptions of leadership can be measured in four dimensions called

libertarianism/pluralism, justice-orientation, participation, and accountability. With the scale that allows double-sided evaluation, people can evaluate themselves as well as the opposite side.[20]

In the field of political psychology, the lack of psychometric scales that can measure these contexts and reveal the relationship between the existing political situation and its psychological effects on the person is noted. The lack of measurement tools for psychopolitical safety indicates that the scale developed in this study will be the first in the literature and will meet the need in this regard. In this study, it is aimed to develop a scale of psychopolitical safety that is thought to contribute to the field of political psychology.

Materials and Methods

This study was performed in line with the principles of the Declaration of Helsinki, as revised in 2013. The ethics committee approval has been obtained from the Uskudar University Noninterventional Research Ethics Committee on the date of 23/09/2019, with the number of 61351342 /2019 404.

The validity and reliability studies of PSS were carried out with 6420 participants throughout Turkey. When the literature is examined, various opinions about the sample size to be reached are found in the multivariate analyses to be carried out for the development of a scale.[21,22] When these opinions are examined, it is stated that the minimum sample size should be between 100 and 250, and it should be at least five times or even ten times, the number of substances on the scale. The sample size in this study is more than 100 times the number of items. Thus, it was found to be sufficient due to it was well above the minimum number of samples required.

The sample of the study consisted of 3419 women (53.3%) and 3001 male (46.7%) participants in various regions of Turkey. When the participant characteristics were examined, it was determined that 42.2% of their education level was university and 30% was high school. In addition, when the marital status was questioned, it was determined that 46.2% of the participants were married, 48.1% were single and 5% were separated.

Measurement instrument

Psycho-political Safety Scale

Psycho-political Safety Scale (PSS) validity and reliability studies were carried out with scope content validity, structure validity, discriminant validity, confirmatory validity, and internal consistency reliability studies. Accordingly, the substance pool of the scale in the scope validity studies was formed from 33 items in the first stage. There was a 3-rated Likert type prepared as a scale and participation in each item is designated as "I do not feel safe," "I am undecided" and "I feel safe" to determine how safe the person feels for the relevant item. The high score from the draft scale indicates that the person feels safe from a psycho-political point of view, while the low score indicates that the person does not feel safe.

After the expressions and contents of the items were edited by taking expert opinions, the draft scale was applied to a pilot group of 10 experts. To evaluate draft scales, the expert opinion inventory includes the options "The item is appropriate to remain on the scale," "The item may remain on the scale but is unnecessary" and "The item is not appropriate to remain on the scale." After that, the adaptation rates of the items were calculated using the formula proposed by Tavşancıl and Aslan.[23]

Interrater reliability rates are calculated using the ratings contained in the inventory for each item. Accordingly, it was noted that the relevant item does not stay below 80, scoring between 0 and 1. Furthermore, according to the opinions of experts, the items have been revised and arranged in terms of spelling and grammar. After this stage, the data obtaining phase and the explanatory factor analysis (EFA) phase have been started.

In the EFA studies, the items that entered each dimension were examined in terms of item-total analysis and contribution to internal consistency, and items were eliminated in cases where low relationship values were present or where the removal of the items increased internal consistency. However, EFA was applied with the Varimax Rotation technique to determine the structure validity of the dimensions. In the first stage, several trial tests were performed with the Varimax Rotation technique, and then the Promax Rotation technique was applied due to the size of the data set. It is stated that the Promax Rotation technique, which is indicated to work better in big data sets, is one of the closest techniques to the Varimax Technique.[24] In this research, it was seen to work better either.

Bartlett Sphericity test was performed with Kaiser Meyer Olkin (KMO) coefficient to determine the suitability of the data for factor analysis.[25] There are some opinions regarding the evaluation of the KMO value. It describes having a KMO value of. 90 and above as "excellent," being in the range of 0.80–0.89 as "very good," being in the 0.70–0.79 range as "good," being in the 0.60–0.69 range as "moderate," "weak" and "unacceptable" being below 0.50.[26] In general, 0.70 and above is considered "good" in terms of providing sample size, and. 80 and above are considered "excellent."[27,28] In addition, Bartlett Sphericity is expected to be $P < 0.05$ for factor analysis with the data set.

In addition, the variance rate explained by the scale of factor analysis is ideal in social sciences when it varies in the range of 40%–60%.[29] The found ratio of 65% in the study is considered fairly well in social sciences.

Correlation values have been reviewed in the relations of the scale within the scope of structural validity studies.

In the interpretation of correlation values, it is taken into account that the relationship values between 0.30 and 0.70 indicate the medium and the values >0.70 indicate a high relationship.[29]

Within the scope of validity studies, the volume of each item for the discriminant validity of the scale was viewed to the total volume of the scale and the lower scales. The item discriminant index (D) shows how many of the items are measured, in particular, relevant to their contacts. In other words, this is the power to distinguish between individuals who have a high level of the feature that the scale aims to measure, and individuals who have a low level. The item discriminant index can vary from −1 to +1. The fact that this value is negative indicates that the item inversely distinguishes individuals in terms of the measured feature. Therefore, such items should be removed from the test.[30] After the scale was scored, the scores were sorted and the lower and upper groups were separated by the 27% sub-quarter and the upper quarter, and the independent group *t*-test was applied.

In the confirmatory factor analysis studies, the scale structure that consisted of dimensions was verified in terms of structural equation modeling. In this stage, the goodness of fit index (GFI) values of PSS were verified (Chi-square/degrees of freedom value, Root mean square error of approximation [RMSEA], Normed fit index [NFI], Nonnormed fit index [NNFI], Comparative fix index [CFI], GFI, Adjusted goodness of fit index [AGFI]).

Within the scope of the reliability studies of the scale, the coefficients of internal consistency Cronbach Alpha (α) were calculated by item analysis. Cronbach Alpha value is considered reliable in cases of. 70 and above. In this study, this criterion was accepted when interpreting the internal consistency value of Cronbach Alpha.

Implementation

The data obtaining was carried out according to the principle of volunteerism through an face to face survey between January 1 and 30, 2020. The study group consisted of people aged 18 and elder through randomly selected sampling. Attendees were given a questionnaire consisting of the PSS questions. An average of 12 min to complete the applied survey was enough.

Data analysis

EFA was applied to 5920 participants for PSS structure validity studies. Twenty-seven percent slices were taken from the upper group and the lower group in the discrimination validity studies, and the difference between the two groups was looked at with an independent group *t*-test. Confirmatory factor analysis was applied to 500 participants for PSS confirmatory validity and was calculated GFI values (Chi-square/degrees of freedom value, RMSEA, NFI, NNFI, CFI, GFI, AGFI). The reliability coefficient of the scales was determined by the Cronbach alpha value. SPSS 26.0 (IBM Corp. Released. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.) and AMOS (These statistical programs by IBM were used for all validity and reliability analyses) statistical program was used for all validity and reliability analyses.

Results

Validity and reliability studies of the psycho-political safety scale

In this part of the study, evaluations were made for the PSS. Content validity, structure validity, discrimination validity, confirmatory validity, and internal consistency reliability studies.

Content validity

The PSS item pool was formed 33 items in the first stage and presented to expert opinions. To include interdisciplinary views, the items were examined by ten experts accompanied by an expert opinion inventory. A content validity study was conducted with data provided from opinions received from each expert through the expert opinion inventory, and interrater reliability was calculated. Accordingly, in the study, the compliance rates of. 80 were sought and 23 items were found to remain on the draft scale. Thus, EFA was applied to the data obtained by applying the 23-item draft scale to 5920 participants.

Structure validity-explanatory factor analysis

To determine the factor structure of PSS, EFA was first studied with KMO coefficient and Bartlett Sphericity Analyses. Accordingly, KMO value was found to be 0.931 at this stage where it was decided whether the data set was suitable for factor analysis. This test demonstrates the suitability of the data set for factor analysis. In addition, the Bartlett test applied to the data set was found to be significant (χ^2 = 45,405,749, sd: 120, P = 0,000). These results showed a high correlation between the variables and the appropriateness of the data set for factor analysis was decided.

Since in factor building after factor analysis is made, eigenvalues for PSS > 1 are accepted, it is obtained that it is four-factor structure. In Table 1, the eigenvalue of the factors obtained as a result of factor analysis and the variance amounts, they explain are given.

As shown in Table 1, the variance rate explained by the first factor with equity of 7,001 is 43.757%; the variance

Table 1: Factor structure and explained variance rate

PSS	Eigenvalue	Variance	Cumulative variance
1st dimension	7001	43,757	43,757
2nd dimension	1265	7905	51,661
3rd dimension	1045	6530	58,191
4th dimension	1012	6326	64,517

PSS: Psycho-political Safety Scale

rate explained by the second factor with equity of 1.265 is 7.905%; the variance rate explained by the third factor with eigenvalue of 1.045 is 6.530%; the variance rate explained by the fourth factor with eigenvalue of 1.012 is 6.326%. The total variance rate explained was 64.517%.

Another method used to determine the number of factors is the scree plot test. Accordingly, the factor analysis scree plot test determines the number of factors indicated by the point at which the slope begins to disappear. The scree plot for dimensions is given in Figure 1.

When the line chart in Figure 1 is examined, a fracture is observed around the fourth factor. Accordingly, high acceleration and rapid decreases in the graph were effective in determining the number of factors.

In the next stage, the rotation of the factors was made with the Promax Rotation technique to associate the substances with the factors. Accordingly, the factors under which the items are under the four factors obtained in the study and the factor loads of the items are given in Table 2.

The factor load values seen in Table 2 are sorted from large to small in each dimension. The load values here are coefficients that describe the relationship between dimensions and factors and items and are decisive in the emergence of the factor structure. In the study, the lower cutting point was considered, 55. Accordingly, items that exhibit a load value below this value have been removed from the scale. Thus, 7 items were eliminated and it was observed that the measuring tool, which was 23 items before the factor analysis, was reduced to 16 items at this stage.

When Table 2 is examined, it is seen that the load values of the first factor consisting of 5 items range from 0.886 to 0.694, the load values of the second factor consisting of 4 items range from 0.833 to 0.597, and the load values of the third factor consisting of 3 items range from 0.932 to 0.608, and the load values of the fourth factor consisting of 4 items range from 0.916 to 0.510.

After the factor load values were found, the dimensions were named according to the variance ratio described before the item discriminant validity studies were started and the contents of the items were taken into account when naming the dimensions.

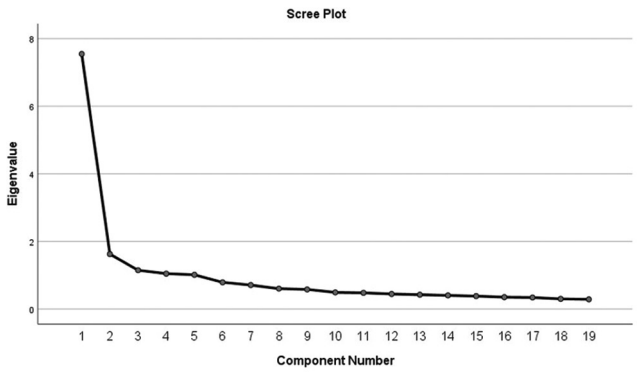

Figure 1: Scree Plot of Psycho-political Safety Scale

Accordingly, items 12, 13, 14, 15, 16 in the measuring instrument constituted the first dimension and it was seen that this dimension was related to "economy." The dimension of the economy is related to one's confidence in the country's economic policies. When the items in this dimension are examined, it is seen that "About the future of my livelihoods and my economic situation," "About that I can protect the work I am still working in, in the near future," "About that Turkey's economy will get better," "About that the economic bureaucracy is doing its job well," "About that the Turkish currency can maintain its value against foreign currencies such as dollars/euros." are taking there their place.

It is seen that the 6th, 10th, 18th, and 19th items in the measuring instrument constitute the second dimension called "homeland security." This dimension is about whether one feels safe against domestic security policies. When the contents of the items are examined, it is seen that "About to live my beliefs freely," "Whether we can succeed in defending our country in the event of an attack," "About the adequacy of the fight against terrorist organizations," "The Turkish armed forces have been completely purged from terrorist organizations and gangs" are taking there their place.

Items 23, 25, 26 in the measuring instrument constitute the third dimension and are called "education." The training dimension is about safety in training policies. When the contents of the items are examined, it is seen that "About the current state of the education system in our country," "Our universities provide adequate education," "Our universities produce objective scientific studies" are taking their place.

Items 1, 2, 3, 4 in the measuring instrument constitute the fourth dimension and are called "domestic policy." The domestic policy dimension is about the person feeling safe from domestic policies. The person responds to the expressions in the substances that make up this dimension by considering whether they feel safe. Accordingly, it is seen that the items; "When I have a job with the judicial authorities, I will be judged fairly," "About the fact that the mainstream media impartially conveys the news," "About being able to express my thoughts freely," "About the reality of the agenda produced on social media" are taking place.

The final form of the scale consisting of 16 items and 4 factors obtained by reordering the substances after the descriptive factor analysis studies carried out within the scope of the structure validity is included in Annexure 1. Thus, the PSS factor structure was determined, and the relationship of each factor was determined. Accordingly, the results are in Table 3.

When Table 3 is examined, the PSS total and subscales are associated with each other at the level of 0.001 signation.

Table 2: Factor load values of Psycho-Political Safety Scale items

	Items	F1	F2	F3	F4
M12	About the future of my livelihoods and my economic situation …	0.886			
M13	About that, I can keep the job I'm still working on in the near future …	0.839			
M14	About that Turkey's economy will get better …	0.778			
M15	About that the economic bureaucracy is doing its job well	0.704			
M16	About the Turkish currency's value against foreign currencies such as Dollar/Euro	0.694			
M10	Whether we can succeed in defending our country in the event of an attack …		0.833		
M18	On the adequacy of the fight against terrorist organizations …		0.811		
M6	About living my beliefs freely …		0.753		
M19	Turkish armed forces have been fully purged of terrorist organizations and gangs.		0.597		
M25	About that our universities provide adequate education …			0.932	
M26	About that our universities produce objective scientific studies …			0.897	
M23	About the current state of the education system in our country.			0.608	
M4	About the reality of the agenda produced on social media.				0.916
M2	About that the mainstream media is impartially reporting the news.				0.795
M1	When I'm in the judicial authorities, I'll get a fair trial.				0.555
M3	About being able to express my thoughts freely.				0.510

Table 3: Psycho-Political Safety Scale and its dimensions related to each other

Subscale/Scale	Economy	Homeland security	Education	Domestic policy
Homeland security	0.627			
Education	0.577	0.502		
Domestic policy	0.622	0.564	0.563	
PSS	0.878	0.833	0.878	0.823

PSS: Psycho-Political Safety Scale

Accordingly, it is understood that the relationship of dimensions with the sum varies between medium and high (r: 0,502 ve r: 0,878).

Discriminant validity

At this stage, item discriminant validity studies were carried out to determine whether the items on the scale measured the desired property. Data collected from 1730 participants were sorted from large to small and independent group *t*-test was applied to data in the upper 27% and subgroups of 27%.

When Table 4 is examined, the results were significant, it was concluded that PSS is a scale that measures the desired properties. Thus, it was observed that the highest score taken from the PSS of 3-rank Likert type, which consisted of 16 items and 4 factors, was 48, the lowest score was 16, and the arithmetic average obtained from the sum of the scale (n = 5920) was 26.56.

Confirmatory validity-confirmatory factor analysis

Validation factor analysis was also applied in the AMOS program with 500 participants to test whether the scale resulting from the structure validity of PSS, the relationship of factors with each other and the validity of items and factors was verified in terms of items and factors. Accordingly, the resulting structural equation model is given in Figure 2.

When Figure 1 is examined, it is seen that the structure revealed in the confirmatory validity studies is verified by the confirmatory factor analysis. Accordingly, the dimensions revealed by EFA are statistically verified and the results are given in Table 5.

Table 5 shows the GFI values of PSS. As a result of confirmatory factor analysis, it was found that Chi-square/freeness value is: 3.15; RMSEA is: 0.069; NFI is: 0.93; NNFI is: 0.93; CFI is: 0.96; GFI is: 0.93 and AGFI is: 0.91. Thus, these values are considered to meet the GFI values reasonably. It has been concluded that PSS is verified by four factors.

Reliability studies

The Cronbach Alpha (α) internal consistency coefficient of PSS and dimensions were determined within the scope of reliability studies. Cronbach Alpha internal consistency coefficients calculated based on the variance of items are included in Table 6.

As shown in Table 6, the 0.911 Cronbach α found in the sum of the PSS revealed a high degree of reliability. When the scale was examined, the Cronbach α value was found to be the lowest with 0.757 (domestic policy) and the highest with 0.845 (economy). It has been concluded that PSS total and dimensions provide reliability.

Conclusion

The PSS is a measuring tool developed by researchers to measure whether people feel safe on a political level. After validity and reliability studies, it reveals that PSS is a structure consisting of 16 items and four factors.

PSS is a three-type Likert scale rated as "I don't feel safe," "I am undecided," "I feel safe," the highest score from the entire scale is 48 and the lowest score is 16. Thus, the increase of PSS means an increase in confidence. To interpret the scores to be obtained from PSS, the highest

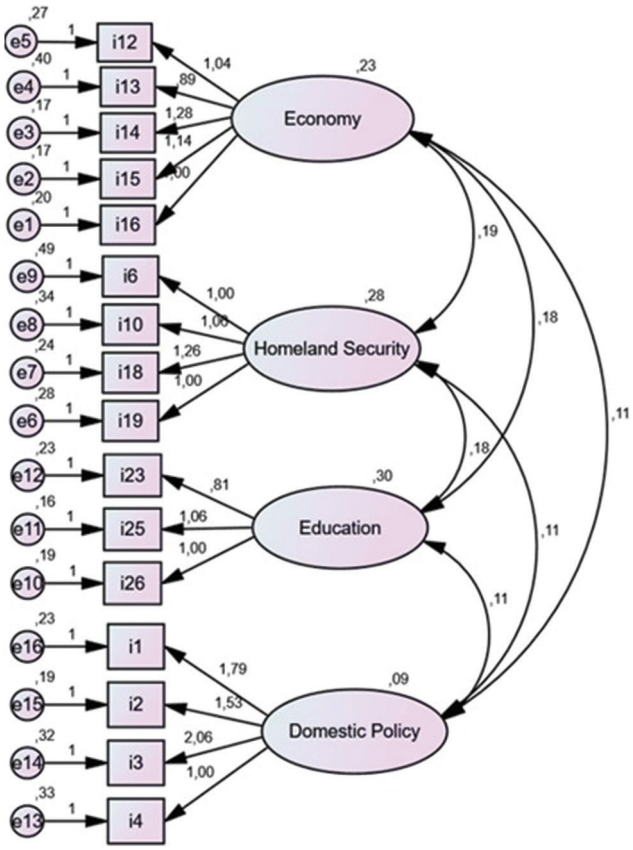

Figure 2: Confirmatory factor analysis of Psycho-political Safety Scale

and lowest score range that can be taken from the scale was determined and the range coefficients were calculated according to the triple Likert scale. The total score from the scale means "Unsafe" in the range of 16–29, "Undecided" in the range of 30–38, and "Safe" in the range of 39–48.

PSS's explanation of 64.5% of the total variance is considered quite high in terms of social sciences. In addition, the internal coefficient of consistency of the scale, Cronbach α value was found to be. 91. Dimensions have also been found acceptable in themselves, providing internal consistency. As a result of the confirmatory factor analysis, the goodness of fit values of the factors and the scale were found to be acceptable. Studies have shown that PSS is a valid and reliable scale. Thus, it is thought that the scale developed will contribute to addressing the lack of measuring instruments in measuring psycho-political safety in Turkey.

Dimensional examinations can also be carried out with the factorial structure of PSS, which will allow measurements to be made to reveal the relationship of people's feelings of safety with the country's policies and what their perceptions of security are. Accordingly, the perception of security to sustain the work achieved by livelihoods can be examined with the dimension of "economy," the perception of security that beliefs can be lived freely, the perception of security in the case of an attack can be examined with the dimension of "homeland security,"

Table 4: PSS and total score differentiations of dimensions

PSS and dimensions	Group	*N*	*X*	SD	df	*t*	*P*
Economy	Upper group	1730	10.3	2.86	3451	53.22	0.000
	Lower group	1730	6.09	1.64			
Homeland security	Upper group	1730	9.66	2.07	3452	53.65	0.000
	Lower group	1730	5.92	2.01			
Domestic policy	Upper group	1730	9.13	1.35	3458	157.4	0.000
	Lower group	1730	4.00	0.00			
Education	Upper group	1730	6.03	1.81	3455	47.02	0.000
	Lower group	1730	3.63	1.09			
PSS	Upper group	1730	34.6	5.67	3455	49.80	0.000
	Lower group	1730	22.1	8.73			

PSS: Psycho-political Safety Scale, SD: Standard deviation

Table 5: Goodness of fit index values of Psycho-Political Safety Scale

GFI	Acceptable GFI values	PSS's GFI values
χ^2/SD	<5	3091.965/980=3.15
RMSEA	<0.08	0.069
NFI	>0.90	0.93
NNFI	>0.95	0.93
CFI	>0.95	0.96
GFI	>0.90	0.93
AGFI	>0.85	0.91

GFI: Goodness of fit index, PSS: Psycho-political Safety Scale, SD: Standard deviation, RMSEA: Root mean square error of approximation, AGFI: Adjusted goodness of fit index, CFI: Comparative fix index, NNFI: Nonnormed fit index, NFI: Normed fit index

Table 6: Psycho-Political Safety Scale and the reliability of dimensions

Scale/dimensions	Item number	Cronbach alpha coefficient
Economy	5	0.845
Homeland security	4	0.788
Domestic policy	4	0.757
Training	3	0.800
PSS	16	0.911

PSS: Psycho-political Safety Scale

the perception of security regarding the adequacy and objectivity of the education system can be examined with the dimension of "education," and the perception of security regarding the impartiality of the judicial authorities, the mainstream media, and the security perception of freedom of thought can be examined with the dimension of "domestic policy."

The validity and reliability studies of the scale developed in this study were carried out with a wide-ranging sample of Turkey. It is thought that the results of new studies with smaller focus groups will contribute to the literature in the future.

Patient informed consent

Informed consent was obtained.

Ethics committee approval

The ethics committee approval has been obtained from the Uskudar University Noninterventional Research Ethics Committee on the date of 23/09/2019, with number of 61351342-/2019-404.

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Conflicts of interest

There are no conflicts of interest.

Author contribution subject and rate

- Gökben Hızlı Sayar (%20) contributed with scale items, theoretical background, and data collect.
- Aylin Tutgun Ünal (%20) contributed with scale development process, data analysis and wrote the whole manuscript.
- Hüseyin Ünübol (%20) contributed with scale items, theoretical background, and data collect.
- Nevzat Tarhan (%20) contributed with scale items revision and theoretical background.
- Deniz Ülke Arıboğan (%20) contributed with scale items revision and theoretical background.

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Annexure 1: Psycho-political Safety Scale

Item number	Items	I don't feel safe	I am undecided	I feel safe
1	About the future of my livelihoods and my economic situation			
2	About that, I can keep the job I'm still working on in the near future …			
3	About that Turkey's economy will get better …			
4	About that the economic bureaucracy is doing its job well…			
5	About the Turkish currency's value against foreign currencies such as Dollar/Euro…			
6	About to live my beliefs freely…			
7	Whether we can succeed in defending our country in the event of an attack …			
8	On the adequacy of the fight against terrorist organizations …			
9	Turkish armed forces have been fully purged of terrorist organizations and gangs.			
10	About the current state of the education system in our country.			
11	About that our universities provide adequate education …			
12	About that our universities produce objective scientific studies …			
13	When I'm in the judicial authorities, I'll get a fair trial.			
14	About that the mainstream media is impartially reporting the news.			
15	About being able to express my thoughts freely…			
16	About the reality of the agenda produced on social media…			

PSS consists of 16 substances and 4 factors. Items 1, 2, 3, 4, 5 on the scale measure "economy"; items 6, 7, 8, 9 measure "homeland security"; items 10, 11, 12 measure "education"; items 13, 14, 15, 16 measure "domestic policy". Evaluation: The total score from the scale is evaluated as "Unsafe" in the range of 16–29, "Undecided" in the range of 30–38, and "Safe" in the range of 39–48. PSS: Psycho-political Safety Scale

Original Article

Depression, Anxiety and Anger Levels in Spouses of Hemodialysis Patients

Abstract

Aim: Different and changing roles in the lives of the spouses of hemodialysis patients could be perceived as a major stress factor due to their partners' diseases with their emotional burden and certain responsibilities related to the disease. Along with these stressors, people could manifest certain symptoms of depression and anxiety and have difficulty adapting to changing living conditions. The aim of this study is to determine the depression, anxiety and anger levels in spouses of hemodialysis patients. **Materials and Methods:** The study consisted of 50 spouses whose partners were currently receiving hemodialysis and 50 healthy controls in Istanbul in Turkey. Both groups were matched based on their gender and ages. Participants in the study were asked to complete the Beck Depression Inventory, Beck Anxiety Inventory, Spielberger Trait Anger and Anger Expression Inventory for collecting data. **Results:** The findings indicated that the treatment process of hemodialysis patients and the disease itself had negative outcomes on the mental health of their spouses. Anxiety, depression, and anger scores were found to be significantly higher among hemodialysis patients' spouses as compared to healthy controls. **Conclusion:** As a result of these findings, possible psychosocial needs of patients undergoing hemodialysis and their spouses should be evaluated together and psychological support and interventions should be provided for improvement of their stress-coping skills.

Keywords: *Anger, anxiety, chronic kidney failure, depression, hemodialysis*

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Introduction

Chronic kidney failure is defined as a progressive and irreversible deterioration in kidney functions. Hemodialysis, which can be applied 2–3 times a week for 4–6 h, is commonly used in the treatment of chronic kidney failure.[1,2] In the hemodialysis process, toxic substances accumulated in the patient's blood due to kidney failure are removed. Although this treatment has vital importance, it usually affects the daily routines and quality of life of the patient and his family. In addition, it significantly restricts the patient and his family in terms of social, economic, and psychological functions.[3] Having a family member who receives hemodialysis treatment brings new responsibilities and dynamics to the family. In these families, the spouses often become a primary caregivers and have to deal with all dialysis-related problems.[4] Fort the patients, dialysis procedures could give rise to break some of their habits and replace older ones with newer and more adaptive habits. This process can be also considered as a transition for both the patient and his spouse. For the spouse, dialysis treatment for their partners represents the process that changes in all areas of their lives, along with adapting to newer living conditions.

Studies have shown that the caregivers of hemodialysis patients, especially spouses, have difficulty with time management for themselves. They mostly have difficulty with meeting the patient's care needs and feel insufficient from time to time. Moreover, due to the disease burden that the family currently encounters, they can have financial difficulties.[5] Due to their increasing responsibilities, the spouses of the patients could feel deprived and restricted for not being able to get together with other members

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of the family and their friends. Therefore, social isolation is mostly observed among them.

Based on the previous studies regarding the psychosocial outcomes of the dialysis process for the patients' family, this study was aimed to compare the psychological symptoms including depression, anxiety, and anger levels of the spouses whose partners had hemodialysis and the healthy controls.

Materials and Methods

This study was performed in line with the principles of the Declaration of Helsinki, as revised in 2013. The compatibility of the study with the Principles of Helsinki Declaration was ensured and the approval of the ethics committee was obtained by Üsküdar University Non-Invasive Research Ethics Committee with the number B.08.6. YÖK.2. ÜS.0.05.0.01/2018/013. The research was carried out in March 2018 at Kosuyolu Ata Dialysis Center and Atasehir and Umraniye Fresenius Medical Care Dialysis Centers located in the city center of Istanbul. All participants were informed about the research in the written and oral form for their consent.

The study group of the research consisted of 50 healthy participants who are between the ages of 25–65, and spouses of hemodialysis patients. The control group consisted of 50 healthy participants who were matched with the spouses in the research group in terms of age and gender, and spouses of people without any chronic diseases. While the study group was selected from the spouses accompanying the hemodialysis patients in the treatment sessions, the control group was formed from healthy spouses of healthy people living in Istanbul.

Measurement instruments

Beck Depression Inventory

It was developed in 1961 by Beck *et al*.[6] Turkish adaptation of the scale was done by Hisli in 1988.[7]

The highest score that can be obtained from the scale is 63.

Beck Anxiety Inventory

It was developed in 1988 by Beck *et al*.[8] It measures the number of anxiety symptoms. It was adapted to Turkish by Ulusoy *et al*.[9] Beck Anxiety Inventory (BAI) consists of 21 Likert-type items and each item has a score range of 0–3. The highest score that can be taken from the inventory is 63.

Spielberger Trait Anger and Anger Expression Inventory

It was developed in 1988 by Spielberger *et al*.[10] It was adapted into Turkish by Özer in 1994.[11] The scale consists of two main subscales: Trait Anger and Anger Expression Style Subscales. Trait Anger Subscale consists of items that show what the individual generally feels in his life or to what extent they feel angry. The Anger Expression Style Subscale is divided into three subcategories: expressing anger, suppressed anger, and controlling anger. Spielberger Trait Anger and Anger Expression Inventory (STAXI) is a Likert-type scale with 34 items.

Data analysis

The data obtained in the research were subjected to statistical analysis with SPSS v. 21 (Statistical Package for Social Sciences, IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) software. In comparative analysis, independent sample *t*-test was used for scores with normal distribution and Mann–Whitney *U*-test was used fort the comparison of mean scores which do not have normal distribution. Pearson correlation analysis was used for examining the relationship among depression, anxiety, and anger in both research groups. In addition, due to the differences observed between the distributions in terms of the problems experienced after hemodialysis, depending on the existence or disappearance of any problem, the Mann-Whitney U test was also used to compare the average scores obtained from the scales in terms of presence of the problems experienced after hemodialysis.

Results

The findings obtained from the research are listed in detail in the tables below. The frequency distributions, percentages, and the Chi-square findings for the comparison of demographic characteristics of the hemodialysis patients' spouses and the control group are shown in Table 1.

As indicated in Table 1, a significant difference was found between the educational status of the hemodialysis patient spouses and the control group. While the number

Table 1: Frequency distributions and percentages regarding the demographic features of hemodialysis patients' spouses and healthy controls

	Patients' spouses, *n* (%)	Healthy control, *n* (%)	Total, *n* (%)	χ^2	*P*
Gender					
Female	24 (48.0)	26 (52.0)	50 (50.0)	0.160	0.689
Male	26 (52.0)	24 (48.0)	50 (50.0)		
Employment					
Public sector	6 (12.0	7 (14.0)	13 (13.0)	10.024	0.018*
Private sector	16 (32.0)	30 (60.0)	46 (46.0)		
Other	13 (26.0)	5 (10.0)	18 (18.0)		
Unemployed	15 (30.0)	8 (16.0)	23 (23.0)		
Education					
Primary school	5 (10.0)	10 (20.0)	15 (15.0)	10.804	0.029*
Secondary school	8 (16.0)	3 (6.0)	11 (11.0)		
High school	20 (40.0)	9 (18.0)	29 (29.0)		
Undergraduate	12 (24.0)	20 (40.0)	32 (32.0)		
Graduate	5 (10.0)	8 (16.0)	13 (13.0)		
Total	50 (100.0)	50 (100.0)	50 (100.0)		

*<0.5

Table 2: The frequencies and percentages of the type of problems after hemodialysis

Problems experienced after hemodialysis	Answers	*n* (%)
Unemployment	Yes/No	9 (18.0)/41 (82.0)
Financial difficulties	Yes/No	26 (52.0)/24 (48.0)
Psychological problems in the patient	Yes/No	33 (66.0)/17 (34.0)
Having problems with accessing health services	Yes/No	4 (8.0)/46 (92.0)
The problems related to children	Yes/No	16 (32.0)/34 (68.0)
Sexual problems	Yes/No	31 (62.0)/19 (38.0)
Problems with relatives	Yes/No	11 (22.0)/39 (78.0)
Other issues	Difficulties related to traveling	14 (28.0)
	Difficulty accepting disease	1 (2.0)
Total	No other problems	35 (70.0)

of university graduates was higher in the healthy control group, the number of high school graduates was higher in the research group including the patients' spouses ($\chi^2[4] = 10.802$; $P = 0.029$).

According to the frequencies in Table 2, 52% of spouses of hemodialysis patients had economic problems and 66% had psychological problems.

Table 3 indicates the average scores, standard deviations, and independent-sample *t*-test findings of the spouses of hemodialysis patients and the control group with their scores in BAI, Beck Depression Inventory (BDI), and STAXI. Based on the findings, a significant difference was found between the mean scores of hemodialysis patients' spouses and the control group in their anxiety scores ($t[98] = 9.610$; $P = 0.000$). The mean anxiety ($\bar{X} = 20.92 \pm 10.62$) of the spouses of the patients was found to be significantly higher than the mean of the control group ($\bar{X} = 5.06 \pm 4.82$). A significant difference was found between the mean scores of hemodialysis patient spouse and control group obtained from BDI ($t[98] = 9.465$; $P < 0.01$). The mean depression scores ($\bar{X} = 18.50 \pm 9.002$) of the patients' spouses were found to be significantly higher than the mean scores of the control group ($\bar{X} = 5.42 \pm 3.80$). A significant difference was found between the mean scores of the hemodialysis patient spouse and the control group in the Trait Anger and Anger Expression Inventory Trait Anger Subscale ($t[98]$ 3.614; $P < 0.01$). The mean trait anger of the spouses ($\bar{X} = 23.96 \pm 6.40$) was found to be significantly higher than the mean of the control group ($\bar{X} = 19.82 \pm 4.96$).

Table 4 shows the Pearson correlation analysis findings between the hemodialysis patients' spouses' and the control group's anxiety, depression, and trait and state anger and anger expression styles.

It was observed that the anxiety level of the spouses of the patients was associated with trait anger ($r = 0.336$) and expressing anger ($r = 0.452$), while the anxiety level of the control group was associated with trait anger ($r = 0.344$) and depression with suppressed anger ($r = 0.351$).

Discussion

Hemodialysis affects the patient's working capacity, physical activity, family life, and individuals who support the patients during the treatment process negatively, despite it is a treatment that prolongs life.[12] In this study, people with healthy spouse were compared with people with hemodialysis patient spouse in terms of depression, anxiety, and anger levels; in demographic characteristics, the education level and working status of the study group including the spouses of the patients were lower than those of the control group and when the problems experienced after hemodialysis were examined, it was seen that 52% of the spouses of the patients had economic problems and 66% had psychological problems.

There was a significant difference between the spouses of hemodialysis patients and the control group in terms of anxiety ($t = 9.610$; $P = 0.000$), depression ($t = 9.465$; $P = 0.000$), trait anger ($t = 3.614$; $P = 0.000$), state anger ($t = 3.292$; $P = 0.000$), anger retained ($t = 4.777$; $P = 0.000$), anger expressed ($t = 2.133$; $P = 0.036$) levels, and the levels of the spouses of the patients was found to be significantly higher than the control group. It was observed that the control group was significantly higher than the spouses of the patients in the controlled anger ($t = -3.072$; $P = 0.003$). The difference between the control group and the spouses of the patients may occur due to factors such as the care burden of the spouses of the patients and the distress caused by this, their social limitations, nostalgia for the past, the chronicity of the disease, and the fear of losing their spouse. At the same time, the higher level of education in the control group was compared to the patient's spouse group and the fact that most of them are in working positions can be counted among the effective reasons for controlling anger. In another study on the relationship between the burden of care and anger expression styles of family members caring for cancer patients, it was shown that as the burden of care increases, trait anger, suppressed anger, and expressing anger increase, and anger control decreases in relatives and spouses of the patient.[13]

Negative effects on social life, increased responsibility, emotional burnout, and efforts to support the diseased spouse psychologically cause an increase in the level of anger and

cause difficulties in controlling anger in the spouses of the patients compared to the control group. It is seen that the process and the requirements of the process affect the anger level of the person, the way of dealing with anger and the ability to control anger.[14] In another study conducted to determine the anger and anxiety levels of the spouses of patients, it was observed that the individuals included in the research group had high levels of anxiety and trait anger.[15]

It has been reported in studies that the hemodialysis process, which causes psychological symptoms, causes changes in the lives of the patient's relatives and spouses.[16] In the study conducted by Keçecioğlu *et al*.,[17] on patients who receiving hemodialysis and chronic ambulatory peritoneal dialysis, and their spouses, it was found that the level of anxiety and depression is high in spouses of patients receiving hemodialysis treatment.

In another study conducted in the same direction, a positive and significant relationship was found between anxiety levels and depression levels in the relatives of the patients.[18] In Ozsaker's study[19] on the quality of life of kidney patients and their relatives, it was found that the spouses of patients without depressive symptoms had a high quality of life in physical, mental, social, and environmental areas, while anxiety scores were found to be high in spouses of patients with depressive symptoms. In the same study, there was a significant relationship between depressive symptoms and social area in the healthy control group, but no significant relationship was found in the level of anxiety.

Participation of the patient's spouses in the treatment process, accompanying the patient, following the medication, not allocating enough time for their own physical, mental and social needs, and concurrent problems cause depression, anxiety, and anger symptoms in the spouses of the patients. As stated in Meric and Oflaz's study,[20] the psychological problems experienced by the patient revealed that the patient's spouse also experienced emotional and experiential tides and anxiety about the future.

The study has limitations considering that it was conducted only with 50 patients and their spouses who were treated in two dialysis centers in Istanbul, Turkey. It is thought that the findings to be obtained by including the spouses who are not with the dialysis patient during the treatment process and by studies with a larger sample will provide more detailed information in terms of evaluating the psychological symptoms.

Table 3: Independent sample *t*-test findings of hemodialysis patients' spouses' and control groups' scores in Beck Anxiety Inventory, Beck Depression Inventory and trait anger and anger expression inventory

Groups	*n*	$\bar{x}$	SS	*t*	*P*
Anxiety					
The patients' spouses	50	20.92	10.625	9.610	<0.01**
Control group	50	5.06	4.825		
Depression					
The patients' spouses	50	18.50	9.002	9.465	<0.01**
Control group	50	5.42	3.802		
Trait anger					
The patients' spouses	50	23.96	6.405	3.614	<0.01**
Control group	50	19.82	4.960		
State anger					
The patients' spouses	50	23.68	3.000	3.292	0.001**
Control group	50	21.58	3.369		
Controlling anger					
The patients' spouses	50	19.56	4.895	-3.072	0.003**
Control group	50	22.56	4.870		
Expressing anger					
The patients' spouses	50	16.94	5.208	2.133	0.036*
Control group	50	14.96	3.995		
Suppressed anger					
The patients' spouses	50	18.22	3.721	4.777	<0.01**
Control group	50	14.64	3.773		

*<0.05 **P<0.01. SD: Standard Deviation

Conclusion

This research was conducted to reveal how the treatment process of patients receiving hemodialysis treatment affects their mental health as well as their spouses' in terms of their depression, anxiety, and anger levels. Based on the findings, the anxiety levels of the spouses in the clinical group were significantly higher than the spouses in the control group. Furthermore, the patients' spouses reported significantly higher scores in depression as compared to the control group. According to the findings indicating the relationship between patients' spouses' the anxiety and depression levels, it was

Table 4: Pearson correlation findings of hemodialysis patients' spouses and the control group's anxiety, depression and trait and state anger and anger expression styles

	r				
	Trait anger	State anger	Controlling anger	Expressing anger	Suppressed anger
The patients' spouses					
Anxiety	0.336*	−0.017	−0.293	0.452**	−0.083
Depression	0.063	−0.054	0.008	0.122	−0.179
Control group					
Anxiety	0.344*	0.206	−0.162	0.121	0.211
Depression	0.145	0.154	−0.231	0.169	0.351*

*P<0.05, **P<0.01

found that there was a positive significant relationship between the spouses' anxiety and depression scores. According to the study, it can be understood that the spouses of the patients can be exposed to certain stressors related to the course of illness and treatment. In this stressful process which basically starts with the diagnosis of chronic renal failure, it is important to cooperate with doctors, nurses, and other health-care workers about the treatment process and home care requirements. Patient–family group meetings, support meetings for the spouses of patients, and psychoeducation for the caregivers will be beneficial in terms of increasing awareness about the effects of the disease and coping with the disease. In addition, programs can be organized to strengthen social relations of the patients and the caregivers. Through these effective interventions, patients' spouses will maintain their functionality, adaptive emotions, and behaviors. Besides, they can be prevented from having psychological symptoms in this process. The success in these intervention strategies is mainly based on revealing functional coping methods for the stressors that the caregivers may encounter.

Patient informed consent

Informed consent was obtained.

Ethics committee approval

The ethics committee approval has been obtained from the Uskudar University Committee on Non-Interventional Research Ethics (B.08.6.YÖK.2.ÜS.0.05.0.01/2018/013).

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Conflicts of interest

There are no conflicts of interest to declare.

Author contribution subject and rate

- Rahel Karako Kampeyas (35%): Design the research, data collection and analyses and wrote the whole manuscript.
- Huseyin Unubol (25%): Designed and organized the research and supervised the article write-up.
- Busra Ozdogan (10%): Contributed with comments on manuscript organization and write-up.
- Remziye Keskin (10%): Contributed with comments on research design.
- Idil Arasan Dogan (%10): Contributed with comments on research design.
- Gokben Hizli Sayar (%10): Contributed with comments on research design.

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Original Article

Electrophysiological Features of Hypnotic State in Healthy Volunteers

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Abstract

Aim: Hypnosis is treated as a state of mind. An individual depending on his/her social and psychological features follows suggestions and applies the requirements concerning time and space. With the advancement in brain-imagining techniques, viewing neuropsychological features of hypnosis has become a possibility. This article investigates the neuropsychological properties of hypnosis. The present study examines the electrophysiological features of the hypnotic minds of healthy individuals. This study aims to detect whether there is a change in and, if yes, in what region of suggestible individuals' minds during hypnosis. **Materials and Methods:** In this study, 34 highly suggestive individuals were selected out of 150 healthy individuals and were subjected to multidimensional Iowa suggestibility scale inventory and electroencephalogram (EEG). Due to technical problems during EEG, 24 data could be used cleanly. Using a correlational design, 34 healthy, suggestive individuals between the ages of 18–55 were included in the study. These participants have gone through an EEG procedure using the oddball paradigm. EEG and oddball were administered to 17 participants with and without hypnosis. Seventeen participants were administered without and with hypnosis. Twenty-four participants whose data was clear were included in the analyses. **Results:** When the groups were compared, it was seen that there was no significant difference in P300, P200, and P100 activities. There was also no significant difference in N200 and N100 activities. **Conclusions:** In this study the authors administered oddball paradigm with hypnosis and without hypnosis. The authors do not report any differences between conditions in terms of enterprise resource plannings. Although there was no statistically significant difference in this experimental design, studies with new and different designs should be continued.

Keywords: *Electroencephalogram, Event Related Potentials, hypnosis, P300*

Introduction

Electroencephalogram (EEG) studies are widely used to measure brain activity (specifically brain oscillations) associated with brain states such as wakefulness, sleep, and attention. Therefore, EEG can be beneficial for deciphering activities such as hypnosis associated with procedures thought to be produced and operated by changes in brain states.

EEG evaluates brain activity using electrodes placed on the scalp using a high conductivity paste. However, given the high level of the brain's interconnectivity, it is essential to know that the activity assessed from either electrode cannot simply reflect the activity in the neurons located below. EEG indirectly measures more of what happens in the brain.

Hypnosis is when the person accepts and applies the suggestions that he/she should take depending on the appropriate time and place depending on their natural, social, and psychological characteristics. Therefore, individuals with much more predispositions are more likely to be hypnotized more easily. Today, hypnosis, in which patients are informed and approved, is called conscious hypnosis. The doctor must use verbal repetitions and mental images, and the hypnotized patient is calm, relaxed, and open to suggestions. Hypnosis is thought to be related to proper brain hemisphere activity and the prefrontal region. Studies have been made that hypnosis causes some changes in brain functions, and it has been observed that there are motor, sensory and autonomic changes in the brain.[1]

As a result, it has been shown in almost all of the studies that the EEG waves of

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the hypnotic trance are pretty different from the EEG waves taken during normal sleep. However, the EEG waves belonging to the hypnotic trance are different from the Alpha waves seen in the EEGs taken during wakefulness. According to the alpha waves of the normal state of wakefulness, EEGs taken without hypnosis and any suggestion may cause excitement or fear; Waves with more regular frequencies and smaller amplitudes are observed. These waves seen on EEGs taken in a hypnotic trance state resemble alpha waves of a state of alertness in which attention and consciousness increase over an object or a thought. If various emotional suggestions are given to the person in hypnosis, it can be seen that there are some changes in EEGs in line with these suggestions.

The aim of this study is to understand the neurophysiological features of hypnosis and to contribute to the literature. Based on the literature, many studies have been done to investigate the neurophysiological effects of hypnosis. However, a hypnosis EEG research with controlled enterprise resource planning (ERP) and oddball paradigm has not been conducted in itself. In this context, as researchers, it was investigated whether hypnosis has a neurophysiological effect with this EEG hypnosis study, which has an ERP exposure process with visual oddball paradigm.

Materials and Methods

This study was performed in line with the principles of the Declaration of Helsinki, as revised in 2013. The ethics committee approval has been obtained from the Uskudar University Non-Invasive Research Ethics Committee (867/25.10.2018).

Research pattern

"Relational scanning model" has been used in this study. The relational screening model is defined as "the research model that aims to determine the existence and degree of change between two or more variables."[2] The relational scanning model is examined in two ways. Correlation type tries to determine whether the variable changes together in relational scans and, if there is a change, how this change is. In the comparison-type relational screening model, there are at least two variables. Groups are formed according to one of them, the independent variable. It is examined whether there is a difference between them according to the dependent variable. In this study, a correlation-type relational scanning model has been used.

Research area and sample

The area of this research is healthy individuals who are prone to suggestions between the ages of 18 and 55 years in the 2018–2019 academic year. The sample representing the universe comprises individuals who have a high suggestibility score and accept the research. The study was carried out with 34 volunteers. The participant group was composed of volunteers who were not diagnosed with any psychiatric or neurological diagnosis using the results of the Miss Inventory application and who were susceptible to suggestion.

Data collection tools

Multidimensional Iowa suggestibility scale-Iowa multidimensional suggestibility test

In this study, the multidimensional Iowa Suggestibility scale test[3] was used to determine the susceptibility levels of the participants. While the alpha value of six factors of the scale with eight factors and 95 items was determined as 0.80, the alpha value of the two factors was determined as more significant than 0.74. These results indicate that the scale is reliable. Consumer suggestibility, persuasiveness, physiological predisposition, physiological reactivity, partner compatibility, psychosomatic control, and stubborn mindset are the sub-dimensions of the scale.

Positive and negative affect scale

In this study, the Positive and Negative Affect Scale (PANAS) scale, adapted into Turkish by Gençöz[4] was used to determine the emotion measurements of the participants. The emotion assessment of the scale participants, consisting of 10 items measuring positive emotions and 10 items measuring negative emotions, was made in two dimensions. Gençöz (2000) found the internal consistency coefficients of the scale as 0.83 and 0.86 for positive and negative dimensions, respectively. The retest consistency of the scale was determined as 0.40 for the positive dimension and 0.54 for the negative dimension. Based on these results, the emotion assessment of the participants in this study was made with this scale.

Wisconsin card sorting test

In this study, the Wisconsin card sorting test (WCST) test was used to determine the effect of participants' reactions on the event-related potentials of the brain. Heaton[5] finalized the scale, which was first developed in.[6] The computer form of WCST was used in the study.

D2-attention test

Developed by Brickencamp[7] the D2-Attention test, which measures selective attention, was used in this study to determine the time-dependent selective attention of the participants. The form adapted to Turkish by Yaycı[8] was used in the study. The test can be applied to all groups between the ages of 9 and 60. There are 14 rows and 47 figures in each row. The adaptation of the test to Turkish was first carried out by (Toker, 1990). Çağlar[9] retested the validity and reliability of the test. In his study, Çağlar found the internal consistency coefficient of the D2 test to be between 0.93 and 0.96 and the reliability coefficient

as 0.86. These numbers indicate that the scale is valid, reliable, and suitable for use.

SCL-90-symptom screening test

SCL-90, a psychiatric self-report test, was used to screen the participants' symptoms in this study. The scale was first developed by Cleary,[10] and the final version was given by Derogatis (1994) (cited in Koğar, 2019). "Scale; It consists of 90 items and nine dimensions: Somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid thinking and psychoticism" Koğar[11] The form adapted to Turkish by (Koğar, 2019) was used in the study. Koğar found confirmatory findings for the 9-factor structure of the scale in his study. "After 11 items removed from the scale in line with the confirmatory analyzes, the Hi coefficients of 72 items preserving their place in the dimensions vary between 0.30 and 0.57. In addition, H coefficients vary between 0.37 and 0.50" (Koğar, 2019).

Sociodemographic form

In the study, a sociodemographic form was used to obtain whether the participants had chronic illnesses, whether they used medication, whether they had psychiatric/psychological disorders, gender, educational status, marital status, and age. When we look at the sociodemographic data of the study, we see that women are more dominant. It is seen that most of our participants have either a bachelor's or master's degree [Table 1].

Research processes

The miss inventory was applied to the individuals during the test phase to see whether they were hypnotizable or not. Thirty-four suggestive volunteers were selected for the study.

Before the test, the participants were informed in writing about the risk and safety factors of the study, and they were asked to sign the consent form.

SCL-90, D2 test, PANAS, and Wisconsin card matching inventories were applied to 34 selected volunteers.

EEG was taken for the first 5 min, and the ERP oddball technique was applied to the person immediately after.

Table 1: Sociodemographic characteristics of the participants

	n (%)	The average age (ss)
Gender		
Female	20 (83.3)	37.05 (10.7)
Male	4 (16.7)	38.75 (7.1)
Total	24 (100)	37.33 (10.1)
Education status		
High school	1 (4.2)	
University degree	14 (58.3)	
Masters	9 (37.5)	

Subsequently, the participants were placed in a hypnotic state, and while they were hypnotic, EEG was applied for the first 5 min. The ERP oddball technique was applied immediately after that.

The research took place in the EEG laboratory. The practice room is 20 square meters. The temperature is 23°. The light is close to daylight. There is no sound. The subjects are seated in front of the computer in front of the table and ERP to the oddball paradigm. Subjects stand motionless with their eyes open depending on the EEG on their heads. Oddball paradigm is constructed visually. Ys appear on the black screen on the computer. One hundred and fifty Y appears in 4 min. In addition, random Xs are interspersed between Ys. There are 36 randomly appearing Xs in total. Subjects are asked to count the Xs that appear randomly during these four minutes. Subjects under hypnosis open their eyes while in the hypnotic state after being hypnotized and are exposed to the oddball paradigm, and then removed from the hypnotic state.

Data analysis

T-test and McNemar analysis were used to analyze the data collected in line with the purpose of the study. Before analyzing the data, it was checked whether the data set met the necessary assumptions for parametric tests and multivariate analysis. The data were analyzed using the SPSS Statistics 23 statistical package program (IBM Inc. SPSS program. USA). While evaluating the data, frequencies (number, percentage) for categorical variables and descriptive statistics (mean, standard deviation, minimum, maximum) for numerical variables were used.

A brain vision analyzer was used for EEG analysis. The extracted parameters were analyzed again with the SPSS program.

Results

Thirty-four suggestion-prone individuals were selected from 150 healthy individuals and EEG/ERP was applied. Some EEG data could not be used after the applications. In this context, since 24 of 34 data are clean and useful, we transfer this part in the experiment.

After clearing out the unusable data, 24 volunteers participated in the second phase of the study. 83.3% (n = 20) of these participants are female and 16% (n = 4) are male. While the average age of female participants was 37.05, the average age of men was 38.75.

Table 2 shows the paired sample *t*-test results of the participants. Accordingly, the attention and awareness parameters of the participants were analyzed in hypnotic and nonhypnotic groups. According to the analysis results, no significant difference was found between the p300 values in the hypnotic state (X = 4.04, ss = 2.7) and the p300 values in the nonhypnotic state (X = 3.11, ss = 2.0) (t = 1.612, P = 0.121). There was no significant difference between

Table 2: Paired sample *t*-test results

	Average	SS	Average difference	df	95% CI		*t*	*P*
					Lower	Upper		
Pairing 1								
HYPP300std	4.04	2.7	0.93	23	–0.26	2.13	1.612	0.121
NHYPP300std	3.11	2.0						
Pairing 2								
HYPp200std	3.22	2.1	0.03	23	–0.80	0.85	0.068	0.946
NHYPp200std	3.19	1.5						
Pairing 3								
HYPn100std	–1.19	1.5	0.18	23	–0.57	0.93	0.502	0.620
NHYPn100std	–1.37	1.7						
Pairing 4								
HYPn200std	–1.61	2.8	0.63	23	–0.89	2.15	0.861	0.398
NHYPn200std	–2.24	3.4						
Pairing 5								
HYPn200nonstd	–1.48	2.7	0.09	23	–1.83	2.02	0.100	0.921
NHYPn200nonstd	–1.58	4.7						
Pairing 6								
HYPn2b	0.12	2.2	–0.54	23	–1.75	0.67	–0.924	0.365
NHYPn2b	0.66	2.8						

CI: Confidence interval, SS: Standard deviation

the p200 values of the participants in the hypnotic state (X = 3.22, ss = 2.1) and the p200 values in the nonhypnotic state (X = 3.19, ss = 1.5) (t = 0.068, *P* = 0.946). Based on these findings, it is possible to state that hypnosis has no effect on the participants' attention value. No significant difference was found between the n100 values of the participants in the hypnotic state (X = −1.19, ss = 1.5) and the n100 values in the nonhypnotic state (X = −1.37, ss = 1.7) (t = 0.502, *P* = 0.620). No significant difference was found between the n200 values of the participants in the hypnotic state (X = −1.61, ss = 2.8) and the n200 values in the nonhypnotic state (X = −2.24, ss = 3.4) (t = 0.861, *P* = 0.398). There was no significant difference between the n200nonstd values of the participants in the hypnotic state (X = −1.48, ss = 2.7) and the n200nonstd values in the nonhypnotic state (X = −1.52, ss = 4.7) (t = 0.100, *P* = 0.921). There was no significant difference between the n2b values of the participants in the hypnotic state (X = 0.12, ss = 2.2) and the n2b values in the nonhypnotic state (X = 0.66, ss = 2.8) (t = −0.924, *P* = 0.365). From these findings, it is possible to state that hypnosis has no effect on the awareness parameter of the participants.

Table 3 shows the results of the independent samples *t*-test prepared within the framework of the attention and awareness parameters of the groups. Accordingly, no significant difference was found between the participants' HYPp300std value in the nonhypnotic state (x = 3.3711, ss = 2.69) and the HYPp300std values in the hypnotic state (x = 4.7188, ss = 2.65) (t = −1.236, *P* = 0.229). No significant difference was found between the NHYPp300std value in the nonhypnotic state (x = 2.4528, ss = 1.41) and the NHYPp300std values in the hypnotic state (x = 3.9897, ss = 2.52) (*t* = −1.846, *P* = 0.078). No significant difference was found between the participants' HYPp200std value in the nonhypnotic state (x = −1.2736, ss = 1.18) and the HYPp200std values in the hypnotic state (x = −1.1046, ss = 1.83) (*t* = −0.269, *P* = 0.791). No significant difference was found between the NHYPp200std value in the nonhypnotic state (x = −2.0711, ss = 3.03) and the NHYPp200std values in the hypnotic state (x = −1.1420, ss = 2.56) (*t* = −0.812, *P* = 0.426). No significant difference was found between the participants' HYPn100std value in the nonhypnotic state (x = −1.8997, ss = 3.11) and the HYPn100std values in the hypnotic state (x = −1.0662, ss = 2.39) (*t* = −0 736, *P* = 0.470). No significant difference was found between the NHYPn100std value in the nonhypnotic state (x = 0.1715, ss = 2.25) and the NHYPn100std values in the hypnotic state (x = 0.0758, ss = 2.25) (*t* = 0.104, *P* = 0.918). No significant difference was found between the participants' HYPn200std value in the nonhypnotic state (x = 2.8274, ss = 1.61) and the HYPn200std values in the hypnotic state (x = 3.4013, ss = 2.38) (t = −0.691, *P* = 0.497). No significant difference was found between the NHYPn200std value of the participants in the nonhypnotic state (x = 3.0600, ss = 1.78) and the NHYPn200std values in the hypnotic state (x = 3.3284, ss = 1.23) (t = −0.430, *P* = 0.672). No significant difference was found between the participants' HYPn200nonstd value in the nonhypnotic state (x = −1.7551, ss = 1.30) and the HYPn200nonstd values in the hypnotic state (x = −0.9865, ss = 2.06) (t = −1.094, *P* = 0.286). No significant difference was found between the NHYPn200nonstd value in the nonhypnotic state (x = −2.2397, ss = 2.55) and the NHYPn200nonstd values in the hypnotic state (x = −2.2394,

Table 3: Independent sample *t*-test results

	Average	SS	Average difference	df	95% CI		*t*	*P*
					Lower	Upper		
HYPP300std								
Nonhypnotic	3.3711	2.69	−1.3477	22.00	−3.61	0.91	−1.236	0.229
Hypnotic	4.7188	2.65						
NHYPP300std								
Nonhypnotic	2.4528	1.41	−1.5369	22.00	−3.26	0.19	−1.846	0.078
Hypnotic	3.9897	2.52						
HYPp200std								
Nonhypnotic	−1.2736	1.18	−0.1691	22.00	−1.47	1.14	−0.269	0.791
Hypnotic	−1.1046	1.83						
NHYPp200std								
Nonhypnotic	−2.0711	3.03	−0.9291	22.00	−3.30	1.44	−0.812	0.426
Hypnotic	−1.1420	2.56						
HYPn100std								
Nonhypnotic	−1.8997	3.11	−0.8335	22.00	−3.18	1.52	−0.736	0.470
Hypnotic	−1.0662	2.39						
NHYPn100std								
Nonhypnotic	0.1715	2.25	0.0956	22.00	−1.81	2.00	0.104	0.918
Hypnotic	0.0758	2.25						
HYPn200std								
Nonhypnotic	2.8274	1.61	−0.5739	22.00	−2.30	1.15	−0.691	0.497
Hypnotic	3.4013	2.38						
NHYPn200std								
Nonhypnotic	3.0600	1.78	−0.2684	22.00	−1.56	1.03	−0.430	0.672
Hypnotic	3.3284	1.23						
HYPn200nonstd								
Nonhypnotic	−1.7551	1.30	−0.7686	22.00	−2.22	0.69	−1.094	0.286
Hypnotic	−0.9865	2.06						
NHYPn200nonstd								
Nonhypnotic	−2.2397	2.55	−0.0004	22.00	−2.90	2.90	0.000	1.000
Hypnotic	−2.2394	4.13						
HYPn2b								
Nonhypnotic	−0.4961	3.41	2.1602	22.00	−1.79	6.11	1.133	0.269
Hypnotic	−2.6564	5.66						
NHYPn2b								
Nonhypnotic	1.7436	2.47	2.1606	22.00	−0.04	4.36	2.040	0.054
Hypnotic	−0.4170	2.72						

CI: Confidence interval, SS: Standard deviation

ss = 4.13) (t = 0.000, P = 1.000). No significant difference was found between the participants' HYPn2b value in the nonhypnotic state (x = −0.4961, ss = 3.41) and the HYPn2b values in the hypnotic state (x = −2.6564, ss = 5.66) (t = 1.133, P = 0.269). No significant difference was found between the NHYPn2b value in the nonhypnotic state (x = 1.7436, ss = 2.47) and the NHYPn2b values in the hypnotic state (x = −0.4170, ss = 2.72) (t = 2.040, P = 0.054).

Table 4 shows the repeated measurement differences between the ERP amplitudes according to the hypnotic and nonhypnotic groups. The effect of hypnosis on the p300 attention amplitude measurement was not significant F (1, 22) = 2.534, P = 0.126, partial η^2 = 0.10. When the group effect is included in the effect equation, it is understood that the amount of difference decreases even more F (1, 22) = 0.438, P = 0.515, partial η^2 = 0.020. The effect of hypnosis on the p200 attention amplitude measurement was not significant F (1, 22) = 0.005, P = 0.945, partial η^2 = 0.000. When the group effect is included in the effect equation, it is understood that the said difference amount increases F (1, 22) = 2.712, P = 0.114, partial η^2 = 0.110. No significant effect of hypnosis on n100 awareness amplitude measurement F (1, 22) = 0.249, P = 0.623, partial η^2 = 0.011. When the group effect is included in the effect equation, it is understood that the amount of difference increases F (1, 22) = 0.678, P = 0.419, partial η^2 = 0.030. No significant effect of hypnosis on n200 awareness amplitude measurement F (1, 22) = 0.722,

Table 4: Differences in repetitive measurement between ERP amplitudes according to hypnotic and nonhypnotic groups

	SS²	df	Avareage²	*F*	*P*	η^2_p
Attention (p300)	10.39	1	10.39	2.534	0.126	0.10
Attention (p300)*Group	1.79	1	1.79	0.438	0.515	0.020
Attention (p200)	0.009	1	0.009	0.005	0.945	0.000
Attention (p200)* Group	4.82	1	4.82	2.712	0.114	0.110
Awareness (n100)	0.396	1	0.396	0.249	0.623	0.011
Awareness (n100)* Group	1.078	1	1.07	0.678	0.419	0.030
Awareness (n200)	4.807	1	4.807	0.722	0.405	0.032
Awareness (n200)* Group	2.588	1	2.588	0.388	0.540	0.017
Awareness (n200non)	0.104	1	0.104	0.011	0.918	0.000
Awareness (n200non)* Group	26.887	1	26.887	2.796	0.109	0.113
n2b	3.494	1	3.494	0.944	0.342	0.041
n2b* Group	12.792	1	12.792	3.456	0.076	0.136

SS: Standard deviation

$P = 0.405$, partial $\eta^2 = 0.032$. When the group effect is included in the effect equation, it is understood that the said difference amount decreases F (1, 22) = 0.388, $P = 0.540$, partial $\eta^2 = 0.017$. No significant effect of hypnosis on n200nonstd awareness amplitude measurement F (1, 22) = 0.011, $P = 0.918$, partial $\eta^2 = 0.000$. When the group effect is included in the effect equation, it is understood that the said difference amount increases F (1, 22) = 2.796, $P = 0.109$, partial $\eta^2 = 0.113$. No significant effect of hypnosis on n2b amplitude measurement F (1, 22) = 0.944, $P = 0.342$, partial $\eta^2 = 0.041$. When the group effect is included in the effect equation, it is understood that the said difference amount increases F (1, 22) = 3.456, $P = 0.076$, partial $\eta^2 = 0.136$

Table 5 shows the correlations between the amplitudes of the participants' hypnotic states and psychological factors. Significant correlations draw attention according to the findings. According to these analyses, there is a moderately positive and significant relationship between HYPp300 and HYPp200 ($r = 0.569$, $P < 0.001$). There is a moderate, positive and significant relationship between HYPp200 and HYPn200 ($r = 0.428$, $P < 0.005$) and Panas Negative ($r = 0.493$, $P < 0.005$)

Between HYPn100 and HYPn200 ($r = 0.551$, $P < 0.001$) moderately positive, SCL90Anxiety ($r = -0.438$, $P < 0.005$), SCL90Depression ($r = -0.432$, $P < 0.005$), SCL90Interpersonal Sensitivity ($r = -0.487$, $P < 0.005$), SCL90PsychoticSymptom ($r = -0.498$, $P < 0.005$), SCL90ParanoidSymptom ($r = -0.450$, $P < 0.005$), SCL90Anger ($r = -0.466$, $P < 0.005$) 0.005), SCL90Phobic Symptom ($r = -0.576$, $P < 0.001$), SCL Extra Score ($r = -0.520$, $P < 0.001$), and SCL General Symptom Index ($r = -0.425$, $P < 0.005$). There are moderately significant relationships.

There is a positive and moderately significant correlation between HYPn200 and HYPn200nonstd ($r = 0.683$, $P < 0.001$). HYPn200 vs. HYPn2b ($r = -0.411$, $P < 0.005$), SCL90Anxiety ($r = -0.538$, $P < 0.001$), SCL90Obsession ($r = -0.464$, $P < 0.005$), SCL90Depression (r = −0. 446, $P < 0.005$), SCL90Interpersonal Sensitivity ($r = -0.446$, $P < 0.005$), SCL90Psychotic Symptom ($r = -0.475$, $P < 0.005$), SCL90Paranoid Symptom ($r = -0.448$, $P < 0.005$), SCL90Anger ($r = -0.580$, $P < 0.001$), SCL90Phobic Symptom ($r = -0.470$, $P < 0.005$), SCL Additional Score ($r = -0.562$, $P < 0.001$), and SCL General Symptom Index ($r = -0.485$, $P < 0.005$), there are negative, moderately significant relationships.

HYPn200nonstd parameter did not correlate with any variable except HYPn200 variable. The HYPn2b parameter has a moderately significant negative correlation with the SCL90 Additional Score ($r = -0.471$, $P < 005$). WCSTY True variable has a moderately significant negative correlation with SCL90EkScore ($r = -0.486$, $P < 005$).

SCL90Somatization variable with SCL90Anxiety ($r = 0.681$, $P < 0.001$), SCL90Obsession ($r = 0.757$, $P < 0.001$), SCL90Depression ($r = 0.686$, $P < 0.001$), SCL90Interpersonal Sensitivity ($r = 0.604$, $P < 0.001$), SCL90PsychoticSymptom ($r = 0.613$, $P < 0.001$), SCL90Paranoid Symptom ($r = 0.751$, $P < 0.001$), SCL90Anger ($r = 0.671$, $P < 0.001$), SCL90PhobicSymptom ($r = 0.470$), $P < 0.718$), SCL Additional Score ($r = 0.820$, $P < 0.001$), SCL common symptom index ($r = 0.791$, $P < 0.005$), and PANAS negative score ($r = 0.427$, $P < 0.005$) moderate to high severity positive and significant relationships were determined.

SCL90Anxiety variable with SCL90Obsession (r = 0.782, $P < .001$), SCL90Depression ($r = 0.757$, $P < 0.001$), SCL90Interpersonal Sensitivity ($r = 0.641$, $P < 0.001$), SCL90Psychotic Symptom ($r = 0.770$, $P < 0.001$), SCL90Paranoid Symptom ($r = 0.928$, $P < 0.001$), SCL90Anger ($r = 0.836$, $P < 0.001$), SCL90Phobic Symptom ($r = 0.864$, $P < 0.718$), SCL additional score ($r = 0.570$, $P < 0.001$), and SCL general symptom

Table 5: Correlation table between hypnotic amplitudes and psychological factors

	1	2	3	4	5	6	7	8	9	10	11
HYPP300std (1)	1										
HYPp200std (2)	0.569**	1									
HYPn100std (3)	0.134	0.231	1								
HYPn200std (4)	0.294	0.428*	0.551**	1							
HYPn200nonstd (5)	0.269	0.401	0.390	0.683**	1						
HYPn2b (6)	−0.036	−0.040	−0.210	−0.411*	0.385	1					
wcstyTrue (7)	−0.022	−0.101	0.296	0.310	0.087	−0.283	1				
SCL90 Somatization (8)	0.259	0.080	−0.403	−0.403	−0.191	0.271	−0.367	1			
SCL90Anxiety (9)	0.034	−0.208	−0.438*	−0.538**	−0.365	0.224	−0.130	0.681**	1		
SCL90Obsession (10)	0.261	0.064	−0.401	−0.464*	−0.383	0.108	−0.169	0.757**	0.782**	1	
SCL90 Depression (11)	0.310	−0.005	−0.432*	−0.446*	−0.221	0.288	−0.142	0.686**	0.757**	0.907**	1
SCL90 Interpersonal Sensitivity (12)	0.338	0.124	−0.487*	−0.446*	−0.321	0.163	−0.195	0.604**	0.641**	0.849**	0.880**
SCL90 Psychotic Symptom (13)	−0.046	−0.171	−0.498*	−0.475*	−0.348	0.165	−0.199	0.613**	0.770**	0.719**	0.769**
SCL90 Paranoid Symptom (14)	0.104	−0.087	−0.450*	−0.448*	−0.297	0.195	−0.131	0.751**	0.928**	0.822**	0.781**
SCL90Anger (15)	0.104	−0.129	−0.466*	−0.580**	−0.377	0.261	−0.238	0.671**	0.836**	0.835**	0.841**
SCL90 Phobic Symptom (16)	0.164	−0.228	−0.576**	−0.470*	−0.245	0.288	−0.169	0.718**	0.864**	0.678**	0.734**
SCL90 Additional Points (17)	0.066	−0.063	−0.520**	−0.562**	−0.192	0.471*	−0.486*	0.820**	0.570**	0.685**	0.652**
SCL90General Symptom Index (18)	0.229	0.069	−0.425*	−0.485*	−0.308	0.228	−0.237	0.791**	0.830**	0.914**	0.896**
PANASPositiveScore (19)	−0.145	−0.168	0.367	0.244	0.111	−0.171	0.091	−0.307	−0.324	−0.451*	−0.570**
PANAS Negative Score (20)	0.208	0.493*	−0.226	−0.127	−0.053	0.095	−0.366	0.427*	0.290	0.441*	0.420*
d2testiTNE (21)	0.299	0.180	0.023	−0.038	0.003	0.052	0.278	0.272	0.305	0.339	0.362
Suggestiblity score (22)	−0.004	0.125	−0.182	−0.123	−0.322	−0.247	0.011	0.332	0.293	0.529**	0.456*

	12	13	14	15	16	17	18	19	20	21	22
HYPP300std (1)											
HYPp200std (2)											
HYPn100std (3)											
HYPn200std (4)											
HYPn200nonstd (5)											
HYPn2b (6)											
wcstyTrue (7)											
SCL90 Somatization (8)											
SCL90Anxiety (9)											
SCL90Obsession (10)											
SCL90 Depression (11)											
SCL90 Interpersonal Sensitivity (12)	1										
SCL90 Psychotic Symptom (13)	0.611**	1									
SCL90 Paranoid Symptom (14)	0.733**	0.786**	1								
SCL90Anger (15)	0.746**	0.800**	0.863**	1							
SCL90 Phobic Symptom (16)	0.542**	0.752**	0.779**	0.690**	1						

Contd...

Table 5: Contd...

	12	13	14	15	16	17	18	19	20	21	22
SCL90 Additional Points (17)	0.590**	0.573**	0.627**	0.657**	0.594**	1					
SCL90General Symptom Index (18)	0.860**	0.777**	0.880**	0.876**	0.711**	0.782**	1				
PANASPositiveScore (19)	−0.613**	−0.452*	−0.443*	−0.373	−0.313	−0.381	−0.538**	1			
PANAS Negative Score (20)	0.489*	0.451*	0.415*	0.363	0.260	0.378	0.515*	−0.572**	1		
d2testiTNE (21)	0.232	0.182	0.254	0.131	0.329	0.103	0.275	−0.386	0.067	1	
Suggestiblity score (22)	0.528**	0.467*	0.357	0.369	0.187	0.154	0.425*	−0.385	0.539**	0.062	1

*P<0.05, **P<0.001. PANAS: Positive-negative affect scale

index (r = 0.830, P < 0.005), high-intensity positive significant relationships were detected.

SCL90Obsession variable with SCL90Depression (r = 0.907, P < 0.001), SCL90Interpersonal Sensitivity (r = 0.849, P < 0.001), SCL90Psychotic Symptom (r = 0.719, P < 0.001), SCL90Paranoid Symptom (r = 0.822, P < 0.001), SCL90Anger (r = 0.835, P < 0.001), SCL90Phobic Symptom (r = 0.678, P < 0.718), SCL Additional Score (r = 0.685, P < 0.001), and SCL common symptom index (r = 0. 914, P < 0.005), high-intensity positive significant relationships were detected. There is a moderately positive and significant relationship between the SCL90Obsession variable and the Suggestibility score (r = 0.529, P < 0.001) variable and the PANAS Negative Score (r = 0.441, P < 0.005). There is a moderately negative and significant relationship between the SCL90Obsession variable and the PANAS Positive Score variable. relationship exists (r = −0.451, P < 0.005).

SCL90 Depression variable vs. SCL90Interpersonal Sensitivity (r = 0.880, P < 0.001), SCL90 Psychotic Symptom (r = 0.769, P < 0.001), SCL90 paranoid symptom (r = 0.781, P < 0.001), SCL90 Anger (r = 0.841, P < 0.001), SCL90Phobic Symptom (r = 0.734, P < 0.718), SCL Additional Score (r = 0.652, P < 0.001), and SCL General Symptom Index (r = 0.894, P < 0.001) with high severity of positive significance relationships have been identified. There is a moderately positive and significant relationship between the SCL90Depression variable and the suggestibility score (r = 0.456, P < 0.005) variable and the PANAS negative score (r = 0.570, P < 0.001). Relationship exists (r = −0.420, P < 0.005).

SCL90Interpersonal Sensitivity variable with SCL90Psychotic Symptom (r = 0.611, P < 0.001), SCL90Paranoid symptom (r = 0.733, P < 0.001), SCL90Anger (r = 0.746, P < 0.001), SCL90Phobic symptom (r = 0.542, P < 0.718), SCL additional score (r = 0.590, P < 0.001), and SCL general symptom index (r = 0.860, P < 0.001) were found to have significant positive correlations. There is a moderately positive and significant correlation between the SCL90Interpersonal Sensitivity variable and the Suggestibility score (r = 0.522, P < 0.001) variable and the PANAS Negative Score (r = 0.489, P < 0.005). Relationship exists (r = −0.613, P < 0.005).

SCL90Psychotic symptom variable with SCL90ParanoidSymptom (r = 0.786, P < 0.001), SCL90Anger (r = 0.800, P < 0.001), SCL90Phobic Symptom (r = 0.752, P < 0.718), SCL additional score (r = 0.573, P < 0.001), SCL General Symptom Index (r = 0.777, P < 0.001), PANAS negative score (r = 0.451, P < 0.005), and Suggestibility score (r = 0.467, P < 0.005) moderately and highly positive significant relationships were found. There is a moderately negative significant relationship between the

SCL90OPpsychotic Symptom variable and the PANAS Positive Score variable ($r = -0.452$, $P < 0.005$).

SCL90 Paranoid Symptom variable with SCL90Anger ($r = 0.863$, $P < 0.001$), SCL90Phobic Symptom ($r = 0.779$, $P < 0.718$), SCL Additional Score ($r = 0.627$, $P < 0.001$), SCL common symptom index ($r = 0.880$, $P < 0.001$), and PANAS negative score ($r = 0.415$, $P < 0.005$), moderate and high-intensity positive correlations were found. There is a moderate negative significant relationship between the SCL90O Psychotic Symptom variable and the PANAS Positive Score variable ($r = -0.443$, $P < 0.005$).

SCL90Anger and SCL90Phobic Symptom ($r = 0.690$, $P < 0.718$), SCL Additional Score ($r = 0.667$, $P < 0.001$), and SCL General Symptom Index ($r = 0.876$, $P < 0.001$) moderate and high-severity positive significant relationships detected. Moderate and high-intensity positive correlations were found between SCL90Phobic Symptom and SCL Additional Score ($r = 0.594$, $P < 0.001$), and SCL General Symptom Index ($r = 0.711$, $P < 0.001$). A significant positive correlation was found between SCL Additional Score and SCL general symptom index ($r = 0.782$, $P < 0.001$).

There is a moderately positive and significant relationship between the SCL90OGeneral Symptom Index variable and the PANAS Negative Score variable ($r = 0.515$, $P < 0.005$) and Suggestibility score ($r = 0.425$, $P < 0.005$). There is a moderate negative significant relationship between the SCL90OGeneral Symptom Index variable and the PANAS Positive Score variable ($r = -0.538$, $P < 0.005$). There is a moderately negative and significant relationship between the PANAS Negative Score variable and the PANAS Positive Score variable ($r = 0.572$, $P < 0.001$). There is a moderately positive and significant relationship between the PANAS Negative Score variable and the Suggestibility score variable ($r = 0.539$, $P < 0.001$).

Table 6 contains the results of the regression analysis that predict the suggestibility scores of the participants. SCL90Obsession ($t = 1.911$, $P = 0.070$), SCL90Depression ($t = 1.445$, $P = 0.163$), SCL90Interpersonal Sensitivity ($t = 1.764$, $P = 0.092$), SCL90Psychotic Symptom ($t = 0.092$), which were associated with the Suggestibility Score 1.427, $P = 0.168$), and the SCL90 General Symptom Index ($t = 0.956$, $P = 0.350$) variables did not have the power to predict participants' suggestion susceptibility. In the calculation performed by step-by-step linear regression analysis, it was observed that the only variable that significantly predicted the suggestion susceptibility score was PANAS Negative ($x^2 = 8317$, 6; F (1.22) = 9.030, $P = 0.007$). According to the model, the predictive power of the PANAS Negative variable was found to be 29.1% ($R^2 = 0.291$).

Discussion

This research investigated the electrophysiological properties of the hypnotic state of mind in healthy individuals. In this context, the study aims to determine in which areas changes occur in the brain of individuals susceptible to hypnosis and determine whether a change in attention and awareness parameters of the person will occur in the hypnotic state.

Different types and patterns have been studied to examine the effects of hypnosis. One of the notable ones is the research by Barabazs and Londsdale (1983).[12] In this study, the effects of a hypnotic negative hallucination state on olfactory potentials were tested. Fully controlled EEG was performed for the first time in the study, which was carried out with 4 highly hypnotizable and 5 low hypnotic participants from a pool of 93 participants. Researchers observed significant increases in p300 amplitude. In another study, a similar research setup was carried out, this time using positive hallucination suggestion, and in this study researchers focused on the effect of hypnosis on visual potential.[13] In this study, it was observed that the p300 amplitude was suppressed. These two studies found conflicting results. It seems possible to explain this contradictory result with methodological differences. In the first study, negative hallucination and olfactory potential were the focus, while in the second study, positive hallucination and visual potential were the focus. This difference also shows us the effect of the research method on the results to be obtained. A similar effect may be in question in this study. The lack of difference between the

Table 6: Variables that predict suggestibility score

	Avarege	SS	β	SE	*B*	*t*	Significant
SCL90 Obsession	0.900	0.68	-	-	0.361	1.911	0.070
SCL90 Depression	0.700	0.65	-	-	0.279	1.445	0.163
SCL90 Interpersonal Sensitivity	0.517	0.50	-	-	0.347	1.764	0.092
SCL90 Psychotic Symptom	0.337	0.35	-	-	0.280	1.427	0.168
SCL90 General Symptom Index	0.567	0.49	-	-	0.201	0.956	0.350
PANAS Negative Score	19.38	10.3	1.846	0.61	0.54	3.005	0.007
R^2					0.291		
χ^2					8317.6, *F* (1.22)=9.030		
P					0.007		

PANAS: Positive-negative affect scale, SE: Standard error, SS: Standard deviation

groups in the research results can be explained by the experimental setup used. Barabasz (1992)[14] later stated that the reason for this difference was due to the hypnotic suggestions used in research.

Perlini, *et al*.,[15] examined the potential of responses to verbal and nonverbal tasks with 9 participants with a high tendency to hypnosis. Researchers reported that they found results consistent with Spiegel *et al*.(1989), who found that the p300 component was attenuated. The authors of this study suggested an alternative explanation to Barabasz (1983),[12] stating that the P300 component could be attenuated when the participant needed to distract between two tasks by participating in the stimulus and hallucinatory object. They offered an explanation that some of the positive results from other studies may be due to the participant's blurred vision, which may have been unconscious to meet the experimental commands. There are other studies showing that visual blurring affects p100 and p300 amplitudes (Sokol and Moscowitz, 1981).[16]

DePascalis,[17] investigating the effects of hypnotic hallucination on evoked potentials and Spiegel *et al*.[13] conducted a study to confirm their results. This study used a group of seven highly hypnotizable participants, a group of nine highly hypnotizable participants, and a group of eight moderately hvpnotizable participants as a control group. The intermediate group of hypnotizable participants was not subject to hypnotic induction and only passive attention served as the button-pressing control group. Both the high and low groups were subjected to a hypnotic induction at the experimental stage and encouraged to try to experience the hypnotic suggestions. Two hypnotic suggestions were used for hallucinations, a visual flash and a brighter and more easily detectable version of the visual flash. This study tested several visual evoked potential components, including n100, n250, P100 and P300. Research findings partially confirmed the findings of Spiegel *et al*., DePascalis found a decrease in the amplitudes of p100 and p300. Unlike Spiegel *et al*., findings, DePascalis did not obtain statistically significant results despite the decrease in p300. Researchers stated that this partial difference may be related to the quality of the commands.

In general, as examples given above, researchers found statistically significant results on the effects of hypnosis. As in the study of Perlini *et al*., no such effect was observed in this study. It is possible to list the main reasons for the few insignificant findings regarding the effects of hypnosis on evoked potentials, such as insufficient measurement of high and low hypnotizability groups, vague instructions, or mixed designs. These reasons are not put forward to explain the results obtained in this study. However, only one group was used in this study. A one-group and two-measure experimental setup was used with 24 participants with high suggestibility scores (100 and above). It seems possible to explain the nonsignificant results obtained with this experimental setup.

The limitations of this study are gathered in a few essential points. The first of these is that the participants are volunteers and therefore self-selected. Personality variables can be expected to affect individuals' preferences to participate, which can reduce the generalizability of the findings. Another point concerns the experimental setup of the study. Although it has its advantages, the setup used in this study does not allow comparing individuals with high hypnotizability versus low individuals. Another limitation is related to the generalizability of the research results. This study was conducted with a limited number of participants. Therefore, the generalizability of the study findings is low. These limitations also bring new research opportunities. At this point, it is possible to offer different suggestions.

Finally, considering that the study was conducted in the laboratory environment, the laboratory environment may have harmed the hypnotic effect. Factors such as the high light level in the environment, the tight fit of the EEG electrodes to the head, and the discomfort of the fluid used for electrode passage may have limited hypnotic induction.

Conclusions

In this study, the neurophysiological effects of hypnosis on the brain were investigated by dividing 34 healthy suggestion-prone individuals into two different groups and measuring their P300 activities under hypnosis and in the normal awake state with the erp/oddball paradigm. The results show that there is no significant difference in EEG results between hypnotized and nonhypnotized subjects. To increase the generalizability of the research results, it is beneficial to repeat a similar study to different populations. However, it is beneficial to repeat the research with a different experimental setup. This setup includes groups with high hypnotizability, and low groups will help determine the effects of suggestion. There is also a need for studies measuring the effectiveness of different suggestion commands. Such studies will help determine the most effective suggestion commands. In addition, it is thought that studies aiming to determine the effectiveness of hypnosis are also needed.

Patient informed consent

Informed consent was obtained.

Ethics Committee Approval

The ethics committee approval has been obtained from the Uskudar University Non-Invasive Research Ethics Committee (867/25.10.2018).

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Conflicts of interest

There are no conflicts of interest to declare.

Author contribution subject and rate

- Metin Çınaroğlu (50%): Data collection and analyses and wrote the manuscript.
- Cumhur Taş (50%): Data collection and analyses and wrote the manuscript.

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Original Article

Investigation of the Relationship between Eating Attitudes, Self-Esteem, Anxiety, and Depression Levels of Postmenopausal Women

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Abstract

Aims: The aim of this study is to evaluate the relationship between hormonal and psychological processes and eating attitudes, self-esteem, anxiety, and depression levels in postmenopausal women. **Materials and Methods:** This study was carried out by applying demographic information form, Beck depression, anxiety inventory, Self-Esteem Scale, and eating attitude test to 100 female participants who entered the menopause period. The research method is the relational screening method. Online and face-to-face surveys were administered to the participants. Data obtained from the scales SPSS software version 25.0. analyzed with the program. **Results:** In 100 menopausal women, 9% were low, 68% moderate, and 23% were at the good material level, body mass index was 14% normal, 61% were slightly obese, 17% were 1st class obese, and 8% were 2nd class obese. When the association between menopausal women's eating attitudes and depression levels was investigated, it was shown that there was a moderately negative relationship between the Beck Depression Scale and the eating attitude scale, as well as between the eating attitude and self-esteem. It has been found that there is a high level of positive correlation between the self-esteem and anxiety levels of menopausal women and between eating attitudes and anxiety levels. **Conclusion:** There is a negative relationship between eating attitude and depression and there is a positive relationship between self-esteem and trait anxiety. Depression, anxiety, nutritional obsessions, and low self-esteem can be seen in women with menopause, and there are relationships among these. For the health and rehabilitation of women with menopause, these parameters should be taken into account and preventive measures should be understood.

Keywords: *Anxiety, depression, eating attitudes, postmenopausal, self-esteem*

Introduction

Menopause is the reduction of follicular activity, which is characterized by hormonal changes and the cessation of the menstrual cycle. It is one of the absolute periods that most women experience between the ages of 45 and 52 years.[1-3] By 2030, it is estimated that 1.2 billion women would be postmenopausal.[4] In line with this physiological change, more than 85% of menopausal women experience vasomotor symptoms (VMS) as sudden warmth, night sweats, and sleep disturbances, and also due to the decrease in estrogen sexual dysfunction, mood disorders, and weight gain can experienced VMS is associated also with cognitive declines and poor quality of life.[1,5,6] VMS typically occurs between 5 and 7 years after menopause but can also last for 15 years or longer.[7,8] Mood swings such as irritability, sadness, and tension, as well as cognitive deficits such as impaired concentration and verbal memory decline, can occur during menopause; social disorders such as deterioration of family relations, social isolation, embarrassment, anxiety, fatigue, and decreased work productivity can also occur.[9] Its effects on psychosocial deterioration can lead to severe mood disorders, therefore, depression[10,11] and anxiety[12] are common in women during the menopausal transition, and both disorders are known to have a ratio approximately twice as high as men.[13,14] Women, who have anxiety and stress and also have low self-esteem, have been shown to experience psychological and VMS more intensely[15,16] and have low self-esteem

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in correlation with symptoms.[17] Similarly, it has been reported that body awareness and self-esteem are associated related to coping with menopausal transition.[18] During this period, some eating behaviors such as uncontrolled eating, restricted eating, and emotional eating may cause a change in eating attitude.[19,20] Uncontrolled eating is a defining actor of binge eating disorder and refers to the urge to overeat. Emotional eating is a pattern of eating that develops in response to and as a result of stress or bad conditions. Restricted eating is the intentional restriction of food consumption for the purpose of weight control.[21-24] It can also be hypothesized that these situations result from a negative perception of the changes that occur during menopause.[16] However, even though menopause is seen as a universal change, it is influenced by sociocultural norms. Women are perceived differently by women because of their menopausal transition experiences.[25] Women, on the other hand, have an inactive approach to managing menopausal symptoms due to their traditional and cultural beliefs.[26] They may use natural nonpharmacological means such as diet and exercise to cope with menopausal symptoms.[27]

Understanding the symptoms of menopause and preventing possible complications are of great importance in terms of process management. This study provides preliminary data on the relationship between psychosocial symptoms of menopause and eating attitudes. Natural interventions based on these data can play a role in the process management.

Materials and Methods

This study was performed in line with the principles of the Declaration of Helsinki, as revised in 2013. Ethics Committee Approval for the study was received from Üsküdar University Noninterventional Research Ethics Board on 31.12.2020 (No: 61351342/2020-634).

Participants

An exploratory and descriptive methodology adopted on an inductive qualitative approach was used to gain an understanding of postmenopausal women's menopausal experiences.

Data were collected from a total of 100 females during their menopausal period who were evaluated for eligibility to participate in the study. The inclusion criteria for the participants were as follows: (i) postmenopausal women, (ii) voluntary participation, and (iii) the ability to fill the inventories by having no mental or physical impairment to prevent reading and writing properly.

Data collection

This study was conducted between February and June 2021 through online platforms. A web-based report form was used to collect data on personal characteristics (age, body weight, body mass index (BMI), marital status, education status, employment status, and monthly income). In addition to this form, Eating Attitudes Test Short Form (EAT-40), Beck Depression Scale (BDS), the State-Trait Anxiety Inventory, and Rosenberg Self-Esteem Scale (RSES) were applied. To develop recommendations, the World Health Organization (WHO) data were used in the calculation and classification of BMI values.[28]

Eating Attitudes Test Short Form

Garner and Garfinkel[29] developed the EAT-40 in 1979, and Savaşr and Erol[30] converted it to Turkish in 1989. EAT-40 is a Likert type and 40-item self-report format questionnaire presented with a 6-point mandatory choice. Severity is measured on a 0–3 scale with "sometimes," "rarely," and "never" responses being scored as 0 each, and "often," "very often," and "always" being scored as 1, 2, and 3, respectively.[29]

Beck Depression Scale

The Beck Depression Inventory was constituted by Beck *et al*.[31] in and concerted to Turkish by Hisli[32] in 1988. The scale consists of 21 items self-report questionnaire and measures the somatic, emotional, motivational, and cognitive symptoms of depression. Each question contains four options numbered 0, 1, 2, and 3. The sentence numbered "0" indicates that there are no depressive symptoms in that item, while other numbers indicate that symptom is experienced more and more intensely. The total score derived from the inventory ranges from 0 to 63, with higher values indicating an increase in depression symptoms.

Rosenberg Self-Esteem Scale

Rosenberg constituted the RSES in 1965.[33] RSES is a 10-item scale administered by self-report. It has been validated for assessing sentiments of self-worth.[33,34] Individual item scores are added together to provide a total RSES score ranging from 0 to 30. Scores <15 indicate probable self-esteem issues, whereas scores 15–25 indicate average self-esteem and scores 26–30 indicate high self-esteem.

State and Trait Anxiety Inventory

Spielberg *et al*.(1970) discovered the State and Trait Anxiety Inventory and the Turkish adaptation and standardization of State-Trait Anxiety, developed by Necla Öner and Ayhan Le Compte. The inventory includes two separate scales consisting of a total of 40 items. The State Anxiety Inventory allows the individual to describe how he or she feels at a certain moment and under certain conditions, and to answer them by taking into account their feelings about the situation they are in; the Trait Anxiety Scale, on the other hand, requires the individual to describe how he or she usually feels.[35] In both scales consisting of 20 statements, there are four answer options, and the weight values of each option vary from 1 to 4. The total score obtained from each scale varies between 20 and 80. An elevated anxiety level is indicated by a high score of the scale.[36]

Table 1: Descriptive data of the participants

	n (%)
Marital status	
Single	19 (19.0)
Married	81 (81.0)
BMI (kg/m^2)	
Healthy weight	14 (14.0)
Overweight	61 (61.0)
Obesity Class I	17 (17.0)
Obesity Class II	8 (8.0)
Education status	
Primary school	43 (43.0)
Middle school	49 (49.0)
High education	8 (8.0)
Employment status	
I am not working	84 (84.0)
I am working	16 (16.0)
Monthly ıncome	
Low	9 (9.0)
Middle	68 (68.0)
Good	23 (23.0)

BMI: Body mass index

Statistical analysis

All the data were entered IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp.). The frequency and percentage tests were applied in demographic information, and minimum, maximum, mean value, and standard deviation tests were applied in the descriptive information of the scales in the analysis of the data. Parametric tests were used since the scales showed normal distribution. To compare more than two independent groups, the one-way analysis of variance (ANOVA) test was utilized. A multiple linear regression model was applied to determine the Pearson correlation and effect levels to determine the relationship between the scales. The results were evaluated at the 95% confidence interval, and the significance level of $P < 0.05$ was considered.

Results

The ages of the participants ranged from 50 to 89 years (60.94 ± 8.4). One hundred participants completed the questionnaires [Table 1].

When the results of the applied scales are evaluated, the total values of the BDS range from 0 to 63, with an average of 16.5 (±17.5) points. Participants are at an average level of mild depression. The values of the eating attitude scale range from 8 to 105, with an average of 43.97 (±37.4) points. Since the cutoff point of the scale is 30, the participants have an eating disorder on average. The total values of the self-esteem scale range from 15 to 40, with an average of 23.3 (±5.3) points. The total values of the State Anxiety Scale range from 20 to 71, with an average of 39 (±8.5) points. The total values of the Trait Anxiety Scale range from 20 to 67, with an average of 48.3 (±9.98) points [Table 2].

ANOVA analyses were performed to compare the data. There was no significant difference between the results obtained from the eating attitudes and the BMI ($P > 0.05$) when compared the scale scores of the depression and anxiety scale subdimensions of state anxiety and trait anxiety to BMI was no significant difference ($P > 0.05$).

Pearson correlation analysis was applied to examine the relationship between the data [Table 3]. There was no significant difference between the State Anxiety Scale and the EAT-40 ($P > 0.5$). Conversely, there was a strong positive correlation between the Trait Anxiety Scale and the eating attitude scale ($r = 0.520$; $P < 0.01$). In other words, as the Trait Anxiety Score increases, the eating attitude score also increases. There was a moderate negative correlation between the BDS and the eating attitude scale ($r = –0.412$; $P < 0.01$). As the depression score increases, the eating attitude score also decreases. There was a moderate negative correlation between the Self-Esteem Scale and the Eating Attitude Scale ($r = –0.326$; $P < 0.05$). While the self-esteem score increases, the eating attitude score decreases.

There was a high positive correlation ($r = 0.936$; $P < 0.05$) between the Self-Esteem Scale and the Trait Anxiety Scale and a moderate negative correlation ($r = –0.416$; $P < 0.05$) between the BDS. There was no significant correlation between the BDS and the anxiety scale subdimensions of Trait Anxiety and State Anxiety Scale and BDS ($P > 0.05$).

In Table 4, multiple linear regression analysis was applied to reveal the extent to which participants' trait anxiety, Beck depression, and self-esteem scale scores predicted the eating attitude scale. Accordingly, there is a significant relationship between trait anxiety, Beck depression, and self-esteem scale and food intake scale ($F[4\text{-}95] = 19.127$; $P < .01$). Trait anxiety, Beck depression, and self-esteem scale scores explain 44.6% of the eating attitude scores. According to the standardized regression coefficients, the relative importance of the predictor variables on the eating attitude score is trait anxiety ($\beta = 0.564$), Beck depression ($\beta = –0.396$), and self-esteem ($\beta = 0.042$). When the significance levels of the regression coefficients are examined, it is seen that Trait Anxiety Scale ($P < 0.01$) and BDS ($P < 0.01$) variables, which are predictive variables, are significant predictors of eating attitude.

Discussion

Menopause includes difficult psychosocial processes for women. During this period, every woman's eating habits, health, quality of life, and mental well-being are affected by menopause. In our study, the relationship between eating attitude and psychosocial data was examined. Eighty-one percentage of the participants were married and 19% were divorced. Duç[37] reported that 82% of the women

Table 2: Descriptive statistics of scales

	n	Minimum	Maximum	Mean (±SD)
BDS	100	0.00	63.00	16.4800 (±17.51160)
EAT-40	100	8.00	105.00	43.9700 (±37.38753)
RSES	100	15.00	40.00	25.3200 (±5.28936)
State Anxiety Scale	100	20.00	71.00	39.0000 (±8.48647)
Trait Anxiety Scale	100	20.00	67.00	48.3000 (±9.97725)

SD: Standard deviation, BDS: Beck Depression Scale, EAT: Eating attitude test, RSES: Rosenberg Self-Esteem Scale, SD: Standard deviation

Table 3: The relationship between participants' eating attitude and mood scales

	EAT-40	
	R	***P***
Trait Anxiety Scale	0.520	0.000**
State Anxiety Scale	−0.017	0.868
BDS	−0.412	0.000**
Self-Esteem Scale	−0.326	0.001*

*P<0.05, **P<0.01. EAT: Eating attitude test, BDS: Beck Depression Scale

participating in the study were married and 21 of them were divorced. Gündüz[38] determined that 71.0% of the women in the study were married and 16.0% of them were single. In our study, 84% of the participants are not working and 16% are working. Oskay[39] reported that the working rate of women was found to be 28.3%. Our results showed parallelism with the literature. In this age group, it is normal to have a low working rate due to the fact that the majority of women are married and their average age is high. Only 8% of the women in our study were graduates of higher education. In Fakili's[40] study, this rate was 58%, in Duç's[37] study, 28.9% were college or university graduates and 2.3% were postgraduate or doctoral graduates. According to TUIK data, as a result of the increase in literacy rates every year and education campaigns for women, the level of education is as expected in the studies.[41]

When the income levels of the women participating in our study were examined, 23% of them were good. In the study of Duç,[37] this good rate was 6%. It is assumed that this difference may be due to the participation of the participants from different regions. When the BMI values of the participants in our study were examined according to the WHO classification, 61% were slightly obese, 17% were 1st degree obese, and 8% were 2nd degree obese. In the study of Fakılı,[40] 47% were found to be slightly obese, 27% to be 1st degree obese, and 8% to 2nd degree obese. In the study of Gümüşay and Erbil,[42] 41.6% were slightly obese, 29.9% were 1st degree obese, and 2% were 2nd degree obese. High BMI values were detected in women in this period; it is predicted that it is caused by high average age, hormonal changes, and inactivity.

Emotional eating is a tendency of eating behavior that develops in response to and in response to moods such as depression, anger, and anxiety.[24] Positive (joy and happiness) and negative (fear, stress, and depression) emotional stimuli have an effect of 30% on appetite, and it has reported that their effect on reducing appetite is can be reached 48%.[43,44] Ünsal *et al*.[45] reported a positive relationship between eating attitudes and depression. Similarly, Linde *et al*.[46] showed a relation between depression and binge eating disorder. On the contrary, in our study, for the examination between eating attitudes and depression levels, it is found a moderate negative correlation among the BDS and the eating attitude scale (r = –.412; P < 0.01). In other words, while the depression score increases, the eating attitude score decreases. The reason for this difference is assumed to be due to the different demographic characteristics of the sample groups. When the relationship between self-esteem and anxiety levels is examined, there is a high level of positive correlation between the self-esteem scale and the Trait Anxiety Scale (r = 0.936; P < 0.05). In other words, as the Trait Anxiety Score increases, the self-esteem score also increases. When we look at the literature, Özcan *et al*.[47] found a high level of relationship between self-esteem and anxiety level in their study on adolescents and young adults. The results of our studies are similar although our sample group is different. When the relationship between the eating attitude and anxiety levels of my participants was examined; there is a strong positive correlation between the Trait Anxiety Scale and Eating Attitude Scale (r = 0.520; P < 0.01). As the Trait Anxiety Score increases, the eating attitude score also increases, and as the anxiety levels of the participants increase, so do the eating disorders. Demir[48] found a positive relationship between eating attitudes and anxiety levels among adolescents. Although our sample group was different, similar results are the result of the existence of a relationship between eating disorders and anxiety. The relationship between the eating attitude of my participants and their self-esteem was examined and there was a moderate negative correlation between the Self-Esteem Scale and the Eating Attitude Scale (r = –0.326; P < 0.05). While the self-esteem score increases, the eating attitude score decreases, and the self-esteem of the participants increases, the eating disorder decreases. Tanrıverdi *et al*.[49] found a statistically significant relationship between the high school students self-esteem levels and

Table 4: The effect of anxiety, Beck depression, and self-esteem scale scores on eating attitude scale scores

Predicted	Predictor	*B*	SE_B	*B*	*T*	*P*
Eating attitude	Constant	−18.590	30.848		50.600	0.556
	Trait Anxiety Scale	2.115	0.390	0.564	5.424	0.000
	BDS	−0.846	0.164	−0.396	−5.162	0.000
	Self-respect	0.298	0.726	0.042	0.410	0.682
R=0.668	R^2=0.446		$F_{(4\text{-}95)}$=19.127, P=0.000			

SE: Standard error, BDS: Beck Depression Scale

their eating attitudes. Moreover, when the relationship between the depression level of my participants and their self-esteem was examined; there was a moderate negative correlation between the self-esteem scale and the BDS (r = –0.416; P < 0.05). As the depression score increases, the self-esteem score decreases. On the other hand, Gündüz (50) did not find a relationship between self-esteem levels and depression levels in menopausal women in his study.

Conclusion

There is a negative correlation between eating attitude and depression; conversely, there is a positive relationship between self-esteem and trait anxiety. Depression, anxiety, nutritional obsessions, and low self-esteem can be seen in women with menopause, and there are relationships among these.

Menopausal women should be evaluated and counseled by the nearest health institution in terms of their basic needs during this period. It can be suggested that there should be continuing education programs in a way that will ensure that menopause is perceived as a change and that women participate in these programs.

Public education centers should emphasize healthy eating. Women should be followed not only during pregnancy but also during menopause, which is one of the important nodes of the life cycle. Informative training should be given to women before, during, and after menopause, and they should be followed up continuously. Regular training should be done in the Women's Health Center. Brochures relating to these should be prepared and distributed. Today, modern methods and treatment perspectives for menopause include cardiology, nutrition and diet, psychiatry and physical therapy, gynecology and obstetrics, and multidisciplinary. It should not be forgotten that the menopause period requires a multidisciplinary approach.

Patient informed consent

Informed consent was obtained.

Ethics committee approval

Ethics Committee Approval for the study was received from Üsküdar University Non-Interventional Research Ethics Board on 31.12.2020 (No: 61351342/2020-634).

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Conflicts of interest

There are no conflicts of interest to declare.

Author contribution subject and rate

- Aleyna ÖZKAN (%15): Data acquisition, interpretation of data for the study.
- Şeyma ÇAYIRCIOĞLU (%15): Data acquisition, interpretation of data for the study.
- İlke KARAGÖZ (%15): Collection of review of literature, wrote the manuscript.
- Rümeysa Rabia KOCATÜRK (%15): Collection of review of literature, wrote the manuscript.
- Öznur Özge ÖZCAN (%20): Conception/design of the work, help in data analysis and wrote the manuscript.
- Mesut KARAHAN (%20): Guided in developing the extent of the study and contributed to the manuscript with his critiques.

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Original Article

The Impact of Perceived Stress on Risk Evaluations among Health-Care Students during Coronavirus Disease-2019 Outbreak

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Abstract

Aims and Objectives: Perception has an important role in managing crisis situations such as pandemics. While studies have been conducted on the risk and stress perceptions of health-care workers, there has not been any study on the stress and risk perceptions of health science students who have not yet started this profession, which was investigated herein. **Materials and Methods:** Participants (n = 225) reported their physiological changes, the level of perceived stress (PSS) caused by the coronavirus disease-2019 (COVID-19) outbreak, and the evaluations of the risk perception through questionnaire form. Two cut-off scores of the PSS-14 were calculated as low (<M-SD), moderate (>M-SD and <M + SD), and high level (>M + SD) of perceived stress. The correlation between the PSS-14 and risk perception scores was analyzed using Spearman's rho correlation coefficient. The Wilcoxon Signed Rank test was used to evaluate pairwise risky situation comparisons. Two logistic regression was conducted to test the association between PSS-14 scores and appetite routine. **Results:** Mean PSS was higher among female students. The participants with a high level of perceived stress have a higher difference between the own risk perception and own risk perception referred to others, and there was a difference between own and own referred to others in the items of risk perception for shaking hands, prayer room, protection against disease, and protection against COVID-19 virus. **Conclusions:** Finally, people's perception of risk could be biased regarding their perceived stress level, and this may lead to not make the right judgments for the risky decisions.

Keywords: *Coronavirus disease-2019, health care students, pandemic, perceived stress, risk perception*

Introduction

On December 31, 2019, 27 cases of pneumonia of unknown etiology were detected in Wuhan City, Hubei Province, China.[1] Wuhan is the most populous city in the center of China with a population of over 11 million. It is reported that patients had clinical symptoms such as dry cough, shortness of breath, and fever. The causative agent of the disease was identified from the throat swab samples run by the Chinese Center for Disease Control and Prevention on January 7, 2020, and later called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses in the wake of an outbreak of pneumonia of unknown cause in Wuhan city, China.[2,3] Furthermore, another diagnose was made by the detection of bilateral lung infiltrates on tomography images. Some patients had shown various fatal complications such as organ failure, septic shock, edema, severe pneumonia, and Acute Respiratory Distress Syndrome (ARDS).[4-6] The WHO global health emergency declared China's coronavirus disease-2019 (COVID-19) epidemic on February 11, 2020, as the International Public Health Emergency, which poses a high risk for countries with vulnerable health systems. The emergency committee advised to prevent the spread of COVID-19 with preventions such as early detection, isolation, rapid treatment, and restriction on people's contact with each other may be useful protection for controlling the disease.[7] According to the WHO recommendation, governments took precautions to prevent contamination for public health. Authorities in Turkey recommended the public to minimize

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face-to-face interaction and socially isolate themselves for preventing the spreading of virus almost 1.5 years.

The sudden and unexpected situations caused some psychological reactions among people. It is known that perception is very important for these unexpected situations, as well as, there are individual differences in the perceived stress levels in society. People who experienced fear and anxiety may be more tending to think negatively, and their risk perceptions can be exaggerated.[8] It has shown that the psychological consequences of the previous outbreak (SARS-CoV-1 in 2002) are more evident in health-care workers.[9,10] Furthermore, there are recent studies indicated that health-care workers reported a higher risk perception and higher anxiety compared to general population.[11] The researchers suggested that the other demographics such as psychological state, sex, and living area are less related to the risk and stress perceptions. Taken all together, there has not been any study on the stress and risk perceptions of health science students who have not yet started this profession, which was investigated herein.

In this study, we used two self-report surveys. We used the Perceived Stress Scale with 14 items (PSS-14) which created by Cohen[12] in Turkish version[13] to determine the perceived stress caused by the COVID-19 outbreak. It is known that increased perceived stress events are associated with more negative perceptions, and lead to depression, for this reason, we preferred to use PSS-14 with adding "COVID-19 related" before the evaluation of all items. Measuring and determining the risk perception is substantial for risky individuals, which have a negative bias on information processing.[14] Since the pandemic is a recent phenomenon and a proper task has not yet been developed to assess the risk perception for the pandemic situations. We were inspiring Knoll *et al*. and used the risk perception task without social influence effect and modified the risky situations related to COVID-19.[15] To evaluate risk perceptions of the participants, we showed some photographs to state the situations that might pose a risk, related to the COVID-19 outbreak. The participants supposed to evaluate their own risk perception and others' risk evaluation for all photos. In this way, we hypothesized to find a difference between their risk evaluation and their risk perception referred to others for the pandemic process. Moreover, we examine whether there is a relationship between a self-report perceived stress of the participants and risky situation evaluations. As the perceived stress level increases, we expect to find the difference between their own and others' risk assessments to widen. Therefore, the purpose of this study is to measure the perceived stress in health sciences students and to evaluate their risk evaluations according to perceived stress. Furthermore, the association between perceived stress and self-report physiological and psychological behaviors such as sleep quality and appetite was also examined.

Materials and Methods

This study was performed in line with the principles of the Declaration of Helsinki, as revised in 2013. Our study protocol was approved by the Uskudar University Ethics Committee on non-Interventional Research Ethics (with the number 61351342-2020-0016and date 04.05.2020). All respondents provided written informed consent. We conducted the study on the different departments of faculty of health science students to investigate their COVID-19-related perceived stress and perception of risk (n = 225). Faculty of health science consists of different departments such as perfusion, midwifery, child development, and neuroscience. The targeted population has to spend 1 or 2 years of their education in university hospitals as a clinical course before their graduation. We selected the group who has not begun the clinical course in the hospital to control the perception of stress and risk related to COVID-19. Participants with access to internet connection, able to write and read in Turkish, and willing to give informed consent were included. We conducted our study using an online survey from March 30 to April 30.

On the date March 18 with the guidance of authorities, dialog education replaced to online education classes for the protection and prevention of COVID-19. We announced our study on our online lessons and posted on social platforms for whom in our inclusion criteria. Our surveys were completed on free online survey platform using Google Docs (https://docs.google.com/forms/u/0/).

To get some background information on participant's demographics gathered from the survey included gender, level of education, some information about health statuses such as chronic illness, heart failure, or respiratory diseases, constantly used drugs and current location. In this study, we used the PSS-14 which is consisted of 14 questionnaires created by Cohen[12] to assess the degree to which the participant has appraised the situations in their life as stressful over the past month. It is validated in Turkey by Eskin and Demirkiran. The scale has two factors; factor I: insufficient self-efficacy perception and factor II: stress/discomfort perception.[13] Participants rated items on a 4-point Likert scale ranging from 1 "Never" to 4 "Very often" ranging from 1 to 56 with higher scores indicating greater perceived stress. PSS-14 has some reverse scoring items, which are positively stated items with the questions numbered 4, 5, 6, 7, 9, 10, and 13 and the total score consists of summing the scores across all 14 items. PSS-14 has two subscales named as Factor I: Insufficient self-efficacy perception and Factor II: Stress/discomfort perception. The items numbered 4, 5, 6, 9, 10, and 13 are considered as Factor I, and others as Factor II. This test is suitable to administrate mailed out or over the phone with the average response time 8–10 min. Moreover, some questions are about the difference in their lifestyle during the COVID-19 outbreak. For example, we added

some items whether they had physiological changes such as a disturbance in their sleep quality and they have to scale to the level of anxiety (between 1 and 10) about developing CoV-like symptoms tomorrow. Another item was related to their self-report about the risk of infecting with COVID-19 with a short answer. In addition, other items are about if they were avoided to being in crowded places before the officials announced the outbreak in the country. These additional items were developed for this particular research based on previous studies, and the purpose of doing this was to obtain additional information about COVID-19. Besides, we were inspiring the risk perception task created by Knoll *et al*. with 15 items without social influence effect.[15] We prepared some photographs related to pandemic to manipulate risky situations that may cause infection. All questions had two sections. One for own risk evaluation for the risky situations between a scale 0 and 10 and other with a question "what do you think about others risk evaluation for this risky situation' to consider own risk evaluation referred to others. The items of the form and mean values and standard deviations for risk evaluation are shown in Table 1.

Statistical analysis

The independent samples *t*-test was used to compare the mean scores of perceived stress scale between female and male participants. Two cutoff scores of the PSS-14 were calculated using the mean score (M) and standard deviation (SD) of the participants to divide into three groups; low (<M-SD), moderate (>M-SD and <M + SD), and high level (>M + SD) of perceived stress. Furthermore, we calculated difference scores between the subjective and others risk perception by subtracting the others' scores from the subjective ones for 15 risky situations mentioned above. Then, one-way analysis of variance (ANOVA) was used to determine whether the evaluation of 15 risky situations differed based on the three PSS-14 groups and whether the difference between the subjective and others' risk perceptions differed based on the PSS-14 scores. Moreover, the correlation between the PSS-14 and risk perception scores was analyzed using Spearman's rho correlation coefficient. Furthermore, total scores were computed for risky situations by summing up the scores of 15 risky situations, and the mean scores were compared between subjective and others risk perception using paired *t*-test. Since the risk perception scores were not normally distributed, the Wilcoxon Signed Rank Test was used to evaluate pairwise (subjective vs. others) risky situation comparisons. Two logistic regression was conducted to test the association between PSS-14 scores and low sleep quality and between PSS-14 scores and appetite routine. Statistical analyses were conducted by the SPSS (IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp). $P < 0.05$ was considered statistically significant.

Results

All the participants were students in health-related departments and aged between 18 and 25 years (34% of the participants were ergo therapy, 32.4% child development, 28.9% perfusion, and 4% neuroscience). Among the participants, 84.4% were females and 15.6% were males. About 77% of the participants were from urban areas.

Among the participants, 76.9% reported that they had some changes in their sleep quality and 54.2% indicated that they had some problems in their appetite during the ongoing pandemic. 55.1% of the responders specified that they would be "highly" or "extremely" worried if they had some CoV such as symptoms tomorrow. 23.6% of the participants stated that they were "always" or "highly" worried about being infected by CoV within last week. Among the participants, 10.2% believed that they would be infected "high probability" or "absolutely" by CoV in the next month [Figure 1]. Nearly 72.4% of the participants regarded that the other people in the society would be infected "high probability" or "absolutely" by CoV in the next month [Figure 2]. A Wilcoxon Signed Rank Test indicated that there was a significant difference between

Table 1: Description items of risk perception with mean±standard deviation according to the photos that presents situations may cause COVID-19 outbreak

Evaluation of risk perception	Mean±SD	
Situations	Own risk perception	Evaluation of others risk perception
Shaking hands is safe	7.4±3.523	7.12±3.141
Online education will have a positive effect on my education life	4.59±2.676	4.8±2.617
My religion highly provides to protect me against COVID-19 disease	6.37±2.99	6.54±2.687
I can change my prayer room for my health	7.6±3.065	6.74±2.956
I can protect myself against the disease caused by the corona virus	7.06±2.338	6.5±2.409
Science will rush to find COVID-19 cure	7.19±2.213	6.73±2.238
The quality of internet information is high to learn about outbreak	6.36±2.496	6.56±2.467
Hospitals are accessible and safe for patients care during COVID-19 outbreak	5.72±2.917	5.89±2.771
Taking public transport is safe during outbreak	5.12±4.174	5.15±3.945
It is safe to cuddle with friends during the coronavirus disease	5.39±3.984	5.37±3.785

Evaluation of risk perception between 0 and 10 score. SD: Standard deviation

the probabilities of themselves and others being infected in the next month ($Z = -11.516$, $P < 0.001$). About 80.4% of the responders mentioned that they avoided going to crowded places before the quarantine started. Among the participants, 67.1% reported cleaning their hands "always" or "often" after touching something, which might cause contamination.

The PSS-14 mean score of the participants was 37.29 and the standard deviation was 6.32. The mean scores of two subscales were as following: insufficient self-efficacy: M = 18.78, SD = 3.46 and stress/discomfort perception: M = 18.52, SD = 3.89. The mean score of PSS in women (M = 38.09, SD = 6.16) was significantly higher than in men [M = 32.94, SD = 5.40; $P > 0.001$; Figure 3]. Furthermore, female (insufficient self-efficacy: M = 19.07, SD = 3.73; stress/discomfort perception: M = 19.03, SD = 3.84) has also higher scores compared to male (insufficient self-efficacy: M = 17.20, SD = 3.58; stress/discomfort perception: M = 15.74, SD = 2.95) for the two subscales of PSS-14, but this result was not significant.

According to the one-way ANOVA, there was a significant difference in online education scores among PSS groups (F (2, 222) = 2.993, $P < 0.05$). A Tukey *post hoc* test revealed that the participants with a low level of PSS evaluated the online education riskier compared to a moderate level of PSS during the pandemic ($P < 0.05$). There was no statistically significant difference among other PSS groups or risky situations. Moreover, there was a significant finding for the difference scores of prayer rooms among PSS groups (F (2, 222) = 3.216, $P < 0.05$). Pairwise *post hoc* comparisons showed that the participants with high level of PSS have more difference between the subjective and other risk perception for the prayer rooms compared to moderate level of PSS during pandemic ($P < 0.05$). There was a significant finding for difference scores of crowded places among PSS groups (F (2, 222) = 3.59, $P < 0.05$). A Tukey *post hoc* test indicated that the participants with low level of PSS have more difference between the subjective and other risk perception for the crowded places compared to moderate level of PSS during pandemic ($P = 0.06$).

Figure 4 shows the items that participants reported own risk perception and own risk perception referred to others.

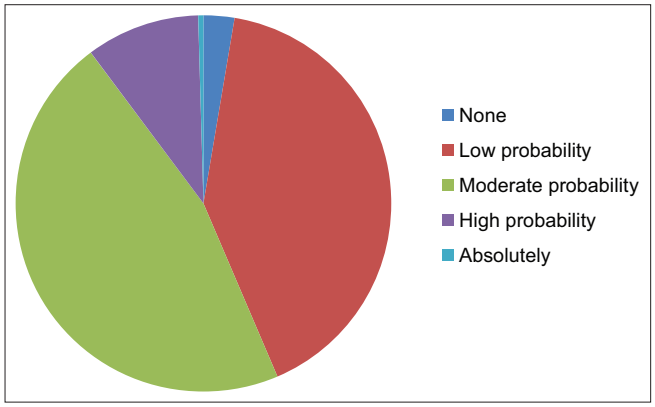

Figure 1: The participants' risk evaluations of the probability of own being infected in the next month

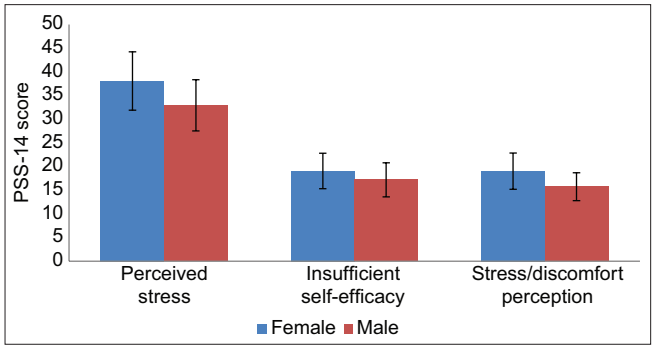

Figure 3: The mean scores and standard deviations for the PSS-14 score and two subscales in females and males. Factor I: insufficient self-efficacy perception and Factor II: stress/discomfort perception.

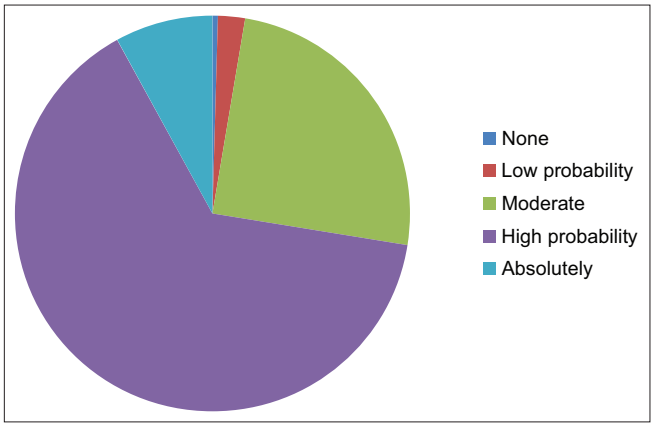

Figure 2: The participants' risk evaluations of the probability others being infected in the next month

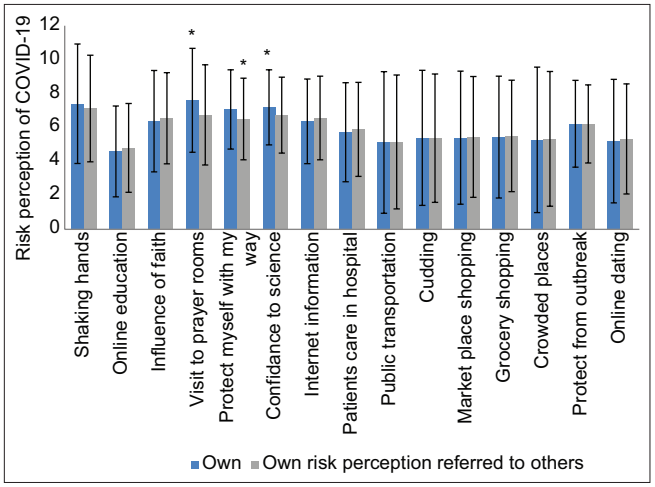

Figure 4: The mean scores and standard deviations for own and own risk perceptions referred to others. A logistic regression showed a significant association between PSS scores and alterations on sleep quality (B = −0.083, *$P < 0.05$) and appetite (B = 0.067, *$P < 0.05$). In the participants with an increasing level of perceived stress was associated with alterations on sleep quality and appetite routine

Pairwise comparisons of risky situations (subjective vs. others) showed that there was a significant difference between the subjective and others risk perception for shaking hands ($Z = -2.175$, $P < 0.05$; subjective: M = 7.40, SD = 3.52, others: M = 7.12, SD = 3.14; prayer room ($Z = -5.678$, $P < 0.01$; subjective: M = 7.60, SD = 3.06, others: M = 6.74, SD = 3), protection against disease ($Z = -4.569$, $P < 0.01$; subjective: M = 7.06, SD = 2.34, others: M = 6.5, SD = 2.41), and protection against COVID-19 virus ($Z = -4.087$, $P < 0.01$; subjective: M = 7.19, SD = 2.21, others: M = 6.73, SD = 2.24).

Moreover, there was not any significant difference between the total scores of subjective and others risk perception. There was not any significant correlation between difference scores (subjective vs. others) of 15 risky situations and PSS scores after correcting the *P* values for multiple comparisons.

A logistic regression showed a significant association between PSS scores and alterations on sleep quality ($B = -0.083$, $P < 0.005$) and appetite ($B = 0.067$, $P < 0.005$). Increased perceived stress was correlated with alterations in sleep quality and appetite routine.

Discussion

The aim of the current study was to investigate the perceived stress in health sciences students and to measure their evaluations of risky situations according to perceived stress. In the findings, the PSS was found higher in female students compared to men. The participants with a high level of perceived stress have a higher difference between the own risk perception and own risk perception referred to others. Moreover, there were differences between own and own referred to others in the items of risk perception for shaking hands, prayer room, protection against disease and protection against COVID-19 virus.

This paper presents that there are some significant differences on COVID-19-related perceived stress and risk perception on health-related students. The health-related students reported that the most changed physiological processes based on self-report were related with sleep quality and routine appetite during the pandemic. The results showed that these physiological changes can be explained with alterations in perceived stress, and the increased level of perceived stress was associated with big changes in physiological processes. Besides, the students reported that "highly" or "extremely" worried if they had some CoV-like symptoms tomorrow. An important finding was some of the participants reported that they are "always" or "highly" worried about being infected by CoV within the last week. The score was very high and indicated that the health-care students were highly worried during the pandemic. One of our finding was about the perceived stress score (PSS-14), the stress level was more significant on female than men were. Studies showed that[16] PSS-14 scores were moderately correlated with depression scores. For this reason, young and women health-related groups need more attention. Researchers showed that, during COVID-19, there are similar results about anxiety and perceived mental health needs on different societies.[17] Furthermore, there is similar study, which was written during and after SARS outbreak to investigate the effect of stress among survivals. Chua *et al*. showed the increase of general stress and negative physiological effects during outbreak among health-care workers. In our study, we showed that not only health-care workers but also health-related students had general stress and negative psychological effects during outbreak.[18] As it is known that health-care workers are very essential and important, this may lead to a difference in their preference for health-related departments.

Lee *et al*. studied on SARS survivors during the outbreak and 1 year after, to evaluate stress and physiological distress. Their findings showed that the survivals still had elevated stress levels and psychological distress 1 year after SARS. In addition, they reported participants showed high levels of depression, anxiety, and posttraumatic symptoms. An alarming proportion (64%) scored with a psychiatric morbidity.[19] Both SARS and COVID-19 viruses presented a global epidemic threat but has spread rapidly around the world with the cases more than 1,290,000 with over 76,000 deaths. Considering these results, we think that, for the COVID-19-related high-stress level, authorities should take preventions for mental health well for COVID-19 survivors.[20]

In our study, there were significance on avoiding going to crowded places before the quarantine started and washing hands "always" or "often" after touching something could be protective for COVID-19. Kim and Kim reported for Middle East Respiratory Syndrome (MERS) outbreak responders believed that washing hands with soap and water and keeping away from the crowded places were protective for MERS[21] besides Smith reported the same beliefs and responses for SARS outbreak[22]. Our participants reported very similar responses for COVID-19. Our results are coherent to SARS and MERS risk perception.

Another interesting result was about the relationship between the beliefs about the online education and perceived stress level. Participants with low score of PSS-14 evaluated the quality of education will decrease with online education compared to the participants with moderate score of PSS during pandemic. This could be interpreted as students with low perceived stress are interested in and worried about their education rather than their health-related issues. Moreover, the participants with high level of PSS and not moderate level believe that they can change more the prayer rooms for their health compared to other people in the society. Besides, participants with low level of PSS and not moderate level

believe that the other people in the society will avoid more being crowded places compared to them. When all results evaluated together, it can be interpreted that if the perceived stress get higher, health-related students are more likely willing to change their habits in daily life.

Our results showed that the health-related students have a belief that the other people in the society would be infected in with a "high probability" or "absolutely" by CoV in the next month. Furthermore, pairwise comparisons of risky situations showed that there was a difference between own and own referred to others in the situations of risk perception for shaking hands, prayer room, protection against disease, and protection against COVID-19 virus. Overall, participants believe that their behaviors are less risky than others' behaviors related to COVID-19. Based on this finding, we can speculated that the health-care students believe that own risk behavior is more accurate than others' behavior. According to the social influence, it is not consistent with our results, which regarded due to the pursuit of acceptance by others as well as the belief that others' behavior is more accurate than our own.[23] This is an unexpected finding and might be related with the increase in conformity and more confidence in their own perception of a situation though their young age. Otherwise, this result might be interpreted with error management theory.[24] According to his theory, the perceptual judgments under uncertainty can contain errors or biases. Error management biases can be observed in both nonsocial and social domains.[25] COVID-19 is an uncertain and completely new pandemic situation. However, none of the available models reflects the symptoms of the disease and the outbreak is a completely new situation, no one has experienced this situation before. We can interpret that, in such cases, people's perception of risk can be biased, and this may lead to not make the right judgments for the risky decisions.

The present study has some limitations. First, only students who can reach to the Internet and speak Turkish participated to the study. Second, the proportion of male and female participants are not equal, more women participants joined to the present study. Indeed, there are more women students in the health-related majors compared to men. The unequal distribution of study population can be found in the sample itself. Moreover, the sample of the study consists of the health-related students, so the results cannot be generalized to the whole population. The perceived stress, belief to the other people's behaviors may be different in the other groups like nonhealth-related students.

Conclusions

Unfortunately, there is no definite antiviral therapy for COVID-19 yet. The recommendations for the personal guarding rules for health care and community are hypnotized to change the progression of the clinical outcomes of the COVID-19 outbreak. This present study, as well as an outbreak report of actual evaluation of COVID-19 by health-related students, shows that people have perceived needs to deal with their mental health difficulties. There is a need to intensify the awareness program and address the mental health issues of people during this COVID-19 pandemic.

Consequentially, coordinated mental health services, specific rehabilitation applications, and improved follow-up during and after outbreak should be delivered. In addition, increased stress could lead to the risk of mood and stress-related disorders. Besides, we offer that an urgent strategic planning and coordination are required for the confidence of health-care workers around the world, otherwise, the number of students preferring to health-related departments could decrease, which could lead to problems in public health services.

Patient informed consent

Informed consent was obtained.

Ethics committee approval

The ethics committee approval has been obtained from the Uskudar University noninterventional research ethics committee (61351342/2020-5).

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Conflict of interest

There are no conflicts of interest to declare.

Author contribution subject and rate

- Zozan Guleken (50%) designed the research, data collection, and wrote the whole manuscript.
- Bernis Sutcubasi (50%) contributed with comments and data analysis.

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Original Article

CYP2C9 Genotype and Phenotype Profile of Cross-Country Skiing Athletes

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Abstract

Aim: Most tissues in the body contain cytochrome P450 enzymes, which play an important role in many functions, especially metabolizing drugs and other xenobiotics. The CYP2C9 gene in humans codes for an enzyme called CYP2C9. The goal of this study was to figure out the genotype and allele distributions of the *CYP2C9* gene rs1799853 (CYP2C9*2), rs1057910 (CYP2C9*3), rs28371686 (CYP2C9*5) and rs28371685 (CYP2C9*11) polymorphism in our cohort study. **Materials and Methods:** For this purpose, 19 cross-country skiing athletes took part in our research. After DNAs were extracted from buccal epithelial cells, real-time polymerase chain reaction was used to genotype them. **Results:** When we looked at the genotype distributions, we found that, the CC genotype was higher than CT and TT genotype for CYP2C9*2. For CYP2C9*3, the AA genotype was higher than the AC genotype and no CC genotype was found. Besides for the CYP2C9*5, only the CC genotype was found. In addition, only the CC genotype was found for CYP2C9*11. For The genotypic and predictive phenotype distribution of *CYP2C9* polymorphisms, it was determined that 11 athletes (57.9%) were *1/*1 (extensive metabolizers), and 5 athletes (26.3%) were *1/*2 (intermediate metabolizers). As a poor metabolizer, one athlete *2/*2 (5.3%) and two athlete *2/*3 (10.5%) were determined. **Conclusion:** This study is the first study investigating the relationship between the CYP2C9 polymorphism in Turkish cross-country skiing athletes.

Keywords: *Cross-country skiing athletes, CYP2C9, genetics, polymorphism, sports*

Introduction

Athletic performance is the combination of an individual's innate genetic gains and skills acquired under the influence of environmental factors.[1] The determination of gene variants that affect athletic performance, molecular pathways governed by those genes, and predispositions to better athletic performance are all part of sports genetics research.[2,3]

Cytochromes are a varied groups of proteins that share only a few characteristics. They are found in almost every type of life, including bacteria, protozoa, yeasts and all higher species. Most cytochromes are proteins that contains heme group involved in electron transfer to produce ATP.[4] Cytochrome P450 (CYP) is known a group of monooxygenases and is distinct family of cytochromes. CYPs are a superfamily of enzymes that contains heme as a cofactor that functions as a monooxygenase.[5] Steroids, fatty acids, and xenobiotics are all oxidized by CYP proteins in mammals. Xenobiotic metabolism takes place in two main stages. The main reaction of the first stage (Phase I) is hydroxylation catalyzed by CYP. In addition, CYP is important in hormone synthesis, degradation and cleansing of various compounds.[6] CYP enzymes involved in active metabolism consist of approximately 99 isoenzymes synthesized from 55 separate gene families.[7] The human genome contains at

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Table 1: Sequences of the TaqMan probe used for genotyping *CYP2C9*2* rs1799853, *CYP2C9*3* rs1057910, *CYP2C9*5* rs28371686, *CYP2C9*11* rs28371685 polymorphisms

qPCR	*CYP2C9 polymorphism*	Sequence, 5'-3'
VIC/FAM	*CYP2C9*2* rs1799853	GATGGGGAAGAGGAGCATTGAGGAC[C/T] GTGTTCAAGAGGAAGCCCGCTGCCT
	*CYP2C9**3 rs1057910	TGTGGTGCACGAGGTCCAGAGATAC[C/A] TTGACCTTCTCCCCACCAGCCTGCC
	*CYP2C9*5* rs28371686	TGCACGAGGTCCAGAGATACATTGA[C/G] CTTCTCCCCACCAGCCTGCCCCATG
	*CYP2C9**11 rs28371685	GATTGAACGTGTGATTGGCAGAAAC[T/C] GGAGCCCCTGCATGCAAGACAGGAG

Table 2: Genotypic and allelic distribution of the *CYP2C9*2* rs1799853, *CYP2C9*3* rs1057910, *CYP2C9*5* rs28371686 and *CYP2C9*11* rs28371685 polymorphisms in the cross-country skiing athletes

CYP2C9*2	**Genotype**			**Allelic frequency**	
	CC	**CT**	**TT**	**C**	**T**
Athlete (19)	12	5	2	29	9
Percentage	63.2	26.3	10.5	76.3	23.7
CYP2C9*3	**Genotype**			**Allelic frequency**	
	CC	**AC**	**AA**	**C**	**A**
Athlete (19)	-	2	17	5	36
Percentage	-	10.5	89.5	5.3	94.7
CYP2C9*5	**Genotype**			**Allelic frequency**	
	CC	**CG**	**GG**	**C**	**G**
Athlete (19)	19	-	-	38	-
Percentage	100	-	-	100	-
CYP2C9*11	**Genotype**			**Allelic frequency**	
	TT	**CT**	**CC**	**T**	**C**
Athlete (19)	-	-	19	-	38
Percentage	-	-	100	-	100

least 57 CYP genes. CYP2 functions are drug and steroid metabolism. There are 13 subfamilies and 16 genes such as *CYP2A6, CYP2A7, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6*.[8,9]

CYP2C9 is an enzyme that in humans is encoded by the *CYP2C9* gene. *CYP2C9* gene is localized on chromosome 10q24.2. The CYP2C subfamily of human liver microsomal CYP enzymes are known to catalyze the oxidation of mephenytoin and to show genetic variability in drug metabolizing enzymes in humans.[10] In excess of 2000 changes have been depicted, and certain single nucleotide polymorphisms (SNPs) have been appeared to generally affect CYP action.[11] Major *CYP2C9* variant alleles result in SNP leading to nonanonymous amino acid changes that differ in only a few residues in the coding region: A cytosine to thymine (C > T) rs1799853 polymorphism at base pair 430, encoding for an Arg144Cys amino acid substitution (*CYP2C9**2). An adenine to cytosine (A > C) rs1057910 polymorphism at base pair 1075, encoding for an Ile359 Leu amino acid substitution (*CYP2C9**3). A cytosine to guanine (C > G) rs28371686 polymorphism at base pair 1080, encoding for an Asp360Glu amino acid substitution (*CYP2C9**5). A cytosine to thymine (C > T) rs28371685 polymorphism at base pair 1003, encoding for an Arg335Trp amino acid substitution (*CYP2C9**11).[12]

The purpose of this study is to analyze the distribution of *CYP2C9* rs1799853 (*2), rs1057910 (*3), rs28371686 (*5), rs28371685 (*11) polymorphisms and phenotype of CYP2C9 enzyme in Turkish cross-country skiing athletes.

Materials and Methods

Nineteen Turkish cross-country skiing athletes participated in the study. Üsküdar University Ethical Committee permission was obtained for study protocol and performed following the principles of the Declaration of Helsinki II World Medical Association WMA 2018. B.08.6. YÖK.2.ÜS.0.05.0.06 /2013/09, date:07.03.201. Before the study, all the participants signed consent forms containing relevant information such as the study protocol and the intended use and evaluation of the results.

Genotyping

DNA isolations from the buccal cells of the athletes participating in the study were performed with a commercially obtained PureLink DNA isolation kit (Invitrogen, Thermo Fisher Scientific, Inc.). Genotyping of the *CYP2C9**2 rs1799853, *CYP2C9**3 rs1057910, *CYP2C9**5 rs28371686 and *CYP2C9**11 rs28371685 polymorphisms were performed using Real-Time polymerase chain reaction on a StepOnePlus (Thermo Fisher Scientific, Inc.) device and Taqman SNP Genotyping Assays genotyping kits according to the manufacturers' protocols (cat. no. 4362691, Thermo Fisher Scientific, Inc.). For a total volume of 10 µl reaction, 5 µl of Genotyping Master Mix (Applied Biosystems, Foster City, CA), 3.5 µl of nuclease-free H2O (Thermofisher, USA), 0.5 µl of genotyping test (Applied Biosystems), and 1 µl of DNA were used. The sequences of the TaqMan Probe used for genotyping are listed in Table 1.

Results

In the *CYP2C9* analysis, genotypes of *CYP2C9**2 was determined in our cohort group that 12 (63.2%) of them had CC, 5 (26.3%) of them CT and 2 (10.5%) had the TT genotype. *CYP2C9**3 was determined that 17 (89.5%) of them had AA, and 2 (10.5%) of them had the AC genotype. No CC genotype was found for *CYP2C9**3. *CYP2C9**5

Table 3: Genotypic and predictive phenotype distribution of the *CYP2C9* polymorphisms in the cross-country skiing athletes

Players	Genotype	Predictive phenotype
1	*2/*3	PM
2	*2/*3	PM
3	*2/*2	PM
4	*1/*2	IM
5	*1/*1	EM
6	*1/*1	EM
7	*1/*2	IM
8	*1/*2	IM
9	*1/*2	IM
10	*1/*1	EM
11	*1/*1	EM
12	*1/*1	EM
13	*1/*1	EM
14	*1/*1	EM
15	*1/*1	EM
16	*1/*2	IM
17	*1/*1	EM
18	*1/*1	EM
19	*1/*1	EM

*EM: Extensive metabolizer, IM: Intermediate metabolizer, PM: Poor metabolizer

was determined that all of them (100%) had CC. No CG and GG genotypes were found for *CYP2C9**5. *CYP2C9**11 was determined that all of them (100%) had CC. No CT and TT genotypes were found for *CYP2C9**11.

When allele distributions were studied, *CYP2C9**2 was observed that the values were 76.3% for C allele and 23.7% for T allele. *CYP2C9**3 was observed that the frequencies were 94.7% for A allele and 5.3% for C allele. *CYP2C9**5 was observed that the results were 100% for C allele and *CYP2C9**11 was observed that the allelic percentage were 100% for C allele. The genotype and allele number distributions of the athletes are summarized in Table 2.

Discussion

High performance in elite athletes improves with environmental factors, training and genetic characteristics.[13] Investigating the effect mechanisms of genetic parameters on athletes contributes significantly to the regulation of athletic performance of athletes. These genetic parameters affect the physiological, psychological characteristics or nutritional metabolism of the athletes.[14]

In the human liver, CYP2C9 is one of the most significant drug metabolizing CYP isoforms. CYP2C9 is a catalytic enzyme that catalyzes the metabolism of a wide range of therapeutically significant medications. Changes in the amino acid arrangement of the CYP2C9 enzyme have been demonstrated to alter its activity and substrate selectivity, as well as the metabolism of medications like warfarin.[15] *CYP2C9**2, *CYP2C9**3, *CYP2C9**5 and *CYP2C9**11 Polymorphisms affect not just the metabolic function of CYP, but also the vulnerability to CYP-related disorders.[16] Clinical trials have been carried out to characterize the contribution of *CYP2C9**2 and *CYP2C9**3 polymorphisms to pharmacokinetic variability in humans, and major effects have been found for a number of drugs.[17]

In our study, the CC genotype was higher than CT and TT genotype for *CYP2C9**2 rs1799853 polymorphism. Also, when we compared the C allele with the T allele, it was found that the C allele was higher in percentage. For *CYP2C9**3 rs1057910 polymorphism, the AA genotype was higher than the AC genotype and no CC genotype was found. At the same time, while comparing the A and C alleles, we discovered that the A allele had a larger percentage. For the *CYP2C9**5 rs28371686 polymorphism, only the CC genotype was found. In addition, only the CC genotype was found for the *CYP2C9**11 rs28371685 polymorphism. When we looked at our court, it was determined that 11 athletes (57.9%) were *1/*1 (EM), and 5 athletes (26.3%) were *1/*2 (IM). As a PM, one athlete was *2/*2 (5.3%) and two athlete were *2/*3 (10.5%). The genotypic and predictive phenotype distribution of the *CYP2C9* polymorphisms in the cross-country skiing athletes are summarized in Table 3.

For the athletes to perform better, metabolisms like vitamin and drug should proceed in proper ways. In which most of the drug metabolism is carried out by CYP2C9. In other words, *1/*1 phenotypes is considered to be an advantage for better athletic performance.

To date, studies including CYP2C9 phenotype and athletes are not enough to speculate on their association. This study is the first study investigating the relationship between *CYP2C9* polymorphism distribution and the predictive phenotype in Turkish cross-country skiing athletes. Therefore, there are not many studies that we can compare our findings. Thus, our work will contribute to the genetic information pool and support other studies in this field.

One of the main limitations of the study is the low number of the participants. Our aim was to analyze the athletes at the same level. That was the reason we conduct the study with the same team athletes, who had the same training programs in our study. Another limitation was that we did not perform CYP2C9 metabolite analysis in our cohort. In further studies, we aim to increase the number of athletes and strengthen our data with metabolite analysis.

Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

Üsküdar University Ethical Committee permission was obtained for study protocol and performed following the principles of the Declaration of Helsinki II World Medical Association WMA 2018. B.08.6. YÖK.2.ÜS.0.05.0.06 /2013/09, date:07.03.2013

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Conflicts of interest

There are no conflicts of interest to declare.

Author contribution subject and rate

- Beste Tacal Aslan(%25): Literature search, data analysis, manuscript preparation, manuscript editing
- Özlem Özge Yılmaz (%20): Literature search, experimental studies, manuscript preparation
- Tolga Polat (%15): Experimental studies, data analysis, statistical analysis
- İpek Yüksel Gözler (%10): Experimental studies
- Muhammed Fatih Bilici (%5): Data acquisition
- Ömer Kaynar (%5): Data acquisition
- Korkut Ulucan (%20): Concept/design of the work, the definition of intellectual content, data analysis, manuscript review.

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Review Article

Is Obsessive–Compulsive Disorder Preventive Against Addiction?

Abstract

Obsessive–compulsive disorder (OCD) is unique among mental illnesses in that its comorbidity with alcohol use disorders (AUD), substance use disorders (SUD), and smoking has been reported to be common in the community but surprisingly less frequent in clinical settings. To better investigate this dual diagnosis, we screened the Medline, PsychInfo, and Scopus databases. We did not apply strict criteria for the selection of articles because this article is a narrative review. Relatively, mild OCD is characterized by a high prevalence of AUD/SUD. Comorbidity becomes less frequent as OCD grows more distressing up to a certain degree of illness severity, above which it rises once more. In contrast, the prevalence of AUD/SUD in anxiety disorders, depression, and bipolar disorder is higher in clinical samples than in the community. The high prevalence of AUD/SUD accompanying OCD in community settings may be accounted for by self-medication, whereas decreasing prevalence in clinical samples may reflect personality traits common among obsessive-compulsive people, such as an elevated sense of harm and risk avoidance. An increase in more severe patients may imply the interplay between impulsiveness and compulsiveness. The distinct symptom dimensions of OCD, such as washing, checking, and having taboo thoughts, may be associated with varying degrees of predisposition to AUD/SUD as well as with different rates for seeking treatment, thus affecting the contradictions in the comorbidity rates of OCD and AUD/SUD. Our search confirms the U-shaped curve model put forward to explain the intricate relationship between OCD and AUD/SUD.

Keywords: *Alcohol use disorder, compulsiveness, impulsiveness, obsessive–compulsive disorder, obsessive-compulsive traits, self-medication, smoking, substance use disorder, symptom dimensions*

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Introduction

It is well-known that substance use, including illicit drugs, alcohol, and tobacco, is exceedingly common among people with psychiatric illness.[1-6] Almost all of the studies done either in clinical or in community samples have revealed a high prevalence of harmful consumption of various substances. Notwithstanding this finding, an exception is obsessive–compulsive disorder (OCD), which has been found to be accompanied by a frequency of alcohol/substance or tobacco use that is similar to or even lower than that of the general population.[7-30]

Indeed, OCD sets a good example of discordant findings between clinical and epidemiological research when both are investigating the same disease. Epidemiological surveys generally denote a frequent co-occurrence of OCD with alcohol use disorders (AUDs), substance use disorders (SUDs), and nicotine use,[31-43] whereas studies conducted in clinical samples[7,9,10,13-19,21-30] have usually failed to show an increased risk in patients with OCD.

Cuzen *et al*.[44] provide a U-shaped curve model as an attempt to designate the relationship between OCD and AUD/SUD. The U-shaped curve model suggests a tripartite pattern characterizing the dual diagnosis. The people who meet the diagnostic criteria for OCD in community studies are commonly afflicted with AUD/SUD as compared with the general population. The patients visiting psychiatric settings for a cure for OCD, although they suffer from a more severe illness, have a lower prevalence of AUD/SUD than community members with OCD. However, the dual diagnosis becomes more frequent again as the OCD becomes more severe and reaches a critical threshold.

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One must ask if the-U shaped curve is unique for OCD. A plethora of studies have shown that anxiety disorders, depression, and bipolar disorder are associated with a high prevalence of AUD/SUD in the community as compared to the general population.[2-4,6,45] Yet, AUD/SUD has a considerably higher prevalence among patients with anxiety disorders, depression, or bipolar disorder who apply to clinics, disproving the U-shaped curve model.[2-4,6,45] Among the mental maladies psychiatrists frequently encounter in their everyday practice, only schizophrenia keeps pace with OCD across epidemiological and clinical studies.[5]

In this paper, we first highlight the evidence supporting the U-shaped curve, which characterizes the comorbidity of OCD with AUD/SUD. Then, we discuss the studies on smoking and OCD. Since smoking is the most common addiction in the world, and, to the best of our knowledge, no paper has reviewed the comorbidity of OCD with smoking, this topic deserves further investigation in a separate section. To explain the U-shaped curve, we suggest a multifaceted model that involves some fundamental aspects of OCD, including self-medication, the interplay between impulsiveness and compulsiveness, obsessive-compulsive traits, such as an increased sense of danger and risk avoidance, as well as symptom dimensions producing a substantially heterogeneous phenomenology.

Materials and Methods

There is no need for ethics committee approval. We searched the relevant English literature in the Medline, PsychInfo, and Scopus databases using the following terms: OCD AND addiction or dependence or substance abuse or SUD or alcohol abuse or AUD or nicotine or tobacco or smoking or cigarette AND comorbidity or community from 1990 to 2020.

Since we aimed to produce a narrative review, not a systematic analysis, we did not assess well-defined eligibility criteria. We included all of the articles that estimated the comorbidity of AUD, SUD, and smoking in the community as well as in the clinical populations diagnosed with OCD. We did not inquire about OCD in individuals who sought treatment for AUD/SUD, since we particularly focused on those who principally complained of the symptoms of OCD rather than alcohol/substance problems.

Various diagnostic tools, such as the DSM-IV and DSM-5, were used in these studies, but this was not as important for our aim as ascertaining the exclusive relationship between OCD and AUD/SUD. Some studies employed the diagnosis "dependence" rather than "use disorder," which includes dependence as well as abuse; we also avoided using the terms "AUD" and "SUD" when investigating these studies. Since hardly any study on SUD included nicotine, we noted the findings concerned with smoking when occasion arose. The criteria concerning the timeframes for which AUD and/or SUD occurred (i.e., lifetime, 12 months, or current prevalence) were also specified in the text when citing the studies.

Obsessive-compulsive disorder and alcohol use disorder/substance use disorder

Obsessive-compulsive disorder and alcohol use disorder/substance use disorder in community settings

The US National Comorbidity Survey Replication found the lifetime prevalence of SUD in people meeting the criteria of OCD in community samples more than four times higher than in the general population.[36,42] SUD, but not AUD, had been estimated to be one and a half times as high in OCD sufferers as in the general population of the US in an earlier survey.[46] Ecker *et al*.[35] examined OCD and SUD rates among nearly 40,000 American veterans and observed a co-occurrence of 36.7%. Two epidemiologic studies in Canada also revealed a high rate of comorbidity,[37,38] involving approximately one-third of individuals with OCD.[38] Adam *et al*.[31] detected an odds ratio (OR) of 3.3 for any SUD, as compared to those having no obsessive-compulsive symptoms, including for nicotine, in 113 German communities. The OR for the association between OCD and AUD was 2.7 in a cross-sectional analysis of more than 10,000 adults in the Australian general population when the people with and without AUD were compared.[33] Individuals with OCD screened among the Dutch population also showed a high prevalence of AUD/SUD.[32,34]

In contrast, several community studies disavowed the high comorbidity of OCD with AUD/SUD. One is a Zurich cohort study, which showed no significant difference in AUD/SUD between those having and not having OCD.[8,12] In the Greek general population, OCD was found to be associated with neither frequent alcohol consumption nor current cannabis consumption.[47] AUD was as equally common in OCD as in the general population in an American study, although the prevalence of SUD was high.[46] Furthermore, Hofer *et al*.[48] found no association between OCD and the subsequent onset of SUD in a population of nearly 3000 adolescents and young adults from Munich, Germany.

The major part of the literature confirms that people having OCD detected during community screenings have a remarkably increased risk of AUD/SUD, although a few exceptions do exist.

Obsessive–compulsive disorder and alcohol use disorder/substance use disorder in clinical settings

Table 1 summarizes many of the clinical studies on the comorbidity of OCD and AUD/SUD. The Netherlands OCD Association (NOCDA) study, which followed up a clinical cohort of about 400 patients with OCD, calculated that the lifetime and current prevalence for SUD + AUD as a whole was approximately 13% and 5%, respectively.[15,24]

Table 1: Clinical studies on the prevalence obsessive-compulsive disorder-alcohol use disorder/substance use disorder comorbidity (the findings pertaining to the US and Holland general population are also shown to allow comparison)

Study and country	AUD Lifetime prevalence (%)	SUD Lifetime prevalence (%)	AUD Current or 12-month prevalence (%)	SUD Lifetime current or 12-month prevalence (%)
Lochner *et al*.[18] International	3.3	0.5		
Torres *et al*.,[28] Torresan *et al*.,[29] Kim *et al*.[16] Brazil‡	8.5	3.3		
Schuurmans *et al*.,[24] Hofmeijer-Sevink *et al*.[15] Holland§		13 (including alcohol)		5 (including alcohol)
Mancebo *et al*.[49] US		27		
Nestadt *et al*.[21] US	15	8		
LaSalle *et al*.[17]‖ US	23.4	13.8		
Maina *et al*.[19] Italy		9.7		
Sbrana *et al*.[22] Italy	4	4		
Italy; control group of Sbrana *et al*.[22]	6	6		
Holland general population de Graaf *et al*.[11]¶	16.3	19.1	4.4	5.6
US general population Kessler *et al*.[50]	23.5	11.9		

‡Brazilian Research Consortium on Obsessive-Compulsive and Related Disorders, §NOCDA study, ‖*Both a clinical sample and participants invited through a media campaign* were *included*, ¶NEMESIS-2. AUD: Alcohol use disorder, SUD: Substance use disorder, NOCDA: The Netherlands Obsessive-Compulsive Disorder Association, NEMESIS-2: The Netherlands Mental Health Survey and Incidence Study-2

These figures are quite low when compared to the Dutch general population. In that country, the lifetime prevalence for AUD and SUD is 16.3% and 19.1%, respectively, and the 12-month prevalence for AUD and SUD is 4.4% and 5.6%, respectively, as shown by the Netherlands Mental Health Survey and Incidence Study-2.[11]

A Brazilian multicenter sample consisting of 630 participants showed a lifetime frequency of 7.5% for AUD.[13] This sample grew to approximately 1000 subjects by the recruitment of succeeding patients over time and produced three publications, which reported a lifetime prevalence of 8%–9% for AUD and 3.3% for SUD, figures similar to the Brazilian general population.[16,28,29]

Only 1.2% of 169 Turkish OCD patients had comorbid current alcohol dependence.[30] Maina *et al*.[19] detected a lifetime prevalence of 9.7% for SUD in 216 Italian people. A separate Italian sample of OCD sufferers had a low prevalence of SUD (4%) and AUD (4%) when compared to control groups, of which 6% had SUD and an additional 6% had AUD.[22] A multinational study on 457°CD patients found AUD and SUD lifetime comorbidities of 3.3% and below 0.5%, respectively.[18]

The US data derived from clinical settings also generally confirm that OCD patients are not considerably affected with AUD/SUD. Eighty patients recruited from clinics as a part of the Johns Hopkins OCD Family Study showed a lifetime prevalence of 15% for AUD and 8% for SUD.[21] These figures are apparently low when one takes into account the high rates of AUD and SUD in American society, which are 23.5% and 11.9%, respectively.[50] The findings by LaSalle *et al*.,[17] which were from a study of 344 individuals including not only treatment seekers but also the subjects invited through media advertisements, indicated a lifetime prevalence AUD and SUD, 23.4% and 13.8%, respectively, which were not substantially different from the findings for the general population. Out of the 409 patients from Yaryura-Tobias *et al*.'s study,[51] 9.8% had substance dependence. Twenty-seven percent of the 323 people recruited for Mancebo *et al*.'s study[49] admitted to having a lifetime history of SUD, which is the one study showing remarkably high comorbidity in clinical OCD studies.

The literature convincingly illustrates that OCD patients visiting clinics are not prone to AUD/SUD, which is in contrast to those with other psychiatric disorders. This surprising finding merits further consideration. Many of the subjects with OCD who were detected in community studies probably had been undiagnosed and probably had a less distressing disease and were much more predisposed to AUD/SUD, which further confuses the picture.

The U-shaped curve of the relationship between obsessive–compulsive disorder and alcohol use disorder/substance use disorder

Two articles[8,12] based on the same cohort from Zurich, Switzerland seem to provide the greatest support for the U-shaped curve model.[44] The studies analyzed not only the people meeting the diagnostic criteria for OCD but also two other groups having so-called obsessive-compulsive syndrome and obsessive–compulsive symptoms, terms describing several clinical manifestations of OCD not reaching the diagnostic threshold. The "obsessive–compulsive symptoms" group had the mildest symptoms, whereas "obsessive–compulsive syndrome" ranked between it and full-blown OCD. The fact that OCD corresponded to the most severe end of the spectrum was reflected by the considerably different rates of those

seeking treatment, which was one-third for OCD and 6% for obsessive–compulsive syndrome.

Table 2 shows the prevalence of AUD/SUD in the Zurich cohort classified into four groups, according to the level of obsessive-compulsive symptoms.[8] It is striking that the prevalence of AUD/SUD in OCD was not only lower than the prevalence of AUD/SUD in the people having obsessive-compulsive symptoms, not meeting the criteria of a full-blown illness, but also lower than the prevalence those having no obsessive-compulsive symptoms. It appears that the co-occurrence of AUD/SUD first rose as the spectrum advanced from cases with no symptoms towards the symptomatic but subthreshold cases. The dual diagnosis then declined to even lower levels for patients having full-blown OCD than for those people reporting no symptoms. Although the differences observed in this Zurich sample did not reach the level of significance, a clinical psychiatric condition not associated with a notably high risk of AUD/SUD is on its own well worth attention.

A Dutch study also supports this finding. In a large Dutch representative population, cases without obsessive-compulsive symptoms, subthreshold cases, and cases meeting OCD criteria exhibited no differences in comorbidity with AUD/SUD.[34]

In a study of the Greek general population, people with subclinical obsessive-compulsive symptoms were shown to consume alcohol and cannabis more frequently than those with full-blown OCD as well as those having no obsessive-compulsive symptoms.[47]

Cuzen *et al*.[44] took one more step to test their U-shaped curve hypothesis. They subdivided their 588°CD cases into higher and lower severity subgroups, relying upon a cut-off score of 25 on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). They estimated that the patients with graver OCD were less likely the victims of AUD/SUD, confirming the U-shaped curve model.

Interim conclusion

The comorbidity of OCD and AUD/SUD is common in community settings as is the case with other psychiatric disorders. Yet, it is intriguing that this familiar finding is contradicted by some data[8,12,47,48] that deny the vulnerability of OCD patients to AUD/SUD.

The bulk of the literature suggests that the individuals visiting psychiatric settings to seek treatment for their OCD are not at an elevated risk for AUD/SUD when compared to the general population, in contrast to the figures seen in anxiety disorders, depression, and bipolar disorder.[5]

Smoking and obsessive–compulsive disorder

A noticeably high prevalence of smoking in individuals with mental illness has convincingly been demonstrated.[52] Regarding OCD, smoking parallels the relationship seen with AUD/SUD.

Community samples in the UK,[41] Greece,[39,47] and the US[35] have been characterized by a high prevalence of smoking for individuals with OCD. Two community studies done in the US[43] and Singapore[40] also indicated an increased association between OCD and smoking, although it was accounted for by only female subjects. The sole community-based sample that lacked a relationship between OCD and smoking was adolescents and young adults living in the US.[53]

Individuals seeking treatment for OCD smoke as much as, or even sometimes less than, the general population does, as shown by various studies done in the US,[7,9,14] Canada,[20] the UK,[23] Sweden,[10] and Turkey.[25-27] Dell'Osso *et al*.[54] looked at cigarette use in OCD patients from ten countries over three continents and found great differences across nations, suggesting a low cooccurrence at least in some societies.

Two studies of ours that investigate the smoking behavior of patients with OCD can shed some light on the subject.[25,27] The more recent one had fewer limitations because it included not only a clinical sample that was large enough to produce sound results but also a matched control group recruited from the general population. That study, which compared 319 control individuals and 317 subjects with OCD who visited our outpatient clinic in Istanbul (Turkey), showed that the percentage of current smokers was lower

Table 2: The prevalence of alcohol use disorder and substance use disorder in a Zurich cohort classified according to obsessive-compulsive symptomatology[8]

	Obsessive-compulsive disorder‡	Obsessive-compulsive syndrome§	Obsessive-compulsive symptoms‖	No obsessive-compulsive symptoms¶
AUD (%)	13.3	23.5	27.3	19.5
SUD (%)	16.7	38.3	31.2	25.5

‡Obsessive-compulsive disorder denotes the clinical picture corresponding to the criteria of the DSM-IV. The criterion stipulating loss of functioning could be replaceable by "significant distress" (i.e., >49 in an analogue scale ranging from 0 to 100), §Obsessive-compulsive syndrome denotes the symptoms specified by the DSM-IV, but the distress is "moderate" (i.e., between 29 and 49 in the analogue scale, ranging from 0 to 100), ‖Obsessive-compulsive symptoms denote a group reporting obsessive-compulsive symptoms but denying loss of functioning or moderate or significant distress, ¶The condition of no obsessive-compulsive symptoms represents those who do not report such symptoms at all. AUD: Alcohol use disorder, SUD: substance use disorder

in the patient group (31% vs. 36%), albeit not reaching the significance level.[27]

The aforementioned two studies of ours[25,27] are unique in that they estimated not only the prevalence but also the relationships between the severities of OCD and comorbid addiction. The severity of nicotine addiction measured by the Fagerström Test for Nicotine Dependence was higher in OCD patients than in the controls.[27] We also found a positive correlation of the severity of addiction with the severity of OCD but not with that of anxiety or depressive symptoms. Age, gender, and educational status did not influence the severity of addiction.[27]

In addition, we subdivided our participants into three groups: current smokers, former smokers, and never smokers.[27] Never and current smokers had similar scores in the Y-BOCS total and its subscales. These two subcategories (never and current smokers) had higher scores of compulsions and total Y-BOCS than former smokers did. The scores of anxiety and depressive symptoms were, unlike OCD, similar in all three categories of cigarette use.[27]

Addiction and Symptom Dimensions in Obsessive–Compulsive Disorder

An impressive aspect of OCD is its heterogeneity of clinical manifestations, as it appears as virtually disparate diseases. Distinct symptom dimensions of OCD are associated with significant differences in age of onset, clinical course, comorbidity, family history, insight into illness, gender preponderance, response to treatment, and neurobiology.[55-59]

Unfortunately, little research has been done on the distribution of AUD/SUD among different symptom types of OCD. Torres *et al*.[28] estimated an elevated risk of AUD only in the patients with sexual or religious obsessions when compared to individuals having aggressive, symmetry/ordering, washing, or hoarding symptoms. A low prevalence of AUD as well as diminishing numbers in comparison subgroups after the subclassification of the whole sample (although it was actually large) did not produce significant results. Brakoulias *et al*.[60] also found a relationship between taboo thoughts and past nonalcohol SUD.

We paid attention to this issue in two studies,[26,61] both of which showed a significant difference in the prevalence of smoking among the subjects with religious, sexual, or aggressive obsessions and those with symmetry, counting, repetition, or ordering symptoms [Table 3]. It seems that the latter group smoked more commonly than the general population did in the area where our patients lived,[62] in contrast to the case in which washing and taboo thoughts were associated with a low frequency of cigarette use.

A few studies screening the association of obsessive-compulsive symptoms (not full-blown OCD) with AUD/SUD have produced significant results. In a New Zealand birth cohort, the risk for alcohol, drug, and cannabis addiction was highest for individuals with taboo thoughts and lowest for individuals who washed excessively, whereas harm/checking and symmetry/ordering fell in between.[63] In the general population of six European countries, AUD was most commonly associated with washing, followed respectively by sexual/religious obsessions, moral issues, harm/checking, symmetry/ordering, and somatic obsessions.[64]

Table 3: The prevalence of smoking with respect to symptom dimensions in obsessive-compulsive disorder

Study	Washing (%)	Religious/ sexual/ aggressive obsessions (%)	Symmetry/ counting/ repetition/ ordering (%)
Tan and Taş[26]	30	37	68
Tan and Çoban[61]	23	30	63

Dirice,[65] who investigated the relationship between smoking and obsessive-compulsive symptoms among the general population of Istanbul (Turkey), found that nicotine addiction was negatively (significantly albeit weakly) correlated with checking and repetitive behavior (precision). Repetitive behavior was related to moderate smoking, whereas the impulses subscale was related to heavy smoking.

It has been reported that obsessive-compulsive patients with taboo thoughts had the highest rate of treatment-seeking behavior, whereas patients suffering from other symptom dimensions tend to remain untreated.[66,67] That finding along with the low frequency of cigarette use in our patients with religious, sexual, or aggressive obsessions may at least partially account for the inconsistent prevalence of smoking, which is high in community settings but low in treatment settings. It is apparent that the relationship of symptom dimensions with addiction and abuse merits further research.

Personality Traits Accompanying Obsessive–Compulsive Disorder: Increased Sense of Harm and Risk Avoidance

OCD must have some unique characteristics accounting for its extraordinary tripartite effect on abuse and addiction. Some features characterizing OCD including an inflated sense of danger and propensity to avoid possible harm, have been suggested as putative mechanisms to account for the relatively low prevalence of a dual diagnosis among these patients.[68]

Increased fear of possible danger, ensuing risk avoidance, and excessive future-oriented planning at the cost of current pleasure, albeit not specified in the diagnostic guidebooks such as the DSM or ICD-10, have traditionally been appraised to be the properties of both OCD and

obsessive-compulsive personality disorder (OCPD).[69] OCD plus OCPD is a common comorbidity.[69,70] OCPD is the most common personality disorder accompanying OCD, and as one expects, OCD is pretty frequent in OCPD, as compared with other neurotic disorders, including generalized anxiety disorder, panic disorder, phobias, depressive episodes, and mixed anxiety and depressive disorder.[70] OCD plus OCPD predicts more severe OCD.[71] Yet OCPD is associated with the lowest prevalence of cannabis use disorder compared with all of the other personality disorders.[72] Cocaine use disorder and AUD are also less common in OCPD than in many other personality disorders.[72]

Compulsiveness and Impulsiveness

The right leg of the U-curve proposed by Cuzen *et al*.[44] is supposedly generated by the treatment seekers who have relatively severe OCD. The positive relationship between the severity of OCD or compulsiveness and addiction[25,27,44,65] may give rise to the right upward ascent of abuse or addiction problems.

Indeed, compulsiveness and impulsiveness, despite once considered to reflect the antithetical poles of a spectrum, have increasingly been understood to have not only discrepancies but also striking similarities with respect to phenomenology, comorbidity, heredity, neurobiology, and medication.[73] The scientific journey of these two behaviors, emerging from disparate starting points, has ended up being classified as OCD and impulse control disorders under the same title "obsessive–compulsive and related disorders" in the DSM-5.[74]

Research has shown that OCD patients have high impulsiveness when compared with the general population.[27,74,75] The intricate interaction of compulsiveness with impulsiveness, which has a well-established association with substance abuse or addiction,[76] can, at least, partially be responsible for the abstruse picture of AUD/SUD among the OCD patients.[77] Our finding that smokers with OCD had increased impulsiveness compared with never smokers with OCD is a further example of this tripartite figure.[25] We also estimated that the correlations between the severities of addiction and impulsiveness were more significant in the OCD group than in the controls.[27] Other studies also demonstrated a relationship between impulsiveness and smoking in patients with OCD,[7,78] as is the case with the general population.[79]

Discussion

Sufficient evidence shows that the comorbidity of AUD/SUD with OCD is high in epidemiological studies, whereas it is low among patients applying to psychiatric facilities, which is in contrast to the figures seen in anxiety disorders as well as for people with depression or bipolar disorder. Moreover, the individuals with obsessive-compulsive symptoms who do not meet the criteria for OCD are more often the victims of AUD/SUD than those having a full-blown OCD. Yet, less robust findings suggest that once OCD has reached a critical severity, its co-occurrence with AUD/SUD exhibits a second increase. Thus, the relationship between OCD and AUD/SUD follows a U-shaped curve. Beyond self-medication, which supervenes upon many other psychiatric disorders, obsessive-compulsive traits (such as heightened feeling of danger and avoidance from risk-taking behavior), distinct symptom dimensions of OCD, compulsiveness, and impulsiveness differentially interact at different stages of disease, thus generating the U-shaped pattern of OCD and AUD/SUD coexistence.

Increased predisposition to AUD/SUD and smoking in community surveys represents the left leg of the U-shaped curve. So-called self-medication is a commonly accepted explanation in order to comprehend the frequent comorbidity of mental illnesses with AUD/SUD.[80] Among community members meeting the criteria for any psychiatric diagnosis, OCD acts like other disorders in its association with AUD/SUD. Accordingly, self-medication may be a satisfactory explanation for the frequent dual diagnosis in epidemiological studies. Although this illness is not as severe in community settings as in clinical settings, even subthreshold OCD is a serious condition, as it decreases quality of life and psychosocial functioning.[81] Yet a few community studies have failed to find a high prevalence of AUD/SUD in people with OCD, as compared to the general population.[8,12,34,47] Since self-medication is a common reaction to mental illness, evidence denying it implies the unique character of OCD and the necessity for explanations other than self-medication.

The inadequacy of self-medication hypothesis becomes more obvious when one considers the reduced susceptibility to AUD/SUD for patients whose OCD grows distressing enough to warrant a visit to the clinic. These patients constitute the basal (horizontal) part of the U-shaped curve and require an account specific for OCD. Low proclivity toward AUD/SUD in clinical samples can be explained by two factors. The first one is the predominance of typical obsessive traits, including an elevated sense of harm and risk avoidance in OCD. To the best of our knowledge, no study has examined whether classical obsessive traits are more widespread or more oppressive in more severe cases of OCD. What we know is that OCPD frequently accompanies OCD and results in a more severe condition.[71] OCPD is associated with the lowest risk of AUD/SUD among other personality disorders.[69,70,72] The second factor is directly related to the essential phenomenological disposition of OCD. Disparate symptom dimensions, such as washing, checking, symmetry, and taboo thoughts (i.e., sexual, aggressive, and religious obsessions), distinctively affect the susceptibility to AUD/SUD SUD.[26.60] Research mostly denotes a marked susceptibility of the sufferers of taboo thoughts to AUD/SUD,[28,60,63] whereas excessive

washing stands out in a study comprising six European countries.[64] We observed that taboo thoughts are less likely associated with smoking than are washing and symmetry, counting, repetition, or ordering.[26,61] Although the findings are discordant, the differential relationship of distinct symptom dimensions with AUD, SUD, and smoking is apparent. Furthermore, particular subtypes of OCD regarding symptoms are associated with varying rates of treatment-seeking behavior,[66,67] influencing the appearance of a dual diagnosis in clinics.

Beyond a critical point of illness severity, OCD once more entails the high risk of AUD/SUD.[44] This stage represents the right upward leg of the U-shaped curve. Evidence confirming this view is limited. Our findings on smoking could support Cuzen *et al*.[44] The high severity of addiction in smokers with OCD, as compared to the controls and despite a similar prevalence, denotes that OCD is associated with not commencing but aggravating addiction.[27] The positive correlation between the severities of OCD and addiction affirms the deteriorating intercourse between OCD and addiction. Another finding corroborating the apparent role of OCD in addiction is that addiction severity in our clinical sample of OCD victims was related to neither gender nor educational status.[27] The fact that the severity of nicotine addiction was not correlated to the severity of anxiety or depressive symptoms[25] further confirms the effect of OCD as an independent factor in intensifying addiction. However, the relationship between anxiety and depression and addiction must be regarded with caution, since this relationship is not parabolic, in contrast to the case seen in OCD. Thus, the findings relying on correlational analysis could be a result of sampling or of not having a broad categorical perspective.

Compulsiveness, which is essentially higher in more severe OCD, may be blamed for the increase in the co-occurrence with AUD/SUD. It has been alleged that there is a link between compulsiveness and addiction.[82,83] Impulsiveness, which is infamous for its noxious effect in predisposing someone to AUD/SUD,[76] in contradiction to what traditional thinking has assumed, is often intrinsic to OCD.[27,74,75,84] A shift from impulsiveness toward compulsiveness has been seen as responsible for the development of addiction.[85] Compulsiveness may enhance the effects of impulsiveness, laying a bridge that accelerates the transition toward AUD/SUD and plays a detrimental role in aggravating addiction.[77]

Our patients with elevated impulsiveness, albeit with a lack of higher prevalence of smoking[27] may suggest a possible explanation for the paradox of OCD: Smoking provoked by the impulsiveness accompanying OCD, while it is counteracted by some other biological and/or psychological traits intrinsic to OCD. The orbitofrontal cortex (OFC), which is responsible for the inhibitory control of behavior, is well-known to be hyperactive in OCD and can account for risk aversion. Nicotine can enhance frontal neurocircuitry, which is already hyperactive in OCD, thus neutralizing positive reinforcement.[78] Yet the damage or degeneration of the OFC results in increased impulsiveness. OCD also involves the striatum, which interacts with the OFC, encoding the shift between goal-directed and habitual action.[86] The deviation from goal directed to habitual behavior can lead to an increased susceptibility to addiction. Impulsiveness and compulsiveness seem to be mediated to a certain extent by the common anatomical pathways, an imbalance of which results in the marked cautiousness inherent in OCD as well as the recklessness often accompanying AUD/SUD. The biochemical viewpoint also denotes a conspicuously overlapping etiology.[87] The serotonin, dopamine, and opioid system are implicated in OCD as well as in addiction and impulsiveness. Several pharmacological agents used for the treatment of AUD/SUD, including buprenorphine, topiramate, and ondansetron, may help alleviate OCD, whereas opioid antagonists may deteriorate it.[84] Yet OCPD, involving the same biological circuits as OCD,[88] frequently accompanies OCD,[69,70] and results in a harsher illness (hence, essentially higher compulsiveness),[71] but is associated with an opposition to AUD/SUD.[72]

The comorbidity pattern of OCD with AUD/SUD is only taken after by schizophrenia, which is associated with a higher propensity for AUD/SUD in community settings rather than in clinical ones.[5] It might be assumed that patients with schizophrenia visiting clinics have relatively high insight, better compliance to treatment, and firmer psychosocial support, which all drive them away from AUD/SUD.

The current paper differs from Cuzen *et al*.'s[44] in several ways. First, we proposed symptom dimensions, which make OCD quite a heterogeneous clinical phenomenon, as factors responsible for the contradictions in the research on dual diagnosis. Moreover, we addressed typical traits of obsessive-compulsive individuals, such as an increased fear of danger, harm-avoidance, and decreased risk taking. These features instantly occur to a clinician when he or she looks at the relationship between OCD and AUD/SUD. We also addressed the interplay between impulsiveness and compulsiveness. We screened the literature as thoroughly as possible, included studies on the comorbidity of OCD with smoking, and supported Cuzen *et al*.[44] with our own findings.

Limitations

The most important limitation of this narrative review is the scarcity of evidence on the right upward leg of the U-shaped curve, which represents the increased prevalence of AUD/SUD in severe OCD. Two points must be considered when evaluating our assumptions. First, researchers tend to recruit into their studies those patients who regularly visit clinics; however, addicts and abusers

are less likely to be regular visitors. Second, physicians are inclined to refer the patients with AUD/SUD to addiction clinics, regardless of whether they suffer from any other mental illness.

We did not look at OCD among individuals who seek treatment for AUD/SUD, since we particularly focused on those whose principal trouble was OCD rather than AUD/SUD. OCD is frequently diagnosed among alcohol and substance abusers and addicts. The fact that we ignored OCD comorbidity in addiction clinics is justifiable for two reasons. First, other psychiatric disorders, especially mood disorders, are also quite widespread in AUD/SUD. Second, the inclusion of studies done in the people with AUD/SUD would confound our results, since individuals complaining primarily of OCD or AUD/SUD have separate characteristics.

Conclusions and Future Directions

It is impressive that, as OCD worsens, the frequency of AUD/SUD accompanying it decreases at first and then begins to increase again after a critical threshold. Self-medication, acute cautiousness commonly characterizing the people with OCD, disparate symptom dimensions associated with different biological and clinical manifestations, as well as compulsiveness and impulsiveness all could affect individuals with OCD, resulting in a tripartite effect on AUD/SUD or the so-called U-shaped curve. Although our presumptions are corroborated by obvious evidence in part, some of our views remain to be investigated by further studies. Introducing the cut-off points of severity to the research of OCD (i.e., classifying OCD into mild, moderate, and severe categories) will be useful because obsessive-compulsiveness at different stages may interact contradictorily with impulsiveness and addiction. A viewpoint that remains to be investigated is to explore the relationship of OCD with AUD/SUD concerning rumination, cognition, emotion regulation, and coping with stress.

Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

There is no need for ethics committee approval.

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Conflicts of interest

There are no conflicts of interest to declare.

Author contribution subject and rate

- Oguz Tan (100%): Data collection and wrote the manuscript

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