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*Ε. Στράτου, Αικ. Τόσκα, Αικ. Γαμβρούλα, Στ. Αντωνόπουλος, Α. Μουλόπουλος, Θ. Ρηγοπούλου, Κ. Σουλιώτης, Μ. Σαρίδη* ..... 244

# Autism spectrum disorder in adulthood: Diagnostic and training challenges in Greece

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Autism spectrum disorder (ASD) is classified among the neurodevelopmental disorders, which are described in the early chapters of DSM-5<sup>1</sup> and ICD-11.<sup>2</sup> These disorders emerge in childhood, persist across the lifespan, and are characterized by deficits or diversities that affect personal, social, academic, and occupational functioning. Although the two major diagnostic systems have converged in terminology and criteria –with only minor differences in the categorization of co-occurring language and intellectual development disorders– Greece continues to rely on ICD-10, leading to difficulties in the consistent use of terminology among mental health professionals.

The global rise in ASD prevalence over recent decades has been widely discussed, largely attributed to broadened diagnostic criteria and increased recognition in groups where autism was previously considered rare, such as women and individuals with milder symptoms. In the United States, current estimates suggest that 1 in 31 children may be diagnosed with ASD.<sup>3</sup> In adults, the prevalence is consistently found to be lower. In Greece, the estimated prevalence based on diagnoses recorded by the Diagnostic, Assessment, and Counseling Centers (KEDASY) is 1.15%,<sup>4</sup> while no epidemiological data exist for adults.

The lifetime cost of care for an individual with autism may exceed 2 million USD.<sup>5</sup> The socioeconomic burden in Greece has been exacerbated by the financial crisis, which had a more detrimental impact on families of individuals with autism than the COVID-19 pandemic.<sup>6</sup>

A critical gap in care has been documented internationally during the transition from adolescence to adulthood. Adults with autism frequently encounter the “double empathy problem,” referring to reciprocal difficulties in their communication with neurotypical individuals. This, coupled with the stigma surrounding the diagnosis, often results in misjudgments regarding the abilities and needs of people with autism.

Among adults with ASD, depression is the most prevalent and impairing co-occurring psychiatric disorder, often accompanied by anxiety disorders, both of which contribute to marked reductions in functioning, particularly during transitional periods.<sup>7–9</sup> For the so-called “lost generation” of adults with autism –those with normal intelligence and relatively functional profiles whose diagnosis was missed earlier– an ASD diagnosis may resolve longstanding diagnostic uncertainty and explain treatment resistance in psychiatric disorders.

Management of ASD and psychiatric comorbidities requires individualized treatment planning that integrates psychosocial interventions and targeted, when needed, pharmacological strategies. Multidisciplinary collaboration among professionals is essential, while active family involvement is of fundamental importance.<sup>10</sup> In the era of precision medicine, its applicability to ASD depends on a comprehensive understanding of genetic, temperamental, and environmental factors, enabling personalized interventions that may enhance treatment effectiveness and reduce costs. Implementation of such approaches presupposes specialized training of mental health professionals.

In Greece, structured training in adult autism for psychiatrists is limited or absent, resulting in delayed or inaccurate diagnoses, reduced access to appropriate services, and inadequate psychiatric care for adults with autism. While the curriculum of the child psychiatry specialty provides training for autism in childhood, there is no continuity into adult psychiatry, even though adulthood spans the majority of life. The lack of training contributes to frequent misdiagnoses (particularly among women and individuals from the “lost generation”), inappropriate pharmacological treatments, and the mischaracterization of adults with autism as “non-compliant.” Consequently, many individuals with autism and their families are deprived of psychoeducation and necessary support.

To address these shortcomings, we propose the integration of a dedicated module on adult ASD into the official psychiatry residency curriculum in Greece, alongside clinical training in autism-specialized services and acquisition of experience in the use

of standardized assessment tools. Such measures are essential to improve diagnostic accuracy, ensure continuity of care, and enhance the quality of psychiatric services for adults with autism.

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## Άρθρο σύνταξης

# Διαταραχή του αυτιστικού φάσματος στην ενηλικίωση: Διαγνωστικές και εκπαιδευτικές προκλήσεις στην Ελλάδα

ΙΣΤΟΡΙΚΟ ΑΡΘΡΟΥ: Παραλήφθηκε 20 Αυγούστου 2025/Δημοσιεύθηκε Διαδικτυακά 2 Σεπτεμβρίου 2025

Η διαταραχή αυτιστικού φάσματος (ΔΑΦ) ανήκει στις νευροαναπτυξιακές διαταραχές οι οποίες περιγράφονται πλέον στα πρώτα κεφάλαια ταξινόμησης των ψυχικών διαταραχών DSM-5<sup>1</sup> και ICD-11<sup>2</sup> και αποτελούν ομάδα διαταραχών που ξεκινούν κατά την παιδική ηλικία, συνεχίζουν σε όλη τη διάρκεια της ζωής και χαρακτηρίζονται από ελλείμματα ή διαφοροποιήσεις που επηρεάζουν την προσωπική, κοινωνική, ακαδημαϊκή και επαγγελματική ζωή του ατόμου. Τα δύο βασικά διαγνωστικά συστήματα, με μικρές διαφορές ως προς τον τρόπο κατηγοριοποίησης πιθανής συνυπάρχουσας διαταραχής λόγου και νοητικής ανάπτυξης, συγκλίνουν πλέον ως προς την ορολογία και τα διαγνωστικά κριτήρια της διαταραχής αυτιστικού φάσματος. Στη χώρα μας, όμως, όπου ισχύει ακόμη το ταξινομικό σύστημα ICD-10, οι επαγγελματίες της ψυχικής υγείας συχνά δυσχεραίνονται ως προς τις ορολογίες που εφαρμόζονται για τη συγκεκριμένη διαταραχή.

Έχει ευρέως συζητηθεί διεθνώς η εκτίναξη του επιπολασμού της ΔΑΦ τις τελευταίες δεκαετίες, η οποία σχετίζεται με τη διεύρυνση των διαγνωστικών κριτηρίων και τη συμμετοχή στη διαγνωστική αυτή κατηγορία ομάδων, στις οποίες ο αυτισμός θεωρείτο σπάνιος, όπως οι γυναίκες και τα άτομα με ηπιότερα πυρηνικά συμπτώματα. Εκτιμάται ότι 1 στα 31 παιδιά στις Ηνωμένες Πολιτείες μπορούν να λάβουν τη διάγνωση<sup>3</sup> ενώ για τους ενηλικίους ο επιπολασμός ανευρίσκεται συστηματικά μικρότερος. Στην Ελλάδα ο κατ' εκτίμηση επιπολασμός σύμφωνα με την καταμέτρηση των παιδιών που έλαβαν τη διάγνωση από τα Κέντρα Διάγνωσης Αξιολόγησης Συμβουλευτικής και Υποστήριξης (ΚΕΔΑΣΥ) υπολογίστηκε σε 1,15%,<sup>4</sup> δεν έχουμε όμως επιδημιολογικά δεδομένα για τους ενηλικίους.

Το κόστος φροντίδας ενός ατόμου με αυτισμό κατά τη διάρκεια της ζωής του μπορεί να υπερβεί τα 2 εκατομμύρια δολάρια.<sup>5</sup> Στην Ελλάδα, η οικονομική κρίση επιδείνωσε την κατάσταση των οικογενειών με άτομα στο φάσμα του αυτισμού σε μεγαλύτερο βαθμό συγκριτικά με την πανδημία COVID-19.<sup>6</sup>

Διεθνώς καταγράφεται σημαντικό κενό στη συνέχεια της φροντίδας κατά τη μετάβαση από την εφηβεία στην ενηλικίωση για άτομα με ΔΑΦ. Οι ενήλικοι με αυτισμό κατά κανόνα αντιμετωπίζουν το πρόβλημα της «διπλής ενσυναίσθησης», δηλαδή δυσκολίες των ίδιων αναφορικά με την αμοιβαιότητα της επικοινωνίας αλλά και των νευροτυπικών ατόμων μαζί τους. Το φαινόμενο αυτό σε συνδυασμό με το στίγμα που κατά κανόνα συνοδεύει τη διάγνωση, οδηγεί σε λανθασμένες εκτιμήσεις σχετικά με τις δυνατότητες και τις ανάγκες των ατόμων με αυτισμό.

Στους ενηλικίους με αυτισμό η κατάθλιψη είναι η συχνότερη και πλέον επιβαρυντική συνυπάρχουσα ψυχική διαταραχή, η οποία, όπως και οι συχνά συνυπάρχουσες αγχώδεις διαταραχές, οδηγούν σε μεγάλες μειώσεις της λειτουργικότητας του ατόμου ιδίως κατά την περίοδο της μετάβασης προς την ενηλικίωση.<sup>7-9</sup> Σε άτομα της λεγόμενης «χαμένης γενιάς» (ενήλικα άτομα με φυσιολογική νοημοσύνη και ως έναν βαθμό λειτουργικά, στα οποία διέλαθε η ύπαρξη αυτισμού) η διάγνωση ΔΑΦ μπορεί να διαλευκάνει δυσεπίλυτα διαγνωστικά προβλήματα ή/και να δικαιολογήσει την ανθεκτικότητα στη θεραπεία ψυχιατρικών διαταραχών.

Οι θεραπευτικοί σχεδιασμοί για την αντιμετώπιση της ΔΑΦ και των συνυπαρχουσών ψυχικών διαταραχών οφείλουν να συμπεριλάβουν, ανάλογα με το εξειδικευμένο προφίλ του ατόμου, ψυχοκοινωνικές παρεμβάσεις και, όπου αυτό είναι αναγκαίο, στοχευμένες φαρμακολογικές προσεγγίσεις. Είναι απαραίτητη η συνεργασία μεταξύ των επαγγελματιών που εξειδικεύονται στην αντιμετώπιση των προβλημάτων που προκαλεί η ΔΑΦ, ενώ η συμμετοχή της οικογένειας θεωρείται κεφαλαιώδους σημασίας.<sup>10</sup> Σε μια εποχή που μιλάμε για Ιατρική ακριβείας είναι άραγε δυνατή η εφαρμογή της στα άτομα με ΔΑΦ; Απαιτείται καλή γνώση των γενετικών, ιδιοσυγκρασιακών και περιβαλλοντικών παραγόντων, η οποία θα οδηγήσει σε συνολική αξιολόγηση και παρεμβάσεις εξατομικευμένες, που μπορούν να αυξήσουν την αποτελεσματικότητα και είναι δυνατόν να μειώσουν το κόστος περίθαλψης. Οι παραπάνω αρχές εξατομικευμένης αντιμετώπισης για να εφαρμοστούν απαιτούν ουσιαστική εκπαίδευση των επαγγελματιών ψυχικής υγείας στο αντικείμενο.

Η εκπαίδευση ψυχιάτρων στον αυτισμό ενηλικίων στην Ελλάδα είναι ανεπαρκής έως ανύπαρκτη ως οργανωμένο πρόγραμμα, γεγονός που δημιουργεί σοβαρά προβλήματα στην έγκαιρη διάγνωση, στην πρόσβαση σε κατάλληλες υπηρεσίες και στην ποιτική ψυχιατρική φροντίδα των αυτιστικών ενηλικίων. Η παιδοψυχιατρική εκπαίδευση παρέχει την απαραίτητη εξοικείωση με

τον αυτισμό στα παιδιά, όμως δεν υπάρχει συνέχεια της εκπαίδευσης για την ενηλικίωση και συνήθως η ενήλικη ζωή διαρκεί πολύ... Οι επιπτώσεις από την έλλειψη εκπαίδευσης οδηγούν σε λανθασμένες ή καθυστερημένες διαγνώσεις (ιδίως σε γυναίκες και γενικότερα σε άτομα από τη «χαμένη γενιά του αυτισμού»), χρήση ακατάλληλων φαρμακευτικών θεραπειών ή αντιμετώπιση ενηλίκων με αυτισμό ως «μη συνεργάσιμων» με αποτέλεσμα πολλά από τα ενήλικα άτομα με αυτισμό και οι οικογένειές τους να στερούνται ψυχοεκπαίδευσης και της υποστήριξης που δικαιούνται. Προτείνεται η ενσωμάτωση θεματικής ενότητας για ΔΑΦ ενηλίκων στο επίσημο πρόγραμμα ειδικότητας, εκπαιδευτική άσκηση σε δομές εξειδικευμένες στον αυτισμό και εμπειρία στην κλινική χρήση εργαλείων αξιολόγησης.

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## Research article

# Dehydroepiandrosterone sulfate (DHEA-S), cortisol, and adrenocorticotrophic hormone (ACTH) levels in drug-naïve, first-episode patients with psychosis

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### ABSTRACT

The hypothalamic-pituitary-adrenal (HPA) axis plays a crucial role in regulating dopamine activity in specific brain areas, particularly in the limbic system, as well as in the stress response. The assessment of the HPA axis is important for the research of biological mechanisms leading from stressful experiences to the onset of psychosis. The release of adrenocorticotrophic hormone (ACTH) by the anterior pituitary stimulates the production of cortisol and dehydroepiandrosterone (DHEA) by the adrenal cortex as a response to stress. The co-release of DHEA may act as a protective mechanism against the damaging effects of excessive cortisol activity. We aimed to measure and compare serum DHEA-S, as well as ACTH, cortisol levels, and cortisol/DHEA-S ratio in drug-naïve FEP patients and matched controls. Data were included for 110 subjects (70 men and 40 women), comprising 55 patients and 55 controls. The mean age was 31.3 years (SD 8.7) in patients and 31.4 years (SD 8.9) in controls. Serum DHEA-S was higher in patients compared to controls [0.69 (0.40) versus 0.50 (0.19), respectively]. Serum ACTH was similar between patients and controls [28.0 pg/ml (6.2-73.9) versus 22.4 pg/ml (7.0-70.5), respectively]. Serum cortisol levels and cortisol/DHEA-S ratio were lower in patients [12.6 µg/dl (4.5) and 4.4% (1.3-19.5), respectively] compared to controls [15.4 µg/dl (3.7) and 7.0% (2.4-25.5), respectively]. Sub-analysis revealed that in men, serum DHEA-S was similar between male patients and controls [0.53 (0.23) versus 0.48 (0.17), respectively], whereas in women, serum DHEA-S was higher in patients compared to controls [0.97 (0.47) versus 0.55 (0.20), respectively]. ACTH levels were not different in the above subgroups. Serum cortisol in men was lower in patients compared to controls [12.8 µg/dl (4.4) versus 15.9 µg/dl (3.6)]. Additionally, the cortisol/DHEA-S ratio was lower in patients compared to controls in men [4.4% (1.3-19.5) versus 5.8% (2.4-15.4)], as well as in women [4.3% (1.8-15.2) versus 7.9% (4.0-25.5), respectively]. Correlation analysis was performed to examine the association between different psychopathological characteristics in patients and measured hormones. It was found that the PANSS cognitive subscale was positively correlated with DHEA-S in men, and the PANSS positive subscale was negatively correlated with DHEA-S in women. In the linear regression analysis, DHEA-S was positively associated with the PANSS cognitive subscale in men.

**KEYWORDS:** Dehydroepiandrosterone sulfate (DHEA-S), cortisol, adrenocorticotrophic hormone (ACTH), first episode psychosis, drug-naïve.

## Introduction

The hypothalamic-pituitary-adrenal (HPA) axis plays an important role in the regulation of dopamine activity in certain brain areas, in particular in the limbic system, and also in response to stress.<sup>1</sup> Impaired response to stress and a pathological activation of the HPA axis have been implicated in the pathophysiology of schizophrenia.<sup>2,3</sup> Anterior pituitary hormones, among them ACTH, are involved in neurotransmission and neuroregulation, processes associated with schizophrenia.<sup>4</sup> Animal studies found that persistently increased glucocorticoid levels induce hippocampal cell damage.<sup>1</sup> Reduced hippocampal volume is one of the most robust findings observed in patients with schizophrenia and may be correlated with hypercortisolemia.<sup>1,5</sup> Hypothalamus releases corticotropin-releasing hormone (CRH), which in turn stimulates the release of adrenocorticotrophic hormone (ACTH) by the anterior pituitary, which leads to the production of cortisol and dehydroepiandrosterone (DHEA) from the adrenal cortex. Cortisol release inhibits the production of ACTH and CRH in a negative feedback.<sup>6</sup> The co-release of DHEA may have a protective effect against the damage induced by excessive cortisol activity.<sup>7</sup> DHEA-S crosses the blood-brain barrier and acts as a neurosteroid that binds to neurotransmitter receptors  $\gamma$ -aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptors in several brain areas, among them the cortex, the hippocampus, and the amygdala.<sup>8-10</sup> Except for these indirect effects, DHEA-S seems to be produced directly by glial cells and neurons in the central nervous system.<sup>11</sup> Importantly, there is a strong association between DHEA levels in cerebrospinal fluid and those in serum.<sup>12</sup>

The assessment of the HPA axis is important for the research of biological mechanisms leading from stressful experiences to the onset of psychosis.<sup>4</sup>

The results of the studies and meta-analyses regarding ACTH, cortisol, and DHEA-S levels in patients with psychosis remain inconclusive so far. Cavaleri et al (2023)<sup>4</sup> report in a recent meta-analysis, higher levels of ACTH were found in drug-naïve FEP with psychosis compared to controls. Misiak et al (2021)<sup>13</sup> report higher blood cortisol levels in patients with FEP compared to controls, but similar unstimulated salivary cortisol levels between FEPs and controls. In the meta-analysis conducted by Aymerich et al (2023),<sup>14</sup> morning cortisol levels did not differ significantly between antipsychotic naïve patients and controls. Chaumette et al (2016)<sup>15</sup> did not find any difference in cortisol levels between FEP, drug-naïve patients, controls, and Ultra High Risk (UHR)

individuals. Blunted cortisol awakening response in FEP patients,<sup>16</sup> and reduced cortisol response to stress in schizophrenia have also been reported.<sup>17</sup> Misiak et al (2018)<sup>10</sup> in his meta-analysis, which included five studies with FEP patients, report increased DHEA-S levels in FEP male patients, but neither in stable multiple episodes nor in acutely relapsed patients.

Of note, very few studies that measured DHEA-S included drug-naïve, FEP patients, and only one<sup>18</sup> measured ACTH, cortisol, and DHEA-S. Two of them,<sup>19,20</sup> report increased DHEA in the patients' group but similar cortisol levels between FEPs and controls, one finds no statistically significant difference in DHEA-S and cortisol levels and cortisol/DHEA-S ratio between patients and controls,<sup>7</sup> while Beyazyuz et al<sup>18</sup> report elevated DHEA-S but similar ACTH and cortisol levels in a group of FEPs compared both to controls and to a group of drug-free, acutely relapsed patients. Garner et al (2011)<sup>7</sup> reports a positive association between cortisol levels and psychotic symptoms, while DHEA-S levels were negatively associated with negative and depressive symptoms.

Studies in samples consisting of chronic, medicated patients with schizophrenia report higher serum cortisol and DHEA-S levels,<sup>21</sup> elevated cortisol/DHEA and cortisol/DHEA-S ratios,<sup>22</sup> elevated DHEA-S levels,<sup>23-25</sup> increased DHEA levels and decreased cortisol/DHEA ratio,<sup>26</sup> while Huang et al (2017)<sup>27</sup> found reduced levels of DHEA-S and pregnenolone in the male subgroup of patients. Huang et al<sup>27</sup> reported a positive correlation between DHEA and DHEA-S levels and age of onset and a negative one with duration of illness, while Peng et al<sup>21</sup> found a positive correlation between cortisol and the negative symptom score in PANSS and no correlation between DHEA-S and cortisol levels and age of onset or duration of illness.

Given the possible implication of the HPA axis in the onset of psychosis and the inconsistent findings reported so far, we aimed to 1. To measure DHEA-S, ACTH, and cortisol serum levels and to calculate cortisol/DHEA-S ratio in a group of drug-naïve FEP patients and matched controls, and to compare the results 2. To find possible correlations between psychopathology and stress hormone' levels

## Material and Method

### Participants

We recruited fifty-five patients from the "Early Intervention in Psychosis Unit" of the Department of Psychiatry of the University Hospital of Ioannina in Greece from September 2019 to August 2021. Inclusion

criteria were the following: (a) Diagnostic and Statistical Manual of Mental Disorders (DSM-5)<sup>28</sup> diagnosis of schizophrenia, schizophreniform disorder or brief psychotic episode, (b) patients had to experience their first psychotic episode, defined as the first experience of psychotic symptoms and the first contact with psychiatric services,<sup>29</sup> (c) they had to be antipsychotic-naïve, and (d) they were 18–48 years old. Exclusion criteria were the following: (a) past major mental illness (psychotic, mood, anxiety disorder), (b) DSM-5 diagnostic criteria for alcohol or substance abuse, (c) have serious physical disorders and/or take medications that interfere with the measurement of cortisol, DHEA-S, and ACTH, (d) patients refused to give informed consent.

Patients and controls with BMI>25 were excluded from the study. Overweight people are more likely to suffer from subclinical metabolic disorders. DHEA-S may be an insulin sensitizer, and there is also evidence that insulin changes DHEA-S levels.<sup>30</sup> DHEA-S also increases glucose uptake in adipocytes by stimulating GLUT-1 and GLUT-4 to the cellular membrane (Perrini et al 2004, Wang et al 2020).<sup>31,32</sup> It has been suggested that DHEA-S may be implicated in the pathogenesis of type-2 diabetes, and higher levels of DHEA-S are associated with a lower risk of type-2 diabetes.<sup>30</sup> Additionally, in women over 35 years, low cortisol levels have been correlated with overweight, while in women less than 35 years, DHEA-S levels have been correlated with insulin resistance. DHEA-S levels have also been associated with increased BMI in women.<sup>33</sup> For these reasons, we excluded overweight patients. We did not exclude underweight patients; however, we would like to note that no patients in our sample had a BMI<18 kg/m<sup>2</sup>.

Patients and controls had complete physical examinations by an internist and were physically healthy. A urine test was performed to exclude current substance use.

### Clinical assessment

Psychiatric diagnosis was established by an experienced psychiatrist using the Structured Clinical Interview for DSM-5 (SCID-5). Twenty-four males and 16 females were diagnosed with schizophreniform disorder, 8 males and 2 females with schizophrenia, and 3 males and 2 females with brief psychotic episode. The patients' psychopathology was evaluated using the Positive and Negative Syndrome Scale (PANSS)-Greek version,<sup>34</sup> conducted by an experienced psychiatrist on the day of blood sample collection. We further evaluated psychopathology following the five-factor model

by Lykouras et al.<sup>35</sup> The participants received detailed information about the aim of the study and gave informed consent, and their anonymity has been preserved. Control group subjects were matched for age and sex. They were examined by an experienced psychiatrist who ruled out any present or past DSM-5 mental disorder. Mental health history was evaluated using the SCID NP (non-patient) edition, and only those without a past or present history of mental disorder (psychotic, mood, or anxiety disorder) were included in the study. First and second-degree relatives of persons with a history of severe mental illness were excluded as controls from the study.

### Measurements

We measured serum DHEA-S levels in FEP patients and matched controls and compared DHEA-S levels between the two groups in men and women. DHEA-S is expressed as the ratio of each DHEA-S value to the upper limit of normal for the respective age group in men and women. We also measured and compared serum ACTH and cortisol levels between patients and controls. Cortisol/DHEA-S ratio was calculated, representing the relative imbalance of the two hormones.

The study was approved by the ethical committee of the University Hospital of Ioannina, Greece, and conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000).

### Biochemical analysis

Blood samples were collected from all participants between 8.00 a.m. to 9.00 a.m. after a 12-hour fast. For DHEA-S and cortisol measurement, venous blood samples were placed in anticoagulant tubes, and then serum was separated by centrifugation for 10 min, 3000 rpm/min. For ACTH measurement, blood samples were placed in a separate tube with ethylene diamine tetra-acetic acid (EDTA), and then plasma was separated by centrifugation. Serum levels of DHEA-S and cortisol were measured using a Chemiluminescence Immunoassay (CLIA) technique on a CENTAUR XP (SIEMENS) automated immunoanalyzer, by SIEMENS DHEA-S and Cortisol Reagent Kit. Plasma levels of ACTH were measured using CLIA on an IMMULITE 2000 (SIEMENS) automated immunoanalyzer, by SIEMENS ACTH Reagent Kit. The normal range of Cortisol serum levels is 43,0–240,0 ng/ml. DHEAS normal range (<30 years, 18–391µg/ml, 30-50 years: 19-266µg/ml). ACTH normal range 6,0-69,0 pg/ml.

## Statistical analysis

Sample size was calculated (power 80%, significance level 5%, mean of the differences between pairs for DHEA-S 66 µg/dl, standard deviation of the differences for DHEA-S 160 µg/dl). Categorical variables are expressed as a number (percentage). Paired t-test was used for comparison of continuous variables with normal distribution [expressed as mean (standard deviation)], whereas the Wilcoxon matched pairs signed rank test was used for not normally distributed variables [expressed as median (range)]. Correlation analysis was performed to examine the association between psychopathology as expressed in the PANSS scale and subscales, duration of untreated psychosis (DUP, crudely assessed as the time (weeks) elapsed from the onset of psychotic symptoms according to information received by the patient), and different hormones (DHEA-S, ACTH, cortisol, cortisol/DHEA-S ratio). Pearson or Spearman correlation analysis was performed for parameters with or without normal distribution, respectively. Linear regression analysis was also performed using the psychopathological characteristics as the independent variable and the measured hormones as the dependent variable, adjusting for age and sex. The level of significance was set at  $p$ -value < 0.05. Statistical analysis was performed with Stata software version 15.1.

## Results

Data were included for 110 subjects (70 men and 40 women), comprising 55 patients and 55 controls. The mean age was 31.3 years (SD 8.7) in patients and 31.4 years (SD 8.9) in controls. Additionally, the positive, negative, cognitive, depression, and excitement subscales of PANSS (according to Lykouras et al five factor model) 35 were 26.3 (1.7), 19.8 (3.1), 13.1 (3.0), 6.4 (1.6), and 10 (5-19), respectively. Median duration of untreated psychosis was 10 weeks (3-29), with women having a longer time being untreated compared to men. Table 1 describes the different demographic, hormonal, and psychopathology data in patients and controls.

Serum DHEA-S was higher in patients compared to controls [0.69 (0.40) versus 0.50 (0.19), respectively,  $p=0.0022$ ]. Serum ACTH was similar between patients and controls [28.0 pg/ml (6.2-73.9) versus 22.4 pg/ml (7.0-70.5), respectively,  $p=0.6359$ ]. Serum cortisol levels and cortisol/DHEA-S ratio were lower in patients [12.6 µg/dl (4.5) and 4.4% (1.3-19.5), respectively] compared to controls [15.4 µg/dl (3.7) and 7.0% (2.4-25.5), respectively],  $p=0.0015$  and  $p=0.0003$ , respectively.

Sub-analysis revealed that in men, serum DHEA-S was similar between male patients and controls [0.53 (0.23) versus 0.48 (0.17), respectively,  $p=0.2590$ ], whereas in women, serum DHEA-S was higher in patients compared to controls [0.97 (0.47) versus 0.55 (0.20), respectively,  $p=0.0013$ ]. ACTH levels were not different in the above subgroups. Serum cortisol in men was lower in patients compared to controls [12.8 µg/dl (4.4) versus 15.9 µg/dl (3.6), respectively,  $p=0.0048$ ]. Additionally, the cortisol/DHEA-S ratio was lower in patients compared to controls in men [4.4% (1.3-19.5) versus 5.8% (2.4-15.4), respectively,  $p=0.0259$ ], as well as in women [4.3% (1.8-15.2) versus 7.9% (4.0-25.5), respectively,  $p=0.0051$ ].

Correlation analysis was performed to examine the association between different psychopathological characteristics in patients and measured hormones (table 2). It was found that the PANSS cognitive subscale was positively correlated with DHEA-S in men ( $r=0.3822$ ,  $p$ -value=0.0235) and the positive subscale was negatively correlated with DHEA-S in women ( $r=-0.4464$ ,  $p$ -value=0.0485). Additionally, the PANSS cognitive subscale was marginally negatively correlated with cortisol/DHEA-S ratio in men ( $r=-0.3323$ ,  $p$ -value=0.0511). In the linear regression analysis, DHEA-S was positively associated with the PANSS cognitive subscale in men ( $\beta=0.04$ ,  $p$ -value=0.006). The results from the linear regression analysis are presented in table 3 and the Supplementary tables.

## Discussion

In this study, we found higher serum DHEA-S levels in drug-naïve, first-episode female patients with psychosis compared to matched female controls and lower cortisol levels in male patients compared to male matched controls. In the total population cortisol/DHEA-S ratio was lower in FEP patients compared to controls. ACTH levels were similar between patients and controls. DHEA-S levels were positively associated with the PANSS cognitive subscale in men.

This is one of the very few studies in this field where DHEA-S, ACTH, cortisol, and the cortisol/DHEA-S ratio were assessed in a calculated sample of drug-naïve, first-episode patients with psychosis with relatively small DUP, and where sub-analysis in males and females was also performed.

Our findings are in accordance with Beyazyuz et al,<sup>18</sup> Strous et al,<sup>19</sup> and Solanki et al,<sup>20</sup> who report increased DHEA-S levels in FEPs compared to controls, although these studies did not provide separate analysis between

**Table 1.** Demographic, hormonal, and psychopathology data in patients and controls.

|                          | Patients (N=55) | Controls (N=55) | p       |
|--------------------------|-----------------|-----------------|---------|
| Men:Women                | 35:20           | 35:20           | –       |
| Age (years)              | 31.3 (8.7)      | 31.4 (8.9)      | –       |
| DHEA-S <sup>1</sup>      | 0.69 (0.40)     | 0.50 (0.19)     | 0.00222 |
| DHEA-S in men            | 0.53 (0.23)     | 0.48 (0.17)     | 0.25902 |
| DHEA-S in women          | 0.97 (0.47)     | 0.55 (0.20)     | 0.00132 |
| ACTH (pg/ml)             | 28.0 (6.2–73.9) | 22.4 (7.0–70.5) | 0.63593 |
| ACTH in men              | 28.7 (8.0–73.9) | 21.4 (8.6–70.5) | 0.56653 |
| ACTH in women            | 19.0 (6.2–56.3) | 23.3 (7.0–52.8) | 0.97023 |
| Cortisol (µg/dl)         | 12.6 (4.5)      | 15.4 (3.7)      | 0.00152 |
| Cortisol in men          | 12.8 (4.4)      | 15.9 (3.6)      | 0.00482 |
| Cortisol in women        | 12.4 (4.9)      | 14.8 (4.0)      | 0.13112 |
| Cortisol/DHEA-S (%)      | 4.4 (1.3–19.5)  | 7.0 (2.4–25.5)  | 0.00033 |
| Cortisol/DHEA-S in men   | 4.4 (1.3–19.5)  | 5.8 (2.4–15.4)  | 0.02593 |
| Cortisol/DHEA-S in women | 4.3 (1.8–15.2)  | 7.9 (4.0–25.5)  | 0.00513 |
| PANSS-P                  | 26.3 (1.7)      | –               | –       |
| PANSS-P in men           | 26.5 (1.8)      | –               | –       |
| PANSS-P in women         | 26 (23–28)      | –               | –       |
| PANSS-N                  | 19.8 (3.1)      | –               | –       |
| PANSS-N in men           | 20.6 (3.4)      | –               | –       |
| PANSS-N in women         | 18.4 (1.7)      | –               | –       |
| PANSS-C                  | 13.1 (3.0)      | –               | –       |
| PANSS-C in men           | 12 (9–19)       | –               | –       |
| PANSS-C in women         | 13.6 (3.4)      | –               | –       |
| PANSS-D                  | 6.4 (1.6)       | –               | –       |
| PANSS-D in men           | 6 (5–11)        | –               | –       |
| PANSS-D in women         | 5.6 (1.4)       | –               | –       |
| PANSS-E                  | 10 (5–19)       | –               | –       |
| PANSS-E in men           | 10 (8–14)       | –               | –       |
| PANSS-E in women         | 11.9 (3.6)      | –               | –       |
| DUP (weeks)              | 10.0 (3.0–29.0) | –               | –       |
| DUP in men               | 10.0 (3.0–29.0) | –               | –       |
| DUP in women             | 13.1 (6.8)      | –               | –       |

Abbreviations: ACTH, adrenocorticotrophic hormone; DHEA-S, dehydroepiandrosterone sulfate; DUP, duration of untreated psychosis; PANSS-P, positive and negative syndrome scale-positive; PANSS-N, positive and negative syndrome scale-negative; PANSS-C, positive and negative syndrome scale-cognitive; PANSS-D, positive and negative syndrome scale-depression; PANSS-E, positive and negative syndrome scale-excitement

<sup>1</sup>It represents the ratio of each DHEA-S value to the upper limit of normal for the respective age group in men and women

<sup>2</sup>Paired t-test was used

<sup>3</sup>Wilcoxon matched-pairs signed-rank test was used

Variables are expressed as mean (standard deviation) or median (minimum-maximum)

males and females. Misiak et al<sup>9</sup> report elevated DHEA levels but only in the male subgroup of patients. The researchers support the hypothesis that elevated DHEA-S levels in FEPs may be attributed to the increased dopaminergic activity during the acute phase of psychosis

and have a neuroprotective effect, given their anti-glucocorticoid and neuroprotective properties. This effect seems to become blunted as the disease progresses because increased DHEA-S levels were found only in FEPs and not in acutely relapsed, multiple-episode patients.

**Table 2.** Descriptive statistics of sociodemographic and clinical variables as well as of psychopathology and neurocognition.

|                 | Total population |         | Men     |         | Women   |         |
|-----------------|------------------|---------|---------|---------|---------|---------|
|                 | r                | p-value | r       | p-value | r       | p-value |
| DHEA-S          |                  |         |         |         |         |         |
| PANSS-P         | -0.2207          | 0.1055  | -0.0843 | 0.6303  | -0.4464 | 0.0485  |
| PANSS-N         | 0.1248           | 0.3641  | 0.2155  | 0.2137  | -0.0141 | 0.9528  |
| PANSS-C         | 0.3438           | 0.0102  | 0.3822  | 0.0235  | 0.2783  | 0.2348  |
| PANSS-D         | -0.1151          | 0.4029  | -0.0637 | 0.7164  | -0.0283 | 0.9057  |
| PANSS-E         | -0.0211          | 0.8785  | -0.1454 | 0.4046  | 0.1246  | 0.6006  |
| DUP             | 0.0018           | 0.9897  | 0.0223  | 0.8988  | -0.0613 | 0.7974  |
| ACTH            |                  |         |         |         |         |         |
| PANSS-P         | 0.1844           | 0.1777  | 0.1798  | 0.3013  | 0.1828  | 0.4405  |
| PANSS-N         | 0.2311           | 0.0896  | 0.2536  | 0.1415  | -0.0781 | 0.7436  |
| PANSS-C         | -0.0385          | 0.7800  | -0.0274 | 0.8758  | 0.0387  | 0.8714  |
| PANSS-D         | 0.0828           | 0.5478  | -0.0084 | 0.9617  | 0.0100  | 0.9666  |
| PANSS-E         | -0.1343          | 0.3282  | -0.0001 | 0.9997  | -0.1127 | 0.6361  |
| DUP             | 0.0767           | 0.5776  | 0.0713  | 0.6839  | 0.1022  | 0.6682  |
| Cortisol        |                  |         |         |         |         |         |
| PANSS-P         | -0.1733          | 0.2058  | -0.2703 | 0.1163  | 0.0101  | 0.9663  |
| PANSS-N         | -0.0810          | 0.5564  | -0.0741 | 0.6724  | -0.2174 | 0.3572  |
| PANSS-C         | 0.1529           | 0.2650  | 0.0505  | 0.7734  | 0.4085  | 0.0737  |
| PANSS-D         | 0.0791           | 0.5659  | 0.1949  | 0.2618  | -0.1672 | 0.4812  |
| PANSS-E         | -0.1692          | 0.2169  | -0.2689 | 0.1183  | -0.1210 | 0.6114  |
| DUP             | -0.0859          | 0.5327  | -0.1336 | 0.4442  | 0.0077  | 0.9742  |
| Cortisol/DHEA-S |                  |         |         |         |         |         |
| PANSS-P         | 0.0058           | 0.9665  | -0.1972 | 0.2561  | 0.4184  | 0.0664  |
| PANSS-N         | -0.2047          | 0.1338  | -0.2589 | 0.1331  | -0.1692 | 0.4757  |
| PANSS-C         | -0.2367          | 0.0819  | -0.3323 | 0.0511  | 0.0414  | 0.8626  |
| PANSS-D         | 0.0763           | 0.5799  | 0.2006  | 0.2478  | -0.1458 | 0.5398  |
| PANSS-E         | -0.1151          | 0.4025  | -0.0108 | 0.9511  | -0.2226 | 0.3456  |
| DUP             | 0.0662           | 0.6311  | 0.0169  | 0.9234  | 0.1710  | 0.4710  |

Abbreviations: ACTH, adrenocorticotrophic hormone; DHEA-S, dehydroepiandrosterone sulfate; DUP, duration of untreated psychosis; PANSS-P, positive and negative syndrome scale-positive; PANSS-N, positive and negative syndrome scale-negative; PANSS-C, positive and negative syndrome scale-cognitive; PANSS-D, positive and negative syndrome scale-depression; PANSS-E, positive and negative syndrome scale-excitement; r, correlation coefficient

DHEA and its sulfate ester (DHEA-S) take part in brain development by promoting neuronal differentiation, synaptic connectivity, myelination, and neuron growth.<sup>36,37</sup> DHEA reduces pro-inflammatory cytokines both in vivo and in vitro.<sup>26</sup> DHEA administration decreases inflammation by the inhibition of Interleukin-6 (IL-6) and Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ), cytokines whose levels have been found to increase in FEPs.<sup>32,38</sup> DHEA-S is the precursor of the sex hormones testosterone and estrogen, and exerts some of its actions by directly binding and activating estrogen receptors in the brain.<sup>10</sup>

Elevated DHEA-S levels may remain as a compensatory effect or as a neuroprotection against chronic oxidative stress or inflammation, factors strongly associated with schizophrenia and FEP. Decreased cortisol/DHEA-S ratio may represent a prolonged neuroprotective effect or a blunted cortisol response to stress.<sup>26</sup>

We did not find any statistically significant difference in ACTH levels between patients and controls. Similar findings by Beyazyuz et al,<sup>18</sup> Misiak et al,<sup>13</sup> reports increased ACTH levels in FEP patients. As the researchers state, their meta-analysis included only seven studies

**Table 3.** Linear regression analysis between different psychopathological characteristics and measured hormones in patients.

|                        | Total population |             |         | Men   |             |         | Women |             |         |
|------------------------|------------------|-------------|---------|-------|-------------|---------|-------|-------------|---------|
|                        | beta             | 95% CI      | p-value | beta  | 95% CI      | p-value | beta  | 95% CI      | p-value |
| <b>DHEA-S</b>          |                  |             |         |       |             |         |       |             |         |
| PANSS-P                | -0.05            | -0.10, 0.01 | 0.110   | -0.02 | -0.07, 0.03 | 0.422   | -0.10 | -0.27, 0.07 | 0.251   |
| PANSS-N                | 0.02             | -0.02, 0.05 | 0.341   | 0.02  | -0.01, 0.04 | 0.187   | 0.03  | -0.10, 0.17 | 0.589   |
| PANSS-C                | 0.03             | 0.00, 0.06  | 0.027   | 0.04  | 0.01, 0.07  | 0.006   | 0.02  | -0.05, 0.09 | 0.503   |
| PANSS-D                | -0.03            | -0.09, 0.03 | 0.342   | -0.03 | -0.09, 0.02 | 0.220   | -0.04 | -0.20, 0.13 | 0.628   |
| PANSS-E                | 0.01             | -0.02, 0.05 | 0.435   | -0.03 | -0.09, 0.02 | 0.220   | 0.04  | -0.02, 0.10 | 0.139   |
| DUP                    | 0.00             | -0.01, 0.01 | 0.744   | 0.00  | -0.01, 0.01 | 0.877   | 0.02  | -0.02, 0.06 | 0.352   |
| <b>ACTH</b>            |                  |             |         |       |             |         |       |             |         |
| PANSS-P                | 1.39             | -1.27, 4.05 | 0.299   | 1.19  | -1.83, 4.22 | 0.429   | 2.35  | -4.44, 9.14 | 0.476   |
| PANSS-N                | 0.38             | -1.15, 1.90 | 0.621   | 0.56  | -1.03, 2.15 | 0.478   | -0.98 | -6.17, 4.20 | 0.694   |
| PANSS-C                | -0.14            | -1.65, 1.37 | 0.849   | -0.19 | -2.20, 1.81 | 0.840   | -0.07 | -2.72, 2.58 | 0.956   |
| PANSS-D                | 0.98             | -1.99, 3.96 | 0.511   | 1.21  | -2.28, 4.71 | 0.484   | 0.49  | -5.91, 6.89 | 0.875   |
| PANSS-E                | -0.10            | -1.88, 1.68 | 0.911   | -0.15 | -3.73, 3.44 | 0.935   | -0.11 | -2.60, 2.38 | 0.927   |
| DUP                    | 0.23             | -0.35, 0.82 | 0.424   | 0.16  | -0.49, 0.81 | 0.617   | 0.57  | -1.00, 2.14 | 0.453   |
| <b>Cortisol</b>        |                  |             |         |       |             |         |       |             |         |
| PANSS-P                | -0.50            | -1.27, 0.27 | 0.200   | -0.66 | -1.53, 0.20 | 0.126   | 0.58  | -1.29, 2.44 | 0.523   |
| PANSS-N                | -0.17            | -0.61, 0.27 | 0.439   | -0.09 | -0.56, 0.38 | 0.697   | -0.51 | -1.91, 0.89 | 0.453   |
| PANSS-C                | 0.23             | -0.21, 0.66 | 0.301   | -0.04 | -0.63, 0.54 | 0.881   | 0.49  | -0.19, 1.17 | 0.144   |
| PANSS-D                | 0.21             | -0.65, 1.08 | 0.622   | 0.56  | -0.45, 1.57 | 0.264   | -0.77 | -2.48, 0.94 | 0.358   |
| PANSS-E                | -0.28            | -0.79, 0.24 | 0.284   | -0.68 | -1.70, 0.33 | 0.182   | -0.03 | -0.71, 0.65 | 0.931   |
| DUP                    | -0.03            | -0.21, 0.14 | 0.685   | -0.08 | -0.27, 0.11 | 0.418   | 0.25  | -0.16, 0.67 | 0.218   |
| <b>Cortisol/DHEA-S</b> |                  |             |         |       |             |         |       |             |         |
| PANSS-P                | 0.03             | -0.58, 0.64 | 0.928   | -0.28 | -0.99, 0.44 | 0.437   | 0.88  | -0.50, 2.26 | 0.195   |
| PANSS-N                | -0.25            | -0.59, 0.09 | 0.150   | -0.21 | -0.58, 0.17 | 0.268   | -0.69 | -1.73, 0.34 | 0.177   |
| PANSS-C                | -0.29            | -0.62, 0.04 | 0.086   | -0.42 | -0.87, 0.03 | 0.064   | -0.11 | -0.66, 0.45 | 0.693   |
| PANSS-D                | 0.26             | -0.42, 0.93 | 0.446   | 0.45  | -0.37, 1.26 | 0.274   | -0.10 | -1.45, 1.24 | 0.876   |
| PANSS-E                | -0.17            | -0.57, 0.23 | 0.396   | 0.32  | -0.52, 1.16 | 0.446   | -0.41 | -0.89, 0.07 | 0.090   |
| DUP                    | 0.01             | -0.12, 0.15 | 0.862   | 0.00  | -0.15, 0.16 | 0.974   | 0.00  | -0.33, 0.34 | 0.987   |

Abbreviations: ACTH, adrenocorticotrophic hormone; CI, confidence interval; DHEA-S, dehydroepiandrosterone sulfate; DUP, duration of untreated psychosis; PANSS-P, positive and negative syndrome scale-positive; PANSS-N, positive and negative syndrome scale-negative; PANSS-C, positive and negative syndrome scale-cognitive; PANSS-D, positive and negative syndrome scale-depression; PANSS-E, positive and negative syndrome scale-excitement

with FEP patients were included and assessment of publication bias cannot be excluded.

Misiak et al<sup>13</sup> report higher cortisol blood levels but not unstimulated salivary cortisol levels in FEPs, while Aymerich et al<sup>14</sup> did not find any statistically significant difference in cortisol levels between FEPs and controls. According to the researchers, cortisol's little influence on dopamine secretion could explain its absence of elevation during the onset of psychosis. Cortisol level abnormalities observed in samples of chronic patients may indicate the evolution or severity of the disorder. No difference in cortisol levels is reported by

Chaumette et al,<sup>15</sup> Beyazuz et al,<sup>18</sup> Strous et al,<sup>19</sup> Solanki et al.<sup>20</sup> Hubbard and Miller<sup>6</sup> report increased blood cortisol levels in minimally treated FEPs compared to controls. In the same meta-analysis, the stratification by geographic region showed that significantly increased cortisol levels were found in studies from Europe and Asia. On the contrary, studies from the Middle East showed a trend for lower cortisol levels in FEPs compared to controls.

As DHEA-S functions as a cortisol antagonist, it may be implicated in returning cortisol levels to baseline after the stress response. DHEA-S elevations tend to be

observed after psychosocial stress and later than the cortisol peak.<sup>39</sup>

It may be suggested that the increase of DHEA-S levels in female patients may be due to a compensatory mechanism aiming at estrogen augmentation, with lower gonadal levels leading to higher DHEA production as part of negative feedback regulation<sup>26</sup> Estrogens increase synaptic plasticity and reduce neuro-inflammation, have antiapoptotic actions and increase dopamine sensitivity in the Ventral Tegmental Area (VTA), thus leading to the reduction of psychotic symptoms.<sup>40,41</sup>

Cortisol/DHEA-S ratio represents the relative imbalance between these two hormones, suggesting a possible role as an index of the HPA axis state. In our study, the cortisol/DHEA-S ratio was consistently lower in FEP patients compared to controls in the total population, as well as separately in men and women. The lower cortisol/DHEA-S ratio reflects the higher DHEA-S values in female patients and the lower cortisol levels in male patients

Our findings provide evidence for higher DHEA-S levels in females but not in males with FEP. Further studies are needed in this field to elucidate the possible implications of DHEA-S in psychosis.

Our sample consists of First-episode patients. First-episode psychosis diagnoses other than schizophrenia are quite unstable over time, although most of them shift to the diagnosis of schizophrenia (Fousar-Poli et al 2016).<sup>42</sup> Prospective studies with larger sample sizes may account for this limitation.

Hormone stress measurement at one point in time does not permit us to generalize our conclusions or to draw causal relationships. Measurements once a day

are not as reliable as multiple measurements during the day, as stress hormone levels follow a circadian rhythm. Future studies should conduct multiple daily measurements in order to account for hormonal fluctuations during the day.

We could not assess perceived anxiety in our study group during the time they were waiting for blood collection (both patients and controls). This is a limitation of our study, since anxiety could have influenced our results.

We could not take into account the phase/day of the menstrual cycle of the female participants, and this could have influenced our results.

The control group was not a random sample of the population, and this is a critical limitation of our study. Statistical analysis of many sociodemographic variables suggested no differences between our two groups, but we cannot exclude the presence of other confounding factors. Nevertheless, our study still had a higher sample size compared to similar previously published ones.

## Conclusion

Female patients with schizophrenia have a later age of onset, better response to antipsychotic treatment, and better prognosis than men. As DHEA-S acts as a compensatory, neuroprotective mechanism, higher DHEA-S values only in female FEP patients may represent a more effective, gender-dependent, compensatory process.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: <https://doi.org/10.22365/jpsych.2025.016>

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# Ερευνητική εργασία

## Συγκεντρώσεις θειικής δεϋδροεπιανδροστερόνης (DHEA-S), κορτιζόλης και αδρενοκορτικοτρόπου ορμόνης (ACTH) σε ασθενείς με πρώτο ψυχωτικό επεισόδιο άνευ αντιψυχωτικής θεραπείας

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### ΠΕΡΙΛΗΨΗ

Ο άξονας υποθάλαμος-υπόφυση-επινεφρίδια (ΥΥΕ) παίζει σημαντικό ρόλο στη ρύθμιση της δράσης της ντοπαμίνης σε περιοχές του εγκεφάλου, ιδιαίτερα στο λιμβικό σύστημα καθώς και στην απάντηση στο στρες. Η εκτίμηση του άξονα αυτού είναι σημαντική για την αναζήτηση βιολογικών μηχανισμών που οδηγούν από τις στρεσογόνες εμπειρίες στην έναρξη της ψύχωσης. Η έκκριση της αδρενοκορτικοτρόπου ορμόνης (ACTH) από την πρόσθια υπόφυση διεγείρει την παραγωγή κορτιζόλης και δεϋδροεπιανδροστερόνης (DHEA) από τον φλοιό των επινεφριδίων ως απάντηση στο στρες. Η ταυτόχρονη έκλυση της DHEA μπορεί να δρα ως προστατευτικός μηχανισμός ως προς τις τοξικές επιδράσεις της υπερέκκρισης κορτιζόλης. Σκοπός της μελέτης ήταν η μέτρηση στον ορό συγκεντρώσεων DHEA-S, ACTH, κορτιζόλης και ο υπολογισμός του λόγου κορτιζόλης/DHEA-S σε ασθενείς πρώτου ψυχωτικού επεισοδίου που δεν είχαν λάβει αντιψυχωτική αγωγή και σε αντίστοιχη ομάδα ελέγχου και σύγκριση των αποτελεσμάτων. Συμπεριλάβαμε δεδομένα από 110 άτομα (70 άνδρες, 40 γυναίκες), 55 ασθενείς και 55 ως ομάδα ελέγχου. Η μέση ηλικία των ασθενών ήταν 31,3 έτη (8,7) και 31,4 έτη (8,9) για την ομάδα ελέγχου. Η τιμές της DHEA-S στον ορό ήταν υψηλότερες στους ασθενείς σε σύγκριση με την ομάδα ελέγχου [0,69 (0,40) έναντι 0,50 (0,19), αντίστοιχα]. Οι τιμές της ACTH του ορού ήταν παρόμοιες μεταξύ των δύο ομάδων [28,0 pg/ml (6,2–73,9) έναντι 22,4 pg/ml (7,0–70,5), αντίστοιχα]. Οι τιμές της κορτιζόλης ορού και ο λόγος κορτιζόλης/DHEA-S ήταν χαμηλότερα στους ασθενείς [12,6 mg/dl (4,5) και 4,4% (1,3–19,5), αντίστοιχα] σε σύγκριση με την ομάδα ελέγχου [15,4 mg/dl (3,7) και 7,0% (2,4–25,5), αντίστοιχα]. Η επιμέρους ανάλυση έδειξε ότι στους άνδρες, οι συγκεντρώσεις της DHEA-S στον ορό ήταν παρόμοιες μεταξύ ανδρών ασθενών και ομάδας ελέγχου [0,53 (0,23) έναντι 0,48 (0,17), αντίστοιχα] ενώ στις γυναίκες οι συγκεντρώσεις της DHEA-S στον ορό ήταν υψηλότερες στις ασθενείς σε σύγκριση με τις γυναίκες της ομάδας ελέγχου [0,97 (0,47) έναντι 0,55 (0,20), αντίστοιχα]. Οι συγκεντρώσεις της ACTH στον ορό δεν διέφεραν μεταξύ των ανωτέρω υποομάδων. Οι τιμές κορτιζόλης ορού στους άνδρες ήταν χαμηλότερες στους ασθενείς σε σύγκριση με την ομάδα ελέγχου [12,8 mg/dl (4,4) έναντι 15,9 mg/dl (3,6)]. Επιπρόσθετα, ο λόγος κορτιζόλης/DHEA-S ήταν χαμηλότερος στους ασθενείς σε σύγκριση με την ομάδα ελέγχου τόσο στους άνδρες [4,4% (1,3–19,5) έναντι 5,8% (2,4–15,4)], όσο και στις γυναίκες [4,3% (1,8–15,2) έναντι 7,9% (4,0–25,5), αντίστοιχα]. Η ανάλυση συσχετίσεων πραγματοποιήθηκε για τον έλεγχο συσχετίσεων μεταξύ ψυχοπαθολογικών χαρακτηριστικών των ασθενών και των ορμονών που μετρήθηκαν. Έδειξε ότι η νοητική υποκλίμακα της PANSS συσχετιζόταν θετικά με τα επίπεδα της DHEA-S στους άνδρες και η θετική της υποκλίμακα συσχετιζόταν αρνητικά με τη DHEA-S στις γυναίκες. Στην ανάλυση γραμμικής παλινδρόμησης, η DHEA-S σχετιζόταν θετικά με τη νοητική υποκλίμακα της PANSS στους άνδρες.

**ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ:** Θειική δεϋδροεπιανδροστερόνη (DHEA-S), κορτιζόλη, αδρενοκορτικοτρόπος ορμόνη (ACTH), πρώτο ψυχωτικό επεισόδιο, ασθενείς άνευ θεραπείας.

## Research article

# Prevalence of attention deficit hyperactivity disorder in individuals with psychoactive substance dependence

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### ABSTRACT

Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurodevelopmental childhood disorder, which in most cases persists in adulthood, causing severe functional impairment. ADHD constitutes an important risk factor for the onset of use and the development of dependence on psychoactive substances. Impulse control disorders, anxiety, mood disorders, and substance abuse are the most common comorbid disorders. The present study aims to estimate the prevalence of ADHD in adult users of psychoactive substances who have attended a treatment program in a special detoxification unit for psychoactive substances. The study concerns the examination of one hundred eighteen psychoactive substance users using the following diagnostic tools: (a) Section 12 of the semi-structured interview SCAN 2.0, which assesses diagnostic criteria of psychoactive substance abuse and dependence. (b) The structured clinical interview CIS-R, which investigates the presence of psychopathological symptoms of “common mental disorders”. (c) The WURS scale retrospectively probes into ADHD symptoms up to the age of 7. The prevalence of ADHD in the sample of individuals with psychoactive substance use disorders was found to be 38.1%. Analyses were also performed concerning age and the comorbidity of common psychiatric disorders and ADHD. Findings are consistent with the results of other studies. The drug users of psychoactive substances, regardless of the ADHD comorbidity, had an increased prevalence of common psychiatric disorders. The most common comorbidities were other psychoactive substance disorders, anxiety, and depressive disorders. The small number of participants, the exclusive use of a single substance by the participants, and the type of unit where the present study was conducted restrict the generalizability of its results.

**KEYWORDS:** ADHD, psychoactive substance use, WURS scale, prevalence, comorbidity.

### Introduction

Attention-deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder of childhood, which in the majority of cases persists into adulthood, causing significant functional impairment.<sup>1</sup> The main problems of ADHD are considered to be behavioral dysregulation, deficits in executive functions, especially in inhibitory control and active memory, and delayed aversion, i.e., the behavioral tendency of these individu-

als to show a preference for smaller immediate rewards over larger delayed rewards.<sup>2</sup> The prevalence of ADHD in school-age children is 3–7% if DSM-IV<sup>3</sup> criteria are applied, or 1–2% according to the more stringent ICD-10.<sup>4</sup> Longitudinal studies of children and adolescents with ADHD have shown that the disorder persists into adulthood to a significant degree. Another study suggests that the prevalence of ADHD in school-age children is estimated at 2–18%.<sup>5</sup>

The ratio of boys to girls ranges from 3:1 to 5:11.1 ADHD symptomatology varies according to developmental stages and is characterized by age-inappropriate inattention, hyperactivity, and impulsivity.<sup>1,2</sup> Impulse control disorders, anxiety and emotional disorders, and substance abuse are the most common comorbid conditions.<sup>6</sup> The lifestyle of individuals and the impact of comorbid conditions on major areas of functioning form the basis of diagnostic assessment. It is primarily differentiated from bipolar disorder and borderline personality disorder.

ADHD is an important risk factor for initiating and developing dependence on psychoactive substances. The prevalence of ADHD in people with psychoactive substance use disorders varies greatly between studies and across substances of abuse/dependence, between 5.2–50.6%,<sup>7–12</sup> whereas the prevalence of psychoactive substance use in individuals with a history of ADHD was found to be between 15–50.7%.<sup>6,9,13,17</sup> This comorbidity is related to serious personal and social problems and poor academic performance.<sup>18</sup>

Comorbidity between substance-use disorders and ADHD has not been studied so far in Greece. The present study aims to investigate the prevalence of ADHD in adult psychoactive substance users attending a treatment program in a psychoactive substance treatment facility. More specifically, the study aimed to retrospectively investigate the prevalence of ADHD in psychoactive substance users by examining whether they met the criteria for the disorder by the age of 7 years.

Existing literature<sup>6–24</sup> suggests an association between substance use and ADHD, and therefore, we felt it was necessary to study adults with psychoactive substance use for retrospective assessment of ADHD symptoms. The same users would have to meet the ICD-10<sup>4</sup> criteria for psychoactive substance use and dependence. In addition, the presence of co-occurring psychopathology was assessed in them.

## Material and Method

### Sample

The sample consists of 118 adult users of psychoactive substances aged 18–40 with heroin as the main substance of use, either intravenously or as a smoker, and with a frequency of daily use in the last month. The users entered the rehabilitation unit between January 2008 and October 2013. The minimum duration of regular use, at least twice a week, was set at one year. One hundred and one people refused to participate in the survey. The patients (psychoactive drug users) came from

a Rehabilitation Unit where they were undergoing psychotherapy and physical rehabilitation. All patients were included as consecutively registered in the waiting book when they had expressed their request for admission to the program. All patients met the criteria for psychoactive substance use disorder. In the first session, the users were almost always in use. Users with psychotic disorders and persons with irreversible brain damage were excluded from the study.

### Methodology

Individuals participating in the study were screened with three diagnostic tools. Users enter the Addiction Counselling Centre, in Athens (Greece), with the request to detoxify from substances, and are almost always using; they were tested with the following psychometric tools:

- a. Section 12 of the semi-structured SCAN 2.0 interview,<sup>25</sup> which assesses whether users meet the criteria of psychoactive substance abuse and dependence. The reliability of the interview has been tested and found to be high.<sup>26</sup>
- b. The CIS-R structured clinical interview,<sup>27</sup> which examines the presence of psychopathology symptoms of common mental disorders that can be used for diagnostic categorization according to ICD-10. The interview investigates the presence of 14 common symptoms in the last seven days. These symptoms are, in order, the following: physical symptoms, fatigue, concentration and attention, sleep problems, irritability, concern about physical health, depression, depressive ideas, anxious ideas (worries), anxiety (physical), phobias, panic, obsessions, and compulsions. The reliability of the interview has been tested and found to be high.<sup>28–30</sup>
- c. With the WURS scale,<sup>31,3</sup> which retrospectively screens for ADHD symptoms up to the age of 7 years. The diagnostic criteria for ADHD in adults, as defined by the DSM-IV, require a history of ADHD from childhood. Unfortunately, many patients evaluated with the disorder in adulthood were not psychiatrically assessed for ADHD as children. Therefore, a prerequisite for the diagnosis of ADHD in adults is a retrospective assessment from childhood. The Wender Utah Rating Scale (WURS) was preferred because it includes symptoms of other disorders that often coexist with ADHD.<sup>32</sup>

Subjects rate these items, thus describing their childhood behavior, with the following rating: not at all or very mild (0), very little (1), moderate (2), quite a bit (3), or very much (4). Psychometric studies of the Wender

scale<sup>32</sup> demonstrated that ADHD can be diagnosed with as few as 25 of the original 61 items on the scale. According to these studies, if the total score of the 25-item scale is 46 or more, it is considered a positive diagnosis of ADHD. In the present study, for the diagnosis of ADHD, the 25-item scale was used.<sup>32</sup> We requested the author's permission to use the Wender scale in our research in Greece. His reply was positive. We used the scale after first translating it using the translation back-translation method.<sup>33</sup>

Statistical analysis was performed on the relationships between the ADHD status as defined by the WURS questionnaire (WURS score expressed as a dichotomous variable rated as positive for ADHD (score  $\geq 46$ ) or negative (score  $\leq 45$ )), and sociodemographic variables, as well as the presence of other psychiatric disorders, by use of contingency tables (chi square statistic). Reliability of the WURS questionnaire was assessed by measuring internal consistency (Cronbach's alpha).

## Results

### WURS Reliability

In international studies, reliability testing of WURS, both in 61 and 25 scales, using the internal consistency method showed excellent results (alpha 0.87–0.91).<sup>34,35</sup> In the present study, the results were also satisfactory (0.55–0.88). In the following 4 sub-units, the results were: ADHD diagnosis 0.84, unselected items for ADHD assessment 0.70, Health problems 0.55, and School problems 0.59.

### Socio-demographic characteristics of the sample

As shown in table 1, of the 118 users screened with the three diagnostic tools, 96.6% were male and 3.4% female, 93.2% lived alone, 5.1% were cohabiting, and 1.7% were married. 83.9% were unemployed, 7.6% had full-time jobs and 5.9% had part-time jobs, 0.8% were engaged in domestic work, and 1.7% were students. 72.0% had more than 10 years of education.

### Prevalence of ADHD and common mental disorders

Table 2 shows the prevalence of ADHD in phase 1 of the study. 38.1% of subjects met the criteria for an ADHD diagnosis, while 61.9% did not meet the criteria and were therefore classified as having a negative ADHD diagnosis. Due to the small number of women, we did not analyze the prevalence by gender. It also shows the prevalence of ADHD by age in the whole sample. Positive in ADHD was 46.4% of the sample at age 18–25, 40.8% at age 26–30, and 29.3% at age 31–

**Table 1.** Sociodemographic data of the patient group.

|                      | Range | N (118) | (%)  | Mean value | SD  |
|----------------------|-------|---------|------|------------|-----|
| Age                  | 18–25 | 28      | 23.7 | 27.9       | 3.9 |
|                      | 26–30 | 76      | 41.5 |            |     |
|                      | 31–40 | 14      | 34.8 |            |     |
| Gender               |       |         |      |            |     |
| Male                 |       | 114     | 96.6 |            |     |
| Female               |       | 4       | 3.4  |            |     |
| Family Status        |       |         |      |            |     |
| Married              |       | 2       | 1.7  |            |     |
| Cohabiting           |       | 6       | 5.1  |            |     |
| Unmarried            |       | 110     | 93.2 |            |     |
| Professional Status  |       |         |      |            |     |
| Full-time employment |       | 9       | 7.6  |            |     |
| Part-time employment |       | 7       | 5.9  |            |     |
| Unemployed           |       | 99      | 83.9 |            |     |
| Household            |       | 1       | 0.8  |            |     |
| Students             |       | 2       | 1.7  |            |     |
| Years of education   |       |         |      | 11.0       | 1.7 |
|                      | 0–10  | 33      | 28.0 |            |     |
|                      | 11–16 | 85      | 72.0 |            |     |

**Table 2.** Prevalence of ADHD by Age.

|                | Age         |             |             | Total       |
|----------------|-------------|-------------|-------------|-------------|
|                | 18–25       | 26–30       | 31–40       |             |
| ADHD diagnosis |             |             |             |             |
| Negative       | 15<br>53.6% | 29<br>59.2% | 29<br>70.7% | 73<br>61.9% |
| Positive       | 13<br>46.4% | 20<br>40.8% | 12<br>29.3% | 45<br>38.1% |
| Total          | 28          | 49          | 41          | 118         |

40. Comparison results showed non-statistically significant differences between age and ADHD diagnosis (chi-square= 2.33,  $p= 0.311$ ).

Table 3 reports the prevalence of co-occurring psychiatric disorders according to the CIS-R structured interview by age in the total sample. Of the total of 118 users, 75% had psychiatric disorders at age 18–25, 67.3% at age 26–30, and 85.4% at age 31–40. Comparison results showed non-statistically significant differences between age and psychiatric diagnosis (chi-square=3.91,  $p=0.141$ ).

**Table 3.** Prevalence of psychiatric disorders (CIS-R) by age.

| Diagnosis | Age         |             |             | Total       |
|-----------|-------------|-------------|-------------|-------------|
|           | 18-25       | 26-30       | 31-40       |             |
| Negative  | 7<br>25.0%  | 16<br>32.7% | 6<br>14.6%  | 29<br>24.6% |
| Positive  | 21<br>75.0% | 33<br>67.3% | 35<br>85.4% | 89<br>75.4% |
| Total     | 28          | 49          | 41          | 118         |

In table 4, the presence of ADHD is not associated with the high proportion of psychiatric disorders in our sample of heroin users. It is the presence of use that determines the high rate of psychiatric disorders. The comparison results showed non-statistically significant differences between ADHD and psychiatric disorders (chi-square 1.82, p=0.769).

### Discussion

The purpose of this study was to investigate whether psychoactive substance users who were retrospectively screened for ADHD symptoms met the criteria for the disorder by age 7 years. 118 adult psychoactive substance users aged 18–40 years with heroin as the main substance of use, intravenously or smoked, with a frequency of daily use in the last month, were examined. The minimum duration of regular use, at least twice a week, was set at 1 year. The SCAN 2.0 and CIS-R interviews were administered to assess psychopathology and psychoactive substance use, and the Wender questionnaire was administered to assess and diagnose ADHD. The total sample of 118 users consisted mainly of males. The mean age of the sample was 27.8 years. The education level of the group was 11.0 years of education on average, with 72.0% having 11–16 years of education. 83.9% were unemployed, while 5.9% were part-time employed.

The prevalence of ADHD in the first phase of the study was 38.14%. It is observed that the highest prevalence of ADHD was found in the age group of 18–25 years, with

46.4%, perhaps because at this age, due to the proximity to the onset of the disorder, users can recall and distinguish the necessary symptoms. At the age of 26–30 years, the prevalence of ADHD was 40.8. Finally, at the age of 31–40 years, the prevalence of ADHD was 29.3%, perhaps because at this age, the ability to recall the symptoms of the disorder was lower than in other age groups. Our results are like a study that found that 36% of adults who met the criteria for ADHD in childhood continued to meet the criteria as adults.<sup>36</sup> Many cases of ADHD from childhood, around 60% in some studies, continue to have significant symptoms as adults.<sup>37–39</sup>

Regarding the co-occurrence of psychiatric disorders, 75% of the sample were found positive for psychiatric disorders at age 18–25, 67.3% at age 26–30, and 85.4% at age 31–40, respectively. The analysis of the data shows that the presence of psychoactive substance use seems to be associated with a high prevalence of common psychiatric disorders. This finding is consistent with those of other studies,<sup>40–49</sup> which have shown that in heroin-dependent users, major depression, alcohol dependence, antisocial disorder, and borderline personality disorder occurred at a much higher frequency than in the general population. It should be noted here that concentration and memory problems, motor restlessness, irritability, anhedonia, and sleep problems may be symptoms of ADHD and should not be taken as symptoms of depression.<sup>50</sup> Concerning children with ADHD, another earlier study<sup>51</sup> notes that 30–50% of children with ADHD meet the criteria for communication disorder or ADHD, with a prevalence of comorbidity more in boys than in girls.

Regarding the relationship between ADHD and substance use, this has been the subject of research, with the prevailing view that the presence of conduct disorder is necessary for a person with ADHD to develop a substance use disorder. Antisocial personality disorder and substance abuse are more common in adults with a history of childhood ADHD than in individuals without childhood psychopathology. Childhood ADHD can be considered a precursor condition to adolescent antisocial personality disorder.<sup>2</sup> There appears to be a deficit

**Table 4.** Comorbidity (CIS-R) of psychiatric disorders and ADHD.

| Psychiatric disorder                    | ADHD (+)   | ADHD (-)   | Total      |
|---|------------|------------|------------|
| Anxiety disorders                       | 9 (12.3%)  | 3 (6.7%)   | 12 (10.2%) |
| Anxiety disorders + Emotional disorders | 22 (30.1%) | 18 (40.0%) | 40 (33.9%) |
| Emotional disorders                     | 24 (32.9%) | 13 (28.9%) | 37 (31.4%) |
| Without a psychiatric disorder          | 18 (24.7%) | 11 (24.4%) | 29 (24.5%) |
| Total                                   | 73 (100%)  | 45 (100%)  | 118 (100%) |

in behavioral regulation, which explains the comorbidity between ADHD and substance use disorder.<sup>52</sup> Thus, conduct disorder has been found to increase the risk for substance use disorder,<sup>53</sup> while the presence of ADHD or conduct disorder in childhood is also an important predictor of substance use disorder.<sup>54</sup> Adolescents with ADHD are usually immature and engage in high-risk activities such as risky driving, smoking, unprotected sexual intercourse, and hashish use.<sup>55–58</sup> The hyperactivity present in children is experienced by adults as subjective motor anxiety. Adults with ADHD, as discussed above, in addition to a higher prevalence of anxiety and depression, have an increased risk of poor physical health, including serious road accidents.<sup>59–63</sup>

In summary, in our study, the user sample meets the criteria for ADHD, with a higher prevalence compared to most epidemiological studies, whereas both psychoactive substance use and ADHD are associated with a high prevalence of psychiatric disorders, similar to that found in other studies.

Our study has serious limitations in terms of the generalizability of its results. First, it took place in a service that receives the most severe cases of people with psychoactive substance use disorders, mainly heroin. Consequently, we cannot claim that the sample represents the profile of psychoactive substance users in Greece, which may influence the true prevalence of ADHD among psychoactive substance users. Moreover, the sample consists exclusively of people who use heroin, which limits the results to this substance. Secondly, our findings on the prevalence of ADHD in persons with sub-

stance abuse are at high rates, compared with some other studies that reported much lower rates. This is probably because a self-rated questionnaire was used instead of a diagnostic interview. Studies in which the diagnosis of ADHD was made by use of an interview report with much lower rates.<sup>11</sup> Bowling (2005) and Rickwood and Coleman-Rose (2023),<sup>64,65</sup> reported the pros and cons of using interviews and questionnaires. Interviewers may suffer from social desirability bias (i.e., under-reporting undesirable behaviors and over-reporting desirable ones) and self-administered questionnaires from recall effects (i.e., the time frame during which a behavior occurs) and, in addition, respondents are prone to reveal sensitive information they would likely not report in interviews. Nevertheless, interviews, especially semi-structured ones, allow the interviewer to ask additional probes to determine accurately the existence and timing of pathological symptoms and behaviors. Questionnaires must be validated against a “Golden Rule”, that is, the diagnosis, usually obtained using a structured or semi-structured interview. The Greek translation of the WURS scale has not been validated yet using a similar method. In determining the prevalence of ADHD, we used the cut-off points suggested by the creator of the questionnaire. Therefore, although our rates are at the high end, these may have been somehow inflated using the unvalidated instrument. Finally, the small sample size is another drawback, but this is justified by the difficulties in collecting a large sample of people with psychoactive substance use. With these limitations, it is understood that further research into a larger number of subjects is necessary to reach more reliable conclusions.

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## Ερευνητική εργασία

# Επιπολασμός διαταραχής ελλειμματικής προσοχής και υπερκινητικότητας σε άτομα με εξάρτηση από ψυχοδραστικές ουσίες

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### ΠΕΡΙΛΗΨΗ

Η διαταραχή ελλειμματικής προσοχής – υπερκινητικότητας (ΔΕΠΥ) αποτελεί τη συχνότερη νευροαναπτυξιακή διαταραχή της παιδικής ηλικίας, η οποία στην πλειονότητα των περιπτώσεων επιμένει στην ενήλικη ζωή, προκαλώντας σημαντική λειτουργική επιβάρυνση. Η ΔΕΠΥ αποτελεί σημαντικό παράγοντα κινδύνου για την έναρξη χρήσης και ανάπτυξη εξάρτησης από ψυχοδραστικές ουσίες. Οι διαταραχές ελέγχου των παρορμήσεων, οι αγχώδεις και συναισθηματικές διαταραχές, καθώς και η κατάχρηση ουσιών, αποτελούν τις πιο συχνές συννοσηρές καταστάσεις. Στόχος της παρούσας έρευνας είναι η μελέτη του επιπολασμού της ΔΕΠΥ σε ενήλικους χρήστες ψυχοδραστικών ουσιών, οι οποίοι παρακολουθούσαν θεραπευτικό πρόγραμμα σε ειδική μονάδα για ψυχοδραστικές ουσίες. Η έρευνα αφορά στην εξέταση 118 χρηστών ψυχοδραστικών ουσιών οι οποίοι ελέγχθηκαν με τρία διαγνωστικά εργαλεία: (α) την ενότητα 12 της ημιδομημένης συνέντευξης SCAN 2.0 με την οποία εκτιμάται αν οι χρήστες πληρούν τα κριτήρια της εξάρτησης από ψυχοδραστικές ουσίες, (β) τη δομημένη κλινική συνέντευξη CIS-R η οποία διερευνά την παρουσία στοιχείων ψυχοπαθολογίας των «συνήθων ψυχικών διαταραχών» και (γ) την κλίμακα WURS η οποία διερευνά αναδρομικά για συμπτώματα ΔΕΠΥ έως την ηλικία των 7 ετών. Ο επιπολασμός ΔΕΠΥ στο δείγμα ατόμων με διαταραχές από χρήση ψυχοδραστικών ουσιών βρέθηκε στο 38,14% των χρηστών, ενώ αναλύσεις έγιναν και για τον επιπολασμό ανά ηλικιακή ομάδα, όπως και για τη συννοσηρότητα με τις συνήθεις ψυχιατρικές διαταραχές, η οποία βρέθηκε αυξημένη, ανεξάρτητα από την παρουσία ΔΕΠΥ. Οι πιο συχνές συννοσηρότητες ήταν οι διαταραχές χρήσης άλλων ψυχοδραστικών ουσιών, οι αγχώδεις και οι καταθλιπτικές διαταραχές. Ο μικρός αριθμός συμμετεχόντων, η αποκλειστική χρήση από τους συμμετέχοντες μίας και μοναδικής ουσίας, και η υπηρεσία στην οποία έλαβε χώρα η μελέτη περιορίζουν τη γενίκευση των αποτελεσμάτων της.

**ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ:** ΔΕΠΥ, χρήση ψυχοδραστικών ουσιών, κλίμακα WURS, επιπολασμός, συννοσηρότητα.

## Research article

# Picture description impairment and neurocognition in schizophrenia: A pilot study

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### ABSTRACT

Schizophrenia is also manifested in a pattern of impaired speech traditionally considered to reflect thought disorder. This pilot study aimed to investigate the relationship between language impairment and other neurocognitive impairments and psychopathology. The study included 10 patients with schizophrenia (5 males), aged  $45.5 \pm 12.48$  years. They were assessed with the Positive and Negative Syndrome Scale (PANSS), scales of disability, and a neuropsychological battery. The experimental condition included four pictures with concrete everyday life content. The statistical analysis included the calculation of Spearman's rho correlation coefficient. Picture description was significantly correlated with the PANSS – General psychopathology. Non-significant but high correlations included the PANSS – Negative, ratings of disability, and the Graphic Sequence test, the Rey figure, and the Stroop test, but there was a lack of correlation with verbal fluency, abstract thinking, and executive function. Despite the small study sample, it could be said that the impaired performance in picture description in patients with schizophrenia is not a consequence of disordered thought alone, but also of the existence of a dysfunctional processing of visual information and a problematic translation of it into meaningful mental images.

**KEYWORDS:** Schizophrenia; language disorders; formal thought disorder; visuospatial ability; picture description; psychopathology.

### Introduction

Apart from classical positive psychotic symptoms, schizophrenia is also manifested in a pattern of impaired verbal communication.<sup>1</sup> Patients often exhibit flattened prosody and loose semantic associations in their speech that are traditionally considered to reflect thought disorder rather than language impairment per se. The literature supports the understanding that speech disorder in schizophrenia is the direct result of the so-called Formal Thought Disorder (FTD), which includes disturbances in concept formation, semantic issues like neologisms, and

transitions between thoughts, and includes how one perceives, interprets, structures, and responds to information.<sup>2–5</sup> However, problems from basic phonetics to more complex semantic, grammar, and syntactic levels have been reported,<sup>6–10</sup> and a possible relationship with longer duration of illness and severity of both positive<sup>11</sup> and negative symptoms<sup>12–15</sup> has also been proposed.

These impairments were also reported to constitute an endophenotype, as they were frequently observed in healthy relatives of patients and people at high risk.<sup>16–19</sup> Comprehension difficulties also seem to exist, as pa-

tients struggle to process linguistic information.<sup>20–23</sup> The neuropathology underlying language disorders in schizophrenia remains unknown.<sup>11,24–26</sup>

Until now, a variety of methods have been used to study languages in schizophrenia. Studies on verbal fluency suggest the existence of non-disorder-specific inability to distinguish target signal from competing noise and to maintain cues for production of memory probes as a result of impaired cognitive control, and this manifests in variable ways corresponding to different underlying mechanisms.<sup>27–29</sup>

Spontaneous speech research revealed possible disease-specific problems in the temporal organization of speech.<sup>30,31</sup> Research on picture naming or the description of vague pictures revealed the existence of specific action-naming impairments that could arise from problems in both semantic and postsemantic processes.<sup>32</sup> To our knowledge, there is no attempt so far to investigate the performance of patients in the description of simple pictures with clear and concrete content, in a similar way to the testing of dementia,<sup>33–35</sup> and in a manner closer to everyday life demands.<sup>36–39</sup> Also, the data concerning the relationship of language problems with dysfunction in other neurocognitive domains is inconclusive, given the variety of language problems and the assessment methods.

This pilot study aimed to register a possible impairment in patients with schizophrenia in the description of simple pictures and to investigate the relationship of such an impairment with other neurocognitive impairments and psychopathology. As small-scale pilot studies are exploring, the findings of this study will be used to develop and formulate a proper research question to design larger-scale future research.

## Material and Method

### Participants and procedures

The study included 10 physically healthy outpatients (5 males), aged  $45.5 \pm 12.48$  years (range 19–56), suffering from schizophrenia. To be included in the study, the participants should have a normal IQ, should not suffer from any neurological or other somatic disorder, and should not manifest substance or alcohol abuse at present or in the past. Smoking was allowed. Any medication treatment was not a contraindication to participate in the study.

All participants provided written informed consent to participate in the study. The study was approved by the Ethics Committee of the School of Medicine, Aristotle University of Thessaloniki, Greece (ref number 260/2024)

The research protocol included the gathering of socio-demographic data and the registration of medication. Antipsychotics were transformed into olanzapine equivalents.<sup>40</sup> Half of the patients had a family history of any mental disorder. The variable “family history load” was calculated as the number of individual persons in the family with any mental disorder (first and second-degree relatives).

### Measures

The psychotic symptoms were assessed with the Structured Clinical Interview of the Positive and Negative Symptoms Scale (SCI-PANSS),<sup>41,42</sup> disability was assessed with the Global Disability Scale (GloDiS)<sup>43</sup> and the General Assessment of Functioning (GAF),<sup>44</sup> and the quality of life was assessed with the visual analog (thermometer type) Quality of Life (QoL) scale.<sup>45</sup> The neurocognition was assessed with a collection of tests that included the random letter test (attention and concentration) and the Graphic Sequence test,<sup>46</sup> the digit span-backwards and the Trail-making test A and B (working memory and mental speed), copying two- and three-dimensional shapes (visuospatial ability), the clock drawing test (executive functions),<sup>47</sup> copying of the Rey-Osterrieth Complex Figure test (visuospatial perception),<sup>48</sup> word naming (verbal fluency), a variation of the Stroop Test (counting mistakes only; mental inhibition).<sup>49</sup> Three tests are not published, but they are under standardization: a copying of two and three-dimensional scales copying task, a test of encoding strategies, and a story comprehension test (social cognition), while for the digits backwards, TMT A and B, and verbal fluency normative data are currently being collected. For all those tests, normative data are being collected.

Although important alternative theoretical models of the PANSS and schizophrenia exist, including works of our group,<sup>50–52</sup> we chose to use the original PANSS subscales (P-positive, N-negative, and G-general psychopathology).

The experimental condition included four pictures (Pic1-4) with concrete everyday life content, and the subject was asked to describe each of them while observing them. Two had colors, and two were black/white. One in each category had little information, while the other was complex. The description of the pictures is shown in table 1. The first picture is in color and includes a scene of one male adult and three children in a beach, the second is also in color and includes an agricultural scene in the tropics with two female adults around a fire, one male carrying goods, two kids and to farm animals,

**Table 1.** Description and characteristics of the testing pictures.

| Picture No | Color/BW | Description of content   | No of sub-scenes | Information load | No of information elements |
|------------|----------|--|------------------|------------------|----------------------------|
| Pic1       | Color    | Seaside scenery, 4 people sunbathing                             | 3                | low              | 24                         |
| Pic2       | Color    | Tropical scenery, 5 people and 2 animals                         | 5                | high             | 34                         |
| Pic3       | B/W      | A house and a tree   | 1                | low              | 7                          |
| Pic4       | B/W      | Two houses and two trees, a river and a boat with a person on it | 3                | high             | 20                         |

the third is a simple black and white picture of a small house and a tree, and the fourth is a more complex black and white of a house with two trees and a landscape.

### Statistical analysis

The statistical analysis was performed using the IBM SPSS software and included the development of frequency tables and the calculation of Spearman's rho correlation coefficient.

No correction for multiple comparisons was applied since this is a pilot study, with an exploratory purpose on a small study sample.

### Results

The basic descriptive statistics of the study sample, including sociodemographic and clinical variables as well as psychopathology and neurocognition, are shown in table 2. In the same table, patients' performance in the description of the four pictures is shown as percentages of the total number of pieces of information from the picture included in the patient's description. Patients performed similarly in the two low-information pictures (Pic1 and Pic3) and better than in the two high-information pictures (Pic2 and Pic4).

The correlations (Spearman's rho) of the performance in the four pictures with all the sociodemographic, clinical, psychometric, and neuropsychological variables are shown in table 3. The sample was very small (N=10), and the whole study was a pilot one; however, there was a statistically significant result concerning the correlation of PANSS G with Pic2 and Pic4. Non-significant but high was its correlation with Pic1, and the pattern of correlations suggests that the general psychopathology reduces performance to picture description in a direct relationship with their difficulty (as reflected in the patient's performance).

Correlations equal to or above 0.50 were considered important to further investigate the components determining the patients' performance. Interestingly, age,

age at onset, and duration of being ill did not seem to affect performance. A similar pattern with PANSS G was manifested by PANSS N, although the correlations did not reach significance. This was also the case with disability (especially its severity), as assessed by the GloDiS, except for picture Pic2, which was the most difficult one. A surprise was that the GAF manifested no correlations. Interestingly, Pic2 correlated positively with quality of life (QoL).

Maybe the most important finding of the current pilot study was the lack of correlation between verbal fluency, abstract thinking, and executive function on one side and picture performance on the other. Equally important is the observation that this performance seems to show some correlation with the Graphic Sequence test, the Rey figure, and the Stroop test.

### Discussion

The present study is a small-scale pilot study, and its findings should be considered only exploratory and interpreted with caution. It reports that overall, color does not seem to play an important role in the performance of picture description in patients with schizophrenia. On the contrary, the loading with information affects the performance in a non-linear way, since the cognitive demands increase disproportionately. The most robust effect on performance was manifested by general psychopathology and negative symptomatology, as well as by the severity of disability, and especially by the severity of mental disability. No important correlation was observed between picture performance and verbal fluency, abstract thinking, and executive function, and this was a surprise since such a finding was expected as a principal finding from the review of the literature. Instead, picture performance showed some correlation with the Graphic Sequence test, the Rey figure, and the Stroop test, all reflecting attentional processes (frontoparietal attentional network-FAN), and mental imaging in the interaction between the frontal, temporal, and parietal lobes.<sup>46,53-57</sup>

**Table 2.** Descriptive statistics of sociodemographic and clinical variables as well as of psychopathology and neurocognition.

|   | Mean   | Min | Max | SD    |
|---|--------|-----|-----|-------|
| Age (years)                                 | 45.50  | 19  | 56  | 12.48 |
| Paternal age (at delivery)                  | 35.22  | 28  | 51  | 7.41  |
| Maternal age (at delivery)                  | 32.00  | 24  | 40  | 5.63  |
| Olanzapine Equivalents                      | 18.81  | 1   | 77  | 21.26 |
| Total No of episodes                        | 2.50   | 1   | 6   | 1.72  |
| Age at psychosis onset (years)              | 24.80  | 7   | 47  | 13.29 |
| Age at Most Recent Episode (years)          | 34.50  | 7   | 52  | 15.76 |
| Duration                                    | 11.00  | 1   | 42  | 12.65 |
| Family history load                         | 1.90   | 0   | 6   | 2.33  |
| PANSS P                                     | 17.50  | 8   | 30  | 8.06  |
| PANSS N                                     | 18.70  | 9   | 33  | 6.95  |
| PANSS G                                     | 34.90  | 20  | 46  | 8.03  |
| PANSS Total                                 | 71.10  | 37  | 97  | 19.91 |
| GloDiS Everyday Functioning                 | 14.80  | 6   | 36  | 10.46 |
| GloDiS Social and Interpersonal Functioning | 6.40   | 0   | 14  | 4.72  |
| GloDiS Severity                             | 11.40  | 3   | 24  | 6.83  |
| GloDiS Mental Disability                    | 7.70   | 0   | 18  | 5.62  |
| GloDiS Total                                | 32.30  | 9   | 62  | 19.98 |
| GAF   | 53.50  | 35  | 85  | 14.35 |
| QoL Scale                                   | 48.50  | 10  | 100 | 26.88 |
| Digits backwards                            | 3.70   | 3   | 6   | 0.95  |
| Trail Making test A                         | 68.60  | 38  | 95  | 20.69 |
| Trail Making test B                         | 175.10 | 87  | 311 | 70.44 |
| Graphic sequence test                       | 9.50   | 1   | 14  | 3.59  |
| Copy a necker cube                          | 6.30   | 2   | 12  | 3.13  |
| Copy a house                                | 8.90   | 4   | 13  | 2.47  |
| Draw a clock (Mendez score)                 | 18.80  | 14  | 21  | 1.87  |
| Rey figure                                  | 37.90  | 27  | 55  | 7.81  |
| Verbal fluency                              | 45.60  | 36  | 55  | 6.04  |
| Abstract thinking                           | 36.90  | 20  | 50  | 10.75 |
| Social cognition                            | 20.50  | 5   | 30  | 8.20  |
| Stroop test (mistakes)                      | 3.90   | 0   | 23  | 7.11  |
| Picture description (correct information %) |        |     |     |       |
| PIC1  | 47.08  | 25  | 88  | 22.99 |
| PIC2  | 36.47  | 24  | 76  | 15.51 |
| PIC3  | 48.57  | 29  | 100 | 24.47 |
| PIC4  | 38.00  | 15  | 90  | 24.63 |

These correlations could imply that the central role in the impaired ability to process and describe a picture in schizophrenia is held by dysfunction at the level of mental imaging that implicates the right parietal cortex as well as the dorsolateral prefrontal cortex (working memory).<sup>58-60</sup> Since the digits backward test does not man-

ifest any correlation, the most probable interpretation could be that there is a severe dysfunction that affects even less demanding tasks in terms of working memory, with subcortical areas playing a major role.<sup>61</sup> Since the Trail Making test does not correlate with performance, the subcortical dysfunction should be specific, not gen-

**Table 3.** The correlations (Spearman's rho) of the performance in the four pictures with all the sociodemographic, clinical, psychometric and neuropsychological variables.

|  | Pic1%  | Pic2%   | Pic3% | Pic4%   |
|--|--------|---------|-------|---------|
| Age (years)                                  | 0.03   | 0.06    | -0.22 | 0.06    |
| Paternal age (at delivery)                   | 0.22   | -0.10   | 0.37  | -0.18   |
| Maternal age (at delivery)                   | 0.09   | -0.17   | 0.25  | -0.22   |
| Olanzapine Equivalents                       | 0.10   | 0.07    | 0.28  | -0.06   |
| Total No of episodes                         | 0.43   | 0.29    | 0.12  | 0.40    |
| Age at psychosis onset (years)               | 0.00   | 0.43    | 0.03  | 0.17    |
| Age at Most Recent Episode (years)           | -0.04  | 0.20    | -0.08 | 0.08    |
| Duration                                     | 0.07   | -0.06   | 0.11  | 0.08    |
| PANSS_P                                      | -0.26  | -0.42   | 0.03  | -0.33   |
| PANSS_N                                      | -0.50* | -0.44   | 0.09  | -0.45   |
| PANSS_G                                      | -0.56* | -0.69** | -0.21 | -0.65** |
| PANSS total                                  | -0.57* | -0.58*  | -0.16 | -0.57*  |
| Glo.Dis Everyday Functioning                 | -0.31  | 0.16    | -0.20 | -0.34   |
| Glo.Dis Social and Interpersonal Functioning | -0.27  | -0.05   | -0.27 | -0.37   |
| Glo.Dis Severity                             | -0.57* | -0.39   | -0.49 | -0.63*  |
| Glo.Dis Mental Disability                    | -0.49  | -0.15   | -0.48 | -0.56*  |
| Glo.Dis Total                                | -0.44  | -0.11   | -0.33 | -0.50*  |
| GAF  | -0.19  | 0.01    | 0.03  | -0.23   |
| QoL  | 0.06   | 0.51*   | 0.07  | 0.15    |
| Digits backward                              | 0.25   | 0.27    | 0.23  | 0.33    |
| Trail Making Test A                          | -0.14  | -0.46   | -0.09 | -0.26   |
| Trail Making Test B                          | -0.25  | -0.38   | -0.12 | -0.27   |
| Graphic sequence test                        | 0.60*  | 0.25    | 0.62* | 0.49    |
| Copy a necker cube                           | 0.11   | 0.39    | 0.43  | 0.18    |
| Copy a house                                 | 0.27   | 0.27    | 0.18  | 0.38    |
| Draw a clock (Mendez score)                  | 0.08   | 0.11    | 0.49  | 0.00    |
| Rey figure                                   | 0.15   | 0.56*   | 0.26  | 0.38    |
| Verbal fluency                               | -0.30  | -0.25   | -0.02 | -0.28   |
| Abstract thinking                            | 0.21   | 0.21    | -0.02 | 0.34    |
| Social cognition                             | 0.05   | 0.02    | -0.36 | -0.01   |
| Stroop test (mistakes)                       | -0.62* | -0.20   | -0.40 | -0.45   |

\*not significant but >0.50 in numerical value, \*\* p<0.05

eralized, unrelated to general mental speed, and could lead to local dysfunction of connected cortical areas, maybe because of dysfunctional filters and selection processes.<sup>62,63</sup>

In the literature, the basic theory suggests that thought disorder is conceptualized as thought-language-communication disorder (TLC disorder),<sup>64</sup> but another more elaborate conceptualization includes content thought disorder (CTD), which refers to delusions and disorganized thought (and subsequently speech), and formal

thought disorder (FTD), which refers to the disruption of the form (or structure) of thought and unlike hallucinations and delusions, it is an observable, objective sign of psychosis.<sup>26,65,66</sup> FTD is a common core symptom of a psychotic disorder, may include incoherence, peculiar words, disconnected ideas, or a lack of unprompted content expected from normal speech, and may be seen as a marker of severity and as an indicator of prognosis.<sup>67</sup> It is further subdivided into positive formal thought disorder (posFTD; includes pressure of speech, tangenti-

ality, derailment, incoherence, and illogicality) and negative formal thought disorder (negFTD; includes poverty of speech and poverty of content).<sup>65,67</sup> In structured conversations, FTD might be difficult to detect,<sup>3</sup> and research has shown that psychopathology is the prime factor in the shaping of aspects of thought disorder.<sup>2,66</sup> It is FTD specifically that, according to the literature, is behind linguistic problems in schizophrenia, although it seems that linguistic problems in these patients could manifest in a variety of ways, and there is no single clear pattern present.<sup>68</sup>

Although the study sample was small, the current study tends to confirm that psychopathology, especially general psychopathology, and negative symptoms, as well as the severity of disability, play a major role in the impairment of picture description,<sup>31</sup> but on the other hand, it suggests that in neurocognitive terms, attentional and visuospatial processes rather than language and executive function play a role. This supports the concept that FTD is partially responsible for our findings, but alone, it is not an adequate explanation. An additional important finding is that in our small pilot sample, the performance on tests involving the description of relatively simple images was significantly impaired.

Of the neurocognitive tests found to correlate with picture performance, the Graphic sequence test<sup>46</sup> is a variation of the Alternating Sequences Test introduced by Luria<sup>69–71</sup> and assesses the ability of the frontal lobes to inhibit inappropriate responses.<sup>72,73</sup> There is a graphic (drawing) version that demands the patient to copy a simple alternation of rectangles and peaks. Impaired patients tend to repeat the same movement or shape and do not alternate with the other component of the pair. The Rey-Osterrieth complex figure is an objective measure of visuospatial function and does not involve semantic cognition.<sup>74</sup> It reflects measures of visual ex-

ploration and perception, judgment of spatial relations, visual organization, and set-shifting, as well as design fluency.<sup>48,75,76</sup> It seems related to the metabolic rate of the bilateral temporal-parietal cortex and occipital lobe, and the right frontal lobe,<sup>74,77</sup> while its relationship with executive function, specifically planning and organization, seems strong.<sup>78,79</sup>

The error rate of the Stroop test<sup>49</sup> is an index of inhibitory control<sup>80</sup> or an index of impaired working memory.<sup>81</sup> The related brain areas include the anterior cingulate cortex and the dorsolateral prefrontal cortex,<sup>82–84</sup> with the cingulate cortex selecting the appropriate response and allocating attentional resources.<sup>84–88</sup>

## Conclusion

Again, the study sample was small, and the current study was a pilot one. However, taking together the interpretations of the GST, Rey-Osterrieth figure, and the Stroop test, along with the negative findings for the other neurocognitive tests, a possible early conclusion could be that the impaired performance in picture description in patients with schizophrenia is not a consequence of FTD alone, but the existence of a dysfunctional processing of visual information and a problematic translation of them into meaningful mental images significantly contributes. This neurocognitive process demands distributed and alternating attention, working memory to keep information readily available, and the development of mental images as reflections of external reality perceived through visual input.

The current study is a small pilot study, and therefore, its results and their interpretation should be considered with caution until bigger datasets are available. However, the findings are strong enough to trigger a hypothesis to be tested in future research.

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## Έκπτωση της περιγραφής εικόνας και νευρονοητική λειτουργία στη σχιζοφρένεια: Πιλοτική μελέτη

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### ΠΕΡΙΛΗΨΗ

Η Σχιζοφρένεια εμφανίζει επίσης μια μορφή έκπτωσης λόγου η οποία παραδοσιακά θεωρείται ότι αντανakλά διαταραχή της σκέψης. Η παρούσα πιλοτική μελέτη στοχεύει στη διερεύνηση της σχέσης μεταξύ της έκπτωσης της γλωσσικής ικανότητας με άλλες νευρονοητικές εκπτώσεις και την ψυχοπαθολογία. Η μελέτη περιέλαβε 10 ασθενείς με σχιζοφρένεια (5 άνδρες), ηλικίας  $45,5 \pm 12,48$  ετών. Εκτιμήθηκαν με την κλίμακα Positive and Negative Syndrome Scale (PANSS), με κλίμακα αναπηρίας καθώς και με μια νευροψυχολογική συστοιχία. Η πειραματική συνθήκη περιελάμβανε τέσσερις εικόνες με σαφές περιεχόμενο από την καθημερινή ζωή. Η στατιστική ανάλυση περιελάμβανε τον υπολογισμό του Spearman's rho Correlation Coefficient. Η περιγραφή των εικόνων σχετιζόταν σημαντικά με τον παράγοντα PANSS – General psychopathology. Μη σημαντικές αλλά υψηλές αριθμητικά συσχετίσεις παρατηρήθηκαν σε σχέση με την PANSS – Negative, την αναπηρία και τα Graphic Sequence test, Rey figure, και το Stroop test αλλά δεν υπήρχε συσχέτιση με τη λεκτική ευφράδεια, την αφαιρετική σκέψη και τις εκτελεστικές λειτουργίες. Παρά το μικρό δείγμα της μελέτης, θα μπορούσε να ειπωθεί ότι η έκπτωση στην επίδοση της περιγραφής εικόνας σε ασθενείς με σχιζοφρένεια δεν είναι απότοκος μόνο της διαταραχής της σκέψης αλλά επίσης οφείλεται σε μια δυσλειτουργία στην επεξεργασία της οπτικής πληροφορίας και προβληματικής μετάφρασής της σε νοητικές εικόνες με νοηματικό περιεχόμενο.

**ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ:** Σχιζοφρένεια, γλωσσικές διαταραχές, διαταραχή δομής της σκέψης, οπτικοχωρική ικανότητα, περιγραφή εικόνας, ψυχοπαθολογία.

## Research article

# Factor analysis and reliability of the Illness Attitude Scales in senior medical students

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### ABSTRACT

Illness behavior is influenced by subjective, social, and cultural factors and can vary from one person to another and even internally within the same individual, depending on the situation and the type of illness he or she needs to deal with. The Illness Attitude Scales (IAS) were designed by Robert Kellner to assess fears, negative beliefs, and attitudes related to hypochondriasis and abnormal behavior about illness, and it is a reliable tool for detecting them as it does not contain items related to symptoms that are characteristic of other psychiatric symptoms. Although the IAS is commonly used, only a few studies have investigated its factor structure, but no common factor solution has been found. The results of these studies differ, ranging from 2 to 5 factor solutions, as well as which items are assigned to the factors. Since factor analysis for the Greek translation has not been previously researched, we analyzed the factor structure in a Greek sample using exploratory factor analysis to reflect cultural nuances in health perceptions and illness behaviors and to enable meaningful comparisons with other populations. A mixed sample of senior medical students of the Athens Medical School (N = 163) completed the psychometric tool before attending the educational clinics. A percentage of 60.98% were women and 39.02% were men, and the average age of the sample was 23.84 years (SD = 1.67). Data were subjected to Maximum Likelihood Estimation and oblique rotation, which revealed a solution of seven factors: i) Worry about Illness after Pain Sensation, ii) Health Habits, iii) Effects of Symptoms, iv) Hypochondriac Beliefs, v) Thanatophobia, vi) Treatment Experiences, vii) Disease Phobia. The internal consistency of the factors, measured by Cronbach's alpha coefficient, achieved good to acceptable reliability: 0.86, 0.88, 0.68, 0.76, 0.73, 0.65, and 0.81, respectively. The results of the current study, although they cannot be generalized to the general population, provide information on medical students' attitudes towards illness and may pave the way for educational strategies and programs in medical school to improve the detection of negative beliefs and attitudes towards illness in medical students during clinical practice.

**KEYWORDS:** Fear of illness, hypochondriasis, illness behavior, health anxiety, thanatophobia, pain.

### Introduction

Issy Pilowsky introduced the term abnormal illness behavior,<sup>1</sup> arguing that our behavior towards illness is influenced by subjective, social, and cultural factors and can vary from one person to another and also internally, within the same person, depending on the situation and kind of illness they need to deal with. In addi-

tion, our behavior towards illness is also influenced by stigma, and more specifically by stigma about mental illness.<sup>2,3</sup>

The misinterpretation of physical symptoms based on preoccupation with a serious illness is called hypochondriasis. Hypochondriasis can be expressed via 4 symptoms: (i) worry or fear of a serious illness, (ii) worry or fear

that persists after medical confirmation, (iii) worry or fear that significantly affects functionality, and (iv) symptoms persisting for more than 6 months.<sup>4</sup> Hypochondriasis has been replaced by Illness Anxiety Disorder and Body Dysmorphic Disorder in DSM-5, which describes hypochondriac symptoms more comprehensively and is clinically useful for the diagnosis of hypochondriasis.<sup>5</sup>

A measure that is proposed to tap hypochondriacal tendencies is the Illness Attitude Scales (IAS), a psychometric tool created by Robert Kellner<sup>6</sup> for the general assessment of fears, beliefs, and attitudes related to hypochondriasis and abnormal illness behavior, and it provides a validated, comprehensive measure of health anxiety, hypochondriacal concerns, and maladaptive illness behaviors, enabling targeted interventions and research into health-related psychological conditions. The Illness IAS consists of nine scales with three entries each, met on a five-point scale, as follows: (i) "Worry about Illness", (ii) "Concerns about pain", (iii) "Health Habits", (iv) "Hypochondriacal beliefs", (v) "Thanatophobia", (vi) "Nosophobia", (vii) "Bodily Preoccupations", (viii) "Treatment Experiences", (ix) "Effects of Symptoms". Two more questions on the IAS provide additional information (e.g., respondents identify illness and treatment, if available) but are not used for scoring.

Although the IAS is commonly used, only a few studies have investigated its factor structure; however, no common factor solution has been found. The results of these studies differ with regard to the number of factors, ranging from a 2-factor solution and ending up with a 5-factor solution, as well as the items assigned to the factors. In addition, in these studies, there were differences in the sample, clinically and culturally.<sup>4-8</sup> Almost all studies used Exploratory Factor Analysis, while only one submitted its structure to Confirmatory Factor Analysis.<sup>9-14</sup> Finally, their findings indicate that the structure of the IAS is less complex than that suggested by the initial author.<sup>6</sup>

As the literature review does not demonstrate a consensus on the results, it is established that the diversity of the factor structure is based on cultural differences and the sample. To date, the factor analysis has not been investigated in a sample of the Greek population. The research aim is to examine the factor structure of the questionnaire in a different population and investigate possible diverse findings in the literature.

To investigate our research goal, we used a sample of senior medical students from the Athens School of Medicine. It was considered useful to measure a tool that detects hypochondriasis in medical students who come into contact with the disease during their clinical practice and to assess their attitudes towards illness.

During clinical practice, medical students are exposed systematically to diseases, symptom recognition, and correct diagnosis. When students learn about physical illnesses, they can interpret physical disorders as signs of serious illness.<sup>15</sup> The results may be used to generate educational strategies and interventions to detect hypochondriasis in medical students.

## Material and Method

### Participants

The data of a sample of 6th-year students of the Medical School of Athens (N=163) were used for exploratory factor analysis, of which 60.98% were women and 39.02% were men. The average age of the sample was 23.84 years (SD=1.67).

### Procedure

The IAS was administered to students as a group in the lecture hall before attending each educational clinic. All participants were informed about the administration of the psychometric tool and signed a consent form to participate.

### Measures

The IAS psychometric tool was translated into Greek and back-translated (reverse translation) (in a modified yes or no form), using the method developed by Brislin.<sup>16</sup> The translation was realized by the first author, the back-translation by the second author, and proof-reading by an independent reviewer. The translated items were checked to ensure that semantic and syntactic aspects were not lost. The two authors and the independent reviewer were fully bilingual in English and Greek and adhered to Greek standards as much as possible.

### Statistical analysis

In order to investigate the structure of the IAS, as formed by a Greek sample of medical students, the Maximum Likelihood Estimation (MLE) with lateral rotation factor was used. The Maximum Likelihood Estimation is a statistical method used to estimate the parameters of a probability distribution by maximizing a likelihood function and helps the determination of the parameter values that make the observed data more likely under a given statistical model.<sup>17</sup> Oblique rotation (SPSS Oblimin,  $\delta = 0$ ) was used because the original scales of the IAS were designed as dependent scales, and a previous study<sup>8</sup> found a better fit to the data in dependent factor solutions. Tabachnick and Fidell<sup>18</sup> strongly recommend the use of lateral rotation

when factors are expected to be related to each other. This approach was chosen since several previous research findings<sup>7–10,14</sup> have shown that this approach achieves substantial solutions. Factors will be created from factor loadings (>.40), and their reliability and stability will be analyzed. The analysis was conducted with the SPSS program v.23.

## Results

### Factor Structure

Application of Maximum Likelihood Estimation (MLE) as well as the scree test and Kaiser's criterion (eigenvalue >1) indicated a seven-factor solution (figure 1).

The seven factors with the Kaiser criterion (eigenvalue >1) presented the following results: 8.02, 2.53, 1.96, 1.67, 1.52, 1.22, 1.12, with the total variance explained by the model at 66.81%, a particularly significant percentage, especially concerning that found in similar studies (table 1).<sup>8–11,13</sup>

The loadings revealed a 7-factor structure (table 2), which included factor 1 with 5 items and the remaining 6 with 3 items.

The seven factors can be named as follows: (1) Worry about Illness after Pain Sensation, and includes 5 items with three of the original Illness Anxiety scale and two items (4,6) of the Concerns about pain scale, (2) Effects of Symptoms, (3) Health Habits, (4) Hypochondriacal Beliefs, (5) Thanatophobia, (6) Treatment Experiences, (7) Nosophobia. The last 6 factors were equivalent to the original scales of Kellner,<sup>6</sup> a finding that is considered particularly important, especially because the present research is the only one that approaches through factor analysis the original structure proposed by Kellner.<sup>6</sup>

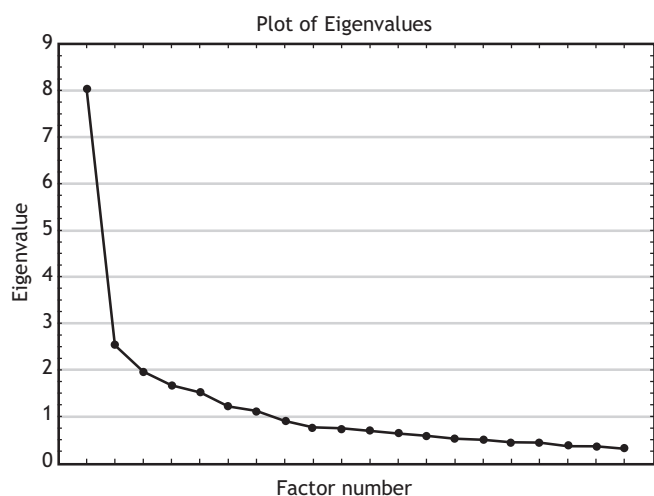


Figure 1. Screen plot from the exploratory factor analysis.

Table 1. Total Variance of the factors.

| Factor | Initial Eigenvalues |               |              |
|--------|---------------------|---------------|--------------|
|        | Total               | % of Variance | Cumulative % |
| 1      | 8.02                | 29.72         | 29.72        |
| 2      | 2.53                | 9.37          | 39.09        |
| 3      | 1.96                | 7.27          | 46.36        |
| 4      | 1.67                | 6.18          | 52.53        |
| 5      | 1.52                | 5.63          | 58.16        |
| 6      | 1.22                | 4.5           | 62.67        |
| 7      | 1.12                | 4.15          | 66.811       |
| 8      | 0.9                 | 30.35         | 70.16        |
| 9      | 0.77                | 20.83         | 72.99        |
| 10     | 0.75                | 20.77         | 75.76        |
| 11     | 0.69                | 20.55         | 78.31        |
| 12     | 0.64                | 20.37         | 80.68        |
| 13     | 0.59                | 20.17         | 82.85        |
| 14     | 0.52                | 10.93         | 84.78        |
| 15     | 0.5                 | 10.85         | 86.62        |
| 16     | 0.45                | 10.65         | 88.27        |
| 17     | 0.44                | 10.63         | 89.9         |
| 18     | 0.39                | 10.43         | 91.33        |
| 19     | 0.36                | 10.32         | 92.65        |
| 20     | 0.34                | 10.25         | 93.9         |
| 21     | 0.3                 | 10.12         | 95.02        |
| 22     | 0.28                | 10.05         | 96.07        |
| 23     | 0.26                | 0.98          | 97.05        |
| 24     | 0.23                | 0.85          | 97.9         |

Note: Total variance explained by the seven factors

The items of the Bodily Preoccupations scale do not represent an integral factor, nor do they belong to another factor, as they present low loadings (0.30–0.33) on factors 1, 4, 5, and 7. Item 19 had loadings on two factors, on 5 (0.33) and 7 (0.32). Also, item 5 from the Concerns about Pain scale showed low loadings on factor 6 (0.35) and factor 7 (0.36).

The maximum absolute correlation was 0.37 between factors 2 and 6, and the minimum was 0.07 between factors 3 and 7. The overall factor correlations were low, supporting this way, the seven-factor solution.

### Reliability

To assess the internal consistency of the IAS questionnaire as formulated by factor analysis, the Cronbach's alpha coefficient was used, with the following measurements for the seven-factor solution: (1) 0.86, (2) 0.88, (3) 0.68, (4) 0.76, (5) 0.73, (6) 0.65, (7) 0.81. The average corre-

**Table 2.** Maximum Likelihood Estimation of the Illness Attitudes Scale: oblique-rotated factor loadings for the seven-factor solution

| Items  | F1    | F2     | F3    | F4    | F5    | F6    | F7    |
|--|-------|--------|-------|-------|-------|-------|-------|
| 1. Do you worry about your health?   | 0.61* | -0.11  | 0.09  | -0.13 | -0.1  | 0.23  | 0.24  |
| 2. Are you worried that you may get a serious illness in the future?   | 0.74* | -0.07  | -0.04 | 0.04  | -0.06 | -0.01 | 0.25  |
| 3. Does the thought of a serious illness scare you?  | 0.65* | -0.08  | -0.06 | 0.04  | 0.07  | 0.07  | 0.1   |
| 4. If you have a pain, do you worry that it may be caused by a serious illness?  | 0.69* | -0.08  | 0.02  | 0.03  | 0.07  | 0.02  | -0.09 |
| 5. If a pain lasts for a week or more, do you see a physician?   | 0.22  | -0.1   | 0.19  | -0.07 | 0.19  | 0.35  | -0.36 |
| 6. If a pain lasts a week or more, do you believe that you have a serious illness?   | 0.66* | 0.02   | 0.09  | 0.14  | 0.17  | 0.01  | -0.24 |
| 7. Do you avoid habits that may be harmful to you, such as smoking?  | -0.02 | -0.07  | 0.72* | -0.17 | 0.1   | 0.03  | 0.08  |
| 8. Do you avoid foods that may not be healthy?   | -0.07 | 0.05   | 0.80* | 0.11  | -0.09 | 0.06  | 0.01  |
| 9. Do you examine your body to find whether there is something wrong?  | 0.29  | 0.04   | 0.39* | 0.19  | 0.05  | -0.04 | -0.12 |
| 10. Do you believe that you have a physical disease but the doctors have not diagnosed it correctly?                           | 0.03  | -0.09  | 0.09  | 0.49* | -0.05 | 0.07  | 0.2   |
| 11. When your doctor tells you that you have no physical disease to account for your symptoms, do you refuse to believe him?   | -0.02 | -0.1   | -0.02 | 0.78* | -0.06 | 0     | -0.07 |
| 12. When you have been told by a doctor what he found, do you soon begin to believe that you may have developed a new illness? | 0.1   | 0      | -0.01 | 0.64* | 0.07  | 0.07  | 0.15  |
| 13. Are you afraid of news that reminds you of death (such as funerals, obituary notices)?                                     | -0.08 | -0.04  | 0.19  | 0.02  | 0.71* | -0.04 | -0.02 |
| 14. Does the thought of death scare you?   | 0.17  | -0.06  | -0.06 | -0.17 | 0.74* | 0.03  | 0.01  |
| 15. Are you afraid that you may die soon?  | 0.1   | -0.05  | -0.17 | 0.15  | 0.49* | 0.04  | 0.2   |
| 16. Are you afraid that you may have cancer?   | 0.32  | 0.06   | 0.04  | 0.08  | 0.09  | -0.06 | 0.54* |
| 17. Are you afraid that you may have heart disease?  | -0.04 | -0.09  | 0.02  | 0.18  | 0.14  | 0.03  | 0.54* |
| 18. Are you afraid that you may have another serious illness?  | 0.29  | -0.07  | 0.05  | 0.13  | 0.11  | -0.03 | 0.57* |
| 19. When you read or hear about an illness, do you get symptoms similar to those of the illness?                               | -0.05 | 0      | -0.01 | 0.17  | 0.33  | 0.09  | 0.32  |
| 20. When you notice a sensation in your body, do you find it difficult to think of something else?                             | 0.07  | -0.14  | 0.07  | 0.3   | 0.25  | 0.15  | 0.11  |
| 21. When you feel a sensation in your body do you worry about it?  | 0.31  | -0.07  | 0.1   | 0.05  | 0.24  | 0.22  | 0.13  |
| 22. How often do you see a doctor?   | 0.08  | 0.09   | 0.02  | 0.17  | -0.04 | 0.67* | -0.09 |
| 23. How many different doctors, chiropractors or other healers have you seen in the past year?                                 | -0.08 | 0.01   | 0     | -0.01 | 0.09  | 0.76* | -0.01 |
| 24. How often have you been treated during the past year? (For example, drugs, change of drugs, surgery, etc.)                 | 0.04  | -0.2   | 0.06  | -0.09 | -0.13 | 0.43* | 0.1   |
| 25. Do your bodily symptoms stop you from working?   | -0.06 | -0.84* | -0.06 | 0.05  | 0.06  | 0.02  | -0.08 |
| 26. Do your bodily symptoms stop you from concentrating on what you are doing?   | 0     | -0.93* | 0.04  | 0.04  | 0.07  | -0.08 | -0.06 |
| 27. Do your bodily symptoms stop you from enjoying yourself?   | 0.12  | -0.78* | 0.01  | 0.02  | -0.12 | 0.02  | 0.08  |

\*Eigenvalues higher than .4 are marked with an asterisk

F1: Worry about Illness after Pain Sensation, F2: Effects of Symptoms, F3: Health Habits, F4: Hypochondriacal Beliefs, F5: Thanatophobia, F6: Treatment Experiences, F7: Nosophobia

lations between items for the factors (including only items with loadings  $r \geq 0.40$  on a single factor) were 0.56, 0.72, 0.43, 0.52, 0.48, 0.40, and 0.58, respectively (see table 3).

The reliability control (alpha coefficients and mean inter-item correlations) of the seven-factor model of the present research is presented below.

The factors of the seven-factor model show very good internal reliability, as shown in table 4, with the max value of factor 2, "Effects of Symptoms", with three items ( $\alpha=0.88$ ), with the minor exception of the factor "Health Habits" ( $\alpha=0.68$ ) and of the "Treatment Experiences" factor ( $\alpha=0.65$ ), which is lower than the recommended 0.7.<sup>19</sup> However, this three-item factor presents a positive correlation coefficient  $r \geq 0.4$  and is above the recommended minimum level for group comparisons.<sup>20</sup>

## Discussion

The results of the present study reveal a seven-factor solution, which, like previous factor analysis,<sup>7-14</sup> is smaller than Kellner's original structure<sup>6</sup> but closer to the original factor structure. The seven-factor structure is different and larger than other sample studies<sup>7,8,10</sup> that reported a four-factor structure and one study<sup>9</sup> that reported a five-factor structure. Moreover, the factor structures of these studies differ partially in terms of the number and items included in the factors. Interpreting these differences is not easy because the studies differ in planning, sample, and methodology. One crucial difference is in the statistical method, as the aforementioned studies used Principal Component Analysis while the present study used Maximum Likelihood Estimation.

In all studies<sup>7-10</sup> with a similar sample, factor 1 emerges, and although each study includes a different number of items, it maintains a relatively similar composition of items. In one research<sup>7</sup> we find 12 items; in another,<sup>9,11</sup> in another,<sup>9,10</sup> and in the last one, 8 items.<sup>8</sup> In the current study, there are the fewest items, 5, which come from the Worry about Illness and Concerns about

Pain scales. As in this study, all studies<sup>7-10</sup> present in factor 1 items from the original Worry about Illness and Concerns about Pain scales, showing that among the respective samples, there is an increased general worry about illness enhanced by the presence of pain. However, the Thanatophobia scale appears integral on factor 1 in three studies,<sup>8-10</sup> connecting, along with other items, the fear of illness to death, in contrast to the current study. The difference in sample composition probably explains this variation, as in the present study, the sample consists of medical school senior students who are sufficiently knowledgeable about disease and illness from their training and probably do not associate it with risk of death, compared to the other studies that had undergraduate students<sup>7-9</sup> and psychology and theology students.<sup>10</sup> Additionally, two of the surveys<sup>8,9</sup> have been conducted in the late 1990s in Canada and share common items on factor 1, and except for Thanatophobia, the same items are observed for Worry about Illness<sup>2,3</sup> and almost the same from the Nosophobia scale, three of them in one survey<sup>9</sup> and two<sup>16,18</sup> in the other.<sup>8</sup> It is possible that the findings for Factor 1 with fear of death were related to Canadians' general dissatisfaction with their country's health care system at the time.<sup>21</sup> Corresponding correlations with factor 1 can be made in another research study<sup>7</sup> conducted in England. It presents 12 items, most on factor 1 from various scales dominated by Concerns about pain and Hypochondriacal Beliefs, and can be related to English people's perceptions of the radical NHS reforms of the 1990s, when new private health providers were created, leading to the closure of public hospitals and causing unrest.<sup>22</sup> The authors of the same research,<sup>7</sup> interpret through the lens of the general population their factor 4, coronary heart disease and health habits, as a separate factor that is not related to the Worry about Illness, but more to the increased knowledge of the general (ordinary people) population on the connection of lifestyle and serious diseases.<sup>23</sup> All three items of the original Worry about Illness scale are found on fac-

**Table 3.** Factor correlation table.

| Factor | 1     | 2     | 3     | 4     | 5     | 6     | 7     |
|--------|-------|-------|-------|-------|-------|-------|-------|
| 1      | 1.00  | -0.34 | 0.27  | 0.29  | 0.35  | 0.34  | 0.23  |
| 2      | -0.34 | 1.00  | -0.12 | -0.21 | -0.22 | -0.37 | -0.20 |
| 3      | 0.27  | -0.12 | 1.00  | 0.13  | 0.19  | 0.35  | -0.07 |
| 4      | 0.29  | -0.21 | 0.13  | 1.00  | 0.24  | 0.17  | 0.31  |
| 5      | 0.35  | -0.22 | 0.19  | 0.24  | 1.00  | 0.17  | 0.21  |
| 6      | 0.34  | -0.37 | 0.35  | 0.17  | 0.17  | 1.00  | 0.08  |
| 7      | 0.23  | -0.20 | -0.07 | 0.31  | 0.21  | 0.08  | 1.00  |

**Table 4.** Internal reliability estimation of the seven factors (Cronbach's  $\alpha$ ).

| Factor                                       | Mean Difference | Std. Error | Cronbach's $\alpha$ | Average inter-item correlation |
|--|-----------------|------------|---------------------|--------------------------------|
| Worry about illness after the pain sensation | 8.21            | 3.96       | 0.86                | 0.56                           |
| Effects of Symptoms                          | 6.74            | 2.76       | 0.88                | 0.72                           |
| Health Habits                                | 2.67            | 2.54       | 0.68                | 0.43                           |
| Hypochondriacal Beliefs                      | 1.53            | 1.93       | 0.76                | 0.52                           |
| Thanatophobia                                | 3.34            | 2.51       | 0.73                | 0.48                           |
| Treatment Experiences                        | 3.47            | 2.03       | 0.65                | 0.4                            |
| Nosophobia                                   | 3.08            | 2.8        | 0.81                | 0.58                           |

tor 1 in one more study,<sup>10</sup> while items 2 and 3 from the same scale are in two studies,<sup>8,9</sup> and 1 and 2 in one.<sup>7</sup>

Items 4 and 6 from the Concerns about Pain scale are found on factor 1 in the current study and in two other studies,<sup>9,10</sup> while in another study<sup>8</sup> we see only 4, and in another<sup>7</sup> all 3 items of the same scale. The two items (4, 6) are semantically very close as they relate to the direct association of pain with serious illness, and this is probably why they are presented in three surveys along with the items of the Worry about Illness scale.

Differences were observed in the evaluation of loadings, with one study<sup>9</sup> calculating significant loadings  $\geq 0.30$  and not excluding any item from Kellner's original scale. No items were excluded in Stewart and Watt's study,<sup>8</sup> where the loadings were  $\geq 0.35$ . The remaining two studies,<sup>7,10</sup> like the current one, assessed loadings  $\geq 0.40$ , and while in the first<sup>7</sup> no item was excluded, in the second<sup>10</sup> 5 items were excluded, while in the current study 4 items did not pass the loading limit, with the latter two studies sharing excluded items 19 and 21 from the original Bodily Preoccupations scale.

The items of the present study that were not included in a factor or did not form a separate factor come from the original Bodily Preoccupations scale. Item 19 from this scale had a defective presence in factors 5 and 7. Item 20 had a presence in factor 4, which is probably related to the wording of the question and is closer to hypochondriasis, as people with hypochondriasis experience difficulty in remaining functional when dealing with a body sensation.<sup>4</sup> Finally, item 21 was present in factor 1, probably because it mentions the word "worry" and was correlated with the items that had the same word. The same items are also excluded in another study<sup>10</sup> and are not included in any factor.

The original Bodily Preoccupations scale does not appear as an independent factor in any other research, regardless of sample, and its items appear on several factors in these studies.<sup>7-10</sup> Similar results to the present study for the items of the Bodily Preoccupations scale

are observed in a study<sup>9</sup> where item 19 presents a loading on factor 4, Disease Conviction. In another study,<sup>8</sup> it is found that loading of all the items of the Bodily Preoccupations scale on their own 4th factor, Beliefs, which includes the items of the Hypochondriacal Beliefs scale. Both studies were conducted in the same country, Canada, which indicates the strong participation of cultural factors in the formation of attitudes towards the disease. The results show that the items of the original Bodily Preoccupations scale can be better understood through other factors related to hypochondriasis, as the questions are not understood as a separate concept.

Item 5 of the original Concerns about pain scale was not included in any of the seven factors of the present study, as it did not show a high loading on any of them. The item appears with low loading on two factors, factor 6 (0.35) and factor 7 (0.36). However, we see the same item loading on the Treatment Experiences factor in other studies<sup>9,10</sup> and factor 2, Behavior, in a study<sup>8</sup> that includes all the items from the original Treatment Experiences scale, which shows that perhaps it can be understood better with the Treatment Experiences factor in a relevant sample. This item mentions the visit to a doctor and is more about a behavior associated with visiting a doctor rather than subjectively interpreting a certain pain.

The lower internal reliability of factor 3, Health Habits, is a finding also observed in previous studies, as none of them has found a satisfactory internal reliability regardless of sample, with a range of values ranging from  $\alpha=0.49$  to  $0.64$ .<sup>8,10,12,14,15</sup> Especially in Kellner's original scale, this factor has  $\alpha=0.44$ .<sup>7</sup> A possible reason for the low internal reliability of the Health Habits factor in the current study, also found in another study,<sup>7</sup> is that the items in this factor are more related to avoiding illness and recording health-promoting behaviors and less with the fear or worry of being ill. A reformulation of the questions to link negative health behaviors with the belief or worry about the disease would probably give

higher reliability to the specific factor and would be better related to the other factors of the psychometric tool.

The same scale also shows defective depiction in Kellner's original study<sup>6</sup> as it fails in clinical samples to distinguish patients diagnosed with hypochondriasis from family practice patients, non-patient employees, and non-hypochondriasis psychiatric patients.<sup>7</sup> Also, the same Health Habits scale does not relate to the criteria defined in the DSM-IV for the diagnosis of patients with hypochondriasis.<sup>4</sup>

The Treatment Experiences factor related to receiving treatment presents in the present study the lowest internal reliability index, however, just below the limit of 0.7.19 Relevant results with low internal reliability in the same factor are also reflected in other studies ( $\alpha=0.649$ ,  $\alpha=0.527$ ), while in another,<sup>10</sup> it is slightly above the limit ( $\alpha=0.75$ ). The low reliability may be related to the participants' perception of their national health care system, as mentioned above, while another reason may be the young age of the sample of students with average of 23.84 years, as they might not have particular experiences of treatments, which could have a different result in a wider age or clinical sample.

However, it is interesting that Ferguson and Daniel<sup>7</sup> examining the internal reliability indices for the original nine scales of the IAS, found that all, except for the scales Thanatophobia ( $\alpha=0.72$ ), Treatment Experiences ( $\alpha=0.75$ ), and Effects of Symptoms ( $\alpha=0.84$ ), were below the recommended 0.7.<sup>19</sup>

The seven-factor solution of the current study explains 66.81% of the variance of the sample, and it is the largest in relation to other studies.<sup>8-11,13</sup> In particular, we observe that the three-factor solution of Dammen et al,<sup>13</sup> in patients with heart disease problems explained 47% of variance, while four- and five-factor solutions, including studies in student samples,<sup>8-11</sup> explained a range of variance from 47.1% to 56.4%.

Studies that used translations of the IAS for factor analysis suggested two<sup>12</sup> and three-factor solutions.<sup>13,14</sup> However, due to the difference in the composition of the sample (patients and general population), these results are difficult to compare with the findings of the present study.

Generally, the current study revealed that the IAS can be captured with a relatively simpler but not radically different hierarchical structure than Kellner's original,<sup>6</sup> supporting a seven-factor solution. Six out of the seven factors hold the original recommendation with the original scales and with good internal reliability, which is interpreted as meaning that in a student sample, the IAS is a tool that can be recommended for investigating hypochondriasis and abnormal illness behavior. Despite different and somewhat inconsistent factor solutions, perhaps due to differences in samples and factor analysis methods used, these studies<sup>7-14</sup> collectively suggest that the IAS tool has multidimensional factors and is not interpreted with a single factor.

A limitation of the current study is the relatively small sample and its specialization. However, the number of subjects was nearly three times the number of subjects in Kellner's original research and also more than three times the number of variables. Another limitation is the low internal reliability of two out of seven factors, Health Habits and Treatment Experiences. Rephrasing questions of the Health Habits factor to connect health behaviors with illness anxiety could give higher reliability. Moreover, in a more general population sample or a clinical sample, a higher reliability might be revealed for the Treatment Experiences factor. Given the specialized and small sample, more research needs to be done in a wider and clinical sample to determine any difference, if there is one, in these factors. Further confirmatory factor analysis research could be done in the future on a similar sample. Finally, there is a need for contemporary factor analysis research of the IAS, as most of the research has been conducted several years ago.

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# Ερευνητική εργασία

## Παραγοντική ανάλυση και αξιοπιστία της Κλίμακας Στάσης για την Ασθένεια σε τελειόφοιτους φοιτητές ιατρικής

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### ΠΕΡΙΛΗΨΗ

Η συμπεριφορά απέναντι στην ασθένεια διαμορφώνεται υπό την επίδραση υποκειμενικών, κοινωνικών και πολιτισμικών παραγόντων, παρουσιάζοντας διαφοροποιήσεις τόσο μεταξύ διαφορετικών ατόμων όσο και εντός του ίδιου ατόμου. Οι διαφοροποιήσεις αυτές εξαρτώνται από τις συγκεκριμένες περιστάσεις και τη φύση της ασθένειας που καλείται το άτομο να διαχειριστεί. Η Κλίμακα Στάσης για την Ασθένεια, σχεδιάστηκε από τον Robert Kellner για να αξιολογήσει τους φόβους, τις αρνητικές πεποιθήσεις και τις στάσεις που σχετίζονται με την υποχονδρίαση και τη μη φυσιολογική συμπεριφορά σε σχέση με την ασθένεια και είναι ένα αξιόπιστο εργαλείο για την ανίχνευσή τους καθώς δεν περιέχει στοιχεία που σχετίζονται με συμπτώματα που είναι χαρακτηριστικά άλλων ψυχιατρικών συμπτωμάτων. Παρόλο που η Κλίμακα Στάσης για την Ασθένεια χρησιμοποιείται ευρέως, μόνο λίγες μελέτες έχουν διερευνήσει την παραγοντική δομή της χωρίς να έχει βρεθεί κοινή παραγοντική λύση. Τα αποτελέσματα αυτών των μελετών διαφέρουν και κυμαίνονται από 2 έως 5 παραγοντικές λύσεις, καθώς και ως προς το ποια στοιχεία αποδίδονται στους παράγοντες. Δεδομένου ότι η παραγοντική ανάλυση για την ελληνική μετάφραση δεν έχει ερευνηθεί στο παρελθόν, αναλύσαμε την παραγοντική δομή σε ελληνικό δείγμα χρησιμοποιώντας διερευνητική παραγοντική ανάλυση για να αντικατοπτρίσουμε τις πολιτισμικές αποχρώσεις στις αντιλήψεις για την υγεία και τις συμπεριφορές απέναντι στην ασθένεια και να είναι εφικτές οι ουσιαστικές συγκρίσεις με άλλους πληθυσμούς. Ένα μικτό δείγμα τελειόφοιτων φοιτητών ιατρικής της Ιατρικής Σχολής Αθηνών (N=163) συμπλήρωσε το ψυχομετρικό εργαλείο πριν από την παρακολούθηση των εκπαιδευτικών κλινικών με το δείγμα να αποτελείται από γυναίκες σε ποσοστό 60,98% και από άνδρες σε ποσοστό 39,02%, με τη μέση ηλικία του δείγματος να είναι 23,84 έτη (SD=1.67). Τα δεδομένα υποβλήθηκαν σε Εκτίμηση Μέγιστης Πιθανοφάνειας και πλάγια περιστροφή, η οποία ανέδειξε μια λύση επτά παραγόντων: (i) Ανησυχία για την ασθένεια μετά την αίσθηση του πόνου, (ii) Συνήθειες υγείας, (iii) Επιπτώσεις των συμπτωμάτων, (iv) Υποχονδριακές πεποιθήσεις, (v) Θανατοφοβία, (vi) Εμπειρίες θεραπείας, (vii) Φοβία για την ασθένεια. Η εσωτερική συνέπεια των παραγόντων, που μετρήθηκε με τον δείκτη άλφα του Cronbach, πέτυχε καλή έως αποδεκτή αξιοπιστία 0,86, 0,88, 0,68, 0,76, 0,73, 0,65, 0,81, αντίστοιχα. Τα αποτελέσματα της παρούσας μελέτης, αν και δεν μπορούν να γενικευτούν στον γενικό πληθυσμό, παρέχουν πληροφορίες σχετικά με τη στάση των φοιτητών ιατρικής απέναντι στην ασθένεια και μπορούν να ανοίξουν τον δρόμο για εκπαιδευτικές στρατηγικές και προγράμματα στην ιατρική σχολή για τη βελτίωση της ανίχνευσης των αρνητικών πεποιθήσεων και των στάσεων απέναντι στην ασθένεια στους φοιτητές ιατρικής κατά την κλινική πράξη.

**ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ:** Φόβος της ασθένειας, υποχονδρίαση, συμπεριφορά ασθένειας, άγχος για την υγεία, θανατοφοβία, πόνος.

## Review

# Bullying's anatomy: How it affects brain structure and function. A systematic review

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### ABSTRACT

Bullying victimization is a common problem among adolescents with many catastrophic sequelae, as it has been associated with psychiatric disorders such as anxiety and depression. Identifying bullying print on the human brain could be useful in clinical practice, specifically in the secondary prevention of the disorders that are related to it. This review aims to explore the potential bullying-related changes of the human brain from a descriptive and functional anatomic perspective. A literature search was performed using the PubMed/Medline database, and, following meticulous screening, 16 articles were finally used. Our review included magnetic resonance imaging (MRI) and functional MRI studies, which were focused on gray and white matter structures of the brain. Bullying affects the morphology and function of gray and white matter structures in both victims and perpetrators. Victims seem to have atrophic hyperactive orbitofrontal cortex, hypertrophic hypoactive amygdalae, and increased cortical activation in almost all brain lobes. Bullies, on the other hand, have hyperactive accumbens nuclei. Fundamental nuclei of the limbic system, namely the nucleus accumbens and amygdala, are affected in both victims and perpetrators. Bullying changes the human brain morphologically and functionally, primarily affecting structures of the limbic system. Identifying these changes early could mainly help in the prevention of the expression of psychopathology and thus improve the quality of life of victims and even help bullies to seek medical help.

**KEYWORDS:** Amygdala, brain imaging, bullying, magnetic resonance imaging, nucleus accumbens, orbitofrontal cortex.

### Introduction

Bullying is defined as a specific form of intentional, repeated aggression that involves a disparity of power between the victim and perpetrator. The aggression can take physical, verbal, or gestural forms.<sup>1</sup> One more common type of bullying is cyberbullying, as people tend to get full access to the internet from a young age. Regarding its prevalence, bullying is a very common phenomenon among adolescents, as has been shown

in numerous cross-sectional studies in various areas around the world.<sup>2,3</sup> Bullying victimization is associated with numerous consequences, including poor mental health, low mood, irritability, nervousness, and sadness.<sup>4</sup> More important, however, is its correlation with many psychiatric disorders such as depression, anxiety, and personality disorders.<sup>5</sup> Attention-deficit hyperactivity disorder has also been related to bullying victimization as well as perpetration.<sup>6,7</sup> Remarkably, bullying

is also a risk factor for suicidal ideation and death by suicide in youth.<sup>8</sup> It is, thus, clear that bullying severely affects worldwide health and societies.

From a neuroanatomic point of view, it would be interesting to approach how bullying affects the human brain. In a clinical context, an easy way to explore this would be via neuroimaging studies. Are there specific imaging findings that correlate with bullying victimization or perpetration? Are brain areas particularly affected? And if so, could these be associated with the above-mentioned vulnerability to psychopathological conditions? And even further, could brain imaging studies help in the prevention of the clinical expression of these psychopathologies? Functional magnetic resonance imaging (fMRI) studies could potentially indicate areas of the brain that are under- or overactivated in response to bullying, whereas regular magnetic resonance imaging (MRI) studies could show areas of the limbic system that underwent structural changes because of bullying. Aiming to find answers to our questions, the purpose of this review is to explore the bullying print on the human brain, as well as its potential usefulness in clinical practice. More specifically, we aim to describe the association between bullying victimization and perpetration of certain imaging findings to potentially help in the secondary prevention of the mental health consequences of it and to motivate bullies to seek medical help.

## Material and Method

Our review follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.<sup>9</sup> Our methodology includes a study selection process, and afterwards, a quality assessment procedure in which we assessed our selected studies for their quality and bias.

### Study selection

A literature search was conducted using the PubMed/Medline database for the terms “bullying” and “brain imaging, which retrieved 61 articles. The authors screened all articles published until December 2024 for potential suitability. Exclusion criteria were (i) reviews, (ii) conference abstracts, (iii) letters to editors and (iv) case reports, and (v) publications for which we could not retrieve the full text. English language publications, including foreign language publications with English abstracts, were included in this review. Articles relevant to the topic concerning brain imaging in bullying, were further analyzed. Overall, 16 arti-

cles were finally used for the analysis of this narrative review (figure 1).

### Quality assessment

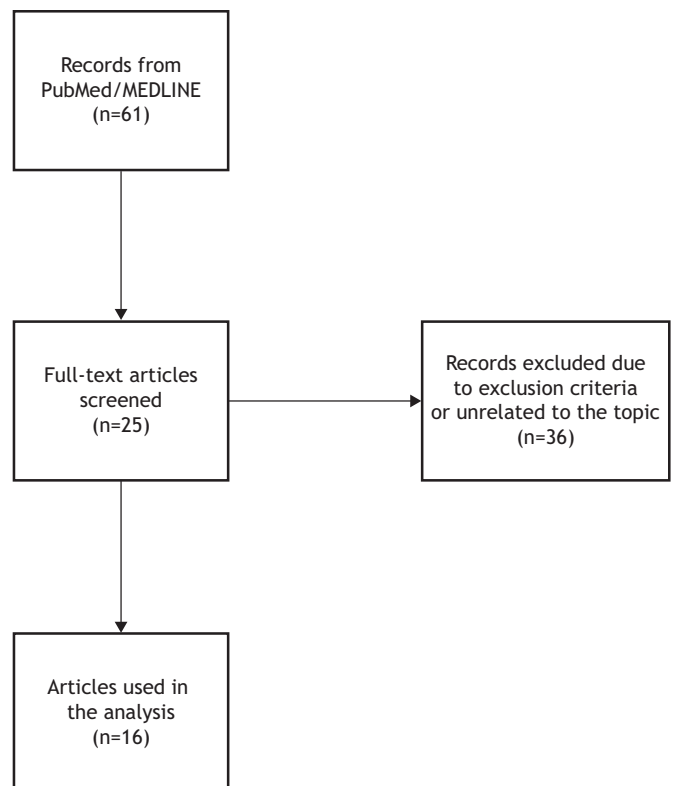
To assess the methodological quality of our selected studies, we used the Newcastle–Ottawa Scale (NOS)<sup>10</sup> to identify potential sources of bias regarding selection, comparability, and bias in outcome assessment of the eligible reports. Given that we used different types of studies, including case-control studies, cohort studies, and cross-sectional studies, we used an adapted NOS for each type of study that we used. A study with an NOS score of 7 or more was considered a “good” study. A quality assessment of our studies can be found in our article’s Supplementary Material.

## Results

Imaging studies on bullying were either MRI or fMRI studies.

### Bullying victimization

Regarding bullying victimization, there were two main categories of studies: those focusing on gray matter areas, mainly the cerebral cortex, and those focusing on white matter tracts.



**Figure 1.** Study selection flowchart.

## Gray matter areas

### Structure

Delaney et al<sup>11</sup> studied bullying effects in brain structure and the role that family plays in minimizing them. More specifically, they reported greater amygdala volume in bullying victims across all family functioning levels, based on the results of the McMaster Family Assessment Device General Functioning Subscale<sup>12,13</sup> (higher score indicated healthier family environment), but the volume was less increased in those from a healthy family environment, indicating the importance of a healthy family environment in mitigating some of the effects of bullying victimization on the human brain.<sup>11</sup>

Without assessing the family environment, the study of Lee et al<sup>14</sup> found no statistically significant change in the volume of the amygdala and hippocampus. However, it was the only study we found that described an association between the volume of the nucleus accumbens and peer victimization. They found that peer problems were associated with adolescent depression through an increase in the volume of the nucleus accumbens, which could indicate increased sensitivity to social threat that resulted from repeated involvement with bullying.<sup>14</sup>

Nolfe et al<sup>15</sup> in their study, which involved patients who experienced bullying at their workplace and were diagnosed with psychiatric disorders (depression, anxiety, or a combination of symptoms), reported a statistically significant reduction in the size of both hippocampi, with a greater decrease in the left. A statistically significant reduction was also found in the volume of cortical Brodmann areas 18 (left inferior occipital gyrus), 19 (left cuneus), and 20 (right inferior temporal gyrus). Interestingly, no difference was found between the hippocampus volume and duration of the work distress, as well as the severity of the psychiatric symptoms.<sup>15</sup>

Quinlan et al,<sup>16</sup> was the first to describe a mechanism of anxiety in victimized peers and connected it to how bullying affects the developing brain. In their study in 2018, they found a connection between chronic peer victimization and reduction in the left putamen volume, which was also unique to peer victimization and unrelated to other types of stress.<sup>16</sup>

Furthermore, Vargas et al<sup>17</sup> in their study regarding bullying in typically developing and clinically high-risk adolescents, used MRI with diffuse tensor imaging (DTI) to examine both the structure of cortical areas of interest, as well as the fractional anisotropy (FA) of

the uncinate fasciculus (white matter tract). Regarding gray matter, they found that increased bullying victimization was associated with smaller orbitofrontal cortex volume, whereas the hippocampi and amygdalae underwent no structural change.<sup>17</sup>

### Function

Lim et al<sup>18</sup> performed a randomized control trial in which they observed the activation of specific brain areas during disgust processing in youth patients who had been victimized either by their peers or by their family, compared to controls. They reported significantly decreased activation in the right amygdala and bilateral posterior insula in bullying victims. They also reported lower activation in areas including bilateral hippocampi, thalamus, striatum, precuneus, inferior temporal areas, lingual and cerebellar regions, and other sensory and motor areas.<sup>18</sup>

Yang et al<sup>19</sup> reported a significant association between bullying and bilateral anterior insula activation, which was further associated with increased suicide risk. Other areas that were found to be activated apart from the insula involved visual regions such as the bilateral middle occipital and fusiform gyri, the supracallosal portion of the left anterior cingulate gyrus, and the medial portion of the left superior frontal gyrus.<sup>19</sup>

Kiefer et al<sup>20</sup> also studied the effect of previous bullying exposure and found that those who had experienced bullying victimization showed greater activation in the subgenual anterior cingulate cortex near the orbitofrontal cortex, pregenual anterior cingulate cortex, inferior frontal gyrus, left insula, dorsolateral prefrontal cortex, medial prefrontal cortex, superior temporal gyrus, and temporal pole. All those results were exhibited when the subjects were in an environment of social exclusion, which was created, meaning that bullying exposure had sensitized these areas.<sup>20</sup>

Finally, Swarz et al<sup>21</sup> in a cross-sectional study using fMRI reported patterns of amygdala activation for both bullying victims and perpetrators. More specifically, firstly, the participants were characterized as either bullying victims or bullies after completing the Peer Experiences Scale,<sup>22</sup> and then their amygdala activity was measured when they were exposed to angry and then fearful faces to see whether a certain pattern of activation could predict their self-reported status regarding bullying. As a result, they found that lower amygdala activity when exposed to both angry and fearful faces was associated with less relational bullying, meaning that bullying victims had higher amygdala

dala activity when exposed to either angry or fearful faces. Interestingly, their study involved only relational bullying, which is the type of aggression in which harm is caused by damaging someone's social status.<sup>21</sup> Table 1 summarizes the studies on gray matter areas affected by bullying victimization.

### White matter tracts

Interesting results were also yielded from studies that focused on the white matter tracts of the brain. Lim et al,<sup>23</sup> apart from their findings on gray matter, also reported interesting findings on the white matter of the brain in another study. More precisely, they performed white matter tractography and tract-based spatial statistics in peer-victimized patients and controls and reported lower FA in the right uncinate fasciculus and bilateral inferior fronto-occipital fasciculi and higher FA in the bilateral inferior longitudinal fasciculi.<sup>23</sup>

Mulder et al<sup>24</sup> found greater global FA and lower global mean diffusivity (MD) in those who were victimized and socially excluded. They specifically reported

greater FA in the corpus callosum, bilateral corona radiata, bilateral sagittal stratum, and left superior longitudinal fasciculus. They suggested that these findings could indicate accelerated white matter microstructure maturation in certain brain areas of children who are victimized.<sup>24</sup>

Graziano et al<sup>25</sup> studied 186 patients with depression, 88 of whom reported a previous history of bullying in their adolescence. DTI was obtained, and images with FA were produced, focusing on white matter tracts of major importance. The results showed that patients who had been bullied showed greater FA in the left posterior corona radiata and right medial lemniscus. These results could be explained by an overactivation of the fear network.<sup>25</sup>

Another study performed by Teicher et al<sup>26</sup> showed that those with exposure to verbal abuse, a major and common form of bullying, showed a significant dose-dependent increase in the MD in the splenium of the corpus callosum, as well as a positive association between exposure and both MD and radial diffusivity (RD) in the

**Table 1.** Summary of the studies on gray matter changes in bullying victims.

| Study profile                    | Type of study | Primary finding   | Secondary findings  | Comments   |
|----------------------------------|---------------|---|---|--|
| Delaney et al 2023 <sup>11</sup> | MRI           | Increase in amygdala volume   | –   | Healthy family environment prevents the increase |
| Lee et al 2020 <sup>14</sup>     | MRI           | Larger nucleus accumbens  | –   | –  |
| Nolfe et al 2018 <sup>15</sup>   | MRI           | Reduction in hippocampus volume                                       | Reduction in Brodmann areas <sup>18–20</sup>  | –  |
| Quinlan et al 2018 <sup>16</sup> | MRI           | Reduction in left putamen volume                                      | –   | Unique to peer victimization                     |
| Vargas et al 2018 <sup>17</sup>  | MRI, DTI      | Smaller orbitofrontal cortex  | –   | –  |
| Lim et al 2024 <sup>18</sup>     | fMRI          | Reduced activation of right amygdala, bilateral posterior insula      | Reduced activation of limbic-thalamic-striatal areas, precuneus/posterior cingulate, temporal, fusiform/lingual and cerebellar regions  | –  |
| Yang et al 2023 <sup>19</sup>    | fMRI          | Anterior insula activation  | Activation of middle occipital gyrus, fusiform gyrus, left anterior cingulate cortex, left superior frontal gyrus                       | Association with suicide risk                    |
| Kiefer et al 2021 <sup>20</sup>  | fMRI          | Greater activation in orbitofrontal cortex                            | Activation of anterior cingulate cortex, inferior frontal gyrus, left insula, prefrontal cortex, superior temporal gyrus, temporal pole | –  |
| Swartz et al 2019 <sup>21</sup>  | fMRI          | Lower amygdala activity when exposed to either angry or fearful faces | –   | –  |

fMRI: functional magnetic resonance imaging; MRI: magnetic resonance imaging; DTI: diffuse tensor imaging

splenium of the corpus callosum and right posterior corona radiata. Regarding FA of the corona radiata and corpus callosum, this was initially found to be negatively associated with exposure to verbal abuse, although it was later proved to be statistically non-significant.<sup>26</sup>

Finally, Vargas et al<sup>17</sup> reported no statistically significant difference in the uncinate fasciculus FA of bullying victims. Table 2 summarizes the studies on white matter areas affected by bullying victimization.

### Bullying perpetration

The study of Mackey et al,<sup>27</sup> although unrelated to bullying, also indicates a connection between lower volume in the frontomedial cortex and bilateral insulae in accordance with greater volumes in the ventral striatum, hypothalamus, and anterior thalamus and impulsivity, which leads to adversity and antisocial behavior.

Swarz et al,<sup>21</sup> apart from their findings regarding bullying victims, also found a pattern of amygdala activation that predicted previously self-reported bullying perpetration. More specifically, they found that increased activity in the bilateral amygdala when exposed to angry faces, in combination with lower amygdala activity when exposed to fearful faces, is associated with bullying perpetration. Finally, they also described a negative association between the activity of the bilateral rostral anterior cingulate cortex and bullying, meaning that those who are less prone to engage in bullying perpetration had higher activation in this area.<sup>21</sup>

Perino et al<sup>28</sup> studied bullying imaging from the perspective of the perpetrator as well. They reported increased activation in the ventral striatum, amygdala, medial prefrontal cortex, and insula. These interesting findings highlight the pathways of reward learning and

motivation that are activated in bullies when experiencing social hierarchy.<sup>28</sup>

Additionally, Kim et al<sup>29</sup> studied the effect of cognitive behavioral therapy in brain imaging of bullying perpetrators. Their results showed decreased fractional amplitude of low-frequency fluctuations (fALFF) in the left lingual gyrus, inferior parietal lobule, left and right inferior frontal gyri, and right middle occipital gyrus. This could indicate a possible association of these areas with bullying perpetration.<sup>29</sup> Table 3 summarizes the studies on brain areas potentially involved in bullying perpetration.

### Discussion

This review approaches the print of bullying on the human brain from both a descriptive and functional anatomic perspective, based on MRI and fMRI data, not only from victimized peers but also from those with an innate tendency to be more impulsive and prone to engage in bullying perpetration.

Regarding bullying victimization, many studies agree on a volume reduction in the orbitofrontal cortex,<sup>17</sup> as well as on its increased activation.<sup>20</sup> The orbitofrontal cortex, which is an important part of the limbic system, plays a critical role in emotion and decision-making by representing the reward or affective value of primary reinforcers like taste and touch, and learning to associate these with other stimuli to predict rewards. It is essential for emotion-related learning, subjective emotional experiences, and modulating these processes through attention and cognitive input.<sup>30</sup> The orbitofrontal cortex has also been found to be affected by environmental stimuli and to be involved in regulating the neurological response to chronic stress.<sup>31</sup> Finally, it can also be affect-

**Table 2.** Summary of the studies on white matter changes in bullying victims.

| Study profile                     | Type of study | Primary finding   | Secondary findings   |
|-----------------------------------|---------------|---|--|
| Mulder et al 2022 <sup>21</sup>   | DTI           | Greater global FA, Lower global MD  | Greater FA in corpus callosum, corona radiata, sagittal stratum, left superior longitudinal fasciculus |
| Graziano et al 2019 <sup>22</sup> | DTI           | Greater FA in left posterior corona radiata                                     | Greater FA in right medial lemniscus   |
| Teicher et al 2010 <sup>23</sup>  | DTI           | Greater MD, RD in corpus callosum (splenium) and right posterior corona radiata | Non-significant trend for decreased FA in corona radiata and corpus callosum                           |
| Vargas et al 2018 <sup>14</sup>   | MRI, DTI      | No statistical significance in the uncinate fasciculus FA                       | --   |

DTI: diffuse tensor imaging; FA: fractional anisotropy; MD: mean diffusivity; MRI: magnetic resonance imaging; RD: radial diffusivity

**Table 3.** Summary of the studies on brain areas involved in bullying perpetration.

| Study profile                   | Type of study | Primary finding  | Secondary findings  |
|---------------------------------|---------------|--|---|
| Mackey et al 2017 <sup>24</sup> | MRI           | Lower volume in frontomedial cortex and insula                         | Greater volume in nucleus accumbens, hypothalamus, anterior thalamus                        |
| Swartz et al 2019 <sup>19</sup> | fMRI          | Increased amygdala activity in angry faces/ decreased in fearful faces | Negative association between the activity of rostral anterior cingulate cortex and bullying |
| Perino et al 2019 <sup>25</sup> | fMRI          | Increased nucleus accumbens activation                                 | Increased activation of amygdala, medial prefrontal cortex, insula                          |
| Kim et al 2018 <sup>26</sup>    | fMRI          | Decreased fALFF in left lingual gyrus and inferior parietal lobule     | Decreased fALFF in right middle occipital gyrus and inferior frontal gyrus                  |

fALFF: fractional amplitude of low-frequency fluctuations; fMRI: functional magnetic resonance imaging; MRI: magnetic resonance imaging

ed by other types of adversities during childhood, such as maltreatment.<sup>32</sup>

The hippocampus was a somewhat controversial structure regarding its association with bullying. Several studies suggested that its volume decreases in victimized peers,<sup>15</sup> while others report no significant change.<sup>14,17</sup> The duration of exposure to bullying could be the reason for this observation. Furthermore, the left putamen seems to suffer atrophy in child victims.<sup>16</sup>

The amygdala was another key nucleus with controversial results, while many studies were focused on it. Delaney et al,<sup>11</sup> studied its specific changes and described greater volume and increased activation in bullying victims. On the other hand, the studies of Vargas et al,<sup>17</sup> Yang et al,<sup>19</sup> Lee et al<sup>14</sup> and Lim et al<sup>18</sup> failed to confirm this finding. Again, the duration of exposure may play a role; however, it could not be proven since most studies did not specify the duration and degree of bullying victimization, and the one that did reported no association.<sup>15</sup> The amygdala was also associated with bullying perpetration, as the pattern of its activation that Swartz et al<sup>21</sup> described can lead to antisocial behavior. Additionally, their pattern of predicting antisocial behavior could potentially help those with the specific pattern of amygdala activation seek medical help and eliminate engagement in this behavior. The amygdala is important in regulating fear and has also been found to be overactive in depressed patients.<sup>33,34</sup>

Other areas that were possibly associated with bullying victimization include the insula and nucleus accumbens. The insula has many functions, including autonomic control, visceral sensations, etc. It also has a significant role in emotional experiences and feelings,<sup>35</sup> which indicates a potential link to bullying. The nucleus accumbens is the ventral portion of the striatum, receives cortical and limbic input, and is a major

pleasure center and regulator of action selection.<sup>36,37</sup> Its overactivation that is suggested to be associated with bullying perpetration could be an interesting topic for future research to better understand how bullies are motivated towards their actions.<sup>14</sup>

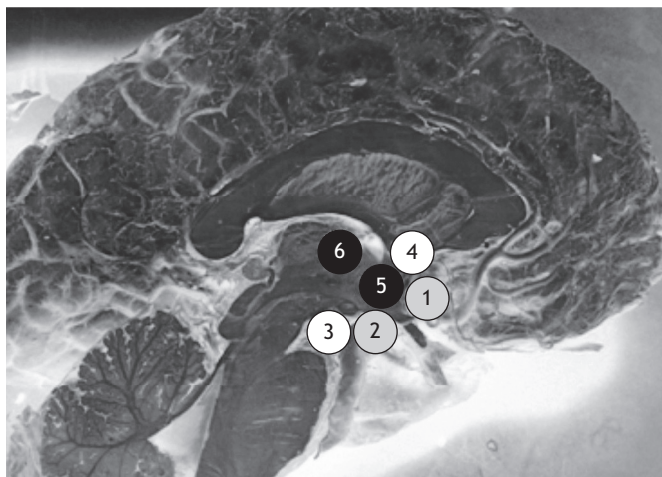
Figure 2 shows a simplification of the current knowledge regarding structural and functional gray matter changes in bullying victims. Notably, these patients seem to have hypertrophic hypoactive amygdalae, atrophic hyperactive orbitofrontal cortex, and increased cortical activation in almost all brain lobes.

Regarding the white matter tracts of the brain, two of the studies showed greater FA (i.e., more homogenous fiber orientation, increased fiber density or axonal diameter, and increased ratio of intracellular/extracellular space) in the corona radiata, whereas another study did not confirm this finding (table 2). The corona radiata is a large white matter bundle that consists of ascending and descending fibers. Ascending fibers primarily connect the thalamus to the cerebral cortex, and descending fibers mainly connect the frontoparietal cortex to subcortical basal ganglia regions and the spinal cord.<sup>38</sup> It is not surprising that abnormalities in this tract have also been linked to other psychiatric conditions, such as depression.<sup>39,40</sup>

Answering our aim's questions, as analyzed above, we did identify specific imaging findings that correlate with bullying victimization and perpetration, namely morphological and functional alterations in many brain areas. And indeed, there are cortical brain areas, nuclei (figure 3), and white matter tracts, particularly affected either morphologically or functionally. As expected, most of them are parts of the limbic system, which plays a crucial role in emotions and behavior and is disturbed in common psychopathologies such as anxiety and depression. It is therefore at least partially explained why alterations in areas like the amygd-

|   | size   | activation   |
|---|--|--|
| ↑ | amygdala<br>nucleus accumbens  | insula<br>orbitofrontal cortex<br>prefrontal cortex<br>anterior cingulate cortex<br>middle occipital gyrus<br>fusiform gyrus<br>superior frontal gyrus<br>inferior frontal gyrus<br>superior temporal gyrus<br>temporal pole |
| ↓ | hippocampus<br>orbitofrontal cortex<br>putamen (left)<br>Brodmann areas 18, 19, 20 | amygdala   |

**Figure 2.** Simplification of gray matter (structural and functional) changes in bullying victims (↑, increase; ↓, decrease).



**Figure 3.** The human brain nuclei affected in bullying conditions (projection on the medial hemispheric surface). (1) nucleus accumbens; (2) amygdala; (3) hippocampus; (4) putamen (left); (5) hypothalamus; (6) anterior thalamus. White circles: nuclei affected in victims, black circles: nuclei affected in perpetrators, gray circles: nuclei affected in both victims and perpetrators (modified from Mavridis<sup>37</sup>).

dala and nucleus accumbens of bullying victims can make them vulnerable to depression and other anxiety disorders.

Given the fact that the imaging findings have been observed after bullying behaviors, it seems unlikely that these could be used in primary bullying prevention. However, they can be useful in secondary prevention by early identification of victims with brain imaging chang-

es before the clinical manifestation of psychopathology. Early interventions could, thus, help in the avoidance of suicidal behaviors and other catastrophic sequelae of bullying on victims. Even for bullies, the evidence of overactive accumbens nuclei, for example, could be a red flag to seek medical help.

## Conclusion

In conclusion, bullying is a serious social and health issue that changes the human brain morphologically and functionally, primarily affecting the limbic system. Fundamental nuclei of the latter, namely the nucleus accumbens and amygdala, are affected in both victims and perpetrators. Bullying victims seem to have atrophic hyperactive orbitofrontal cortex, hypertrophic hypoactive amygdalae, and increased cortical activation in almost all brain lobes. Bullies, on the other hand, have hyperactive accumbens nuclei. These findings can be useful in the early identification of victims before the expression of psychopathology (secondary prevention). Subsequent early interventions could help in the preservation of the victims' lives and their quality. It is certain that we still have a lot to learn about the way that bullying affects the human brain, and further research is needed in this direction, especially at a neurochemical/molecular level. Of course, primary prevention is always better than secondary, and our societies have therefore to maximize their efforts in this direction, i.e., fighting bullying as a social disease.

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## Ανασκόπηση

# Ανατομία του εκφοβισμού (bullying): Πώς επηρεάζει τη δομή και λειτουργία του εγκεφάλου. Συστηματική ανασκόπηση

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### ΠΕΡΙΛΗΨΗ

Ο εκφοβισμός (bullying) είναι ένα κοινό πρόβλημα στους νέους με πολλές καταστροφικές συνέπειες καθώς σχετίζεται με ψυχιατρικές διαταραχές όπως το άγχος και η κατάθλιψη. Ο προσδιορισμός του αποτυπώματος του εκφοβισμού στον ανθρώπινο εγκέφαλο θα μπορούσε να χρησιμεύσει στην κλινική πράξη, ιδίως στη δευτερογενή πρόληψη των διαταραχών που σχετίζονται με αυτό. Η παρούσα ανασκόπηση έχει ως σκοπό να διερευνήσει τις δυνητικές σχετιζόμενες με τον εκφοβισμό αλλαγές του ανθρώπινου εγκεφάλου από μία οπτική περιγραφικής και λειτουργικής ανατομίας. Πραγματοποιήθηκε έρευνα της βιβλιογραφίας χρησιμοποιώντας τη βάση δεδομένων Pubmed/Medline και, μετά από ενδελεχή έλεγχο, χρησιμοποιήθηκαν τελικά 16 άρθρα. Η παρούσα ανασκόπηση περιέλαβε μελέτες συμβατικών και λειτουργικών μαγνητικών τομογραφιών, οι οποίες εστίασαν σε δομές φαιάς και λευκής ουσίας του εγκεφάλου. Ο εκφοβισμός επηρεάζει τη μορφολογία και τη λειτουργία δομών φαιάς και λευκής ουσίας σε αμφοτέρους τους θύτες και τα θύματα. Τα θύματα φαίνεται να έχουν ατροφικό υπερδραστήριο κορχομετωπιαίο φλοιό, υπερτροφικές υποδραστήριες αμυγδαλές και αυξημένη ενεργοποίηση του φλοιού σε όλους σχεδόν τους λοβούς του εγκεφάλου. Οι θύτες, από την άλλη πλευρά, έχουν υπερδραστήριους επικλινείς πυρήνες. Θεμελιώδεις πυρήνες του μεταιχμιακού συστήματος, δηλαδή ο επικλινής πυρήνας και η αμυγδαλή, επηρεάζονται σε αμφοτέρους τους θύτες και τα θύματα. Ο εκφοβισμός αλλάζει τον ανθρώπινο εγκέφαλο μορφολογικά και λειτουργικά, επηρεάζοντας πρωτίστως δομές του μεταιχμιακού συστήματος. Η έγκαιρη ανίχνευση αυτών των αλλαγών θα μπορούσε κυρίως να βοηθήσει στην πρόληψη της εκδήλωσης ψυχοπαθολογίας και συνεπώς να βελτιώσει την ποιότητα ζωής των θυμάτων και ακόμη να βοηθήσει τους θύτες να αναζητήσουν ιατρική βοήθεια.

**ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ:** Αμυγδαλή, απεικόνιση εγκεφάλου, επικλινής πυρήνας, κορχομετωπιαίος φλοιός, μαγνητική τομογραφία, εκφοβισμός.

## Review

# Link between the mechanism of mitophagy and schizophrenia: A narrative review

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### ABSTRACT

Despite extensive research, the precise pathophysiology underlying schizophrenia remains unclear, but accumulating evidence suggests that mitochondrial dysfunction and oxidative stress play significant roles in its development. Mitophagy, the selective degradation of damaged or dysfunctional mitochondria, plays a critical role in maintaining cellular homeostasis and is increasingly recognized for its implications in various neuropsychiatric disorders, including schizophrenia. This review examines current knowledge regarding mitophagy and its association with schizophrenia. The literature was searched in PubMed-Medline and Scopus databases, and as a narrative review, the methodology focuses on the comprehensive coverage and synthesis of relevant studies. The hypothesis of the review claims that there is a link between mitophagy and schizophrenia. The terms used in the search query are “mitophagy”, “schizophrenia” with the Boolean variable “AND”. The relationship between mitophagy and schizophrenia is complex and multifaceted, involving mitochondrial dysfunction, neuroinflammation, and the integrity of oligodendrocytes and microglia. Schizophrenia is associated with dysfunctional mitophagy and elevated oxidative stress. These mechanisms may help to explain overlapping symptoms, particularly cognitive deficits. While the emerging data linking mitophagy and schizophrenia are promising, current research has limitations. Much of the evidence for mitophagy dysfunction in schizophrenia comes from animal models or postmortem studies, which may not fully capture the complexity of the disorder in humans. Moreover, mitophagy is challenging to study *in vivo*, particularly in the human brain, making it difficult to directly observe mitophagy processes in patients with schizophrenia. Mitophagy and its dysfunction may contribute to the pathophysiology of schizophrenia. Evidence suggests that impaired mitophagy can lead to energy dysregulation, oxidative stress, and neuroinflammation, all of which are implicated in schizophrenia. While more research is needed, the potential link between mitophagy and schizophrenia presents an interesting area for future studies and therapeutic development. Targeting mitophagy could offer new approaches for addressing cognitive and negative symptoms, providing hope for improved treatment outcomes.

**KEYWORDS:** Mitochondria, mitophagy, schizophrenia, mitochondrial dysfunction.

### Introduction

Schizophrenia is a chronic and often debilitating psychiatric disorder characterized by a constellation of positive symptoms (such as hallucinations and delusions), negative symptoms (such as apathy and social withdrawal), and cognitive deficits.<sup>1</sup> Despite exten-

sive research, the precise pathophysiology underlying schizophrenia remains unclear, but emerging evidence suggests that mitochondrial dysfunction and oxidative stress have a pivotal role in its development.<sup>2</sup> Given the critical energy demands of neurons, mitochondrial health is essential for maintaining cellular homeostasis and function in neural cells.<sup>3</sup>

Mitophagy, a selective autophagy process that removes damaged or dysfunctional mitochondria, is essential for mitochondrial quality control. By preventing the accumulation of damaged mitochondria, mitophagy plays a crucial role in preventing oxidative damage and sustaining cellular health. Recent research has highlighted disruptions in mitophagy as a contributing factor to neurodegenerative diseases<sup>4</sup> and, increasingly, neuropsychiatric disorders like schizophrenia.<sup>5</sup> Understanding how mitophagy functions in neurons—and how its dysregulation could contribute to the symptoms of schizophrenia—could provide new insights into disease mechanisms and potential therapeutic strategies.

This review examines current knowledge regarding mitophagy and its association with schizophrenia. It starts by examining the process of mitophagy, followed by mitochondrial abnormalities and emerging evidence that links disruptions in mitophagy with schizophrenia's pathophysiology. Finally, it discusses potential therapeutic implications and areas for further research.

## Overview of mitophagy

Mitophagy is a specialized form of autophagy responsible for the targeted removal of damaged or dysfunctional mitochondria, thereby preserving cellular health.<sup>5</sup> Through the process of mitophagy, cells can maintain mitochondrial quality control, preventing the accumulation of malfunctioning mitochondria that might otherwise generate excessive reactive oxygen species (ROS) or trigger apoptotic pathways.<sup>6</sup> This mechanism is particularly critical in neurons, where stable mitochondrial function is essential to meet the high energy demands necessary for synaptic transmission and plasticity.<sup>4</sup>

Several well-characterized pathways regulate mitophagy, each playing a unique role in recognizing and targeting damaged mitochondria for degradation.

- **PINK1/Parkin Pathway:** PINK1 (PTEN-induced kinase 1) accumulates on the outer mitochondrial membrane once the mitochondrion becomes depolarized and loses membrane potential. Due to this accumulation, Parkin, an E3 ubiquitin ligase, is drawn to the membrane. Parkin then ubiquitinates other mitochondrial proteins, indicating the organelle for autophagic degradation. This pathway has been extensively studied in the context of neurodegenerative diseases like Parkinson's, but is also pertinent in schizophrenia.<sup>4,6</sup>
- **BNIP3/NIX Pathway:** BNIP3 and NIX are two proteins that facilitate mitophagy in response to hypoxia. These proteins assist in the engulfment of mitochondria within autophagosomes via interaction with the

autophagic protein LC3. This pathway may also be relevant in the brain, where hypoxic conditions are related to various neuropsychiatric conditions.<sup>4,5</sup>

- **FUNDC1 Pathway:** FUNDC1 is a mitophagy receptor, essential for hypoxia-induced mitophagy. It binds directly to LC3, indicating mitochondria for degradation. Although less studied in schizophrenia, emerging evidence suggests it may contribute to cellular responses to environmental stressors implicated in schizophrenia.<sup>4</sup>

Neurons are uniquely dependent on effective mitophagy. They have a highly polarized structure and are less capable of regenerating compared to other cell types, making mitochondrial quality control essential. Neuronal health relies on continuous mitophagy to meet synaptic demands, support neuroplasticity, and maintain overall brain function.<sup>7</sup> Impairments in mitophagy have been linked to neurodegenerative diseases, but recent findings suggest that similar dysfunctions might also contribute to the pathogenesis of psychiatric conditions, including schizophrenia.<sup>5</sup>

## Mitochondrial dysfunction in schizophrenia

Research has increasingly highlighted mitochondrial dysfunction as a factor in the pathophysiology of schizophrenia.<sup>5</sup> Mitochondria are essential for ATP production, calcium buffering, and regulation of oxidative stress, all of which are critical for neuronal function.<sup>4</sup> Studies have documented various mitochondrial abnormalities in patients with schizophrenia, including structural changes, impaired bioenergetics, and increased oxidative stress.

Postmortem studies have identified structural changes in the mitochondria of individuals with schizophrenia, such as alterations in mitochondrial density and morphology.<sup>8</sup> These changes are thought to compromise cellular energy production, leading to an energy deficit in neurons. Functional imaging studies have also shown reductions in glucose metabolism and ATP levels in specific brain regions associated with schizophrenia symptoms, including the prefrontal cortex and hippocampus.<sup>9</sup>

Mitochondrial dysfunction is a well-documented feature in schizophrenia, with evidence suggesting that impaired mitophagy may contribute to the observed mitochondrial abnormalities.<sup>10</sup> Oligodendrocytes and microglia exhibit mitochondrial dysfunction in schizophrenia, positing that increased mitophagy could be a response to mitochondrial damage, thereby influencing white matter pathology.<sup>11</sup> This aligns with findings by Li et al, who note that mitochondrial dysfunction is prevalent in various psychiatric disorders, including schizo-

phrenia, indicating a broader pattern of mitochondrial involvement in mental health conditions. They argue that increased mitophagy could be a compensatory response to mitochondrial damage, which is prevalent in the prefrontal gray matter of individuals with schizophrenia.<sup>11</sup>

One prominent hypothesis is that the dysregulation of mitochondrial function leads to increased oxidative stress. Neurons are particularly vulnerable to oxidative damage due to their high metabolic demand, and accumulating evidence suggests that schizophrenia is associated with elevated levels of oxidative stress markers.<sup>12</sup> The energy deficits and oxidative stress resulting from mitochondrial dysfunction are thought to contribute to several aspects of schizophrenia pathology. For instance, impaired ATP production may impact neurotransmitter regulation, leading to disruptions in dopamine and glutamate signaling, both implicated in schizophrenia. Additionally, energy dysregulation and increased ROS can lead to cellular damage, potentially contributing to the progressive cognitive decline and negative symptoms observed in schizophrenia.<sup>13,14</sup>

### **Potential mechanisms linking mitophagy to schizophrenia**

Several specific mechanisms could explain the connection between impaired mitophagy and schizophrenia. Since neurons rely heavily on mitochondrial energy production, impaired mitophagy can lead to an accumulation of dysfunctional mitochondria that fail to meet neuronal energy demands.<sup>4</sup> This energy deficit can impair neurotransmission and synaptic plasticity, processes essential for cognition and behavior. The resulting deficits could contribute to both the cognitive and negative symptoms of schizophrenia, such as poor working memory and diminished motivation.<sup>12</sup>

Mitochondria are both sources of oxidative stress. When mitophagy is impaired, damaged mitochondria accumulate, leading to increased production of ROS.<sup>14</sup> Excessive ROS can damage cellular components, including lipids, proteins, and DNA, potentially contributing to the cellular pathology observed in schizophrenia. Increased oxidative stress may also disrupt neuronal signaling and plasticity, further exacerbating cognitive symptoms.<sup>13</sup>

Mitophagy plays a key role in maintaining synaptic health. Mitochondria are essential for supplying ATP at synaptic sites and buffering calcium during neurotransmitter release. When mitophagy is impaired, dysfunctional mitochondria can lead to synaptic deficits, as they fail to support the energy-intensive processes required for proper synaptic transmission and plasticity.

These disruptions may underlie some of the cognitive impairment's characteristic of schizophrenia.<sup>5</sup>

Recent studies suggest that impaired mitophagy may contribute to neuroinflammation, which is increasingly recognized as a factor in schizophrenia. When dysfunctional mitochondria accumulate, they can release pro-inflammatory signals, such as mitochondrial DNA and ROS, that activate the immune system. Chronic neuroinflammation can alter brain function and has been linked to various neuropsychiatric disorders, including schizophrenia.<sup>13</sup>

Moreover, the role of antipsychotic medications in influencing mitophagy has garnered attention. Olanzapine can induce mitochondrial damage and impair mitophagy, thereby influencing mitochondrial dynamics and autophagic processes, potentially leading to accelerated aging effects in neuronal cells.<sup>15,16</sup> This finding underscores the importance of considering how pharmacological interventions may impact mitochondrial function and mitophagy in patients with schizophrenia. Additionally, natural compounds that enhance mitophagy could serve as adjunctive therapies to improve mitochondrial function and reduce oxidative stress in patients with schizophrenia.<sup>17</sup>

### **Mitophagy and neurodegeneration: A mechanistic link to schizophrenia?**

Both neurodegenerative disorders and schizophrenia are associated with dysfunctional mitophagy and elevated oxidative stress. These shared mechanisms may help to explain overlapping symptoms, particularly cognitive deficits.<sup>5</sup> Moreover, mitophagy dysfunction in neurons can result in an accumulation of damaged mitochondria, leading to impaired neuronal function and increased susceptibility to apoptosis.<sup>4</sup> Understanding these shared mechanisms may provide novel treatment potential for schizophrenia, through therapies aimed at enhancing mitophagy.

Research on neurodegenerative diseases has established that mitophagy is crucial for neuronal survival and function.<sup>4</sup> Dysregulation of mitophagy is known to contribute to diseases like Parkinson's and Alzheimer's, and emerging studies suggest that similar mechanisms may be at play in schizophrenia.<sup>5</sup> Although schizophrenia is traditionally classified as a psychiatric disorder rather than a neurodegenerative one, the two categories share common pathological features, including mitochondrial dysfunction and cellular stress responses.<sup>18</sup>

Animal studies have shown that genetic mutations affecting mitophagy (e.g., PINK1, Parkin) can lead to neuropsychiatric symptoms, including behaviors akin to those seen in schizophrenia, such as social with-

drawal and cognitive impairment.<sup>11</sup> Additionally, post-mortem analyses of brain tissue from individuals with schizophrenia have identified alterations in mitophagy-related proteins.<sup>8</sup> This suggests that impairments in mitophagy may play a role in the neuronal abnormalities seen in schizophrenia.

The mechanisms underlying mitophagy are complex and involve various signalling pathways. Wang et al provide a comprehensive overview of the mechanisms of mitophagy, emphasizing the importance of ubiquitin-dependent and receptor-mediated signals in the degradation of damaged mitochondria.<sup>6</sup> This is particularly relevant in the context of schizophrenia, where disrupted signalling pathways—such as those involving PINK1/Parkin, BNIP3/NIX, and FUNDC1—may impair mitophagy, leading to the accumulation of damaged mitochondria. This impairment exacerbates mitochondrial dysfunction, contributing to neuroinflammation and oxidative stress, which are key features of schizophrenia pathology.

The role of mitochondrial dysfunction in psychiatric disorders, including schizophrenia, has been well documented. Impaired mitophagy in neurons and glial cells during aging and age-related disorders can lead to neurodegeneration, which may also be relevant to the pathophysiology of schizophrenia. The accumulation of dysfunctional mitochondria due to defective mitophagy can exacerbate neuroinflammatory processes, further complicating the clinical picture of schizophrenia.<sup>13</sup> Neuroinflammation is another critical factor that intersects with mitophagy in the context of schizophrenia. The activation of microglia, the brain's resident immune cells, can lead to the release of pro-inflammatory cytokines, which may further exacerbate mitochondrial dysfunction and impair mitophagy.<sup>13</sup> Mitochondrial dysfunction can lead to increased oxidative stress and neuroinflammation, both of which are implicated in the pathophysiology of schizophrenia.<sup>14,19</sup> This interplay suggests that impaired mitophagy may not only contribute to mitochondrial dysfunction but also exacerbate inflammatory processes that are characteristic of schizophrenia.

Recent research has identified specific genes associated with mitophagy that may be implicated in schizophrenia. The expression of genes associated with mitophagy, such as those identified by bioinformatic analyses, has been shown to correlate with schizophrenia, indicating a potential genetic basis for impaired mitochondrial quality control in this disorder.<sup>20</sup> The gene BNIP3L, which is involved in mitophagy, has been highlighted in studies linking genetic risk factors to schizophrenia.<sup>20</sup> This gene's expression is altered in the context of neurodevelopmental disorders, suggesting that

disruptions in mitophagy could be a contributing factor to the etiology of schizophrenia. Additionally, MEF2C, a gene enriched in neuronal populations, is involved in regulating mitochondrial function and its potential implications for cognitive function in schizophrenia.<sup>21</sup>

The mechanisms underlying mitophagy are multifaceted and involve various signaling pathways. The involvement of the PINK1/Parkin pathway in mitophagy regulation has been implicated in both neurodegenerative diseases and schizophrenia.<sup>6</sup> Wang et al, provide insights into how mitochondrial biogenesis and mitophagy are regulated through various signaling pathways, including the PGC-1 family proteins and AMPK.<sup>6</sup> These pathways are crucial for maintaining mitochondrial health and could be targeted for therapeutic interventions in schizophrenia, as suggested by the potential of pharmacological agents to modulate these pathways.<sup>3</sup> BNIP3L/NIX, a mitophagy receptor, plays a significant role in recognizing damaged mitochondria and facilitating their degradation.<sup>22</sup> This process is crucial in neurons, which are particularly vulnerable to mitochondrial damage due to their high energy demands. Impaired mitophagy has been linked to the accumulation of dysfunctional mitochondria, leading to increased oxidative stress and neuronal death, which are observed in neurodegenerative diseases and may also be relevant to schizophrenia.<sup>5</sup>

Furthermore, the role of specific proteins, such as Disrupted-in-Schizophrenia-1 (DISC1), has been explored in the context of mitophagy, and synaptic DISC1 acts as a mitophagy receptor, and its dysregulation may contribute to synaptic dysfunction in schizophrenia. This highlights the potential for targeting mitophagy pathways as a therapeutic strategy to restore synaptic integrity and improve clinical outcomes in schizophrenia.<sup>23</sup>

## Current evidence and limitations in mitophagy research in schizophrenia

While the emerging data linking mitophagy and schizophrenia are promising, current research has limitations. Much of the evidence for mitophagy dysfunction in schizophrenia comes from animal models or postmortem studies,<sup>8,11</sup> which may not fully capture the complexity of the disorder in humans. Moreover, mitophagy is challenging to study *in vivo*, particularly in the human brain, making it difficult to directly observe mitophagy processes in patients with schizophrenia.

Further research is needed to clarify the role of mitophagy in schizophrenia, including studies using advanced imaging techniques and biomarkers to measure mitophagy activity *in vivo*. Additionally, research into genetic and environmental factors that influence mito-

phagy in schizophrenia may shed light on individual differences in disease presentation and treatment response.

## Potential therapeutic implications

Understanding the role of mitophagy in schizophrenia opens the door to potential therapeutic interventions aimed at restoring mitochondrial function. Research is exploring pharmacological agents that can enhance mitophagy, including compounds that activate the PINK1/

Parkin pathway.<sup>24</sup> Although many of these agents are still in experimental stages, they may offer a new approach for treating schizophrenia by targeting mitochondrial function and cellular resilience. Lifestyle factors, such as regular physical exercise and caloric restriction, have been shown to stimulate mitophagy and improve mitochondrial function.<sup>25,26</sup> Additionally, certain nutrients (e.g., NAD<sup>+</sup> boosters) may support mitochondrial health and could be considered as adjunctive therapies for schizophrenia.<sup>27</sup> Table 1 summarizes the main findings on

**Table 1.** Summary of key findings on mitochondrial and mitophagy abnormalities in schizophrenia.

| Aspect                    | Key Findings  | Detailed Mechanisms and Observations   | References                                  |
|---------------------------|---|--|---|
| Mitochondrial dysfunction | Structural changes in mitochondria in schizophrenia.    | Postmortem studies show altered mitochondrial density and morphology, particularly in the prefrontal cortex.   | Roberts (2017), Uranova et al (2020)        |
|                           | Impaired energy production and ATP synthesis.           | Glucose metabolism and ATP levels are reduced in brain regions associated with cognitive functions (e.g., prefrontal cortex, hippocampus).                   | Howes et al (2023), Li et al (2021)         |
|                           | Elevated oxidative stress levels.                       | Increased markers of oxidative damage, including lipid peroxidation and protein oxidation, were observed in patients with schizophrenia.                     | Ermakov et al (2021), Stone et al (2022)    |
| Mitophagy pathways        | Dysfunctional PINK1/Parkin pathway.                     | Damaged mitochondria fail to recruit PINK1/Parkin for ubiquitination and degradation, leading to the accumulation of defective mitochondria.                 | Wang et al (2019), Cen et al (2021)         |
|                           | BNIP3/NIX pathway alterations under hypoxic conditions. | BNIP3/NIX proteins are involved in mitochondrial degradation during stress, with potential dysfunctions contributing to neuronal pathology in schizophrenia. | Cen et al (2021), Doblado et al (2021)      |
|                           | FUNDC1 receptor-mediated mitophagy under stress.        | Impairment of FUNDC1 may reduce mitophagy in neurons, exacerbating stress responses in schizophrenia.  | Cen et al (2021)                            |
| Neuroinflammation         | Dysfunctional mitophagy exacerbates neuroinflammation.  | Damaged mitochondria release pro-inflammatory signals such as mitochondrial DNA and ROS, triggering immune responses.  | Sukhorukov et al (2021), Picca et al (2020) |
|                           | Microglial activation contributes to inflammation.      | Persistent microglial activation releases pro-inflammatory cytokines, worsening neuronal damage and cognitive symptoms.                                      | Uranova et al (2020), Ermakov et al (2021)  |
|                           | Excess ROS production leads to neuronal damage.         | Dysfunctional mitochondria generate excessive ROS, causing damage to proteins, lipids, and DNA, and impairing synaptic plasticity.                           | Morris & Berk (2015), Boz et al (2020)      |
|                           | Energy deficits contribute to oxidative stress.         | Reduced mitochondrial bioenergetics impair neurotransmitter systems (e.g., glutamate and dopamine), crucial in schizophrenia pathology.                      | Stone et al (2022), Li et al (2021)         |
| Cognitive deficits        | Linked to mitochondrial and oxidative dysfunctions.     | Impaired ATP synthesis and excessive oxidative stress disrupt neurotransmission and synaptic plasticity, leading to cognitive impairments in schizophrenia.  | Li et al (2021), Howes et al (2023)         |
| Therapeutic implications  | Pharmacological agents target mitophagy pathways.       | Activators of PINK1/Parkin pathways and antioxidants show potential in restoring mitochondrial health and reducing oxidative damage.                         | Wang et al (2019), Stacchiotti et al (2020) |
|                           | Lifestyle interventions enhance mitophagy.              | Physical exercise and caloric restriction promote mitophagy, reduce oxidative stress, and improve mitochondrial function.                                    | Kyriazis et al (2022), Xu et al (2022)      |
|                           | Adjunctive therapies include natural compounds.         | Nutritional supplements (e.g., NAD <sup>+</sup> boosters) and antioxidants may serve as supportive therapies for cognitive and negative symptoms.            | Boz et al (2020), Stacchiotti et al (2020)  |

mitochondrial and mitophagy abnormalities in schizophrenia reviewed in this study.

## Conclusion

Mitophagy is a critical process for maintaining neuronal health, and its dysfunction may contribute to the pathophysiology of schizophrenia. Evidence suggests that impaired mitophagy can lead to energy dysregulation, oxidative stress, and neuroinflammation, all of

which are implicated in schizophrenia. While more research is needed to elucidate the precise mechanisms and the potential link between mitophagy and schizophrenia, it represents a promising field for future studies and therapeutic development. Targeting mitophagy could offer new approaches and explore potential therapeutic strategies for addressing cognitive and negative symptoms, providing hope for improved treatment outcomes.

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# Ανασκόπηση

## Σύνδεση του μηχανισμού της μιτοφαγίας με τη σχιζοφρένεια: Αφηγηματική ανασκόπηση

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### ΠΕΡΙΛΗΨΗ

Παρά την εκτεταμένη έρευνα, η ακριβής παθοφυσιολογία της σχιζοφρένειας παραμένει ασαφής, αλλά αυξανόμενα στοιχεία υποδεικνύουν ότι η δυσλειτουργία των μιτοχονδρίων και το οξειδωτικό στρες παίζουν σημαντικό ρόλο στην ανάπτυξη της. Η μιτοφαγία, η επιλεκτική αποδόμηση των κατεστραμμένων ή δυσλειτουργικών μιτοχονδρίων, διαδραματίζει κρίσιμο ρόλο στη διατήρηση της κυτταρικής ομοιόστασης και αναγνωρίζεται όλο και περισσότερο για τις επιπτώσεις της σε διάφορες νευροψυχιατρικές διαταραχές, συμπεριλαμβανομένης της σχιζοφρένειας. Αυτή η ανασκόπηση εξετάζει τις τρέχουσες γνώσεις σχετικά με τη μιτοφαγία και τη σχέση της με τη σχιζοφρένεια. Η αναζήτηση της βιβλιογραφίας πραγματοποιήθηκε στις βάσεις δεδομένων PubMed-Medline και Scopus, και ως αφηγηματική ανασκόπηση, η μεθοδολογία επικεντρώνεται στην ολοκληρωμένη κάλυψη και σύνθεση σχετικών μελετών. Η υπόθεση της ανασκόπησης υποστηρίζει ότι υπάρχει σύνδεση μεταξύ της μιτοφαγίας και της σχιζοφρένειας. Οι όροι που χρησιμοποιήθηκαν στην αναζήτηση ήταν "mitophagy", "schizophrenia" με τον Boolean όρο "AND". Η σχέση μεταξύ της μιτοφαγίας και της σχιζοφρένειας είναι σύνθετη και πολυδιάστατη, περιλαμβάνοντας τη δυσλειτουργία των μιτοχονδρίων, τη νευροφλεγμονή, και την ακεραιότητα των ολιγοδενδροκυττάρων και των μικρογλοιακών κυττάρων. Η σχιζοφρένεια συνδέεται με δυσλειτουργική μιτοφαγία και αυξημένο οξειδωτικό στρες. Αυτοί οι εμπλεκόμενοι μηχανισμοί μπορούν να συμβάλουν στην εξήγηση των κοινών συμπτωμάτων, ιδιαίτερα των γνωστικών ελλειμμάτων. Παρά τα υποσχόμενα δεδομένα που συνδέουν τη μιτοφαγία με τη σχιζοφρένεια, η τρέχουσα έρευνα έχει περιορισμούς. Μεγάλο μέρος των στοιχείων για τη δυσλειτουργία της μιτοφαγίας στη σχιζοφρένεια προέρχεται από ζωικά μοντέλα ή μεταθανάτιες μελέτες, τα οποία μπορεί να μην αποδίδουν πλήρως την πολυπλοκότητα της διαταραχής στους ανθρώπους. Επιπλέον, η μελέτη της μιτοφαγίας *in vivo* είναι ιδιαίτερα δύσκολη, ειδικά στον ανθρώπινο εγκέφαλο, καθιστώντας δύσκολη την άμεση παρατήρηση των διαδικασιών μιτοφαγίας σε ασθενείς με σχιζοφρένεια. Η μιτοφαγία και η δυσλειτουργία της ενδέχεται να συμβάλουν στην παθοφυσιολογία της σχιζοφρένειας. Τα στοιχεία δείχνουν ότι η εξασθενημένη μιτοφαγία μπορεί να οδηγήσει σε δυσλειτουργία ενεργειακής ρύθμισης, οξειδωτικό στρες και νευροφλεγμονή, όλα εκ των οποίων εμπλέκονται στη σχιζοφρένεια. Παρά το γεγονός ότι χρειάζεται περισσότερη έρευνα, η πιθανή σύνδεση μεταξύ της μιτοφαγίας και της σχιζοφρένειας αποτελεί ένα ιδιαίτερα ενδιαφέρον πεδίο για μελλοντικές μελέτες και ανάπτυξη θεραπευτικών μεθόδων. Η στόχευση της μιτοφαγίας θα μπορούσε να προσφέρει νέες προσεγγίσεις για την αντιμετώπιση των γνωστικών και αρνητικών συμπτωμάτων, δίνοντας ελπίδα για καλύτερα θεραπευτικά αποτελέσματα.

**ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ:** Μιτοχόνδρια, μιτοφαγία, σχιζοφρένεια, δυσλειτουργία μιτοχονδρίων.

## Review

# Barriers to the use of telepsychiatry for the treatment of eating disorders: A systematic review and thematic synthesis

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### ABSTRACT

Eating disorders are mental disorders characterized by disturbed body image and excessive fear of weight gain, leading to disordered eating and weight control behaviour. Studies show that early treatment is one of the most important factors in improving the prognosis of these diseases. Nevertheless, a large percentage of patients with eating disorders do not receive treatment or seek treatment until their disorder has progressed. Telepsychiatry promises to expedite treatment times by resolving geographical and cost barriers. However, there are various shortcomings in using telepsychiatry in eating disorders, including its effectiveness in treating patients with eating disorders, difficulty establishing a strong therapeutic relationship, privacy concerns, security and technological limitations, among others. The purpose of this paper is to review the barriers that limit the usefulness of telepsychiatry in eating disorders. Ultimately, it aims to improve the use of telepsychiatry to better and more safely serve the needs of patients with eating disorders. We conducted a systematic review and thematic synthesis using a mixed PRISMA/ ENTREQ methodology, focusing on research that directly or indirectly investigated barriers to the use of telepsychiatry in the treatment of patients with EDs. Fifty-two studies were included, revealing multifaceted challenges in implementing telepsychiatry for patients with EDs. Specific barriers identified include poor therapeutic relationship and poor treatment adherence, clinical limitations (poor therapeutic effect, illness severity, comorbidity, certain eating disorder types are barriers themselves, impersonal care), and technical limitations (program design issues, privacy concerns), as well as negative patient experience. Telepsychiatry shows promise for treating EDs, but it is important to address these barriers to reach its full potential. Clinical adaptations, technological improvements, and a person-centered approach are essential to fully realize its potential. Online or hybrid treatment models must be highly personalized and multifaceted and have active therapist involvement, particularly for patients with clinical complexity.

**KEYWORDS:** Eating disorders, telepsychiatry, online therapy, barriers, person-centered.

### Introduction

Eating disorders (EDs) are characterized by abnormal eating behaviours and intense preoccupation with food and body image, often driven by dissatisfaction

with body weight and a need to control food intake. Common EDs include anorexia nervosa, bulimia nervosa, and binge eating disorder. These often physically and psychosocially debilitating disorders are commonly comorbid with anxiety, depression, personality disorders,

and substance misuse, and their aetiology is multifactorial, involving genetic, psychological, and environmental factors.<sup>1</sup> The prevalence of EDs has risen from 3.5% in 2000–2006 to 7.8% in 2013–2018, while the prevalence escalates to 17% if atypical presentations are also considered.<sup>2</sup> A significant increase was noted during the COVID-19 pandemic, especially among marginalized groups.<sup>3</sup> Early detection and intervention are critical for improving prognosis,<sup>1</sup> but EDs are frequently underdiagnosed due to factors like shame and denial.<sup>4</sup> Treatment delays are long and vary, with shorter durations for anorexia nervosa and longer for bulimia nervosa and binge eating disorder.<sup>5</sup> EDs are also undertreated, with only an estimated one-third of patients receiving treatment for their disorder. Men, adolescents, patients with high BMI or transgender/gender-diverse individuals, and people from minority groups face additional barriers to accessing treatment.<sup>6</sup>

Telepsychiatry has emerged as a promising approach for treating EDs, offering benefits like early intervention, reduced wait times, better accessibility and engagement, lower treatment costs, reduced stigma, and improvement of both core ED symptoms and comorbid anxiety and depression.<sup>7–9</sup> Although remote care for EDs may be as effective as in-person treatment while offering patients greater access to care,<sup>10</sup> barriers such as compromised therapeutic relationship, treatment adherence, privacy issues, and technical limitations may limit its overall usefulness. This systematic review and thematic synthesis aim to summarize these barriers and to suggest potential improvements to care.

## Material and Method

This systematic review and thematic synthesis utilized a mixed PRISMA/ENTREQ methodology.<sup>11,12</sup> We employed a mixed methodology to enhance the rigor of systematic search and reporting of the thematic synthesis. Risk of bias assessment/study appraisal was not relevant for our study. The study was registered with PROSPERO (registration number: CRD42021265611).

### Search Strategy

We searched PubMed using the following pre-planned search strategy: (telepsychiatry OR internet-based treatment OR online intervention OR online treatment OR videoconference) AND (eating disorder OR anorexia nervosa OR bulimia OR binge eating OR orthorexia), date up to January 2022. Included studies were also cross-checked for references to eligible studies.

### Inclusion/exclusion criteria

Inclusion criteria followed the review's PICOS and included the whole clinical spectrum of disordered eating, with no limitations to patient age or gender, form of telepsychiatry used, or control condition used. To capture barriers comprehensively, we also included studies involving caregivers, qualitative studies of patients lived experience, and studies directly or indirectly investigating barriers. The search included primary research of all types (randomized controlled trials, non-randomized control trials, single group trials, observational studies, and service evaluation papers for qualitative data). Exclusion criteria were systematic and scoping reviews, thematic deviation, and language other than English.

### Study selection and data extraction

Eligible studies were screened independently by two authors (MS, NC), based on the eligibility criteria, as depicted in figure 1. Unresolved cases were externally arbitrated. Data extraction was doubly checked. The following study characteristics were tabulated: authors, publication year, design, sample size, type and duration of telepsychiatry intervention, type of ED, research outcome, dropout rate, and negative consequences.

## Results

### Selection of articles

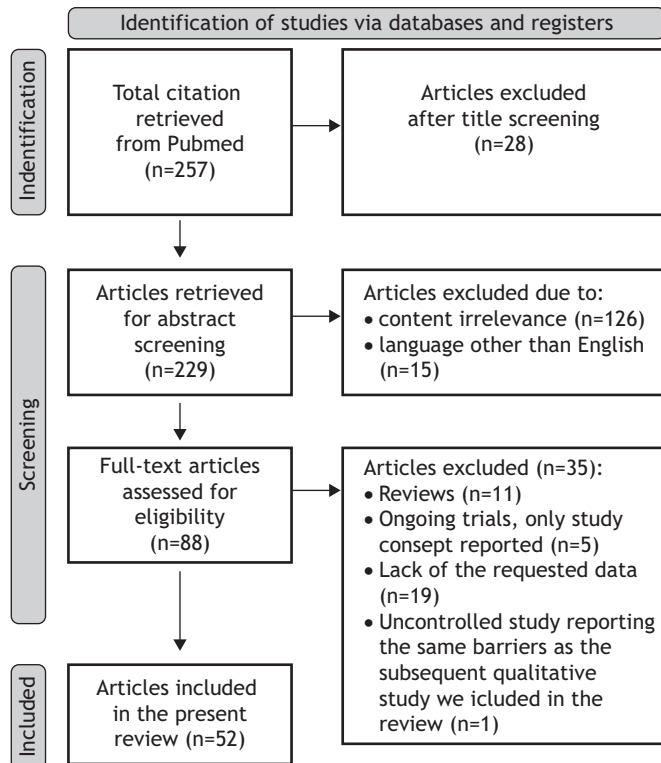
Following screening, 52 studies were included in the current review (PRISMA flow chart, figure 1), which are summarized in tabular form in the supplementary material (table S1). In total, there were 15 studies (n=2,451) with ED (diagnoses were not specified), 7 studies (n=716) with AN, 11 studies (n=1187) with BN, 7 studies (n=615) with BED, and 12 studies (n=1138) with mixed diagnosis (diagnosis was specified). Table S2 in the supplementary material shows the types of intervention in each diagnostic category. There was considerable heterogeneity in interventions, so further analysis of the results in each intervention separately was not possible. Nevertheless, we see that there are more studies and patients for i-CBT and i-GSH interventions.

### Barriers to treatment

A thematic analysis of included studies revealed a total of 10 barriers (figure 2). The most frequently reported barrier was reduced adherence- increased dropout rate (n=29), followed by poor therapeutic result (n=23), and type-severity of ED (n=21).

### Reduced adherence – increased dropout

The most common barrier was reduced adherence and increased dropout, reported by 25 studi



**Figure 1.** PRISMA flow diagram of the study-selection procedure.

es.<sup>15,17–21,25–27,30,31,37,39,40,42,47,50,51,53,56,57,59,60,63,64</sup> Some of the reasons reported were: Technical issues,<sup>20,59</sup> treatment ineffectiveness,<sup>19,58</sup> initial design flaws,<sup>25,59,64</sup> severe types of ED,<sup>19,21,26,30,31,40,57,59,60,64</sup> comorbidities,<sup>26,30,31,40,50,53,59,63,64</sup> personality traits,<sup>24,34,45,47,48,50</sup> social characteristics,<sup>40,42,59</sup> personal obligations,<sup>30,50</sup> family distraction,<sup>19,20,32,52</sup> and privacy and confidentiality.<sup>23,43,55</sup>

### Poor therapeutic result

Twenty three studies reported poor and/or slow therapeutic results of telepsychiatry,<sup>21,35,41,47,54,57</sup> or even no improvement whatsoever (for instance, in binge eating episodes and purging behaviours).<sup>13–15,20,22,30,31,33,39,45,49,56,61,63,64</sup> Motivational support did not improve outcomes<sup>27</sup> and a fully automated online intervention<sup>25</sup> failed to increase initial appointment attendance.

### Types and Severity of ED

Patients with severe body image distortion, frequent binge eating and purging, strict dietary restriction, and longer illness duration show lower adherence,<sup>19,31,40</sup> higher dropout rates,<sup>30,31,48,57,59,60,64</sup> and poorer outcomes.<sup>14,31,35,43,48,56,58,59,64</sup> The type of ED also affects results. Anorexia nervosa is associated with poor outcomes<sup>17,26,32,33</sup> and so is severe bulimia.<sup>14,35,39</sup> Patients prefer online treatment at the early stages of EDs, believing it to be more beneficial then.<sup>43</sup>

### Therapeutic alliance

A very important barrier documented in the literature is the difficulty in developing a strong therapeutic relationship. Seventeen studies<sup>15,20,23,29,32,36,43,44,52,55,57–62,64</sup> refer to the lack of intimacy and the difficulty of recognizing emotions and non-verbal behaviour, resulting in patients feeling the treatment as impersonal and the therapist as unsupportive. The difficulty in developing a therapeutic alliance is often mentioned in combination with a low therapeutic effect and/or a negative patient experience,<sup>15,20,23,36,43,44,58,61,64</sup> low adherence, and/or high dropout from treatment.<sup>18,25,34,43,47–49,55</sup> Also, many studies, such as V C Sánchez-Ortiz et al and Natalie Pretorius et al,<sup>43,44,62</sup> mention that the patients need more support and guidance (via email, phone calls, etc.) during the treatment process.

### Technical difficulties and design issues

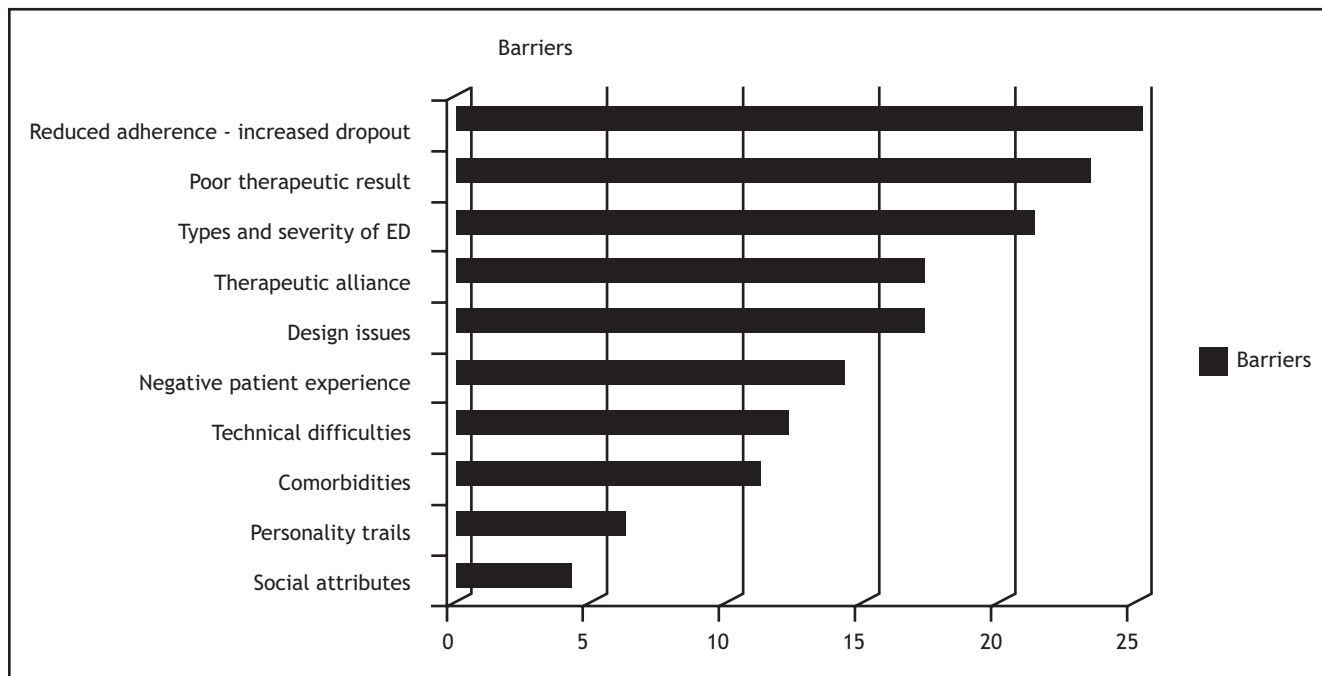
Twelve studies identified technical difficulties as a significant barrier to telepsychiatry,<sup>15,16,20,29,30,32,33,43,44,52,55,59</sup> while 17 studies pointed to poor design of online treatment programs as problematic.<sup>13,15,16,20,25,28,29,34,36,39,44,49,52,55,57,62,64</sup> Factors such as internet access, program workload, required devices, session duration/frequency, and communication methods with mentors/therapists influence patient experience and treatment outcomes. Unstable internet and difficulty using the program (e.g., playing audiovisual modules) led to low adherence to self-help exercises and reduced therapeutic effects.<sup>33,44</sup> Technical limitations hinder the development of a strong therapeutic alliance, reducing patient satisfaction and trust.<sup>29,59</sup> Lastly, poor program design negatively influenced some patients, as they exchanged harmful weight loss ideas with peers.<sup>44</sup>

### Negative patient experience

Many qualitative studies<sup>15,16,24,32,43,44,47,58</sup> report patient experience of online treatment as boring, impractical, less helpful, less personalized, and less satisfying than face-to-face therapy. Also, several studies report that face-to-face treatment is considered necessary, at least in parallel to online treatment, and online treatment alone is inadequate.<sup>16,17,35,39,43,55,56,61</sup>

### Comorbidities, social attributes, and personality traits

Stress, mood disorders, and substance misuse negatively affect patient adherence to treatment.<sup>20,24,32–34,37,45,46,50,56,61</sup> Poor education,<sup>40,42</sup> unemployment<sup>59</sup> and high workload<sup>19</sup> are linked with low adherence to treatment. Finally, personality traits like vulnerability, difficulty in socializing,



**Figure 2.** Frequency of barriers of telepsychiatry in EDs.

low self-esteem, and low self-discipline are associated with poor therapeutic outcomes.<sup>19,38,43,44,59,60</sup>

## Discussion

Internet-based therapy is certainly effective for EDs, as demonstrated by Barakat et al,<sup>65</sup> Samara et al,<sup>10</sup> and Dufour et al.<sup>66</sup> It enhances early intervention and results in symptomatic improvement, especially when CBT-based intervention<sup>10,65</sup> or FBT<sup>66</sup> for adolescents is employed, and when good technical equipment is used and an emphasis on the therapeutic relationship is achieved.

This review aimed to investigate the barriers to using telepsychiatry for treating EDs so that addressing them could make an already effective treatment even more effective.

We identified several barriers, many of which are interlinked, and they may be inductively grouped as follows:

- Therapeutic relationship and adherence to treatment
- Clinical limitations: poor therapeutic effect, illness severity, comorbidity, certain eating disorder types are barriers themselves, and personalised care
- Technical limitations: program design issues, privacy concerns, patient experience

The most frequent barrier was low treatment adherence, which is often linked to several other barriers, including the second most common barrier, poor therapeutic effect.<sup>15,20,21,25,27,30,31,36,37,39,48,57,60,61,63,64</sup> One common and simple strategy to enhance adherence is us-

ing brief telephone prompts, which improve adherence rates in patients with bulimia, even when delivered by non-healthcare professionals.<sup>67</sup> Conversely, rejecting telephone prompts leads to non-attendance at psychiatric outpatient appointments.<sup>68</sup> Treatment adherence can also be improved by making program design more user-friendly and reducing technical difficulties. This is in line with the findings of the review of Barakat et al, who mention that user-friendly utilization of multimedia has been associated with symptomatic improvement in EDs.<sup>65</sup>

Our review also shows that clinical complexity (symptom severity, certain eating disorder (ED) subtypes, and comorbidity) compromises telepsychiatry's effectiveness. Severe symptoms were linked to lower effectiveness, reduced treatment adherence, and higher dropout rates. Anorexia nervosa was often associated with poor results, probably due to the limitations of online treatments to supervise meals, to measure weight, and to check for weight-reduction behaviors.<sup>69</sup> Face-to-face interventions were also found to be more effective than remote interventions in achieving abstinence from binge/purge episodes.<sup>10</sup> Given the importance of weight gain in recovery,<sup>70</sup> it may be useful for patients with very low weight to initially receive face-to-face treatment until some weight gain is achieved before transitioning to online treatment. It is important to individualize online treatment or develop hybrid models that combine online and in-person therapy for patients with anorexia

nervosa, severe bulimia, and other ED subtypes with severe psychopathology or comorbidities.

A careful synthesis of our findings suggests that person-centered care, or the lack thereof, is the common denominator to the barriers highlighted in our report. Among the barriers, the therapeutic relationship, personalized care, privacy, and patient experience are particularly dependent on person-centered care. Equally, the fact that treatment adherence and clinical complexity (illness severity, comorbidity, ED subtypes) also emerge as barriers suggests that telepsychiatry lacks a longitudinal clinical effect. Taken together, even though generally effective, our study suggests that telepsychiatry misses the multifaceted and longitudinal nature of person-centered care.<sup>71,72</sup> Indeed, as suggested by Dufour et al, a sense of connection is crucial for therapeutic success.<sup>66</sup> This is in line with several studies in our review suggesting that more active therapist involvement could improve outcomes.

The reviews by Barakat et al,<sup>65</sup> Samara et al,<sup>10</sup> and Dufour et al,<sup>66</sup> recommend online therapy for EDs but also point out several barriers. More specifically, Barakat et al support that eTherapies currently available for ED treatment are limited in their interactive and personalized design features,<sup>65</sup> which is in line with the findings of Dufour et al, where both patients and clinicians report their experience of decreased connection in exclusively online treatment.<sup>66</sup> Samara et al found that remission was more likely with face-to-face interventions compared to online interventions.<sup>10</sup> Also, even though mobile apps are generally acceptable to youth, they have limited effects on ED psychopathology.<sup>66</sup>

This literature review presents several limitations. Firstly, there was considerable study design heterogeneity, including inconsistent diagnostic criteria, different inclusion/exclusion criteria, and interventions. Anorexia

nervosa was under-represented in this review, rendering the findings more pertinent to bulimia nervosa, binge eating disorder, and eating disorder not otherwise specified (EDNOS) phenotypes. In many studies, comorbidities influenced the response to treatment, and patient characteristics varied significantly, including age, sex, illness duration, and prescribed medication. Furthermore, heterogeneity was evident in the study outcomes, complicating direct comparisons between findings. The nature of this review did not allow a formal risk of bias assessment or meta-analysis. Consequently, this review adhered to a modified PRISMA checklist, adapted to accommodate a more flexible synthetic approach.

Future research should determine the most effective type of telepsychiatry for eating disorders (EDs) and explore different psychotherapy modalities and pharmacotherapy options. Systematic reviews indicate that CBT is superior to pharmacotherapy for binge eating disorder (BED),<sup>73</sup> while pharmacotherapy outperforms placebo for bulimia nervosa<sup>74</sup> and BED.<sup>75</sup> It is essential to investigate if telepsychiatry affects this treatment hierarchy. Additionally, hybrid models combining face-to-face and online therapy, especially for cases with clinical complexity, should be explored for potentially better outcomes.

In conclusion, while this study seems pessimistic, due to the nature of investigating barriers telepsychiatry is very useful and promising for treating EDs. Clinical adaptations, technological improvements, and a person-centered approach are essential to fully realize its potential.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: <https://doi.org/10.22365/jpsych.2025.007>

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# Ανασκόπηση

## Τα εμπόδια της τηλεψυχιατρικής στη θεραπεία ασθενών με διαταραχές πρόσληψης τροφής: Συστηματική ανασκόπηση και θεματική σύνθεση

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### ΠΕΡΙΛΗΨΗ

Οι διαταραχές πρόσληψης τροφής είναι ψυχικές διαταραχές, με κύρια χαρακτηριστικά τη διαταραγμένη εικόνα σώματος και τον υπέρμετρο φόβο για αύξηση του σωματικού βάρους, που οδηγούν σε διαταραχή του τρόπου λήψης τροφής και της συμπεριφοράς ελέγχου του βάρους. Μελέτες δείχνουν πως η έγκαιρη παροχή θεραπείας είναι από τους σημαντικότερους παράγοντες βελτίωσης της πρόγνωσης αυτών των ασθενειών. Παρ' όλα αυτά, μεγάλο ποσοστό των ασθενών με διαταραχές πρόσληψης τροφής δεν λαμβάνουν θεραπεία ή αναζητούν θεραπεία σε προχωρημένο στάδιο της νόσου. Η τηλεψυχιατρική φαίνεται ότι θα μπορούσε να αποτελέσει μια λύση σε αυτό το πρόβλημα, με την άρση των γεωγραφικών εμποδίων και την ελάττωση του κόστους μετακίνησης που προσφέρει. Παρ' όλα αυτά, υπάρχουν ανησυχίες σχετικά με την αποτελεσματικότητά της στη θεραπεία ασθενών με διαταραχές πρόσληψης τροφής, την εγκατάσταση ισχυρής θεραπευτικής σχέσης, τη διασφάλιση της προστασίας προσωπικών δεδομένων, την ασφάλεια και τους τεχνολογικούς περιορισμούς. Σκοπός της παρούσας εργασίας είναι η επισκόπηση των εμποδίων που περιορίζουν τη χρησιμότητα της τηλεψυχιατρικής στη θεραπεία των διαταραχών πρόσληψης τροφής. Ο απώτερος στόχος είναι η βελτίωση των υπάρχοντων υπηρεσιών τηλεψυχιατρικής, ώστε να εξυπηρετούν καλύτερα και ασφαλέστερα τις ιδιαίτερες ανάγκες των ασθενών με διαταραχές πρόσληψης τροφής. Διενεργήσαμε συστηματική ανασκόπηση και θεματική σύνθεση χρησιμοποιώντας μικτή μεθοδολογία PRISMA/ENTREQ, εστιάζοντας στις έρευνες που διερεύνησαν άμεσα ή έμμεσα τα εμπόδια στη χρήση της τηλεψυχιατρικής για τη θεραπεία ασθενών με διαταραχές πρόσληψης τροφής. Συμπεριλήφθηκαν πενήντα δύο μελέτες, οι οποίες απεκάλυψαν πολύπλευρες προκλήσεις στην εφαρμογή της τηλεψυχιατρικής για ασθενείς με διαταραχές πρόσληψης τροφής. Συγκεκριμένα εμπόδια που εντοπίστηκαν περιλαμβάνουν δυσκολίες στη δημιουργία ισχυρής θεραπευτικής σχέσης και στη διατήρηση της συμμόρφωσης στη θεραπεία, κλινικούς περιορισμούς (φτωχό θεραπευτικό αποτέλεσμα, βαρύτητα ασθένειας, συννοσηρότητα, ορισμένοι τύποι διατροφικών διαταραχών που αποτελούν οι ίδιοι εμπόδια, απρόσωπη φροντίδα) και τεχνικούς περιορισμούς (ζητήματα σχεδιασμού προγραμμάτων, ανησυχίες για την προστασία της ιδιωτικότητας), καθώς και αρνητική εμπειρία ασθενών. Η τηλεψυχιατρική δείχνει πολλά υποσχόμενη για τη θεραπεία των διαταραχών πρόσληψης τροφής, αλλά είναι σημαντικό να αντιμετωπιστούν και τα εμπόδια που εντοπίζονται κατά την εφαρμογή της. Η κλινική προσαρμογή, οι τεχνολογικές βελτιώσεις και η προσωποκεντρική προσέγγιση είναι ουσιαστικής σημασίας για την πλήρη αξιοποίηση του δυναμικού της. Τα διαδικτυακά ή υβριδικά μοντέλα θεραπείας χρειάζεται να είναι εξατομικευμένα, πολυδιάστατα και με ενεργή συμμετοχή του θεραπευτή, ιδιαίτερα για ασθενείς με κλινική πολυπλοκότητα.

**ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ:** Διατροφικές διαταραχές, τηλεψυχιατρική, διαδικτυακή θεραπεία, εμπόδια, προσωποκεντρική ιατρική.

## Brief communication

# COVID-19 Fear and coping strategies during the pandemic: Insights from Greek health services units

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### ABSTRACT

This study aimed to assess the fear caused by the COVID-19 pandemic among health service users in Greece. The study involved 1260 participants from three health services units in the prefecture of Corinthia. The COVID-19 Fear Scale (FCV-19S) and the Coping Orientation to Problems Experienced Inventory (Brief-COPE) were used to assess fear levels. Results showed that females experienced a significantly higher fear of COVID-19 (15.9 compared to 15.4), while the age group of >60 years had the highest mean score (16.6). Individuals in retirement showed a greater fear of COVID-19 (16.8), while health sector employees had lower fear scores (15.1). Chronically ill patients had a higher fear of COVID-19 (16.5 as opposed to 15.5 of healthy persons), while people considering that the COVID-19 pandemic will be dealt with soon presented lower levels of fear compared to those not considering it or being uncertain. According to the Brief-COPE questionnaire, fear of COVID-19 total scores were positively correlated with two of the coping subscales; the emotion-focused and the avoidant-coping. The study's findings can contribute to the identification of fear and coping strategies for the development of targeted interventions and mental health support programs during this global crisis.

**KEYWORDS:** COVID-19, fear, fear assessment, fear of COVID-19 scale, coping strategies.

### Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus and its consequent public health measures has significantly impacted global physical and mental health, leading to anxiety, stress, depressive symptoms, insomnia, denial, anger, and fear.<sup>1,2</sup> The rapid proliferation of the disease and measures to mitigate its spread has created a state of emotional and psychological disturbance, causing fear of infection and vaccination

across various age groups and cultural backgrounds.<sup>3</sup> This Fear of COVID-19 (FOC) has been one of the most common psychological reactions in the population during the pandemic.<sup>4</sup> Data from systematic reviews and meta-analyses examining the period of the pandemic have revealed associations between FOC and various mental health factors, such as anxiety and depression.<sup>5,6</sup> These associations were also found in Greek samples.<sup>7</sup> People use various coping strategies to handle stress-

ful situations and fear. These can be adaptive, like positive reframing and social support, or maladaptive, like avoidance, denial, and substance use.<sup>8</sup> Adaptive coping is linked to better psychological well-being, while maladaptive coping is associated with higher distress.<sup>9</sup> This study, taking into account that FOC is high around the world, with varying means in different countries and populations,<sup>4</sup> aims to evaluate the level of FOC in peripheral Greek health services users as well as the associations of FOC with different characteristics and coping styles.

## Material and Method

### Sample

The study, conducted from September 2021 to September 2022, included 1260 individuals assessed at three health services units in Corinthia, Greece: two health centers and a vaccination center. The sample consisted of health service users attending these facilities for regular appointments and vaccinations. These facilities were chosen for their accessibility and because they served a population that was otherwise difficult to reach during the pandemic and lockdown measures.

### Research tools

The study utilized the Fear of COVID-19 Scale (FCV-19S)<sup>10</sup> (translated and validated in Greek<sup>7</sup>), the Coping Orientation to Problems Experienced Inventory (Brief-COPE) questionnaire<sup>11,12</sup> as well as a Socio-demographic Questionnaire.

#### *The Fear of COVID-19 Scale*

The Fear of COVID-19 Scale is a self-reporting tool consisting of seven items that assess fear of COVID-19. The FCV-19S comprises seven items, each with a five-point Likert-type scale (1=strongly disagree to 5=strongly agree). The total score of the FCV-19S ranges from 7 to 35; higher scores represent greater fear against the novel coronavirus disease.

#### *The Coping Orientations to Problems Experienced Inventory (COPE), Brief-Cope*

A total of 28 questions are included being also divided into 3 categories, while the answers are given on a four-point Likert scale where 1: I don't do it at all, 2: I do it a little, 3: I do it to a moderate extent and 4: I do it a lot. The 3 categories of the questionnaire are: (1) Problem-focused coping, (2) Emotion-focused coping (3) and Avoidance Coping.<sup>11,12</sup>

### Statistical analysis

Data were analyzed using SPSS (Statistical Package for the Social Sciences, version 25). Descriptive statistics, percentage distributions, and mean values were employed for socio-demographic, labor, health, and lifestyle variables. Non-parametric tests were applied to assess relationships with FCV-19S total score and Brief-COPE subscales due to their non-normal distribution. Pearson correlation examined the association between FCV-19S total score and Brief-COPE subscales. Significance level was set at 0.05.

## Results

The results of the study provide valuable insights into the fear of COVID-19 within the sampled population. The distribution of responses means, and standard deviations for the items of FCV-19S (table 1) highlights notable agreement, with the highest percentages recorded for items I2, I5, and I1. More specifically, 38.8%, 32.8%, and 29.6% of participants agreed or strongly agreed with these items, indicating a substantial level of fear. Regarding the mean score, the two highest were 3.00 (1.24) of I2 and 2.87 (1.19) of I1. In contrast, items I6 and I3 garnered the lowest mean scores of 1.49 (0.65) and 1.52 (0.72), reflecting variations in fear levels across specific aspects of the pandemic. The overall mean score for the FCV-19 Scale in the sample was  $m=15.65\pm 3.62$ , providing a comprehensive measure of the fear experienced by the participants.

The examination of demographic, labor, health, and lifestyle characteristics (table 2) unveils noteworthy associations with the fear of COVID-19. Females exhibited a significantly higher fear level (15.9 compared to 15.4), while the age group of >60 registered the highest mean score (16.6). Individuals in retirement expressed greater fear (16.8), while unemployed and public servants displayed the lowest scores (15.2 & 15.3). It is worth mentioning that healthcare professionals manifested the lowest fear levels (15.1). Chronically ill individuals reported higher fear levels (16.5 compared to 15.5 in healthy individuals), while individuals being confident in the pandemic's resolution exhibited lower fear (14.7).

The correlation analysis revealed that the Emotion-Focused coping subscale showed a weak but significant positive correlation ( $r = 0.055$ ,  $p = 0.049$ ) with FCV-19S scores, indicating that higher fear of COVID-19 is slightly associated with increased use of emotion-focused strategies. The Avoidant Coping subscale had a weak but significant positive correlation ( $r = 0.093$ ,  $p = 0.001$ ), suggesting that higher fear levels are linked to more frequent use of avoidant coping strategies. Problem-

**Table 1.** Item-wise distribution of responses, means, and SDs.

| Item   | Percentage distribution* |       |       |       |       | Mean (SD)   |
|--|--------------------------|-------|-------|-------|-------|-------------|
|  | 1                        | 2     | 3     | 4     | 5     |             |
| I1. I am most afraid of the coronavirus  | 20.2%                    | 10.4% | 39.8% | 21.7% | 7.9%  | 2.87 (1.19) |
| I2. It makes me uncomfortable to think about coronavirus                         | 18.4%                    | 12.0% | 30.7% | 28.8% | 10.0% | 3.00 (1.24) |
| I3. My hands become clammy when I think about coronavirus                        | 58.3%                    | 33.5% | 6.1%  | 1.8%  | 0.3%  | 1.52 (0.72) |
| I4. I am afraid of losing my life because of coronavirus                         | 34.8%                    | 14.7% | 27.8% | 17.9% | 4.9%  | 2.43 (1.26) |
| I5. I become nervous or anxious when watching news and stories about coronavirus | 32.1%                    | 19.9% | 15.2% | 22.3% | 10.5% | 2.59 (1.40) |
| I6. I cannot sleep because I'm worried about getting coronavirus                 | 58.9%                    | 33.7% | 6.9%  | 0.5%  | 0.1%  | 1.49 (0.65) |
| I7. My heart races or palpitates when I think about coronavirus                  | 46.7%                    | 37.2% | 11.0% | 4.8%  | 0.2%  | 1.75 (0.85) |

\*Five-point Likert scale where score – 1: strongly disagree to score 5: strongly agree

Focused coping subscale had a non-significant negative correlation with the FCV-19S score ( $r=-0.012$ ,  $p=0.647$ ).

## Discussion

The COVID-19 pandemic had a significant impact on the physical and mental health of the general population, leading to increased levels of fear and anxiety. Additionally, it was observed that concerning the socio-demographic characteristics, (gender, age, chronic disease, working status, job sector) fear levels vary.<sup>4</sup>

In our research, females -compared to men- and the age group of >60 years old experienced higher FOC. These findings are in agreement with those measured by the Greek study for the validation of FCV-19S7. A meta-analysis examining gender and FOC has found a moderate and statistically significant effect on FOC and anxiety in favor of females.<sup>13</sup> Conversely, one systematic review and meta-analysis of FOC found no significant association between FOC and gender, while a different one found age not to be significantly associated with FOC.<sup>4,5</sup> These studies suggest that different rates of FOC in different countries can be attributed to contextual and cultural factors and access to medical services.<sup>4</sup>

According to our study's results, there is a statistically significant correlation between fear of COVID-19 and the presence of chronic diseases, with chronically ill individuals reporting higher fear of the pandemic compared to those not suffering from chronic diseases. These findings are in alignment with those from a study from Cyprus.<sup>14</sup> Furthermore, our study revealed that people in retirement experienced greater fear while unemployed individuals as well as public servants showed the lowest fear score. In the lack of data from reviews and meta-analyses, we examined reports from different countries regarding FOC and employment. A study in Saudi Arabia found no significant association between

FOC and employment status,<sup>15</sup> while a Bangladesh study reported that older adults -unemployed or in retirement- were more likely to experience FOC.<sup>16</sup> Research indicates that fear associated with uncertainty about the future impact of the COVID-19 pandemic is lower among those who believe it will be resolved soon.<sup>14,17</sup>

Our study reveals a weak but positive relation between the fear of COVID-19 and the following two coping subscales: emotion-focused and avoidant coping. Emotion-focused coping is a vital aspect of individuals' response to the COVID-19 pandemic, focusing on regulating feelings and emotional reactions to stressors. Higher scores on this coping subscale indicate strategies addressing various emotions, such as fear, anger, sadness, anxiety, and uncertainty.<sup>18,19</sup> Individuals with elevated scores engage in adaptive strategies, express and process their emotions, gaining emotional regulation and mental well-being. Research indicates that emotion-focused coping has a positive impact on long-term mental health outcomes during crises.<sup>20</sup> In addition it entails mindfulness, acceptance of emotions, as well as seeking social support, allowing individuals to navigate the challenges imposed by the pandemic's protracted and unpredictable nature.<sup>21</sup>

Engagement in avoidance-coping strategies, which involves physical or cognitive efforts to disengage from stressors, is an important component of the individual's response to the COVID-19 pandemic.<sup>20</sup> Although it may provide temporary relief, it is often considered maladaptive in the long term, potentially hindering problem-solving and emotional processing. High reliance on avoidance strategies can negatively affect mental health, leading to anxiety and distress. Individuals have been found to shift between regulation strategies, using maladaptive methods, such as avoidance and counterarguing, to manage FOC.<sup>22</sup> Excessive avoidance may

**Table 2.** Demographic, labor, health and lifestyle characteristics

| Variable   | N (%)        | Mean (SD)  | Sig.  |
|--|--------------|------------|-------|
| <b>Gender</b>                                      |              |            |       |
| Male   | 605 (49.1%)  | 15.4 (3.6) | 0.032 |
| Female   | 627 (50.9%)  | 15.9 (3.7) |       |
| <b>Age group</b>                                   |              |            |       |
| 18-29  | 246 (19.5%)  | 15.0 (3.5) | 0.018 |
| 30-40  | 263 (20.9%)  | 15.9 (3.3) |       |
| 41-59  | 648 (51.4%)  | 15.5 (3.5) |       |
| 60 or above  | 103 (8.2%)   | 16.6 (5.1) |       |
| <b>Education level</b>                             |              |            |       |
| Primary or Secondary Education                     | 429 (34.0%)  | 15.6 (4.2) | 0.642 |
| Higher Education                                   | 607 (48.2%)  | 15.6 (3.4) |       |
| Master or PhD                                      | 224 (17.8%)  | 15.8 (3.1) |       |
| <b>Residence (based on population)</b>             |              |            |       |
| City over 100k                                     | 249 (19.8%)  | 15.7 (3.2) | 0.190 |
| City under 100k                                    | 715 (57.0%)  | 15.7 (3.7) |       |
| Village or Island                                  | 291 (23.2%)  | 15.4 (3.8) |       |
| <b>Working status</b>                              |              |            |       |
| Unemployment                                       | 193 (15.4%)  | 15.2 (3.5) | 0.010 |
| Private sector                                     | 309 (24.7%)  | 16.2 (3.5) |       |
| Public sector                                      | 375 (29.9%)  | 15.3 (3.3) |       |
| Freelancer   | 227 (18.1%)  | 15.8 (3.3) |       |
| Retired  | 69 (5.5%)    | 16.8 (5.6) |       |
| Other  | 80 (6.4%)    | 15.2 (3.9) |       |
| <b>Job Sector</b>                                  |              |            |       |
| Health sector                                      | 153 (14.6%)  | 15.1 (3.3) | 0.035 |
| Education sector                                   | 164 (15.6%)  | 15.4 (3.3) |       |
| Foodservice sector                                 | 210 (20.0%)  | 15.8 (3.3) |       |
| N/A  | 523 (49.8%)  | 15.9 (3.1) |       |
| <b>Work during the restrictive measures period</b> |              |            |       |
| On suspension                                      | 188 (15.0%)  | 15.9 (3.5) | 0.180 |
| Yes, at the workplace                              | 651 (52.0%)  | 15.5 (3.6) |       |
| Yes, remotely                                      | 192 (15.3%)  | 16.1 (3.2) |       |
| Employment Termination                             | 124 (9.9%)   | 15.6 (3.5) |       |
| N/A  | 97 (7.7%)    | 15.2 (3.1) |       |
| <b>Chronic disease</b>                             |              |            |       |
| No   | 1066 (84.6%) | 15.5 (3.4) | 0.020 |
| Yes  | 194 (15.4%)  | 16.5 (4.5) |       |
| <b>Mental illness</b>                              |              |            |       |
| No   | 1209 (96.0%) | 15.6 (3.4) | 0.079 |
| Yes  | 50 (4.0%)    | 17.9 (7.1) |       |
| <b>Smoking</b>                                     |              |            |       |
| No   | 844 (67%)    | 15.7 (3.7) | 0.950 |
| Yes  | 415 (33%)    | 15.5 (3.5) |       |

Continues

**Table 2.** Continued.

| Variable  | N (%)        | Mean (SD)  | Sig.   |
|---|--------------|------------|--------|
| Alcohol consumption (drinks per week)                             |              |            |        |
| No consumption at all   | 471 (37.4%)  | 15.7 (3.7) | 0.966  |
| 1 or 2 drinks   | 472 (37.5%)  | 15.8 (3.5) |        |
| 3 or more drinks  | 317 (25.2%)  | 15.6 (3.7) |        |
| Exercise more than 3 hours per week                               |              |            |        |
| No  | 755 (59.9%)  | 15.8 (3.8) | 0.787  |
| Yes   | 505 (40.1%)  | 15.6 (3.4) |        |
| Computer use more than 3 hours daily                              |              |            |        |
| No  | 708 (56.3%)  | 15.6 (3.6) | 0.144  |
| Yes   | 550 (43.7%)  | 15.8 (3.6) |        |
| Mobile use more than 3 hours daily                                |              |            |        |
| No  | 696 (55.3%)  | 15.9 (3.8) | 0.287  |
| Yes   | 563 (44.7%)  | 15.5 (3.4) |        |
| Infection from Covid-19   |              |            |        |
| No  | 1090 (86.5%) | 15.7 (3.6) | 0.156  |
| Yes   | 170 (13.5%)  | 15.3 (4.1) |        |
| Covid-19 vaccinated   |              |            |        |
| No  | 138 (11.0%)  | 15.5 (4.0) | 0.889  |
| Yes   | 1122 (89.0%) | 15.7 (3.6) |        |
| Confidence in the health system to deal with Covid-19?            |              |            |        |
| Not at all  | 87 (6.9%)    | 14.8 (3.5) | 0.430* |
| Moderate  | 613 (48.7%)  | 15.6 (3.4) |        |
| Enough  | 323 (25.7%)  | 15.6 (3.7) |        |
| Much  | 163 (13.0%)  | 16.1 (3.4) |        |
| Very much   | 72 (5.7%)    | 15.6 (5.3) |        |
| Confidence in the medical and nursing staff to deal with Covid-19 |              |            |        |
| Not at all  | 18 (1.4%)    | 13.6 (4.3) | 0.846* |
| Moderate  | 292 (23.2%)  | 15.7 (3.4) |        |
| Enough  | 381 (30.2%)  | 15.8 (3.7) |        |
| Much  | 360 (28.6%)  | 15.7 (3.4) |        |
| Very much   | 209 (16.6%)  | 15.7 (4.1) |        |
| Do you think the Covid-19 pandemic will be dealt with soon?       |              |            |        |
| No  | 508 (40.3%)  | 15.8 (3.5) | 0.000  |
| Yes   | 228 (18.1%)  | 14.7 (3.3) |        |
| Maybe   | 524 (41.6%)  | 15.9 (3.8) |        |

\*Spearman correlations

lead to information overload.<sup>23</sup> Balancing avoidance along constructive coping strategies is of major significance, highlighting the need to address stressors directly and encourage a broader strategy to overcome the difficulties imposed by the ongoing uncertainty.

Our results demonstrate that demographic variables such as gender, age, chronic disease, working status, and job sector significantly influence FOC in the Greek population. This provides significant data for the discussion regarding the characteristics influencing FOC

variance across different countries. The nuanced understanding of fear and coping strategies derived from our findings adhere to targeted interventions regarding

emotion-focused coping strategies, which have been shown to improve mental health outcomes<sup>20</sup> especially among females and older adults.

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## Σύντομο άρθρο

# Φόβος για την COVID-19 και στρατηγικές αντιμετώπισης κατά τη διάρκεια της πανδημίας: Δεδομένα από ελληνικές μονάδες υπηρεσιών υγείας

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### ΠΕΡΙΛΗΨΗ

Σκοπός της παρούσας μελέτης ήταν να εκτιμηθεί ο φόβος που προκαλεί η πανδημία COVID-19 σε λήπτες υπηρεσιών υγείας στην Ελλάδα. Στη μελέτη συμμετείχαν 1260 άτομα από τρεις μονάδες υπηρεσιών υγείας του νομού Κορινθίας. Για την αξιολόγηση των επιπέδων φόβου χρησιμοποιήθηκαν η Κλίμακα Φόβου COVID-19 (FCV-19S) και το Ερωτηματολόγιο Προσανατολισμών στην Αντιμετώπιση Προβλημάτων (Brief-COPE). Τα αποτελέσματα έδειξαν ότι οι γυναίκες είχαν σημαντικά υψηλότερο φόβο για την COVID-19 (15,9 έναντι 15,4), ενώ η ηλικιακή ομάδα των 60 ετών και άνω είχε την υψηλότερη μέση βαθμολογία (16,6). Οι συνταξιούχοι είχαν μεγαλύτερο φόβο για την COVID-19 (16,8), ενώ οι εργαζόμενοι στον τομέα της υγείας είχαν χαμηλότερη βαθμολογία φόβου (15,1). Οι ασθενείς με χρόνιες παθήσεις είχαν υψηλότερο φόβο για την COVID-19 (16,5 έναντι 15,5 των υγιών ατόμων), ενώ τα άτομα με την πεποίθηση ότι η πανδημία COVID-19 θα αντιμετωπιστεί σύντομα παρουσιάζουν χαμηλότερα επίπεδα φόβου σε σύγκριση με εκείνους που ήταν αβέβαιοι και εκείνους που δεν το πίστευαν αυτό. Σύμφωνα με το ερωτηματολόγιο Brief-COPE, η συνολική βαθμολογία του φόβου για την COVID-19 συσχετίστηκε θετικά με δύο από τις υποκλίμακες αντιμετώπισης, την αντιμετώπιση με επίκεντρο το συναίσθημα και την αντιμετώπιση αποφυγής. Τα ευρήματα της μελέτης μπορούν να συμβάλουν στον εντοπισμό του φόβου και των στρατηγικών αντιμετώπισης για την ανάπτυξη στοχευμένων παρεμβάσεων και προγραμμάτων υποστήριξης της ψυχικής υγείας κατά τη διάρκεια αυτής της παγκόσμιας κρίσης.

**ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ:** COVID-19, φόβος, αξιολόγηση του φόβου, Κλίμακα Φόβου COVID-19 (FCV-19S), στρατηγικές αντιμετώπισης.